Byung-Boong Lee
Stanley G. Rockson
John Bergan *Editors*

Lymphedema

A Concise Compendium of Theory and Practice

Second Edition

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Foreword

In the foreword of the first edition of this book, I wrote, «If venous diseases are the Cinderella of the vascular field as the late Michael Hume, former President of the American Venous Forum, called them, then the lymphatics are Cinderella's poor cousin.» This second edition of *Lymphedema: A Compendium of Theory and Practice*, which will be published only a few years after the first edition, is a welcome evidence of the great interest and acceptance that the subject of lymphedema and its challenging pathology has received among the students of vascular disorders. The lymphatics are no more the poor cousin of the vascular system. How pleased would have been the late John Bergan, coauthor of the first edition, to see that the field that he chose and made seminal contributions to during the last two decades of his life is now in its second edition and in the limelight of most vascular meetings. Even a prestigious journal is dedicated solely to diseases of the venous and lymphatic systems!

This book is a welcome update of the first edition and has been elevated to the category of textbook. The addition to every chapter of an abstract, a summary of basic concepts, and a few annotated relevant references is an important contribution to its contents. Almost every chapter has been expanded and revised to include an update of our current knowledge on the subject.

The critically important work of early investigators in the field of the lymphatic physiology and pathophysiology, such as Servelle, Kinmonth, Casley-Smith, Olszewski, Nielubowicz, Földi, and others, established the basis and served as a stepping-stone for many of the subjects covered by recognized specialists in this book. As recognized by all investigators, one of the most important obstacles in the study of the lymphatics has been its visualization. The technique of visual lymphography using intradermal injections of Patent Blue (alphazurine) to study cutaneous and deeper lymphatics followed the technique of oil lymphography and lymphadenography as described by Professor John Kinmonth. These techniques were a useful tool in the study of the lymphatic vasculature and served as the basis for an early classification of lymphedemas. The tedious and time-consuming lymphography has been replaced by new nuclear medicine imaging techniques, radionuclide lymphoscintigraphy, multislice CT scan, magnetic resonance imaging, and computerized axial tomography. These techniques have contributed to guide the clinician in the process of establishing a rational diagnosis and dictating appropriate treatment. Advances in diagnosis have been followed by an array of therapeutic techniques. Many of them are described in this book by their original authors.

At this point, I will take the liberty to narrate a pertinent anecdote that happened during my fellowship at the Peter Bent Brigham Hospital in Boston. It was my fortune that, in the fall of 1957, Professor John Kinmonth from St.

Thomas' Hospital in London came to Boston as a visiting professor invited by my mentor Professor Richard Warren. Mr. Kinmonth gave us a great lecture on lymphatic disorders and the lymphangiography procedure that he pioneered and had performed in more than 2000 patients in London.

During a break, Mr. Kinmonth pulled me aside and gave me a small bag containing one ounce of a blue powder that was his «Patent Blue Violet,» a vital dye that diffuses readily and is absorbed promptly by the lymphatic vessels. He had used it extensively to visualize the lymphatics. He gave me detailed instructions on how to use it and told me: «young fellow, take this powder and prepare an 11% distilled water solution, sterilize it, and start using it!»

Professor Kinmonth's visit to the Brigham sparked the flame of a lifetime interest in the lymphatic system. I became fascinated with the elusive little channels and their physiopathology. The reflections of my mentor's friendship with Professor Kinmonth led him to study the lymphatics. Doctor Warren and I designed an instrument to measure lymphatic pressures and perform direct lymphangiography that is described in this book.

The tedious and time-consuming Kinmonth's lymphography has been replaced by new nuclear medicine imaging techniques, radionuclide lymphoscintigraphy, multislice CT scan, magnetic resonance imaging, and computerized axial tomography. These techniques have contributed to guide the clinician in the process of establishing a rational diagnosis and dictating appropriate treatment. Advances in diagnosis have been followed by an array of therapeutic techniques. Many of them are described in this book by their original authors. Because of my longtime interest on the subject, I have had personal experience with some of the diagnostic and surgical techniques described in this book such as oil lymphography, lymphoscintigraphy, lymphovenous anastomosis, and debulking procedures for massive lymphedema. I consider however that, at present, a program of complex manual decongestive techniques, associated with properly applied intermittent pneumatic compression and followed by a closely supervised compression therapy program in a compliant patient, may achieve long-lasting edema control without the need for surgery. The role of surgery, as described in surgical books and texts of vascular surgery, has been relegated to severe cases of chronic fibro-lymphedema treated by reconstructive plastic surgery to excise the fibrous tissue and remodel the redundant skin folds resulting from a good lymphatic manual decompression program of the extremities.

The science of genetics has found fertile ground in the pathology of the lymphatic vasculature. I am certain that as genetic research on the phenotypes of different lymphedema conditions progresses, our thoughts and concepts on the nature and classification of some primary lymphedemas will change. The same will occur in those cases of lymphedemas associated to other vas-

cular and nonvascular anomalies. We are on the threshold of a true revolution in our understanding of the Kinmonth lymphedemas for the benefit of our own understanding of the disease and, hopefully, for the benefit of the many unfortunate patients suffering from the disabling pathology of the lymphatic system.

J. Leonel Villavicencio, MD, FACS
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Preface

It is indeed gratifying that, a scant 5 years after the first publication of this compendium, we find ourselves in need of a revision and expansion of the text. This fact is testimony to the continued and growing renaissance that is being experienced in the realm of lymphatic science and, specifically, as it impacts the vexing problem of lymphedema and related disorders. The transformation that we sensed in 2011 is far from over.

The last 5 years have witnessed substantial growth of insights within the genetics, developmental biology, and physiology of the lymphatic system, as evidenced by the steady growth of publications devoted to this subject and by the 15% growth in the number of manuscripts indexed by the National Library of Medicine.

While the translation of biomedical science into diagnostic and therapeutic advances can be frustratingly slow, the last 5 years have indeed witnessed a substantial evolution in the evaluation and medical care of these patients. Specifically, significant progress has been made in diagnostic imaging and in reconstructive surgical interventions, with increasing utilization of the various approaches that have been developed. One can say, optimistically, that greater numbers of lymphedema patients now have access to appropriate evaluation and therapeutic interventions. There is substantially greater awareness of the problem, which translates into more effective surveillance mechanisms for the at-risk population.

It has been our intent that this second edition of our compendium accurately reflects the exponential growth in the content of this subject matter. We have had the opportunity to work with our distinguished colleagues in generating new and expanded subject matter. Given the increasing need for clinicians to embrace this material, we have added features that allow this work to be utilized as a textbook of lymphatic medicine, including summaries of the basic concepts inherent in each chapter, and highlighted references that reflect the most important primary sources of information.

For the first edition of this book, we had the honor and privilege to work editorially with our colleague Dr. John Bergan. It is our fervent hope that this edition serves as a fitting tribute to him and to his distinguished career.

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Preface to the First Edition

It is truly fortunate that, as we enter the twenty-first century, the fields of lymphatic biology and medicine are experiencing a highly anticipated renaissance. This much-needed emphasis upon the study of the lymphatic system is predicted to have a transformative impact upon our understanding of physiology, health, and disease.

Inexplicably, the lymphatic system has been the subject of passive neglect for centuries of medical development. This is, indeed, paradoxical, considering that such a very important component of the human circulation plays an equally important role in the normal functioning of the immune apparatus. Awareness of the importance of lymphatic mechanisms to the continuum of human biology and disease is growing. This «lymphatic continuum» now easily encompasses cardiovascular disease, obesity, autoimmune disease, respiratory and other forms of chronic inflammation, and chronic transplant rejection, among many other expressions of human pathology.

Lymphedema is a central manifestation of both peripheral and visceral diseases of the lymphatic circulation. Any pathological condition of the lymphatic vasculature, whether superficial or internal, regional, or systemic, is predominated by the appearance of the characteristic type of tissue edema that occurs when lymphatic dysfunction supervenes. While there is a broad spectrum of lymphatic vascular diseases, the most common diagnosis in lymphatic medicine is, of course, lymphedema.

This patient population is large and, historically, underserved by the medical community. At last, after decades and centuries of relative neglect, these patients are increasingly receiving attention. It is very timely, and gratifying, that there is now a clinical need for a comprehensive textbook that addresses the problem of lymphedema, and it is equally gratifying to acknowledge that this compendium has called upon the expertise of so many authorities to contribute their collective wisdom.

I am especially honored to collaborate with such an inspiring group of colleagues and, in particular, to have had the privilege to work so closely with my esteemed coeditors, Drs. John Bergan and Byung-Boong Lee.

It is an honor to dedicate this volume to the current and future well-being of our patients with lymphedema.

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Introduction

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General Considerations

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1

Summary of Basic Concepts

Over the last 20 years, insight into lymphatic structural biology and function has undergone an unparalleled renaissance. There has been a consequent growth in comprehension of lymphatic function in health and in disease. The diagnosis of lymphatic edema needs a differential diagnostic approach that may require distinct imaging approaches and that will, by inference, lead to precise utilization of treatment resources, including physical modalities, surgical interventions, and, increasingly, pharmacology. These are all intended to improve lymph flow and macromolecular clearance from the affected edematous regions.

- Failure of fluid homeostasis, immune traffic, and/or lipid uptake and transport are the hallmarks of the entire spectrum of lymphatic disease, including both primary and acquired forms of lymphedema, lymphatic inflammatory, lymphatic maldevelopment, and cancer metastasis.
- Insights into normal function, and its aberration in disease, derive from the active investigation of lymphatic vascular development and postnatal remodeling and repair.
- Edema occurs if lymphatic load is abnormally increased, if the transport capacity is reduced (obstructive lymphedema), or if there is any combination of these two.
- Primary lymphedema can be sporadic, hereditary, or syndrome-associated. Secondary lymphedema is acquired and can be further classified as benign (on the basis of trauma, infection, or iatrogenic causes) or malignant (the result of direct neoplastic invasion). Mixed lymphaticovenous edemas are also common.
- Lymphedema is not usually life-threatening, but the presence of lymphatic disease typically has a very deleterious effect on quality of life (▶ Chap. 37), based upon loss of function, restriction of movement, loss of body image and self-esteem, impaired psychosocial adjustment, and the risk of infection.
- The clinical diagnosis of lymphedema relies most heavily upon observations made at the bedside. Discrimination from other non-lymphatic forms of edema requires recognition of the unique cutaneous sequelae of lymphedema. The diagnosis can be confirmed through a variety of imaging modalities, including duplex ultrasonography, lymphoscintigraphy, computed tomography, magnetic resonance imaging, positron emission tomography, near-infrared fluorescent lymphography, and oil-based lymphangiography.
- Treatment of lymphedema is mandatory at the earliest detectable time point in the evolution of the disease. Decongestive physiotherapies been shown to have a very beneficial impact upon edema volume and patient symptomatology.
- Pharmacologic approaches include aggressive control of infection through antibiotic therapy. Molecular modifications, including growth factor-based and cellular therapies (▶ Chap. 36), continue to hold great future promise.
- Surgical therapies for lymphedema are enjoying increasing utilization as these approaches continue to be refined. The surgical approach to the lymphedema patient may include both reconstructive (Part VIII) and excisional (Part IX) techniques.
- Surgical therapies for lymphedema are enjoying ever-increasing utilization as these approaches continue to be refined. The surgical approach to the lymphedema patient can incorporate both reconstructive and excisional techniques.

Lymphedema is a common condition that is still, commonly, underappreciated and undertreated. Thankfully, there is a growing emphasis upon mechanisms related to lymphatic development, function, and repair; these investigations are likely to translate into clinical advances that will stimulate the development of new and efficacious treatment interventions [1].

Fear and frustration are common experiences for the lymphedema patient. It is the purpose of this volume to provide substantive information to assist the clinician in responding to the needs of these complex presentations [2].

The lymphatic vasculature occupies a central role in health maintenance and can participate actively in the progression of various disease states [1, 6]. While the most readily identifiable lymphatic responsibility is the active maintenance of tissue fluid homeostasis (▶ Chaps. 6, 7, 8, and 9), they have a no less important active participation in the activity of the immune system [7]. In the intestinal viscera, intact lymphatic function is essential for lipid absorption and transport to the liver.

Failure of fluid homeostasis, immune traffic, and/or lipid uptake and transport are the hallmarks of the entire spectrum of lymphatic disease, including both primary and acquired forms of lymphedema, lymphatic inflammatory, lymphatic maldevelopment, and cancer metastasis.

Insights into normal function, and its aberration in disease, derive from the active investigation of lymphatic vascular development and postnatal remodeling and repair (▶ Chap. 4) [3, 8, 9]. Under the influence of the recognized molecular regulators of this process, including CCBE, SOX18, vascular endothelial growth factors (VEGFs), Syk and SLP-76, podoplanin, angiopoietins, neuropilins, ephrins, GATA2, and others, the lymphatic circulation develops, remodels, and matures. The list of recognized pathways that contribute to this process continues to grow year by year.

The occurrence of tissue edema reflects a relative imbalance between the rate of interstitial tissue fluid production and the presence of a reduced capacity of the lymphatic vasculature to transport that fluid (▶ Chap. 16). Edema occurs if lymphatic load is abnormally increased, if the transport capacity is reduced (obstructive lymphedema), or if there is any combination of these two.

Primary lymphedema (▶ Chap. 55) can be sporadic, hereditary (▶ Chap. 3), or syndrome-associated (▶ Chap. 56). Secondary lymphedema is acquired and can be further classified as benign (on the basis of trauma, infection, or iatrogenic causes) or malignant (the result of direct neoplastic invasion). Mixed lymphaticovenous edemas are also common (▶ Chaps. 67 and 68).

Lymphedema is not usually life-threatening, but the presence of lymphatic disease typically has a very deleterious effect on quality of life (▶ Chap. 37), based upon loss of function, restriction of movement, loss of body image and self-esteem, impaired psychosocial adjustment, and the risk of infection.

Lymphedema is a chronic debilitating disease that is frequently misdiagnosed, treated too late, or not treated at all [4]. The clinical diagnosis of lymphedema relies most heavily upon observations made at the bedside. Discrimination from other nonlymphatic forms of edema requires recognition of the unique cutaneous sequelae of lymphedema [5] (Part IV).

Where desired, the diagnosis can be confirmed through a variety of imaging modalities, including duplex ultrasonography, lymphoscintigraphy, computed tomography,

magnetic resonance imaging, positron emission tomography, near-infrared fluorescent lymphography, and oil-based lymphangiography (Part V). Bioimpedance spectroscopy is an increasingly employed, sensitive, and specific noninvasive detection method for early stages of edema, but this approach will not distinguish lymphatic edema from other forms. Nevertheless, the technique is very useful for prospective identification of early-stage disease in defined at-risk populations (▶ Chap. 15).

Treatment of lymphedema is mandatory at the earliest detectable time point in the evolution of the disease. Decongestive physiotherapies been shown to have a very beneficial impact upon edema volume and patient symptomatology [5, 10, 11] (Parts VII and VIII). Current therapeutic approaches are time and labor intensive, but have been shown to effectively reduce the impact of the disease upon function and quality of life. Lifestyle modifications, including the implementation of specific exercise regimens [12], can also have salutary effects. Guidelines for the incorporation of intermittent pneumatic biocompression into the treatment regimen continue to evolve, but it appears that these devices can have a significant ameliorative impact on the reduction of disease symptoms and manifestations (▶ Chap. 32).

Pharmacologic intervention is in evolution, but has little current applicability in the management of the lymphedema patient (▶ Chap. 34). Aggressive control of infection through antibiotic therapy is, however, mandatory (▶ Chap. 35). Molecular modifications, including growth factor-based and cellular therapies (▶ Chap. 36), continue to hold great future promise.

Surgical therapies for lymphedema are enjoying ever-increasing utilization as these approaches continue to be refined. The surgical approach to the lymphedema patient can incorporate both reconstructive (Part VIII) and excisional (Part IX) techniques.

This volume is dedicated to the millions of individuals in the world who have lymphedema and the associated lymphatic disorders and to the scientists and clinicians who dedicate their efforts in this direction. With focused attention upon disease mechanisms, diagnosis, and medical and surgical intervention, we can hope that, one day, the impact of these diseases will be eradicated.

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Etiology and Classification of Lymphatic Disorders

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2

Summary of Basic Concepts

Beyond lymphedema, in its diverse manifestations, there is a spectrum of human disease that directly or indirectly alters lymphatic structure and function. Diagnosis and differential diagnosis pose distinct challenges. In this overview, various categories of lymphatic disease are enumerated and viewed through the prism of lymphatic embryological development.

- Defects in the growth and development of lymphatic vessels underlie the lymphatic clinical disorders, including lymphedema, vascular malformations, and lymphangiectasia.
- Lymphedema represents the most commonly encountered disease state of the lymphatics. It can present in both acquired and heritable forms.
- Clinical manifestations of primary lymphedema can be mistaken for secondary lymphedema if edema first appears after an apparent provoking secondary inciting event.
- A genetic predisposition for the development of lymphedema, even when the inciting secondary events are easy to identify.
- There are at least nine causal mutations known for inherited human lymphedema.
- Beyond peripheral lymphedema, the spectrum of lymphatic vascular disease is remarkably diverse. The pathological alterations can be isolated, regionalized, or diffuse and can occur in isolation or in concert with other complex vascular lesions.
- Lymphatic malformations are microcystic, macrocystic, or mixed; generalized lymphatic anomaly is a multifocal lymphatic malformation that can involve the skin, superficial soft tissues, bone, and abdominal and thoracic viscera.
- In protein-losing enteropathy, loss of lymphatic fluid and plasma protein within the lumen of the gastrointestinal tract can lead to edema and hypoproteinemia.

Beyond lymphedema, in its diverse manifestations, there is a spectrum of human disease that directly or indirectly alters lymphatic structure and function. Not surprisingly, the symptomatic and objective presentation of these patients is quite heterogeneous. Diagnosis and differential diagnosis pose distinct challenges. In this overview, various categories of lymphatic disease are enumerated and viewed through the prism of lymphatic embryological development (► Chap. 4).

2.1 Development of the Lymphatic System

It is vital that we understand the processes of normal lymphatic development, since defects in the growth and development of lymphatic vessels (lymphangiogenesis) underlie the clinical disorders of this vascular system, including lymphedema, vascular malformations, and lymphangiectasia [5].

It is now reasonably well established that the lymphatic progenitors arise from the endothelial cell population within embryonic venous structures. Lymphatic endothelial

cell specification entails the expression of the unique molecular markers that impose the characteristic phenotype of this cell. As the lymphatic endothelial cells attain higher levels of differentiation, additional lymphatic-specific markers are expressed, along with concomitant suppression of the markers of blood vascular expression [6]. The committed lymphatic cell population achieves complete autonomy from the local venous microenvironment and migrates peripherally. Thereafter, the formation of primary lymph sacs occurs throughout the embryo. Secondary budding and migration distinguish the final stages of lymphatic development. However, despite this generally described phenomenon, recent studies provide evidence that, in humans and other complex organisms, there are distinct and tissue-specific differences in the mechanisms by which the lymphatic vasculature arises and develops; accordingly, dermal, intestinal, brain, visceral, and cardiac lymphatics each possess a unique and diverse developmental program [7]. Specifically, in embryonic skin, heart, and mesentery, sources of progenitor cells beyond the venous pool have now been identified [7].

2.2 Lymphatic Vascular Disease Classification

Evolving insights into molecular embryology continue to inform our comprehension of lymphatic vascular development. The spectrum of lymphatic vascular disease is broad: an informed classification schema, with therapeutic implications, should ultimately be derived from the insights drawn from developmental biology. In fact, until quite recently, disease classification and risk stratification have been very imprecise, and comprehension of disease natural history and epidemiology has been disappointingly primitive [8, 9]. The recognized categories and representative subsidiary diseases are summarized in Table 2.1.

2.2.1 Lymphedema

Lymphedema represents the most commonly encountered disease state of the lymphatics. It can present in both acquired and heritable forms [8]. Conventionally, a distinction has been established among primary and secondary causes of lymphedema [10]. In approach, primary lymphedemas encompass both the sporadic and hereditary forms, as well as those that are syndrome associated [1]; secondary lymphedema is either *malignant* (i.e., associated with direct neoplastic invasion and/or obstruction of the vascular channels and nodes) or *benign* (acquired as a consequence of infection, trauma, obesity ([11, 12], or iatrogenic causes, including the surgical and radiotherapeutic treatment of malignancies). More recent approaches to the mechanistic classification of lymphedemas suggest that the boundaries that separate the seemingly distinct categories of primary and secondary lymphedema may, in fact, be indistinct: primary cases often declare themselves after a «secondary» provocation, and evolving clinical data suggests that there might be a genetic predisposition for the development of lymphedema, even when the inciting secondary events are easy to identify [13, 14].

At the present time, there are at least nine causal mutations known for inherited human lymphedema [1]. Heritable congenital lymphedema of the lower extremities was first described in 1891 [15]; in 1892, Milroy [16] described the familial distribution of

Table 2.1 Lymphatic disease classification

Disease	Symptoms	Signs	Genetic features	Pathology
I. Primary lymphedema				
Nonne–Milroy lymphedema	Pitting/brawny swellings of ankles and shins apparent at birth or infancy	Firm edema of lower limbs	Autosomal dominant	Inadequate lymphatic drainage (insufficient development of lymphatic vessels)
Milroy disease	Congenital swelling of the lower limbs	Lymphedema confined to lower limbs	Autosomal dominant	Hypoplasia of lymphatic capillary network; fibrosis of limb tissues
Lymphedema tarda (Meige's disease)		Lymphedema of lower extremity; becomes clinically evident near age 35	No family history	Hyperplastic pattern, with tortuous lymphatics increased in caliber and number; absent or incompetent valves
Klippel–Trenaunay syndrome: combination of cutaneous capillary malformation, varicose veins, and hypertrophy of bone and soft tissue		Capillary hemangioma/port-wine stain: distinct, linear border; nevus flammeus (salmon pink patch); large, lateral, superficial vein beginning at the foot/lower leg and traveling proximally until entering the thigh/gluteal area; bony/soft tissue hypertrophies, limb hypertrophies/discrepancies		
Noonan syndrome (congenital)	Decreased appetite	Facial abnormalities, webbing of the neck, and deformities of the chest	Autosomal dominant or sporadic	

	Frequent or forceful vomiting Difficulty swallowing Severe joint or muscle pain	Heart murmur Mental retardation		
Neurofibromatosis	Coffee-colored skin spots, freckling in non-sun-exposed areas, back pain	Neurofibromas Optic glioma hamartomas on the iris Distinctive bony lesions	Autosomal dominant (half of cases have no family history, high mutation rate)	Vasculopathy (arterial stenoses due to proliferation of cells in intima) Fibro-muscular hyperplasia of arteries leads to renal artery stenosis, cerebral infarction, aneurysm (rare)
Lymphedema distichiasis	Onset of edema commonly at or near the time of puberty	Distichiasis Pitting edema	Autosomal dominant inheritance	Abnormal development of intralymphatic valves; enhanced recruitment of vascular mural cells to lymphatic capillaries
Protein-losing enteropathy	Swelling of the legs or other areas Diarrhea Weight loss Abdominal pain	Edema Ascites Pleural effusion Pericardial effusion		
Lymphedema/hypoparathyroidism		Symmetrical congenital lymphedema with pulmonary lymphangiectasia	Pleiotropic effect of an autosomal or X-linked recessive gene	

(continued)

Table 2.1 (continued)

Disease	Symptoms	Signs	Genetic features	Pathology
Turner's syndrome	Short stature Congenital edema of hands/feet at birth; Webbed neck; ptosis; a «shield-shaped» broad, flat chest; absent or incomplete development at puberty, including sparse pubic hair and small breasts Infertility Dry eyes Absent menstruation, absent normal moisture in the vagina, painful intercourse	Ovarian failure Hypoplastic or hyperconvex nails Underdeveloped breasts and genitalia, webbed neck, short stature, low hairline in the back, simian crease, and abnormal bone development of the chest	X-linked dominant inheritance	Absence of one set of genes from the short arm of one X chromosome
Klinefelter syndrome (supplementary X chromosome)	Infertility, gynecomastia	Lack secondary sexual characteristics, lack facial/body/sexual hair, high-pitched voice, female type of fat distribution, testicular dysgenesis		Small, firm testes with seminiferous tubular hyalinization, sclerosis, degenerated Leydig cells; histology of gynecomastic breasts shows hyperplasia of interductal tissue
Patau syndrome	Scalp defects	Holoprosencephaly (the brain does not divide completely into halves)		

Trisomy chromosome 13	Cleft lip/palate Facial defects (absent or malformed nose) Hernias	Hypotelorism Microphthalmia Anophthalmia Rocker-bottom feet Microphthalmia Cutis aplasia Omphalocele		
Edwards syndrome (trisomy 18)	Stop breathing, poor feeding	Apneic episodes, marked failure to thrive; severe growth retardation, mental retardation Malformations (e.g., microcephaly, cerebellar hypoplasia, hypoplasia/aplasia of corpus callosum, holoprosencephaly)		
Triploidy syndrome		General dysmaturity, muscular hypotonia, large posterior fontanel, hypertelorism, microphthalmia, colobomata, cutaneous syndactyly Abnormalities of the skull, face, limbs, genitalia (male karyotype), various internal organs Fetal hypoplasia, microstomia, low-set ears		Triploid cell lines may have disappeared from peripheral blood so evidence of triploidy can only be found in the cultured skin fibroblasts
Yellow nail syndrome	Yellow nails Edema	Triad of lymphedema (symmetrical, non-pitting), slow-growing yellow nails, pleural effusion	Heterogeneous inheritance, both autosomal dominant and recessive	Hypoplastic lymphatics

(continued)

Table 2.1 (continued)

Disease	Symptoms	Signs	Genetic features	Pathology
Adams liver syndrome	Rare syndrome of defects of the scalp and cranium associated with distal limb anomalies and occasional mental retardation		Most autosomal dominant; some autosomal recessive/sporadic	
Proteus syndrome	Partial gigantism, long face, wide nasal bridge, mouth open at rest, upper body wasting, learning disabilities, occasional seizures	Cutaneous and subcutaneous lesions including vascular malformations, lipomas, hyperpigmentation, and several types of nevi	Somatic mosaicism for a dominant lethal gene yet to be identified; mosaicism: a fraction of cells have mutation, a fraction do not	Connective tissue nevi resemble tightly compacted, collagen-rich connective tissue. Epidermal nevi generally exhibit a combination of hyperkeratosis, parakeratosis, acanthosis, and papillomatosis
Hennekam syndrome	Edema Facial anomalies Moderate developmental problems	Lymphedema, lymphangiectasia, facial anomalies, delayed onset of puberty Moderate mental retardation	In one report of ten familial cases, equal sex ratio, increased parental consanguinity, no vertical transmission; consistent with autosomal recessive	

Aagenaes' syndrome (cholestasis with malabsorption)	Predominantly in patients in Norway, jaundice, severe itching	Enlarged liver	Possibly autosomal recessive	Generalized lymphatic anomaly (lymphedema due to lymph vessel hypoplasia) giant-cell hepatitis with fibrosis of the portal tract
Prader-Willi syndrome: genomic imprinting; genes expressed differentially based upon parent of origin (loss of paternal gene or maternal disomy)	Floppy newborn infant (hypotonic), small for gestational age, undescended testicles in the male infant, delayed motor development, slow mental development, very small hands and feet in comparison to body, rapid weight gain, insatiable appetite, food craving, almond-shaped eyes, narrow bifrontal skull, morbid obesity, skeletal (limb) abnormalities, striae	Hypotonia, hypomentia, hypogonadism, obesity	Genomic imprinting; genes expressed differentially based upon parent of origin (loss of paternal gene or maternal disomy)	
II. Acquired lymphedema				
Stewart–Treves syndrome (Cutaneous angiosarcoma induced by radical mastectomy to treat breast cancer; tumor develops 5–15 years after mastectomy)	Recurrent erysipelas	Severe chronic edema of an upper extremity; first appears on the arm on the side operated on; gradually extends from arm to forearm and the dorsal aspect of the hand/fingers		Proliferating vascular channels; tumor endothelial cells lining these channels show marked hyperchromatism and pleomorphism Mitoses commonly seen in these tumor cells; lymphangiosarcoma cells surrounded by complete basal lamina

(continued)

Table 2.1 (continued)

Disease	Symptoms	Signs	Genetic features	Pathology
Hodgkin's disease (potentially curable malignant lymphoma)	Unexplained weight loss, fever, night sweats Chest pain, cough, and/or shortness of breath; hemoptysis	Asymptomatic lymphadenopathy; splenomegaly Hepatomegaly		
	Pruritus Intermittent fever Alcohol-induced pain at sites of nodal disease	Superior vena cava syndrome (rare) CNS symptoms (cerebellar degeneration, neuropathy)		
Filariasis	Fever, inguinal or axillary lymphadenopathy, testicular and/or inguinal pain, skin exfoliation, and limb or genital swelling; cloudy, milk-like urine	Episodic attacks of fever associated with inflammation of the inguinal lymph nodes, testis, spermatic cord, lymphedema, or a combination of these; abscess formation at nodes; cellular invasion with plasma cells/eosinophils/macrophages with hyperplasia of lymphatic endothelium; lymphatic damage and chronic leakage of protein-rich lymph in the tissues, thickening of skin, chronic infections contributing to the appearance of elephantiasis		Fibrosis of affected lymph nodes; stenosis and obstruction of lymphatics with creation of collateral channels; cutaneous hyperkeratosis, acanthosis, loss of elastin fibers, and fibrosis
III. Lymphangiectasia				
Pulmonary lymphangiectasia	May present at birth, tachypnea, cough, wheeze	Increased respiratory effort with inspiratory crackle, respiratory distress, cyanosis; pleural effusion (chylous), lymphedema	Sporadic, a few autosomal recessive	Lung histology reveals large, cystic endothelial-lined lymphatic channels

Intestinal lymphangiectasia	Intermittent diarrhea, nausea, vomiting, steatorrhea,	Growth retardation	Most sporadic	Diffuse or localized ectasia of enteric lymphatics
	Peripheral edema			
Lymphangiomatosis	Presents in late childhood, can occur in any tissue in which lymphatics are normally found, predilection for thoracic and neck involvement; wheezes (misdiagnosed as asthma)			Multiple lymphangiomas (well-differentiated lymphatic tissue that presents as multicystic or sponge-like accumulations; benign proliferations of the lymphatic channels with abnormal connections to the lymphatic system); anastomosing endothelial-lined spaces along pulmonary lymphatic routes accompanied by asymmetrically spaced bundles of spindle cells
Gorham's disease – proliferation of vascular channels that results in destruction/resorption of osseous matrix	Dull aching pain or insidious onset (limitation of motion, progressive weakness); swelling	Massive bone loss	No familial predisposition	Nonmalignant proliferation of thin-walled vessels; proliferative vessels may be capillary/sinusoidal or cavernous Wide capillary-like vessels
Lymphangioleiomyomatosis (LAM)	Shortness of breath, expectoration of chyle or blood	Pneumothorax Chylothorax Chylous, pleural effusions Enlarged lymph nodes	Sporadic	

(continued)

Table 2.1 (continued)

Disease	Symptoms	Signs	Genetic features	Pathology
	Nausea Bloating Abdominal distension Cough Phlegm Crackles Wheezing Chest pain Gurgling in chest			
Diffuse hemangiomatosis	Many newborns have premonitory lesions, such as small red macule, telangiectasias, or blue macule at the hemangioma site	Visceral hemangiomas (in the neonatal period), three or more organ systems were affected, hemangiomas are not malignant	Congenital defect	Lesions have dilated thin-walled channels lined by a single layer of flattened endothelial cells Only a few focal areas of endothelial proliferation, no other cellular hyperplasia or pleomorphism, well-formed vascular channels; abnormal capillaries coursing through muscle suggest that hemangiomas are hamartomas
		Vascular hamartomas		
Lymphangitis (Inflammation of the lymphatic channels that occurs as a result of infection at a site distal to the channel)	Red streaks on the skin Fever, chills, malaise Headache, loss of appetite, muscle aches Recent cut/abrasion that appears infected and spreading	Erythematosus and irregular linear streaks extend from primary infection site toward draining regional nodes Tender/warm Blistering of skin Lymph nodes swollen and tender Children may be febrile/tachycardic		

Maffucci's syndrome	Soft, blue-colored growths of distal aspects of extremities	Enchondroma (benign enlargements of cartilage) with multiple angiomas	Sporadic, manifests early in life (~ 4–5 years); 25% of cases are congenital	Thrombi often form within vessels and develop into phleboliths – appear as calcified vessels under the microscope; chondrosarcomas diagnosed by poorly differentiated pleiomorphic chondrocytes
	Short in stature, unequal arm/leg	Bone deformities Dark, irregularly shaped hemangiomas		
Blue rubber bleb nevus syndrome (multiple cutaneous venous malformations in association with visceral lesions, most commonly affecting GI)	Skin lesions multiple, protuberant, dark blue, compressible blebs, look and feel of a rubber nipple	Lesions asymptomatic but may be painful or tender Increased sweating on skin overlying lesion Fatigue from blood loss Hematemesis, melena, or frank rectal bleeding Joint pain Blindness due to cerebral or cerebellar cavernomas that hemorrhage into occipital lobes	Sporadic, autosomal dominant inheritance also reported	Vascular tissue with tortuous, blood-filled ecstatic vessels, lined by single layer of endothelium, with surrounding thin connective tissue; dystrophic calcification may be present
Cystic angiomatosis	Soft tissue masses, localized pain, and swelling related to pathological fracture	Dyspnea with or without cyanosis, ascites, splenomegaly, hepatomegaly, anemia, soft tissue masses	Vascular malformation of congenital origin	Dilated, cavernous thin-walled vascular channels lined by flat endothelial cells (similar to LAM)
Lymphangioma: (uncommon, hamartomatous, congenital malformations of the lymphatic system that involve skin and subcutaneous tissues)	Verrucous changes, warty appearance; clear or solitary rubbery nodule with no skin changes	Persistent, multiple clusters of translucent vesicles that contain clear lymph fluid; superficial saccular dilations from underlying lymphatic vessels that occupy papilla and push upward against overlying epidermis		Vesicles are greatly dilated lymph channels that cause dermis to expand

(continued)

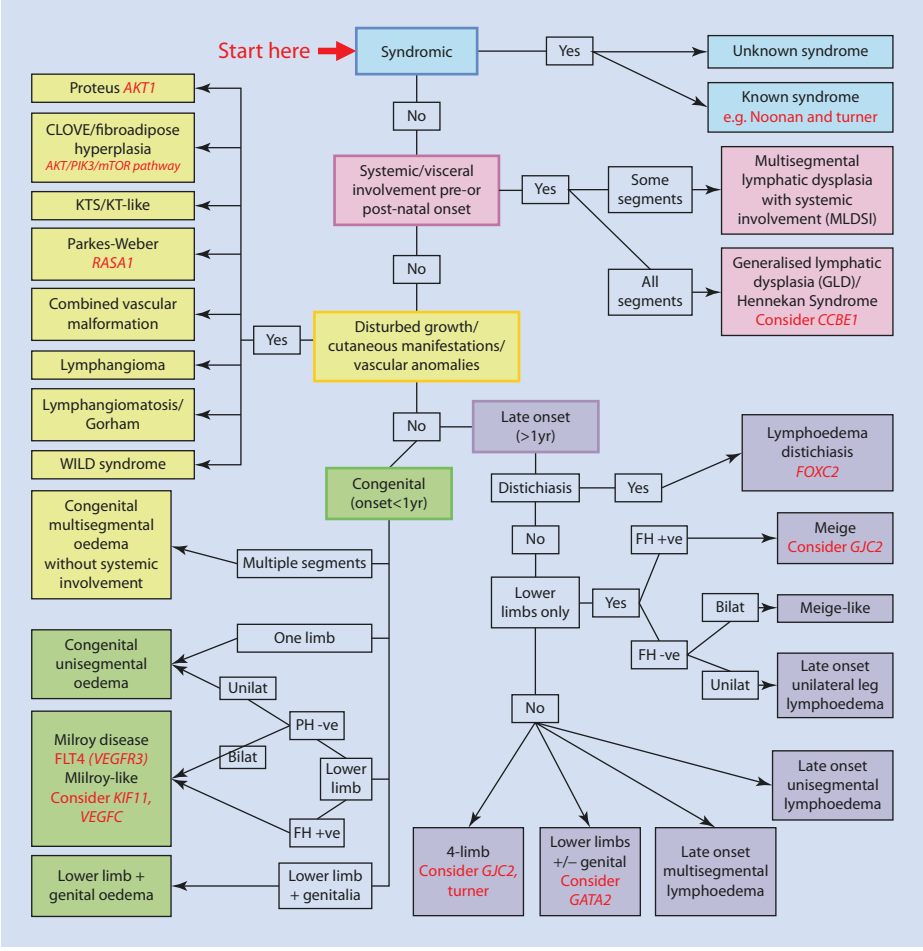
Table 2.1 (continued)

Disease	Symptoms	Signs	Genetic features	Pathology
Superficial vesicles: lymphangioma circumscriptum More deep seated includes cavernous lymphangioma and cystic hygroma				Lumen filled with lymphatic fluid often contains red blood cells, lymphocytes, macrophages, neutrophils; lined by flat endothelial cells Large, irregular channels in the reticular dermis, lined by single layer of endothelial cells
Cystic hygroma (develops in first trimester)	Single or multiple fluid-filled lesions that occur at sites of lymphatic–venous connection; primarily in the neck and axilla	Lymphedema Hydrops fetalis	Congenital; autosomal recessive	Dilated, disorganized lymph channels due to failure of lymph sacs to establish venous drainage
IV. Lipedema				
Lipedema	Insidious onset in adolescence; progressive, swollen legs with foot sparing; range of skin, bruises, pain, varicose veins, weight gain	Edema without pitting, Stemmer's sign negative	Sporadic	Fibro-sclerosis, damage to deep venous system

Modified from Radhakrishnan and Rockson [4]

congenital lymphedema, noting the involvement of 26 persons in a single family, spanning six generations. Nonne–Milroy's lymphedema is characterized by unilateral or bilateral swelling of the legs, arms, and/or face with gradual and irreversible fibrotic changes. Additional, distinct variants of heritable lymphedema have subsequently been described. In 1898, Meige reported cases of lymphedema in which the age of onset was after puberty and that often appeared alongside acute cellulitis [17]. In 1964, another variety of pubertal-onset lymphedema was reported, in which the affected individuals had distichiasis (i.e., an auxiliary set of eyelashes) [18].

In addition to the isolated gene mutations responsible for Milroy's disease and lymphedema distichiasis, there is an array of syndromic heritable disorders that are associated with dysfunction of the lymphatic vasculature (■ Fig. 2.1) [2]. Often, these syndromes are associated with abnormal facial and mental development.



■ **Fig. 2.1** An algorithm for the classification of the primary lymphedemas (Reprinted with permission from Connell et al. [2])

An additional useful organizational schema is to classify the disorders by their autosomal dominant (Noonan syndrome, Adams–Oliver syndrome, and neurofibromatosis) or autosomal recessive (Hennekam syndrome, the Prader–Willi syndrome, and Aagenaes' syndrome) modes of genetic transmission.

Chromosomal disorders can also result in multiple organ defects, in addition to lymphedema when present. These disorders are uncommon; hence, the chromosomal basis can be readily overlooked or misdiagnosed. Confirmatory identification can be achieved only through detailed cytogenetic studies. Many of these disorders severely distort lymphatic function. Turner's syndrome and Klinefelter syndrome are linked to the sex chromosomes, whereas Edwards syndrome and Patau syndrome are linked to autosomal chromosomes. Triploidy syndrome denotes the presence of an extra copy of all of the chromosomes.

Beyond peripheral lymphedema, the spectrum of lymphatic vascular disease is remarkably diverse. Histologically, the vasculature can display any combination of pathological dilation of structures that are normal in number and distribution or abnormal patterns of vascular growth. The pathological alterations can be isolated, regionalized, or diffuse and can occur in isolation or in concert with other complex vascular lesions.

2.3 Lymphatic Vascular Malformation

Lymphatic vascular malformations, formerly known as lymphangiomas [3], arise during embryological development. These lesions may arise from segments of lymphatic vascular tissue that fail to undergo proper anastomosis, or they may represent portions of lymph sacs that become grouped together during development [19]. The presence of multiple or widespread lymphatic vascular malformations, previously designated as *lymphangiomatosis* [4], now more properly implies the diagnosis of *generalized lymphatic anomaly (GLA)* [3]. GLA is characterized as a multifocal lymphatic malformation that can involve the skin, superficial soft tissues, and abdominal and thoracic viscera; they often involve bone, with osseous involvement that is typically nonprogressive and that spares the bone cortical boundaries [3]. Chylous pleural, pericardial, or peritoneal effusions may be present [3]. At least two distinct genetic mutations have recently been linked to heritable forms of GLA [20, 21]. Lymphatic malformations were previously classified by size and depth of formation, with the smaller, superficial form previously designated as *lymphangioma circumscriptum* and the deeper lesions as *cavernous lymphangiomas* and *cystic hygromas*. This terminology has been replaced with the simple designation of the lesions as microcystic, macrocystic, or mixed [3]. Lymphatic malformations can also occur in association with other vascular and structural anomalies.

2.4 Protein-Losing Enteropathy and Intestinal Lymphangiectasia

Loss of lymphatic fluid and plasma protein within the lumen of the gastrointestinal tract can lead to edema and hypoproteinemia [4]. Patients with protein-losing enteropathy typically have local lymphatic obstruction and stasis [22], while those with lymphangiectasia have dilated lymphatic vessels in the intestinal villi [23].

In general, lymphatic obstruction leads to increased hydrostatic pressure throughout the lymphatic system of the gastrointestinal tract, resulting in lymph stasis. Protein-rich lymphatic fluid is consequently lost into the gastrointestinal lumen through the lacteals in the intestinal microvilli.

Intestinal lymphangiectasia is a rare condition characterized by severe edema, thickening of the small bowel wall, protein-losing enteropathy, ascites, and pleural effusion [24]. The condition may be primary, resulting from a congenital lymphatic vascular disorder, or secondary, as a consequence of inflammatory or neoplastic involvement of the lymphatic system [25]. Although intestinal lymphangiectasia can occur in the context of generalized lymphatic dysplasia, the pathogenesis of this disorder is unknown.

2.4.1 Complex Vascular Malformations

Various disorders result from abnormal development of, or insult to, the blood vascular and lymphatic vascular systems [4].

Cystic angiomatosis is a congenital condition of unknown etiology, defined by the presence of numerous cystic skeletal lesions. The lesions are generally round or oval, and they vary widely in size. The cystic lesions may be due to dilated blood vessels or lymphatic channels or both. The cysts are encircled by a single, flat layer of endothelial cells.

Maffucci's syndrome is characterized by the presence of hard subcutaneous enchondromas and hemangiomas due to mesodermal dysplasia [26]. Patients with Maffucci's syndrome are also at risk for the development of a variety of malignant tumors [27]. Maffucci's syndrome is often associated with lymphatic system dysfunction, with consequent edema and secondary infection. Lesions appear during childhood and may progressively worsen.

Gorham's disease results from the uncontrolled growth of nonmalignant vascular channels that lead to lysis of the affected bone [28]. Osteolytic lesions are consecutive and progressive [29], and pathologic fractures can occur [3]. The condition is associated with angiomatosis of blood and lymphatic vessels. Chylous pericardial and pleural effusions are associated with this condition, and chylothorax can sometimes result from dilation of the lymphatic vessels, with reflux into pleural cavity.

Klippel–Trenaunay syndrome consists of a combination of vascular malformations, including capillary anomalies (port-wine stain), varicose veins, and hypertrophy of bone and soft tissue [30]. While Klippel–Trenaunay syndrome generally manifests in a single extremity, it can also affect multiple limbs or the entire body. Histologically, the condition is associated with dilated telangiectatic vessels in the upper dermis that do not spontaneously regress. The etiology of this condition is unknown; it is hypothesized that it might reflect a mutation in a mosaic state, in a gene that would be lethal when mutated in a non-mosaic state [31]. The putative gene(s) have not been identified.

Beyond lymphedema and the primary defects of lymphatic vasculature, there are numerous additional categories of disease that can be considered to be part of the spectrum of lymphatic vascular disease.

2.5 Infectious Diseases

Lymphatic dysfunction can arise as a consequence of invading pathogens.

Globally, more than 129 million patients are afflicted by *lymphatic filariasis* (▶ Chap. 63). This condition is characterized by markedly impaired lymphatic function and lymphangiectasia. Patients are infected by filariae, or parasitic worms, which take up residence in the lymphatic structures. As a result, the lymphatics become compromised; the formation of new lymph channels is impaired by the adenolymphangitis, fibrosis, and stenosis of the lymph nodes.

Lymphangitis is, in general, a consequence of the inflammation of lymphatic channels through tissue infection. Pathogenic organisms can include bacteria, fungi, viruses, and protozoa.

2.5.1 Lipedema

Lipedema [32] was first described in 1940 as a bilateral, gradual accumulation of fatty deposition in the lower extremities and buttocks. The body habitus superficially resembles that of bilateral lower extremity lymphedema, although the involvement of the two limbs is substantially more symmetrical than in lymphedema, and there is almost always sparing of the feet. The condition is found almost exclusively in female subjects. A family history of large legs is commonly encountered [33]. Earlier stages of lipedema are characterized further by the presence of normal cutaneous architecture, lacking the fibrotic changes often seen in lymphedema. The histopathology describes edematous adipose cells that are sometimes hyperplastic. The microlymphatic function can become distorted in lipedema, and a component of secondary lymphedema often supervenes.

2.5.2 Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is a hybrid disorder that has a distinct lymphatic component to the clinical presentation [34]. Among the complex components to the disease are mutational inactivation of the tuberous sclerosis complex genes, TSC1 and TSC2, activation of the mammalian target of rapamycin (mTOR) pathway, enhanced cell proliferation and migration, lymphangiogenesis, metastatic spread through the blood and lymphatic circulations, sex steroid sensitivity, and dysregulated autophagy [35]. The disease is characterized by the spread of abnormal smooth muscle cells (LAM cells) through both the pulmonary interstitium and the axial lymphatics, leading to the cystic destruction of the lung, along with lymphatic wall thickening. LAM is also characterized by the presence of pulmonary cysts and angiomyolipomas, tumors consisting of LAM cells, adipose tissue, and underdeveloped blood vessels. LAM chiefly affects women of childbearing age. It is an extremely rare disease, found in fewer than one in a million individuals. The primary clinical presentation associated with LAM is pulmonary, including pneumothorax, progressive dyspnea, chylous pleural effusions, cough, hemoptysis, and chyloptysis. Non-pulmonary findings include lymphangioleiomyomas, the large cystic masses commonly found in the abdominal and retroperitoneal regions, and chylous ascites [4].

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Hereditary and Familial Lymphedemas

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Summary of Basic Concepts

- Primary lymphedema arises from an inborn, or intrinsic, fault in lymphatic vessel architecture, function, or both and by implication is genetic in origin.
- Not all forms are inherited. For those with germline mutations, the mode of inheritance can be variable.
- A disease-causing mutation may be inherited but not clinically expressed. De novo mutations will have no family history but can be subsequently inherited.
- Classifying primary lymphedema simply as congenital, praecox, or tarda has resulted in a limited number of types (phenotypes) of primary lymphedema being recognized. A clinical approach based on not only the age of onset but also associated abnormalities has been proposed.
- Definitive diagnosis should be through genotyping where casual genes are known.

3.1 Introduction

Primary lymphedema is a visible swelling due to a failure of lymph drainage arising from an inborn, or intrinsic, fault in lymphatic vessel architecture, function, or both. This will be caused by a failure of normal lymphatic development and, by implication, will frequently be genetic in origin.

Primary lymphedemas are considered rare, but an underlying genetic susceptibility may contribute to many forms of secondary lymphedema. For example, podoconiosis, an endemic type of non-filarial elephantiasis, has been shown to have an association between disease expression and variants in HLA class II loci [6]. Similarly there is strong evidence that breast cancer related lymphedema may have a constitutional and therefore genetic basis [7].

3.2 Hereditary and Familial Lymphedema

Familial lymphedema describes any form of lymphedema that is seen in more than one family member. The mode of inheritance can be variable (autosomal dominant, autosomal recessive, or even X-linked). However, genetic disorders may occur as a new dominant event (de novo) in an offspring. In this scenario, there may be no family history, but the condition is hereditary and the proband's offspring are at risk of inheriting the condition, i.e., a sporadic primary lymphedema may have a genetic basis but there is no family history.

Equally, a disease-causing mutation may be inherited but not clinically expressed: the so-called non-penetrance. Nevertheless the mutation can be passed on to the next generation and then lymphedema may be clinically expressed. It should be stressed that the gene mutation does not skip a generation, only the clinical signs of the condition.

There may also be variable expression within families – i.e., different members of the family may present with a differing severity or manifestations of the condition despite all having the same mutation in the same gene.

Some genetic forms of lymphedema are not inherited because the mutation causing the disease is not in the parental germline but arising only in certain somatic cells postfertilization. When some somatic cells possess a disease-causing mutation and others do not, the disorder is referred to as mosaic. Vascular nevi or birthmarks are an example of a mosaic disorder as is lymphedema arising from a localized lymphatic malformation. Germline mutations can be found in the DNA from a blood sample, but mosaic mutations can often only be found in the affected tissue in which case a tissue biopsy will be necessary to detect the mutation. These forms of lymphedema, although genetic in origin, are neither familial nor inherited and not covered in this chapter.

3.3 Methods of Classification

Traditionally primary lymphedema has been categorized according to age of onset, e.g., congenital, pubertal (praecox), or late onset (tarda). This has resulted in a limited number of types (phenotypes) of primary lymphedema being recognized, with most forms of congenital lymphedema being labeled «Milroy disease.» With the discovery of causative genes for lymphedema, we now know that this classification is too restrictive as it failed to facilitate categorization based on more specific phenotypes.

Connell et al. [1] have proposed a new classification based on not only the age of onset but also associated abnormalities. This classification recognizes the highly heterogeneous nature of this disorder. This is described in more detail below.

3.3.1 Genotyping

The discovery of causal mutations for primary lymphedema has radically changed the clinical approach for diagnosis and management. At the time of writing, 12 genes are known to cause non-syndromic and syndromic conditions where the dominant feature is primary lymphedema (there are considerably more if one considers all the syndromes which can be associated with lymphatic problems). In those cases the definitive diagnostic test is to look for the mutation (genotype), but multiple forms of primary lymphedema are now recognized in which the genotype is not yet known. Careful clinical phenotyping, i.e., determining the physical characteristics as carefully as possible, is essential in such cases. At present, it is only through careful phenotyping that one form of primary lymphedema can be discriminated from another [1].

3.4 Diagnostic Algorithm and Classification for Primary Lymphedema

The primary lymphedema classification pathway is presented in the form of a color-coded algorithm to illustrate the five main categories of primary lymphedema and the individual subtypes (including genotypes) within these categories (Fig. 3.1). What

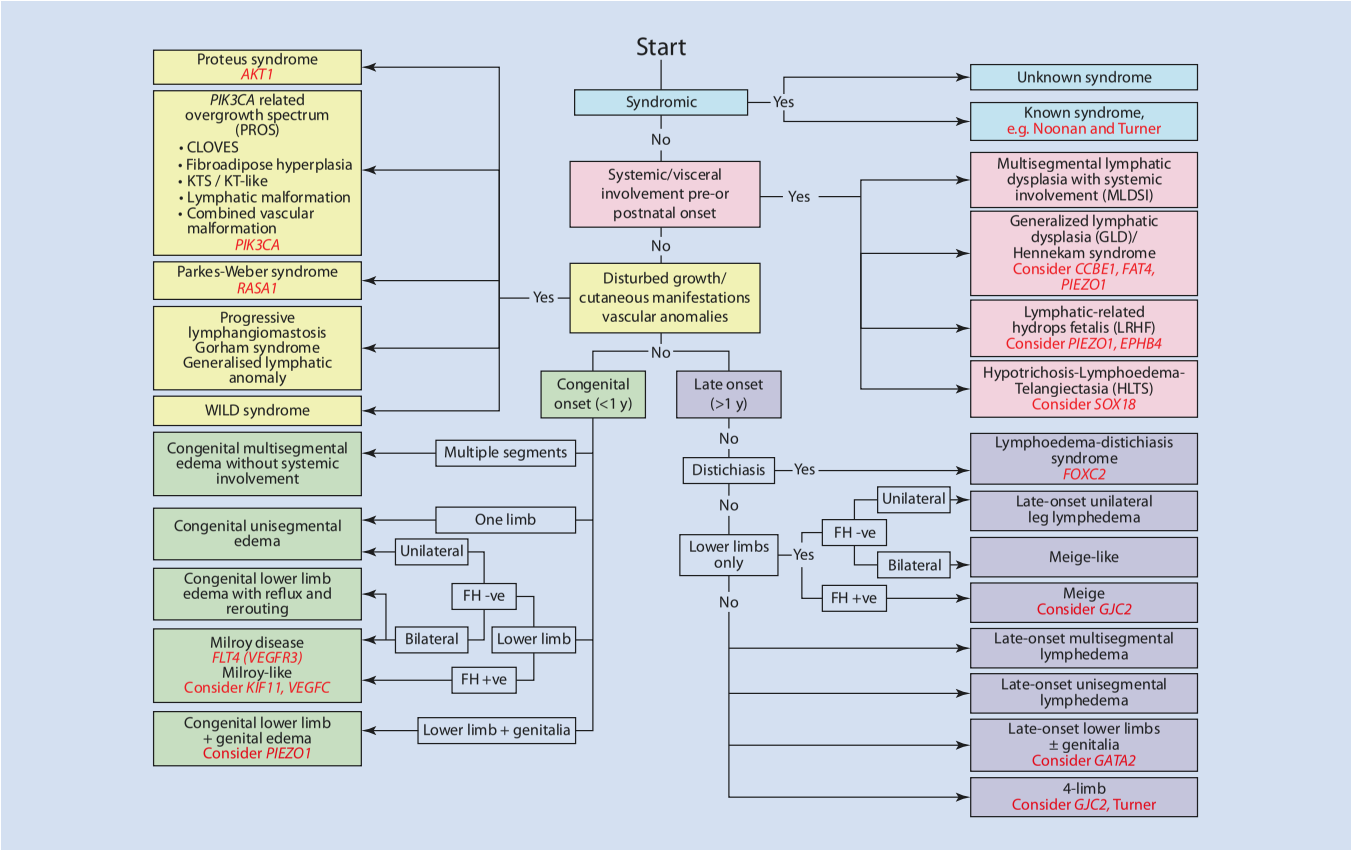

Fig. 3.1 An algorithm to guide clinical practice for the discrimination of different phenotypes with primary lymphoedema. Genotypes identified where known (Adapted from our publication in Clinical Genetics in 2013)

follows is a recommended clinical approach to phenotyping as suggested by Connell et al. [1]. The main categories are:

1. Syndromes associated with lymphedema (but where lymphedema is not the predominant feature) (blue).
2. Localized or generalized lymphedema associated with systemic/visceral lymphatic abnormalities including hydrops fetalis, intestinal lymphangiectasia, pleural effusions/chylothoraces, pulmonary lymphangiectasia, and pericardial effusions (pink).
3. Lymphedema associated with disturbed growth and/or cutaneous/vascular anomalies (yellow).
4. Congenital-onset primary lymphedema, that is, lymphedema that is present at birth or develops within the first year of life (green).
5. Late-onset primary lymphedema, that is, lymphedema that develops after the first year of life (purple).

3.5 Syndromes with Lymphedema

Lymphedema is a recognized feature of many syndromes; however, it is not the primary problem in these conditions but is an associated feature. These include Turner and Noonan syndromes.

Turner syndrome Turner syndrome is a complex disorder caused by an absent or abnormal sex chromosome. It affects 1/2000–1/3000 live-born females. Congenital lymphedema of the hands, feet, and neck region (present in over 60% of patients) is a common and key diagnostic indicator. The majority of fetuses with Turner syndrome present with hydrops fetalis (generalized swelling) in utero and miscarry. Of those that survive, many of the patients present at birth with four-limb lymphedema, which often resolves in early childhood, but may recur in later life. The swelling is confined to the legs and hands with no facial or genital swelling. Systemic involvement (i.e., intestinal lymphangiectasia, chylothoraces, pulmonary lymphangiectasia, pericardial effusions) is very rare in this cohort. Lymphoscintigraphy suggests that the lymphatic phenotype of Turner syndrome may be due to a failure of initial lymphatic (capillary) function [8].

Noonan syndrome The RASopathies, which include Noonan syndrome (NS) and cardiofaciocutaneous syndrome (CFC), are autosomal dominant disorders with genetic heterogeneity associated with germline mutations of genes in the Ras/mitogen-activated protein kinase (MAPK; RAS-MAP kinase) pathway. The conditions overlap and are characterized by facial dysmorphism, short stature, and congenital heart disease. NS and CFC, in particular, are known to be associated with lymphatic problems.

The lymphatic disorders in Noonan and CFC syndrome are rare, but have a characteristic pattern with bilateral lower limb lymphedema, genital swelling with chylous reflux, and frequent systemic involvement, including intestinal lymphangiectasia and chylothoraces, which may be progressive. Lymphoscintigraphy demonstrates reflux and/or rerouting of lymphatic drainage associated with incompetent veins on the venous duplex scans [9].

Other syndromes associated with lymphedema are listed in Table 3.1. The genetic causes of many of these syndromes are known and testing is available.

Table 3.1 Syndromes associated with primary lymphoedema

OMIM	Name	Inheri-tance	Gene/chromosomal location
	Single gene disorders		
214900	Aagenaes syndrome	AR	Unknown/15q
239850	Cantu syndrome	AD	*ABCC9*
115150	Cardiofaciocutaneous syndrome	AD	Ras-MAP kinase pathway (>15 genes)
214800	CHARGE syndrome	AD	*CDH7*/18q
613611	Choanal atresia-lymphedema	AR	*PTPN14*/1q
301500	Fabry disease	XL	*GLA*/Xq
249420	Frank-Ter Haar syndrome	AR	*SH3PXD2B*/5q
615704	Hereditary fibrosing poikiloderma with tendon contractures	AD	*FAM111B*/11q
607823	Hypotrichosis - lymphedema - telangiectasia syndrome	AR	*SOX18*/20q
601927	Irons-Bianchi syndrome	AR	UnknownNKNOWN
152950	Microcephaly with or without chorioretinopathy, lymphedema, and mental retardation (MCLMR)	AD	*KIF11*/10q
247440	Mucke syndrome	AR	Unknown
163950	Noonan syndrome	AD	Ras-MAP kinase pathway (>15 genes) incl. *PTPN11*/12q
164200	Oculo-dento-digital syndrome	AD	*GJA1*/6q
300301	Osteopetrosis, lymphoedema-ectodermal dysplasia, anhidrotic immunodeficiency, OL-EDA-ID syndrome	XL	*IKBKG*/Xq
260565	**P**rogressive encephalopathy with **e**dema, **h**ypsarrhythmia, **o**ptic atrophy	AR	*CCDC88A*/2p
274000	Thrombocytopenia absent radius syndrome	AR	1q21.2 deletion/*RBM8A*
191100	Tuberous sclerosis	AD	*TSC1*/9q, *TSC2*/16p
	Mosaic genetic defect		
612918	CLOVE syndrome	Somatic	*PIK3CA*/3q
	Fibroadipose hyperplasia	Somatic	*PIK3CA*/3q

Table 3.1 (continued)

OMIM	Name	Inheritance	Gene/chromosomal location
602501	Macrocephaly, capillary malformation syndrome (MCAP)	Somatic	*PIK3CA*/3q
176920	Proteus syndrome	Somatic	*AKT1*/14q
	Chromosomal disorders		
190685	Down syndrome		Trisomy 21
606232	Phelan-McDermid syndrome		Chromosome 22q13 deletion
176270	Prader-Willi syndrome	AD/de novo	15q deletion or uniparental disomy of chromosome 15 (imprinting disorder)
	Turner syndrome		X chromosome deletion
192430	Velo-cardio-facial syndrome		22q11 microdeletion
	Predominantly lymphatic		
614038	Emberger syndrome	AD	*GATA2*/3q
235510	Hennekam syndrome	AR	*CCBE1*/18q, *FAT4*/4q
613480	Late-onset four-limb lymphedema	AD	*GJC2*/1q
600011	Lymphatic-related hydrops	AD	*EPHB4*/7q
153400	Lymphedema-distichiasis	AD	*FOXC2*/16q
615907	Lymphedema, hereditary (Milroy-like)	AD	*VEGFC*/4q
153100	Milroy disease	AD	*VEGFR3*/5q
616843	PIEZO1-related generalized lymphatic disorder	AR	*PIEZO1*/16q
153300	Yellow nail syndrome	Unknown	Unknown

3.6 Lymphedema with Systemic/Visceral Involvement

A widespread developmental abnormality of the lymphatic system leads to systemic/visceral involvement and swelling that may not be confined to the limbs. Lymphatic dysfunction may present prenatally with hydrothoraces, ascites, or hydrops fetalis. The development of in utero edema may cause dysmorphic facial features such as epicanthic folds, a broad nasal bridge, and neck webbing with low-set ears [10].

Systemic lymphatic abnormalities may present with pericardial and pleural effusions/chylothoraces, chylous ascites, and pulmonary and intestinal lymphangiectasia in the postnatal period. An individual with intestinal lymphangiectasia will complain of abdominal pain and diarrhea following the ingestion of foods with a high-fat content.

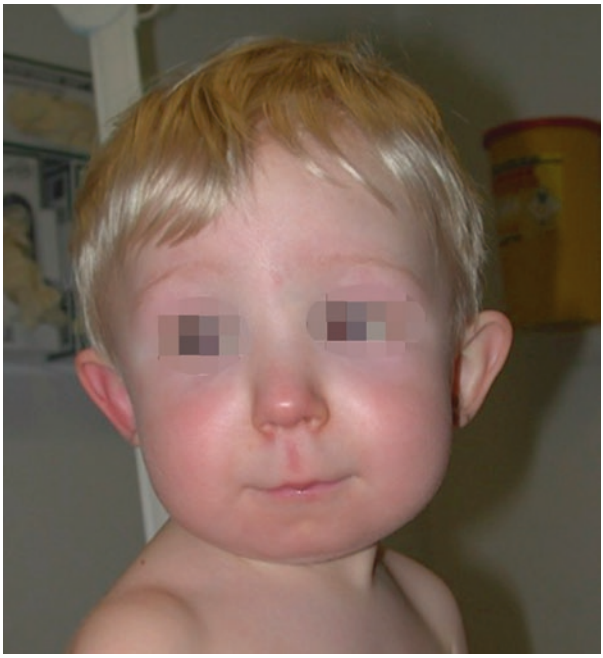

Fig. 3.2 Facial oedema and epicanthic folds in a 2 year old with compound heterozygote mutations in *PIEZO1*

Patients with systemic lymphatic abnormalities can be classified into one of two categories depending upon the clinical presentation: a generalized lymphatic dysplasia (GLD) for which four genes are currently known to be causal, *CCBE1, FAT4, PIEZO1,* and *EPHB4,* and a multisegmental lymphatic dysplasia with systemic involvement which is considered to be due to somatic mutations (Fig. 3.2).

Patients with GLD have a more global pattern of lymphedema. Swelling typically affects all body parts and often presents in utero with hydrops fetalis. Individuals with mutations in *CCBE1*, *FAT4,* or *PIEZO1* may have a family history consistent with autosomal recessive inheritance, whereas *EPHB4* is dominantly inherited.

Management of systemic lymphatic impairment is not straightforward and a multidisciplinary approach is key. Management includes the drainage of effusions and implementation of a medium-chain triglyceride diet to manage intestinal lymphangiectasia and chylous disorders [11].

Generalized lymphatic dysplasia due to *CCBE1* and *FAT4* Hennekam syndrome is one type of autosomal recessive GLD and presents with lymphedema of all four limbs, intestinal and/or pulmonary lymphatic dysplasia, a variable degree of learning difficulties, and characteristic facies (a flat face, flat and broad nasal bridge, and hypertelorism) [12]. Associated problems include hypothyroidism, glaucoma, seizures, hearing loss, and renal abnormalities. Lymphoscintigraphy has rarely been undertaken in this condition, but abnormal drainage in the upper and lower limbs and the thoracic duct has been demonstrated in one patient [13].

Patients with suspected Hennekam syndrome should be screened for mutations in *CCBE1* (collagen- and calcium-binding EGF domain 1) on chromosome 18q21 [14]. However, *CCBE1* mutations only appear to account for approximately 25% of cases,

suggesting genetic heterogeneity. This is supported by the recent identification of homozygous or compound heterozygous mutations of the *FAT4* gene (a member of the protocadherin family and not a recognized component of the lymphangiogenesis pathway) in 4 of 24 *CCBE1* mutation-negative Hennekam syndrome patients [2]. *CCBE1* is essential for embryonic lymphangiogenesis. *CCBE1* acts by regulating the cleavage of pro-VEGFC into its active form [15].

Generalized lymphatic dysplasia due to *PIEZO1* Homozygous and compound heterozygous mutations in *PIEZO1* result in an autosomal recessive form of GLD with a high incidence of nonimmune hydrops fetalis and childhood onset of facial and four-limb lymphedema [3].

There is a high mortality associated with the hydrops fetalis. Survivors may present later with lymphedema of the peripheries (mainly lower limbs but also arms) and genitalia, with or without chylothoraces and pericardial effusions. Intestinal lymphangiectasia is rare. A characteristic clinical feature in patients with *PIEZO1* mutations is severe, recurrent facial cellulitis with significant morbidity (high pyrexia and frequent admission to intensive care).

Lymphoscintigraphy shows distinctive changes with poor uptake of tracer in the groin and axillary lymph nodes with evidence of deep rerouting through the calf muscles in the lower limbs, seen as prominent uptake in the popliteal lymph nodes.

Mutations in *PIEZO1*, which encodes a mechanically activated ion channel, have been reported with autosomal dominant dehydrated hereditary stomatocytosis and nonimmune hydrops of unknown etiology. Besides its role in red blood cells, *PIEZO1* appears to be involved in the development of lymphatic structures. The mechanism is not yet understood.

Generalized lymphatic dysplasia due to *EPHB4* Mutations in the *EPHB4* gene produce a rare, autosomal dominant, inherited form of lymphatic-related (nonimmune) hydrops fetalis (LRHF). Independent exome sequencing projects on two families with a history of in utero and neonatal deaths associated with nonimmune hydrops fetalis uncovered two heterozygous missense variants in the gene encoding Eph receptor B4 (*EPHB4*) [4].

Inactivation of *EPHB4* in lymphatic endothelial cells of developing mouse embryos caused defective lympho-venous valve formation and subcutaneous edema. These findings identify *EPHB4* as a critical regulator of early lymphatic vascular development and demonstrate that mutations in the gene can cause an autosomal dominant form of LRHF that is associated with a high mortality rate.

This phenotype shows highly variable expression. Some individuals present with severe in utero swelling, which may cause perinatal demise or fully resolve to become completely asymptomatic. Others develop no edema and only an atrial septal defect.

Lymphoscintigraphy shows entirely normal levels of transport of lymph within the legs, but imaging is abnormal and suggestive of rerouting through skin and superficial tissues.

Hypotrichosis-lymphedema telangiectasia syndrome The first component of the syndrome, early-onset hypotrichosis with the absence of eyebrows and eyelashes, is present in all patients with *SOX18* mutations [16].

The lymphatic component can present as nonimmune hydrops fetalis, which can be fatal. The age of onset of lower limb lymphedema is highly variable, ranging from 4 to

15 years. Edema of the upper eyelids has been described suggesting a predilection to widespread peripheral lymphedema.

The third component of the syndrome is an anomaly of peripheral blood vessels, manifesting as telangiectasia in three of the four patients.

Both recessive and dominant forms of hypotrichosis-lymphedema-telangiectasia syndrome appear to exist.

Multisegmental lymphatic dysplasia with systemic involvement (MLDSI) Patients with MLDSI have a segmental pattern of lymphedema. The swelling affects different body parts in association with a systemic lymphatic abnormality. For example, they may have lymphedema of one or more limbs or body sites (including the face), in association with previous or current systemic lymphatic abnormalities (e.g., intestinal lymphangiectasia, recurrent chylous pleural effusions). The patient has no syndromic features and is of normal intelligence. The underlying mechanism is thought to be of somatic mosaicism. No known causal genes have been identified to date. There is a low sibling and offspring recurrence risk.

3.7 Congenital-Onset Primary Lymphedema

Historically, all cases of congenital lymphedema were classified as Milroy disease. However, several different types of congenital lower limb primary lymphedema have been recognized. They may all look clinically similar at birth, and it is only with genetic testing can they be distinguished from one another. For example, mutations in *VEGFR3, VEGFC,* and *KIF11* can all present with exactly the same type of lymphedema at birth.

Milroy disease Mutations within the gene that encodes the vascular endothelial growth factor receptor type 3 (*VEGFR3*) on chromosome 5q35 are causal of Milroy disease [17]. Inheritance is autosomal dominant, but de novo cases have been reported [18].

Milroy disease presents with congenital lymphedema of the feet (usually bilateral). The onset of swelling may occasionally be delayed but usually occurs within the first year of life. Lymphedema is typically confined to the feet and ankles, but may progress up to the knees. Up-slanting «ski-jump» toenails are present as a result of disturbance to the nail bed by the edema. Prominent large-caliber veins are frequently present on the feet and pretibial regions. The vein affected is the great saphenous vein, which demonstrates reflux at some point during childhood [19]. A third of affected males have hydroceles and 4% have urethral abnormalities [20].

Ultrasonography during pregnancy may detect swelling of the dorsum of the feet; mild pleural effusions, which often resolve; and (very rarely) more extensive edematous states (hydrops fetalis) in an affected fetus.

Lymphoscintigraphy in Milroy disease confirms failure of the initial lymphatic vessels to absorb fluid. The term «functional aplasia of lymphatic vessels» has been used to describe the characteristic feature of no visible drainage. The initial lymphatic vessels are present (confirmed on histological examination) but unable to absorb interstitial fluid [19].

Mutations in the tyrosine kinase domain of *VEGFR3* are found in 70% of patients with congenital-onset primary lymphedema affecting both lower limbs, so genotyping is not confirmatory in all cases [18].

Milroy-like lymphedema Individuals with congenital lower limb lymphedema who do not have an underlying *VEGFR3* mutation are classified as having «Milroy-like lymphedema.»

Mutations within the *VEGFC* gene have been identified as causal in some families within this category [21]. *VEGFC* is the ligand for VEGFR3 and controls lymphatic sprouting during embryonic development [22]. Affected individuals typically have all the clinical signs of Milroy disease (congenital lower limb lymphedema, prominent large-caliber veins, and hydroceles, inherited in an autosomal dominant pattern), yet their lymph scans are atypical.

MCLMR syndrome Microcephaly with or without chorioretinopathy, lymphedema, or mental retardation syndrome is an autosomal dominant syndrome comprising congenital lower limb lymphedema (mimicking Milroy disease) with microcephaly and variable degrees of learning difficulties that occur as a result of mutations in the *KIF11* gene on chromosome 10q24 [24]. The presence of chorioretinopathy is variable but should always be excluded by an expert ophthalmology opinion. Other eye abnormalities are frequent. Lymphoscintigraphy demonstrates the same pattern of lymphatic functional aplasia as that seen in Milroy disease. The *KIF11* protein product is involved in spindle formation during mitosis, but it is not clear how *KIF11* relates to the lymphangiogenesis pathway. MCLMR should be considered in all patients with congenital, bilateral lower limb lymphedema and microcephaly. Measuring head circumference should be an essential clinical requirement when seeing children with congenital pedal lymphedema (Fig. 3.3).

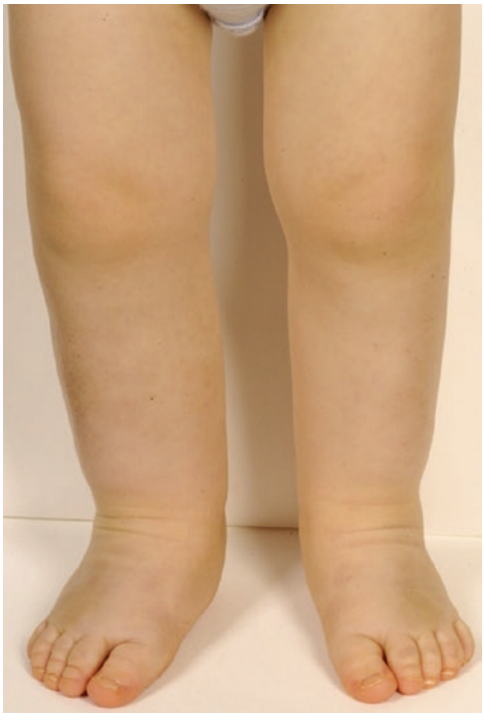

Fig. 3.3 Bilateral lower limb oedema in the same patient as Fig. 3.2. Images courtesy of Professor Mansour with permission

Congenital multisegmental lymphedema Patients with congenital multisegmental lymphoedema without systemic lymphatic impairment have been included within the yellow section of the classification pathway (Fig. 3.1) in order to avoid confusion with multisegmental lymphedema occurring in association with systemic lymphatic abnormalities (in the pink section of the pathway). These patients have an asymmetrical pattern of lymphatic failure with some limb sparing (i.e., some limbs are unaffected) but without overgrowth or cutaneous or vascular abnormalities. It is possible that somatic mosaicism in gene(s) involved in lymphangiogenesis could explain this subtype of congenital primary lymphedema, but the genetic basis is not known.

3.8 Late-onset Primary Lymphedema

The term late-onset lymphedema is used to describe a primary lymphedema that develops after the first year of life (i.e., non-congenital lymphedema). This section contains a number of conditions, some with life-threatening-associated diseases (e.g., Emberger syndrome), but they all share the common finding of non-congenital limb swelling.

Cholestasis-lymphedema syndrome (Aagenaes syndrome) Cholestasis-lymphedema syndrome is characterized by (1) neonatal intrahepatic cholestasis, often lessening and becoming intermittent with age, and (2) severe chronic lymphedema, mainly lower limb [23]. Edema of one or both legs begins in childhood and progresses. Lymphedema of the arms, face, and trunk can also occur. Liver pathology initially shows giant cell transformation in infancy with subsequent development of some fibrosis or cirrhosis in later childhood. Consanguinity was frequent among published cases suggesting autosomal recessive inheritance. The causal gene is not known but a locus has been mapped to chromosome 15q [25, 26].

Lymphedema-distichiasis syndrome Distichiasis (aberrant eyelashes arising from the meibomian glands in the inner eyelid) is present in 95% of affected individuals and is usually present at birth but rarely causes symptoms until childhood. Lymphedema typically appears in late childhood or puberty but may not be evident until the fifth decade. It is confined to the lower limbs, and is often asymmetric but usually bilateral; severity varies within families. Males develop edema at an earlier age and have more problems with cellulitis than females. Other clinical signs include ptosis, cleft palate, and congenital heart disease. The majority of affected individuals have varicose veins often from a very young age [27].

Lymphedema-distichiasis syndrome occurs as a result of mutations in the *FOXC2* gene on chromosome 16q24 and is inherited in an autosomal dominant manner [28]. *FOXC2* encodes a transcription factor necessary for ensuring normal development of the lymphatic collecting vessels and valves. Lymphoscintigraphy of affected individuals demonstrates reflux of lymph within the lower limbs as a result of valve failure within the lymphatic vessels [29]. Similarly, abnormal venous valves lead to early-onset venous reflux in all patients with *FOXC2* mutations [30].

Meige disease Meige disease is the most prevalent subtype of primary lymphedema [31]. It typically presents with bilateral lower limb lymphedema that rarely extends above the knee. The onset of symptoms is in adolescence or adulthood. There are no other associated features of the condition [32]. Lymphoscintigraphy frequently demonstrates abnormal deep rerouting of lower limb lymph drainage as evidenced by an increased uptake of tracer within the popliteal lymph nodes and impaired main superficial lymphatic tract filling. Family history is consistent with an autosomal dominant pattern of inheritance, yet the causal gene of classic Meige disease has not yet been identified.

Late-onset four-limb lymphedema An autosomal dominant pattern of late-onset lymphedema, affecting either the lower limbs or all four limbs, occurs as a result of mutations in the *GJC2* gene [33]. Apart from lower limb varicose veins, no other associated conditions have been reported. Lymphoscintigraphy demonstrates lymphatic tracts that appear normal but with significantly reduced quantification uptake of tracer, reflecting reduced absorption from tissues by peripheral lymphatics in all four limbs. The functional role of *GJC2* within the lymphatic system is unclear as it encodes for the connexin 47 protein located on chromosome 1q42 and is not yet known to be involved in the lymphangiogenesis pathway.

Emberger syndrome Emberger syndrome comprises late-onset (but in childhood) bilateral or unilateral lower limb with or without genital lymphedema together with immune dysfunction and myelodysplasia which may progress to acute myeloid leukemia. It may also be associated with a high-frequency, progressive sensorineural deafness [34, 35].

Severe cutaneous warts occur as a result of the associated immune dysfunction. Myelodysplasia may develop at any stage and will often progress to acute myeloid leukemia with a high mortality rate. Mutations in the *GATA2* gene on chromosome 3q21 are causal and are inherited in an autosomal dominant manner [5]. Mouse studies suggest the lymphedema occurs as a result of abnormal lymphatic valve development. *GATA2* is also involved in the regulation of hematopoiesis, hence the association of lymphedema with myelodysplasia, immunodeficiency, and infections (particularly mycobacterial) in this rare, yet life-threatening, condition [36].

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Embryology, Anatomy, & Histology

Contents

Embryology of the Lymphatic System and Lymphangiogenesis

Stanley G. Rockson

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Summary of Basic Concepts

Recent molecular and structural insights have helped to shed light on the embryological origins of the lymphatic vasculature. These discoveries have distinct implications, not only for molecular therapeutics in lymphatic vascular disease but also for the broad field of tumor biology and for the study of vascular malformations.

- The lymphatic vessels appear substantially later than the blood vascular structures.
- The lymphatics arise from aggregates of endothelial cells through the combined forces of vasculogenesis and angiogenesis. The earliest identifiable embryonic lymphatic precursors are the jugular lymph sacs, paired structures that are adjacent to the jugular section of the cardinal vein.
- Both centrifugal and centripetal models for lymphatic vascular development have been proposed, and both likely play a role in mammalian biology.
- Lymphatic vasculogenesis is thought to occur in four identifiably distinct stages: lymphatic competence, commitment, specification, and vascular coalescence and maturation.
- Lymphangiogenesis is a critical pathway in embryonic development that has an important, clinically relevant counterpart in wound healing and inflammation.

The lymphatic vasculature was first recognized by Gaspare Aselli more than three centuries ago, and the hypothesized embryonic origin of the lymphatic structures was initially investigated more than one century ago [6]; nevertheless, it only has been recently, during the era of molecular biology, that the mechanisms of mammalian lymphatic development have become increasingly well-understood [1, 2, 7].

Still a subject of some unresolved controversy, the embryological origin of the mammalian lymphatic system has been extensively explored over the last two decades. Recent molecular and structural insights have helped to shed light on this complex and important topic, which also has distinct implications, not only for molecular therapeutics in lymphatic vascular disease but also for the broad field of tumor biology. Furthermore, defects in the growth and development of lymphatic vessels (lymphangiogenesis) underlie numerous disorders, including vascular malformations, lymphedema, and lymphangiectasia [3].

As integral elements of the mammalian circulation, the lymphatic conduits, like all vascular structures, arise from aggregates of endothelial cells, through the concerted forces of vasculogenesis and angiogenesis (Fig. 4.1).

The lymphatic vessels appear substantially later than the blood vascular structures [8]. In the human embryo, this occurs at 6–7 weeks, nearly 1 month after the appearance of the first blood vessels [9]. The earliest identifiable embryonic lymphatic precursors are the jugular lymph sacs, paired structures that are adjacent to the jugular section of the cardinal vein. The origin of these lymph sacs and their relationship to the adjacent cardinal vein has, until quite recently, been central to the theoretical controversy [4]. The «centrifugal» model, originally suggested by Florence Sabin, proposes that the primary lymph sacs arise from the endothelial cell population of the embryonic veins, with subsequent, continued endothelial sprouting from the lymph sacs into the surrounding tissues and organs.

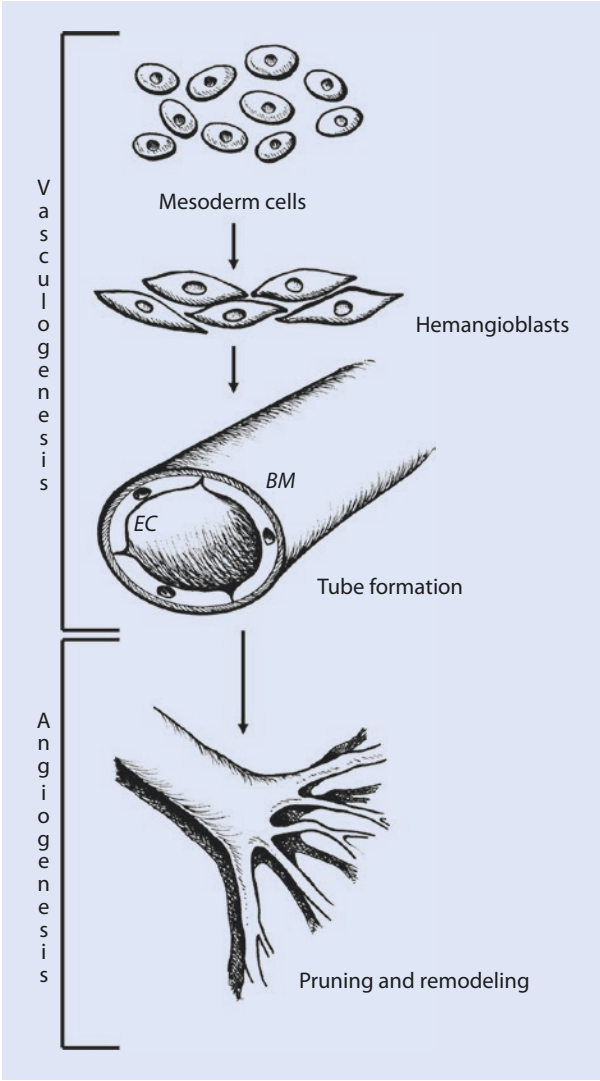

Fig. 4.1 The embryonic development of the vasculature originates from mesodermally derived endothelial cell precursors, termed vasculogenesis. Subsequently, the developing vessels grow and remodel into a mature vascular network by endothelial sprouting and splitting, the process called angiogenesis (Adapted from Oliver [5])

The contrasting «centripetal» model of Huntington relies upon the contribution of mesenchymal precursor cells, termed lymphangioblasts, to give rise to the lymph sacs, a process that occurs independently of the veins.

Although there are lines of evidence to support elements of both of these theories, it seems that the centrifugal model more closely predicts the process in higher mammals.

Support for Sabin's centrifugal model was initially provided by studies in Prox1-deficient mice [10, 11] and has subsequently been confirmed by others [12, 13]. Nevertheless, mesenchymal cells expressing CD31 and CD45, along with lymphatic

endothelial markers (Prox1 and LYVE-1), have been observed in mouse embryos, suggesting that these cells might serve as lymph endothelial precursors [14] . This and other lines of investigation continue to support elements of the centripetal hypothesis [15, 16], particularly in the tissue-specific manner in which brain, cardiac, intestinal, visceral, and dermal lymphatics develop [2].

Prox1 is central to the centrifugal mechanism. This nuclear transcription factor is a homolog of the *Drosophila* homeobox transcription factor *prospero* 7 and serves as a master regulator of lymphatic development. The venous origin of the mammalian lymphatic vasculature has been demonstrated by lineage-tracing experiments [12] and supported by studies in zebrafish [13]. It has furthermore become apparent that CCBE1 is crucial for the initial stages of lymphatic vascular development [17, 18].

According to the current prevailing model, lymphatic vasculogenesis is thought to occur in four identifiably distinct stages: *lymphatic competence, commitment*, *specification*, and *vascular coalescence and maturation* (Fig. 4.2).

Lymphatic competence refers to the cellular capacity to respond to the initial induction signals for lymphatic vascular differentiation [5]. The priming of lymphatic endothelial cells (LECs) to initiate lymphatic development seems to depend on molecular signaling pathways that are distinct from those that direct blood vascular development [17, 18].

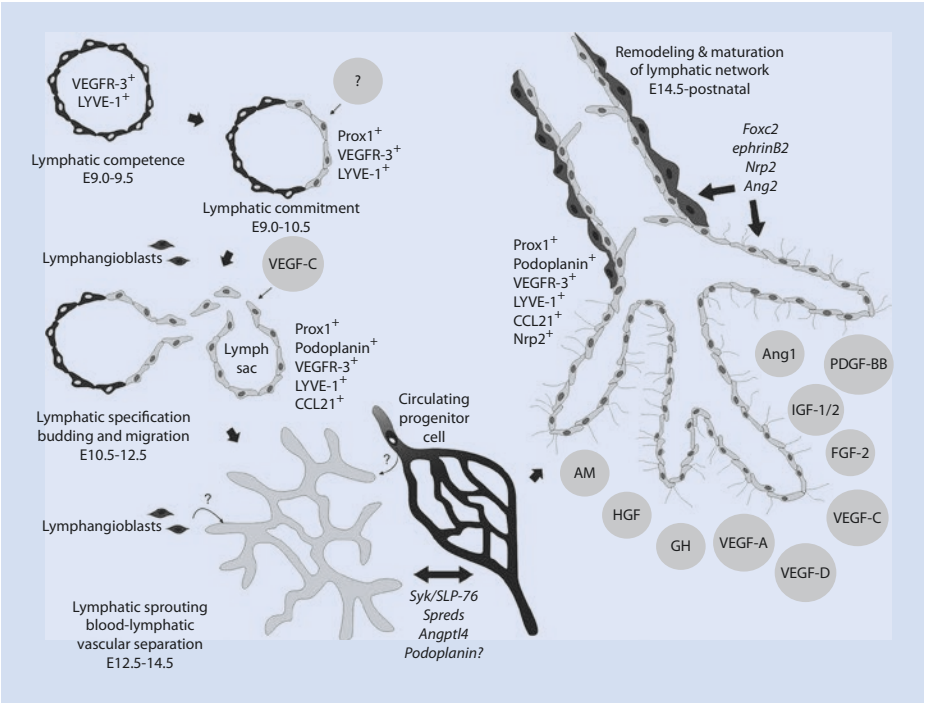

Fig. 4.2 Lymphatic vasculature development and growth. *AM* adrenomedullin, *Ang* angiopoietin, *Angptl* angiopoietin-like protein, *E* mouse embryonic day, *FGF* fibroblast growth factor, *GH* growth hormone, *HGF* hepatocyte growth factor, *IGF* insulin-like growth factor, *Nrp2* neuropilin-2, *PDGF* platelet-derived growth factor, *VEGF* vascular endothelial growth factor (Reproduced with permission from Cueni and Detmar [4])

LEC competence is recognized through cellular expression of lymphatic vessel endothelial hyaluronan receptor-1 (LYVE-1) [10, 19] and vascular endothelial growth factor receptor-3 (the flt4 gene encodes for VEGFR3) [4]. Mouse embryos that lack VEGFR3 expression die without lymphatic development. VEGF-C binding to VEGFR3 transduces signals that promote lymphatic endothelial cell survival, proliferation, and migration [20, 21]. Mouse embryos that lack VEGF-C do not develop lymph sacs [22]. VEGF-C/VEGFR3 signaling plays a key role during multiple stages of lymphatic vascular development; while VEGF-C signals can be transduced by means of multiple receptors, VEGFR3 is undoubtedly the most pivotal of these [3]. In addition, more recently, there has been demonstration of the potential for embryonic mechanosensitive activation of VEGFR3 independently of VEGF-C binding [23]. Various defined roles for VEGFR3 signaling in lymphatic vascular development and maturation are summarized in Table 4.1.

Lymphatic commitment is characterized developmentally and functionally by the expression of Prox1. The expression of this nuclear transcription factor is exclusive to cells of committed lymphatic lineage [10]. Prox1 expression shifts commitment of venous endothelial cells from the default blood vascular fate to a lymphatic lineage [11]. In mammals [2], the initiation of Prox1 expression in venous endothelial cells is dependent on the transcription factors Sox18 [24] and Nr2f2/Coup-TFII [25].

It seems that expression of Prox1 within the embryonic endothelial cell is necessary and sufficient for lymphatic commitment. Prox1-positive lymphatic endothelial.

cells, within both the cardinal and intersomitic veins, subsequently bud and migrate away from the veins in connected streams [2] to form an initial lymphatic plexus and, with further development, lymph sacs [26–28]. In addition, the expression of CCBE1 seems to be essential for the egress of the developing LECs.

Table 4.1 VEGFR signaling in lymphatic vascular development

VEGFR signaling in lymphatic endothelial progenitor cell specification and migration
Exit of lymphatic endothelial progenitor cells from the embryonic veins
VEGFR signaling during sprouting and expansion of the lymphatic vasculature
VEGF-D, but not VEGF-C, is particularly important for development of the lymphatic vasculature in skin
VEGFR2 promotes lymphatic endothelial cell proliferation, but does not result in lymphatic vessel sprouting
Increased embryonic interstitial pressure can drive VEGFR3 phosphorylation independently of VEGF-C, promoting lymphatic endothelial cell elongation, proliferation, and vessel growth
VEGFR signaling during lymphatic vascular remodeling and vessel maturation
Generation of the superficial lymphatic plexus
VEGFR3 signal transduction is like to be important for generation of lymphatic valves

Adapted from Secker [3]

Lymphatic endothelial cell specification entails the expression of the distinguishing molecular markers that lead to the unique lymphatic endothelial phenotype. As the newly developing LECs leave the veins, they express markers of LEC identity; these include podoplanin and higher levels of VEGFR3 and neuropilin-2 [26–28]. Through these developmental steps, the committed lymphatic cell population establishes complete autonomy from the local venous microenvironment. Peripheral migration occurs. Budding and migration precede the formation of primary lymph sacs throughout the embryo. Secondary budding and migration herald the final stages of lymphatic development. The cells thereby form capillaries in a centrifugal fashion, establishing the lymphatic vasculature throughout the bodily tissues and organs [4].

An important event in lymphatic development is the necessary separation between the flow of blood and lymph. A tyrosine kinase, Syk, and an adapter protein, Slp-76, are both critical for lymphaticovenous separation. Deficiency of either *Syk* or *Slp76* has been shown to create abnormal connections between blood vessels and lymphatics, with resultant blood-filled lymphatics and chylous hemorrhage [29]. In the embryo, platelets aggregate at sites of lymphaticovenous connections, triggered by binding of LEC-specific podoplanin to C-type lectin receptor 2 (CLEC-2), which is specifically expressed in platelets; this leads to activation of Syk and Slp-76 [30, 31]. Inadequate megakaryocytes, platelets, podoplanin, CLEC-2, Syk, or Slp-76 in the mouse all can lead to blood-filled lymphatic vessels [2, 29–36].

Vascular Coalescence and Maturation After the appearance of the embryonic peripheral lymphatic vasculature, these vessels must experience substantial maturation and remodeling. One of the important maturational events is the development of the valve apparatus. A forkhead transcription factor, FOXC2, is highly expressed in adult lymphatic valves. It seems that FOXC2 specifies a collecting lymphatic vessel phenotype [37, 38]. Valve development is also dependent on GATA2 [39]: selective deletion of GATA2 in the murine lymphatic endothelium leads to major defects in valve structure and distended collecting lymphatic vessels. Additional signaling pathways, among them BMP [40], Notch [41], and semaphorin3a-neuropilin-1 [42], play important roles in valvular development.

The ephrins and the angiopoietins also contribute to lymphatic vascular maturation. In mutant mice, faulty expression of EphrinB2 leads to hyperplasia of the collecting lymphatics, absent valve formation, and failure of lymphatic capillary remodeling [43]. There is also a role for EphB4 forward signaling in lymphatic vessel valve development [44]. Angiopoietins 1 and 2 (Ang1 and Ang2) also participate in the maturation of the lymphatic vasculature [45–47]. In the lymphatics, Ang2 is a Tie2 receptor agonist, in contradistinction to its role in the blood vasculature [46]. Mice with a deletion of the Tie2 ligand Ang2 exhibit major defects in lymphatic vessel remodeling: their lymphatic vessels prematurely recruit smooth muscle cells and fail to develop valves [45, 46]. The Tie1 receptor also plays a critical role in early stages of lymphatic development [48, 49]. Lymphatic valve development apparently also requires normal expression of integrin-alpha9 and deposition of its ligand, fibronectin-EIIIA, in the extracellular matrix [50]. Reelin signaling apparently participates in vascular maturation, through its regulation of smooth muscle investment of the lymphatic collecting vessels [51].

All of these developmental events are interrelated and complex. New molecular participants in the process continue to be identified. Although lymphangiogenesis is a critical pathway in embryonic development, it has a counterpart in wound healing and inflammation [52, 53]. These molecular pathways may also have direct implications for future molecular therapeutics in lymphedema and other lymphatic vascular disorders [1, 54]. These concepts are further explored in ▶ Chap. 16.

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Anatomy of the Lymphatic System and Its Structural Disorders in Lymphoedema

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Summary of Basic Concepts

A better understanding of normal lymphatic anatomy is essential for recognising the structural disorders that occur in lymphoedema. This chapter describes the micro- and macro-anatomy of the lymphatic system in the normal state and introduces the lymphosome concept, a new anatomical concept proposed by the authors. It then discusses the pathophysiology of lymphoedema, presenting ICG lymphography images in the normal state and different lymphoedema conditions.

Key Points

- Our current knowledge of the lymphatic system still largely depends on the mercury injection technique in cadavers that was developed for dissection studies over 100 years ago.
- The anatomical structure of the lymphatic system is composed of three elements: the lymphatic vessels, lymph nodes and lymph fluid.
- The microstructure of the lymphatic vessels consists of the lymphatic capillaries meeting to create the larger pre-collectors which in turn join to become the lymph collecting vessels.
- The major lymph pathways in the upper and lower extremities connect to a small number of dominant lymph nodes in the axilla or inguinal region. However, some collateral lymph pathways bypass these nodes.
- The skin can be demarcated into lymphatic territories (lymphosomes).
- Structural changes in the lymphatic system can be identified using indocyanine green fluorescence lymphography. This technique enables us to understand the structural disorders in each individual lymphoedema patient.

5.1 Introduction

The blood vascular system in humans is composed of arteries and veins connected to the blood capillary network extending to the peripheral regions. The heart is located at the centre of the vascular system and serves as a mechanical pump that circulates the blood throughout the body. Blood flows from the artery to the vein in a continuous «closed system» that returns to the heart. The blood vascular system is described as «blood circulation» because it works in a closed loop. By contrast, lymph fluid originates from the interstitial fluid exuding from the blood capillaries. Some of the excess interstitial fluid is absorbed by the lymph capillaries, with the rest absorbed by the venules. The lymphatic system is classified as «open system» because lymph capillaries are open-ended. The lymph fluid is transported centrally by the lymphatic system and is eventually retrieved by the venous system. As the fluid flows in one direction and does not circulate, lymph flow is commonly described as «lymphatic transport» or «lymphatic drainage» (◘ Fig. 5.1).

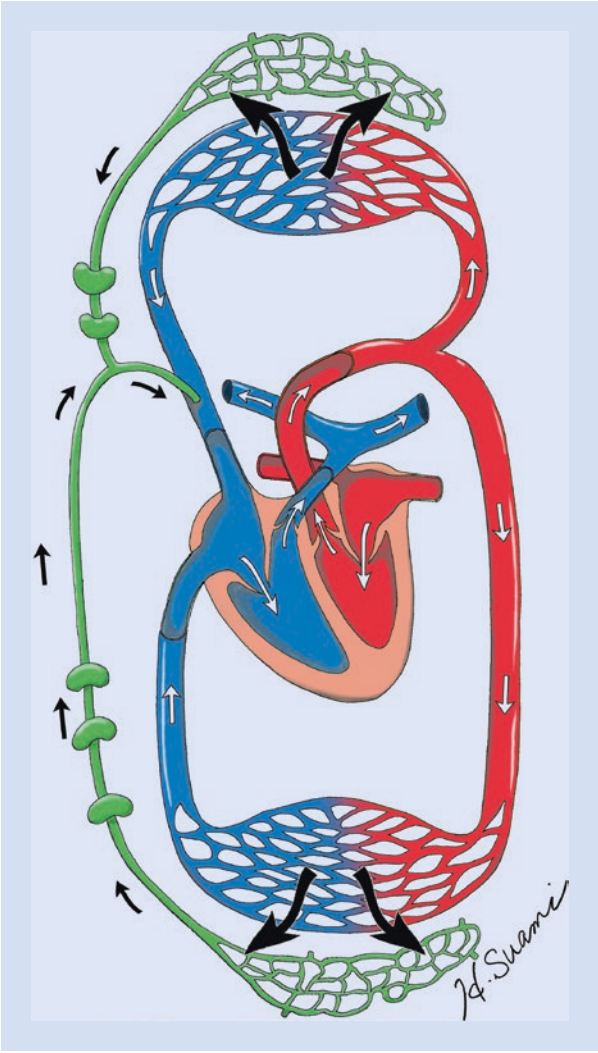


Fig. 5.1 Schematic diagram of the relationship between blood vascular circulation and lymphatic drainage (Published with kind permission of © Hiroo Suami 2017)

The anatomical structure of the lymphatic system is composed of three tissue components: the lymphatic vessel, the lymph node and the lymph fluid [6]. The lymphatic vessel originates as a blind-ended sac in the lymphatic capillary located immediately below the epidermis or mucosa. The lymph capillaries connect to pre-collectors in the deep dermis. The pre-collectors have a valvular structure, and they run deeply from the skin to connect to the lymph collecting vessels in the fat tissue [7, 8] (Fig. 5.2).

While there is no pumping organ like the heart associated with the human lymphatic system, the lymph collecting vessels are surrounded by smooth muscle cells that contract and squeeze to propel lymph flow [1]. There are numerous valvular structures in the

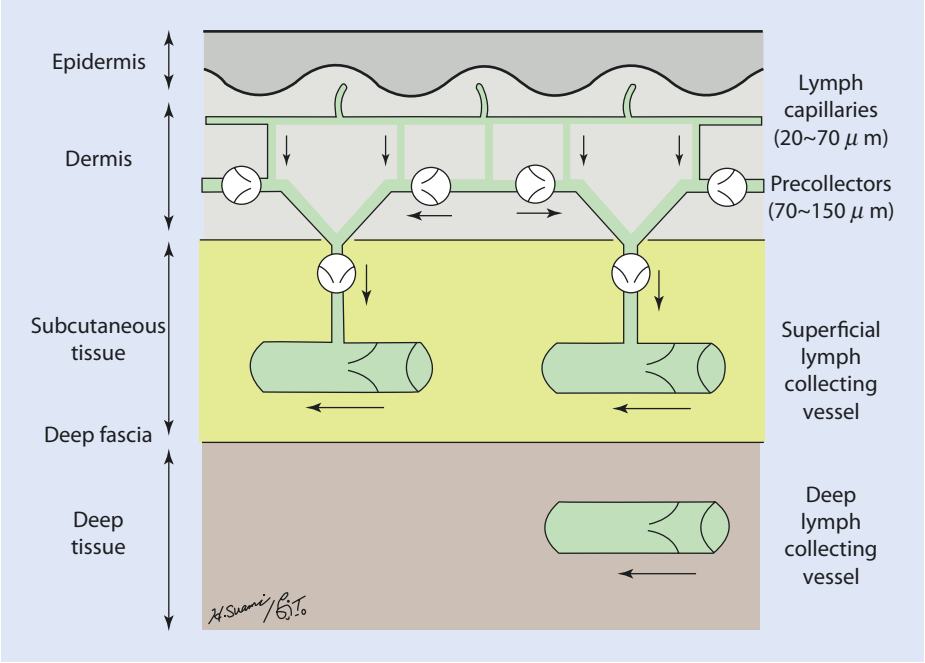


Fig. 5.2 Schematic diagram of the relationship between the lymph capillaries, pre-collectors and lymph collecting vessels (Suami et al. [8]. Published with kind permission of © Hiroo Suami 2017)

lumen of the lymph collecting vessels spaced at intervals of a few millimetres. Between the valves of the lymph collecting vessel is a functional unit called a «lymphangion» [9]. Lymphangions are innervated by the autonomic nervous system, and they contract rhythmically in a coordinated manner. The contraction rate and amplitude of the lymphangions are regulated by the increase or decrease in lymph flow volume and intravascular pressure [10]. Peristaltic contraction of the lymph collecting vessel and the valves facilitates lymph flow to the central region in a mechanism known as the «intrinsic pump».

5.2 Microstructures of the Lymphatic System

5.2.1 Lymph Capillaries

Lymph capillaries are also called «initial lymphatics» or «terminal lymphatics» [6] (Fig. 5.3). The lymph capillaries are composed of a single layer of endothelial cells with a diameter of between 20 and 70 um. There are no valvular structures in the lumen. The endothelial cells are oak leaf shaped and interweave to connect with each other. Electron microscopic observation reveals that gaps exist between the endothelial cells to facilitate permeability of the interstitial fluid [11].

The anchoring filament is a special structure of the lymph capillary that attaches to the outer edge of the endothelial cell at one end and the surrounding tissue at the other [2].

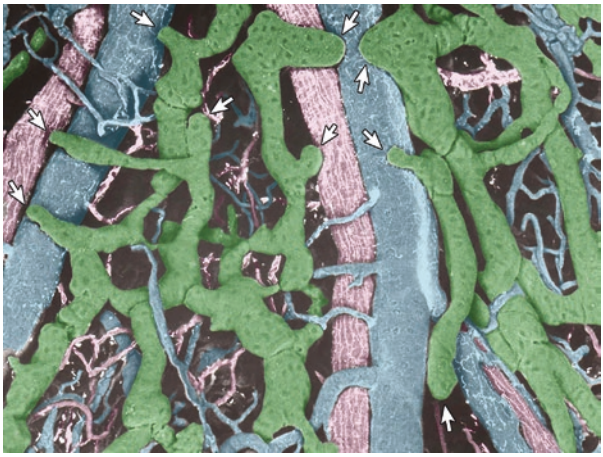


Fig. 5.3 Scanning electron microscopic image of the lymph capillaries (*green*), arteries (*pink*) and veins (*blue*) in the gall bladder of a canine (colours added by author). *Arrows* indicate the blind end of the lymph capillaries (Reproduced from Kato et al. [6])

The anchoring filaments prevent the lumen of the thin-walled lymph capillaries from collapsing. They also pull the endothelial cells outwards to expand the cellular gaps and increase absorption of the interstitial fluid when the amount of interstitial fluid increases in the local tissue and the tissue becomes oedematous [12].

5.2.2 Pre-collectors

Pre-collectors connect the lymph capillaries with the lymph collecting vessels. The lumen of these vessels has a valvular structure and contains smooth muscle cells that are randomly spaced. The lymph capillaries become pre-collectors in the deep dermal layer [7] (Fig. 5.4). At between 70 and 150 um, the diameter of the pre-collector is larger than the lymph capillary.

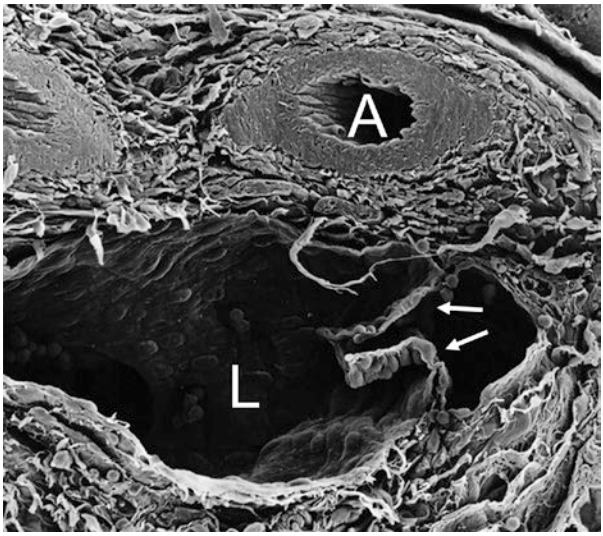


Fig. 5.4 Scanning electron microscopic image of the pre-collector (*L*) and artery (*A*) in the dermis. *Arrows* indicate a valvular structure. (Reproduced from Kato et al. [6])

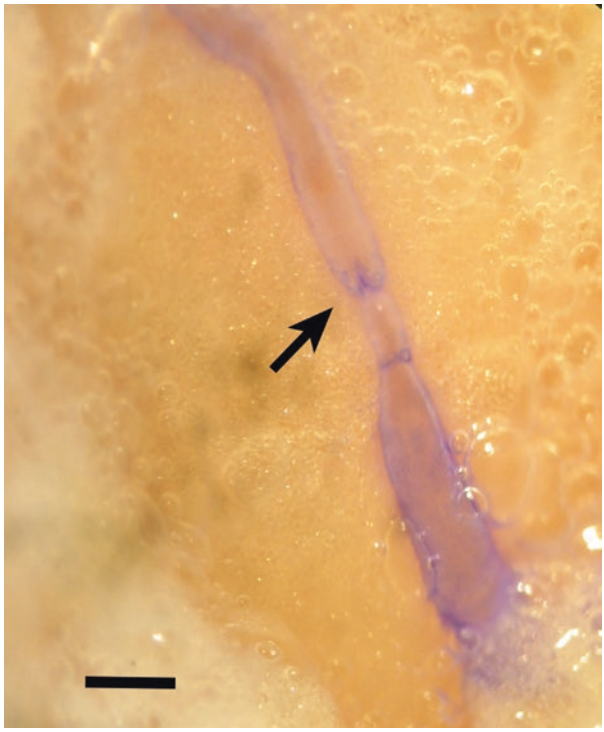


Fig. 5.5 A lymph collecting vessel is shown using a mixture of hydrogen peroxide and *blue* dye in the dorsum of a cadaver foot. *Arrow* indicates the intravascular valves. (Scale bar 1 mm)

5.2.3 Lymph Collecting Vessels

Lymph collecting vessels have a valvular lumen and are outlined with the smooth muscle cells (Fig. 5.5). While the lymphatic capillaries and pre-collectors mainly transport lymph fluid from the superficial layer to the deep layer in a vertical direction, the lymph collecting vessels transfer lymph fluid horizontally, like a highway of lymphatic drainage. The lymph collecting vessels in the extremities form major lymphatic drainage pathways and run longitudinally in the fat tissue towards the lymph nodes.

The lymph collecting vessels are categorised as «superficial» or «deep» depending on their anatomical relationship to the deep fascia [8] (Fig. 5.2). In contrast to the veins, most of the superficial and deep lymph collecting vessels are clearly separated by the deep fascia and are independent of each other. They merge at the regional lymph nodes [13, 14].

5.2.4 Lymph Nodes

The lymph node is a lymphatic organ which intervenes in the lymph collecting vessel. Bartels proposed the «barrier theory» which postulates that each lymphatic vessel passes through at least one lymph node before connecting to the vein [15]. His theory makes

good sense because the lymph node is central to the immune defence mechanism in both humoral and cellular immunity.

Lymph nodes are categorised as «regional» or «interval» depending on their anatomical characteristics. The regional lymph nodes associated with the extremities are located in the axilla and inguinal regions where several lymph nodes concentrate as a group. In contrast, interval lymph nodes are located along the course of the deep lymph collecting vessels which run parallel to the major arteries [16]. The popliteal lymph nodes in the knee fossa and the epitrochlear lymph nodes in the medial elbow are relatively well-known interval lymph nodes. The structural difference between regional and interval nodes arises from the difference in the number of afferent lymph vessels connecting to the node. In the regional lymph node, several afferent lymphatic vessels connect to the node, while a few efferent lymphatic vessels exit from the hilum. In the interval lymph node, one or two afferent lymphatic vessels connect to the node, while one or two lymphatic vessels exit from it.

Lymphatic vessels can regenerate after surgical resection, and this phenomenon is called lymphangiogenesis [17]. However, lymph nodes have no regeneration potential and lose their immunological function after surgical removal [18, 19].

5.3 Macrostructure of the Lymphatic System in the Extremities

5.3.1 Upper Extremities

The lymphatic system in the upper extremities originates in the lymph capillaries in the skin of the fingertips. The capillaries merge to form a pair of lymph collecting vessels on each side of the fingers and run alongside the digital neurovascular bundles [16, 20]. When they reach the meta-pharyngeal joints, all lymph collecting vessels are located in the dorsum of the hand immediately below the cutaneous veins. These vessels continue to run longitudinally in the posterior forearm, diverging around the olecranon to become two streams. They gradually converge in the medial upper arm and connect to the axillary lymph nodes (Figs. 5.6, 5.7 and Supplemental Video 5.1). The lymph capillary network in the palm transforms into superficial lymph collecting vessels at the anterior wrist joint. These vessels are directed straight to the axilla. It is noteworthy that most of the anterior vessels and some of the posterior vessels connect to one or two dominant lymph nodes in the axilla [13]. These nodes are located at the most lateral aspect of the axilla in the level I node group which is located laterally from the pectoralis minor muscle and classified as the region for axillary lymph node dissection. These dominant lymph nodes in the axilla are also considered to be the sentinel nodes for the majority of the skin area in the upper extremities.

In addition to the major pathways, there are also a number of collateral lymph pathways that bypass the dominant lymph nodes. These superficial lymph vessels, which run along the cephalic vein in the upper arm, do not run towards the axilla but connect to the deltopectoral node, which is an interval lymph node at the front of the shoulder. After passing this node, the efferent lymphatic vessels connect to the subclavicular lymph nodes

Fig. 5.6 Radiographic image of the lymph collecting vessels in a cadaver forearm shown using the ICG fluorescence lymphography-assisted microinjection technique performed by the author

[3, 16] (Mascagni's pathway). Knowledge of this pathway is important for management of skin cancer around the cephalic vein, because if axillary lymph node dissection is performed without sentinel lymph node tracking, it is possible that metastatic lymph nodes in the subclavicular area may not be successfully removed. The superficial lymph vessels accompanying the basilic vein usually connect to the dominant lymph nodes, but occasionally angle downwards at the elbow, penetrating the deep fascia and becoming deep lymphatic vessels. These vessels pass through the epitrochlear lymph node en route to the axilla. This pathway may be the reason that lymphoscintigraphy occasionally shows the epitrochlear nodes, while the examination shows mainly superficial lymph pathways [21].

The deep lymphatic system in the upper extremities originates in the lymph capillaries in the deep fascia and periosteum. The deep lymphatic vessels run parallel to the ulnar, radial and humeral arteries. These vessels also bypass the foregoing dominant lymph nodes in level I and connect to the more proximal lymph nodes.

Fig. 5.7 ICG fluorescence lymphography image in upper extremities of a cadaver

5.3.2 Relationship of the Lymphatic System between the Upper Extremities and Torso

The relationship of the lymphatic system between the upper extremities and torso is crucially important for understanding the pathophysiology of secondary lymphoedema [22] (Figs. 5.8 and 5.9, Supplemental Video 5.2). The lymphatic vessels and lymph nodes in the axilla are shown radiographically in three dimensions in one of our cadaver studies. In this study, we applied our radiographic cadaver technique [4, 20] and our microinjection technique guided by indocyanine green (ICG) fluorescence lymphography [23, 24]. The results demonstrated that lymph nodes in the axilla can be divided into subgroups and colour-coded according to the skin region through which the corresponding lymphatic vessels run. For example, the green territory represents the

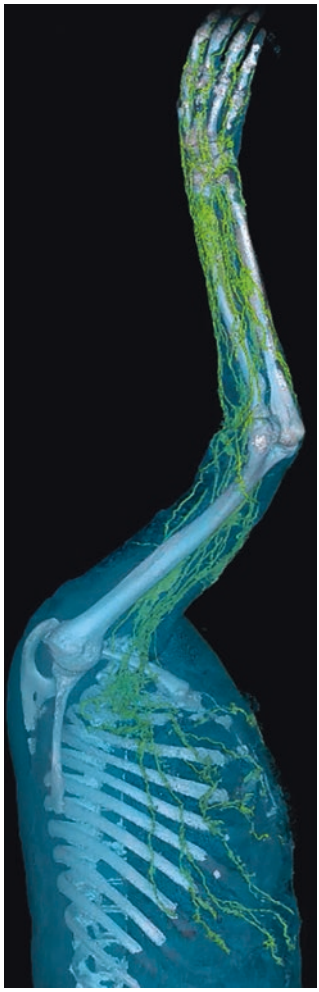


Fig. 5.8 3-dimensional volume-rendering image of the lymphatic vessels (*green*) of the upper extremity and torso in a cadaver forequarter (Published with kind permission of © Hiroo Suami 2017)

overlapping of lymphatic territories between the upper extremities and the breast. The purple lymphatic territory in the upper arm is independent from the green territory that indicates lymphatic drainage in the breast. Theoretically, if oncologists can identify the lymph node group in the purple territory and preserve these nodes during axillary node dissection or radiation therapy, they can potentially preserve some of the lymph drainage capability without compromising oncologic treatment. In this way, precise anatomical knowledge can be applied to prevent secondary lymphoedema.

5.3.3 Lower Extremities

Similarly to the upper extremities, the lymphatic system in the lower extremities originates in the lymph capillaries in the toes and sole of the foot. Lymph capillaries in the

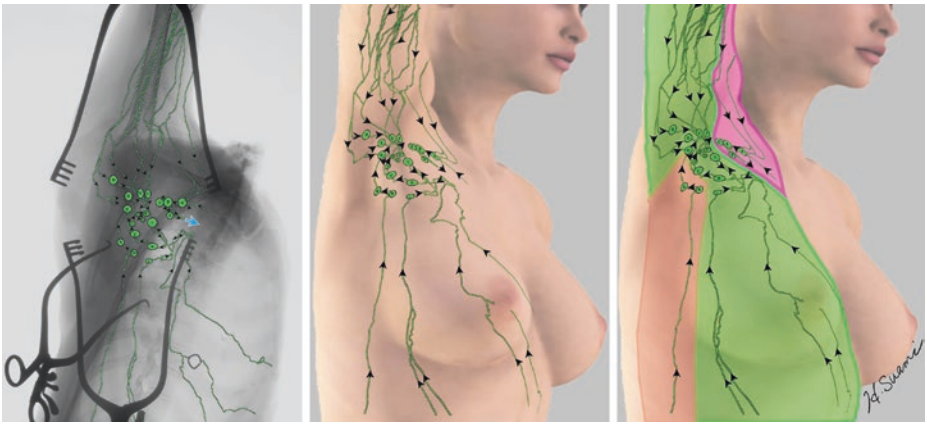


Fig. 5.9 Radiographic image of a cadaver forequarter with tracing of the lymphatic vessels and lymph nodes (*left*). Schematic diagram of the tracing of the lymphatic system (*middle*). Lymphatic territories (lymphosomes) in the forequarter (*right*), overlapping lymphatic territories between the breast and upper extremity (*green*), lymphatic territory in the upper extremity independent from the breast lymph drainage (*purple*) and lymphatic territory in the torso independent from the breast (orange) (Published with kind permission of © Hiroo Suami 2017)

toes merge to form superficial lymph collecting vessels located in the dorsum of the foot. The other lymph collecting vessels originate in the lymph capillary network in the sole and appear on both sides of the foot. The superficial lymph vessels are distributed evenly around the ankle joint and run longitudinally up the lower leg (Fig. 5.10). They gradually change course towards the medial side of the knee and then run parallel to the great saphenous vein in the thigh. Several lymphatic vessels also originate in the posterior thigh. As a result, the superficial lymphatic vessels are concentrated in the medial thigh, but they are sparsely distributed in the lateral thigh. There are also dominant lymph nodes that can be identified in the inguinal region. Most of the lymphatic vessels in the lower extremities connect to two or three dominant lymph nodes located at the base of the inguinal triangle next to the saphenous vein, and these nodes act as the sentinel nodes for the majority of the skin area of the lower extremities [23] (Fig. 5.11).

In addition to the major pathways, there are also a number of collateral lymph pathways that bypass the dominant lymph nodes. The superficial lymphatic vessels originating in the heel run alongside the small saphenous vein in the calf. At the knee fossa, these vessels connect to the interval lymph nodes, known as the popliteal nodes. The efferent lymphatic vessels from the popliteal nodes become deep lymphatic vessels and run alongside the femoral artery [25] (Fig. 5.12).

The deep lymphatic vessels run parallel to the peroneal, anterior tibial and posterior tibial arteries. These vessels pass through several interval lymph nodes in the lower leg and then connect to the popliteal lymph nodes. The efferent vessels of the popliteal nodes do not connect to the dominant inguinal lymph nodes but to the deep inguinal lymph nodes.

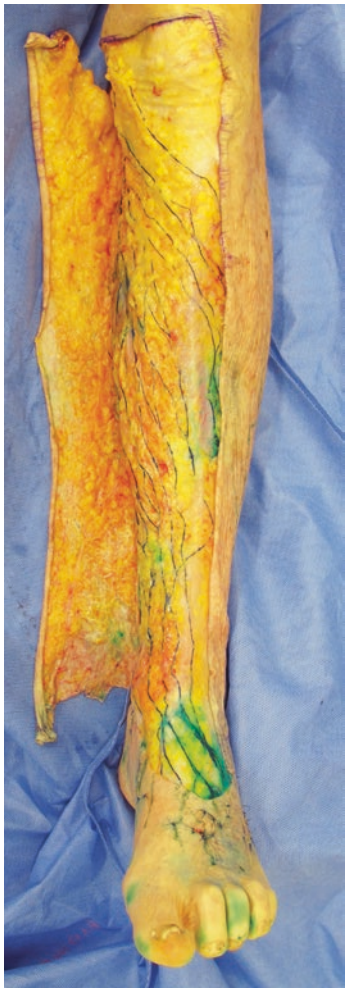


Fig. 5.10 The superficial lymphatic vessels in the lower leg (Dye injection in a cadaver leg)

5.3.4 Relationship of the Lymphatic System between the Lower Extremities and Torso

The inguinal region is one of the common donor sites for harvesting the vascularised lymph node flap, an emerging surgical procedure for the treatment of lymphoedema [26]. However, morbidity of the donor extremity is not negligible because of its potential to develop iatrogenic secondary lymphoedema [27, 28].

Our dissection studies demonstrated that superficial lymph vessels from the abdominal region connect to the lining of the lymph nodes via the superficial circumflex iliac artery or the superficial inferior epigastric artery. We were able to separate the inguinal lymph nodes, which connect to the abdominal lymphatic vessels, from the lymph nodes which connect to the lower extremities, allowing us to divide them into subgroups and identify the corresponding lymphatic territories [4].

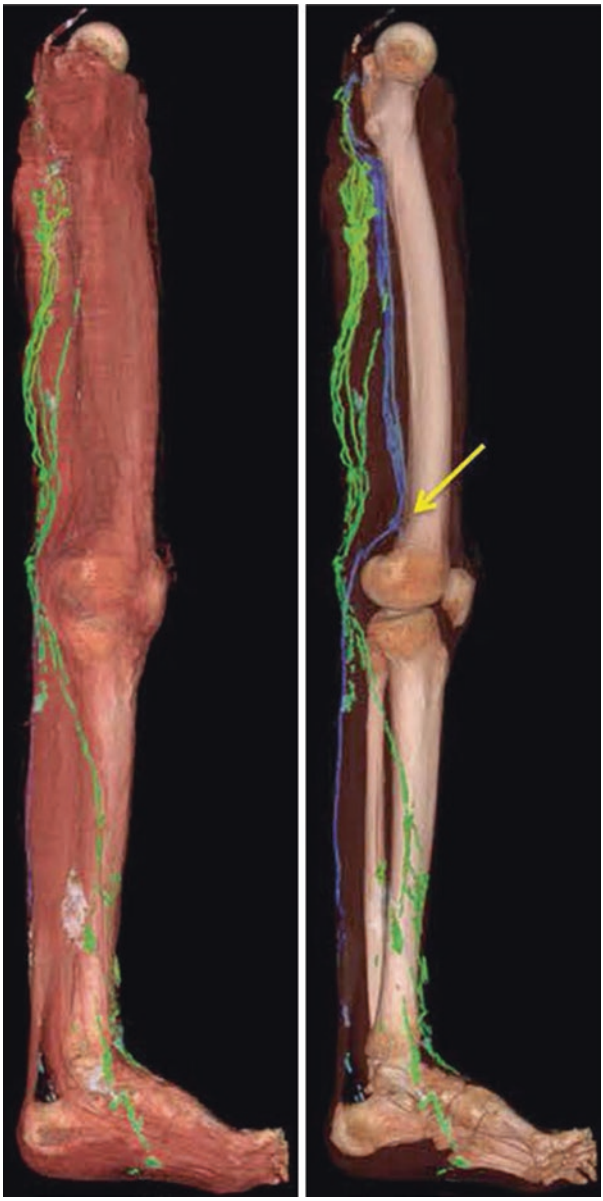


Fig. 5.11 Three-dimensional volume-rendering image of the lower extremity. The superficial lymphatic vessels (*green*) connect to the inguinal lymph node. The collateral lymphatic vessel (*purple*) runs through the calf region, connects to the popliteal lymph node (*arrow*) and becomes a deep lymphatic vessel (Reproduced from Yamazaki et al. [25].

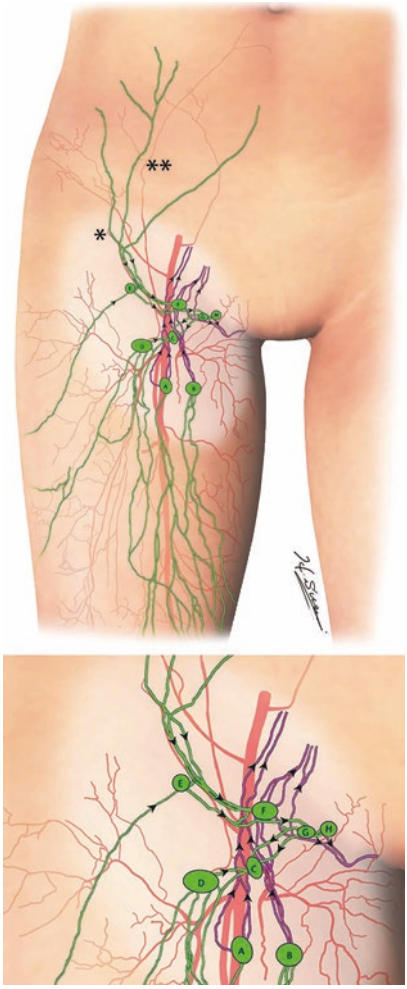


Fig. 5.12 Mapping arteries and lymphatic vessels in a cadaver specimen. The dominant lymph nodes are A, B and C. Superficial lymphatic vessels (*green*), efferent lymphatic vessels (*purple*) and arteries (*red*). * indicates the superficial circumflex iliac artery; ** indicates the superficial inferior epigastric artery. The *black* arrowheads indicate the direction of lymph flow (Reproduced from Scaglioni [23])

5

5.4 Lymphatic Territories, Namely, «Lymphosomes»

Sappey was a nineteenth-century French anatomist who used the mercury injection technique for his cadaver dissection studies. He published his findings in superb diagrams of the lymphatic system in 1874. He may be the first anatomist to recognise that the lymphatic drainage of the skin can be divided into lymphatic territories. His etching diagram showed that the lymphatic drainage of the torso is demarcated into four territories along the anterior and posterior midlines, with the horizontal line at the umbilical level. The lymphatic vessels in each territory are connected to the ipsilateral axillary or inguinal lymph nodes [5] (Fig. 5.13). Sappey's findings became the basic rationale for oncologists in deciding which regional lymph nodes should be targeted for surgical

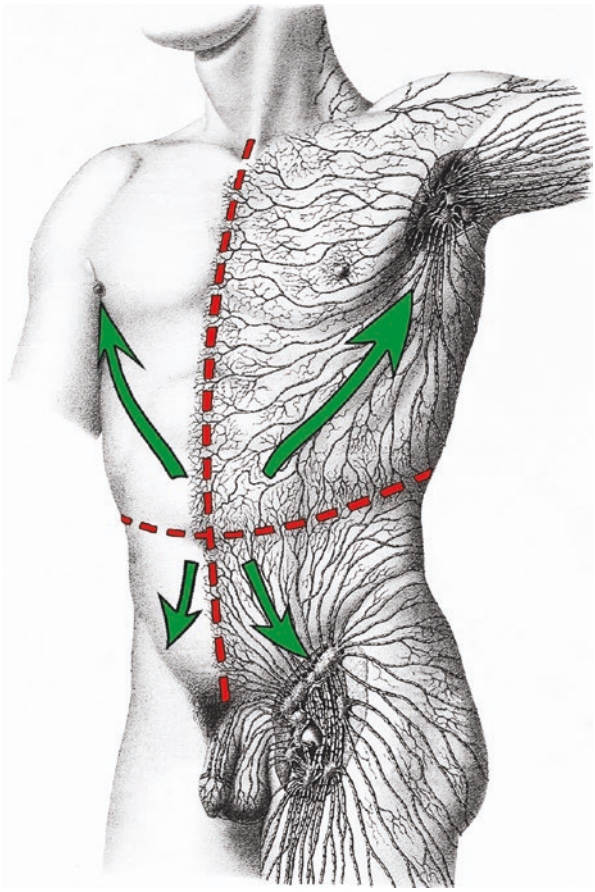


Fig. 5.13 Sappey's diagram of the front torso shows that each lymphatic territory drains to the ipsilateral axilla or inguinal lymph nodes (*arrows* and *dotted lines* added by the author)

dissection and irradiation to prevent skin and breast cancers spreading. Kubik conducted further detailed territorial mapping of the lymphatic system. He divided the skin into lymphatic territories based on bundles of lymphatic vessels and anatomical region. For example, in his system, the thigh skin is divided into three lymphatic territories: dorsolateral, ventromedial and dorsomedial bundle [29].

Our cadaver dissection findings revealed that while each superficial lymphatic vessel diverged and converged, interconnections between the vessels were much fewer than in veins [13, 14, 16]. Superficial lymphatic vessels do not overlap. We identified and traced lymphatic vessels from the peripheral regions until they reached their corresponding lymph nodes. The regional lymph nodes were divided into subgroups and colour-coded according to the skin region through which their corresponding lymphatic vessels run (Fig. 5.9). Finally, retrospective colour-coding was conducted of each superficial lymph vessel to match the colour of its corresponding lymph node. In this way, we were able to demarcate the skin into lymphatic territories for which we coined the term «lymphosomes» [13] (Fig. 5.14).

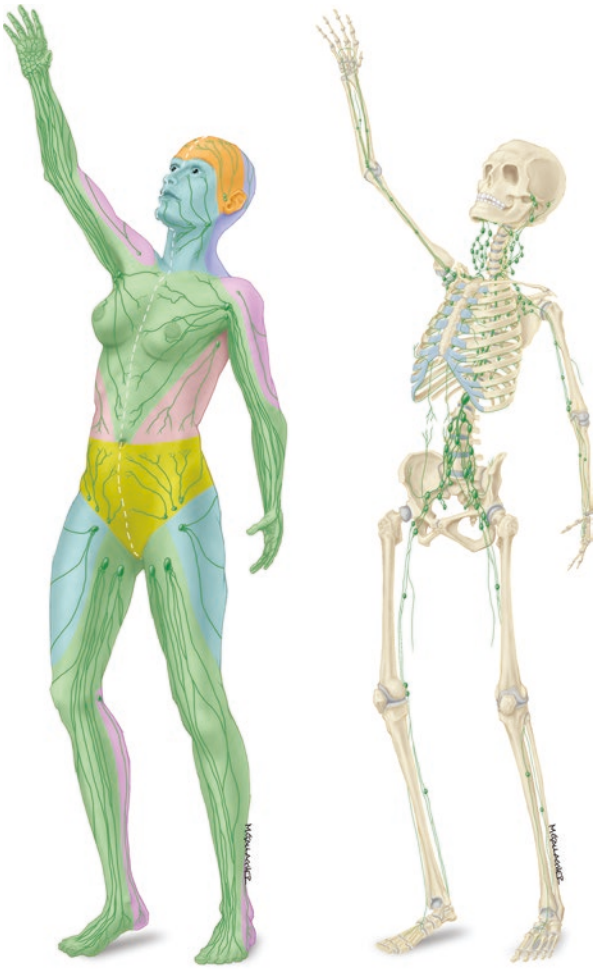


Fig. 5.14 Lymphosomes in the human body: superficial lymphatic system (*left*) and deep lymphatic system (*right*) (Published with kind permission of © Michael Gallagher 2017)

5.5 Structural Disorders in Lymphoedema

In lymphoedema, hypertrophic and proliferative tissue changes occur mainly in tissue above the deep fascia, including the skin and subcutaneous fat tissue. However, the structure of the deeper tissue is maintained [29]. This may be due to the fact that there are fewer connections between the superficial and deep lymphatic vessels and that there are more superficial lymphatic vessels than deep ones.

Structural disorders in primary lymphoedema are not uniform and lymphatic condition varies from aplastic to hyperplastic. For example, patients with «Milroy-Meige syndrome» do not have any apparent structural defects of the lymphatic system, but rather have functional impairment of the lymph capillaries [30]. Patients with «lymphoedema-distichiasis syndrome» have impaired valve development, which causes lymphatic reflux [31].

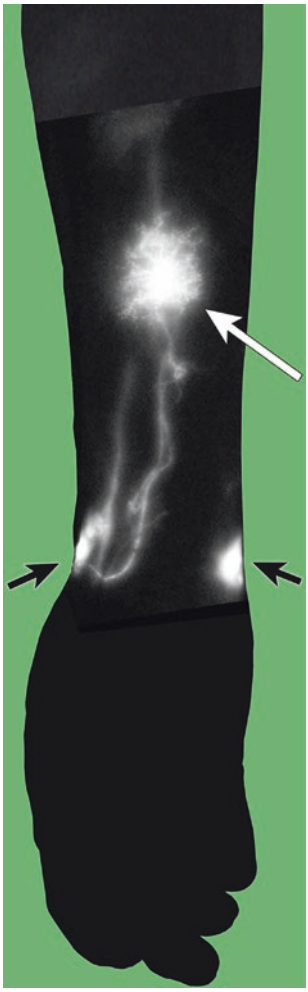


Fig. 5.15 ICG fluorescence lymphography in the anterior forearm of an early lymphoedema patient. Injection sites (*black arrows*) and localised patchy dermal backflow (*white arrow*)

The initial cause of secondary lymphoedema is the obstruction of lymphatic vessels as a result of various factors such as oncological treatment, parasite, trauma or infection. Secondary lymphoedema is signalled by «dermal backflow», which can be shown with dye injection [32], lymphangiography [21, 33], lymphoscintigraphy [34] or ICG fluorescence lymphography in the affected limb [35, 36]. In early lymphoedema (subclinical phase, ISL stage 0), the dermal backflow is localised and is patchy in appearance (Fig. 5.15). This phenomenon indicates that some superficial lymphatic vessels are obstructed in the proximal region, but the nearby lymphatic vessels are patent and functional. Lymph reflux results from incompetent pre-collectors, when the pre-collectors and lymph capillaries dilate and impede proper functioning [37] (Fig. 5.16). The reflux in the skin is absorbed by the nearby patent lymphatic vessel (Fig. 5.17 top). The existence of patchy dermal backflow is a useful sign in diagnosing lymphoedema, especially in the early stage. Structural changes of the lymphatic system in secondary

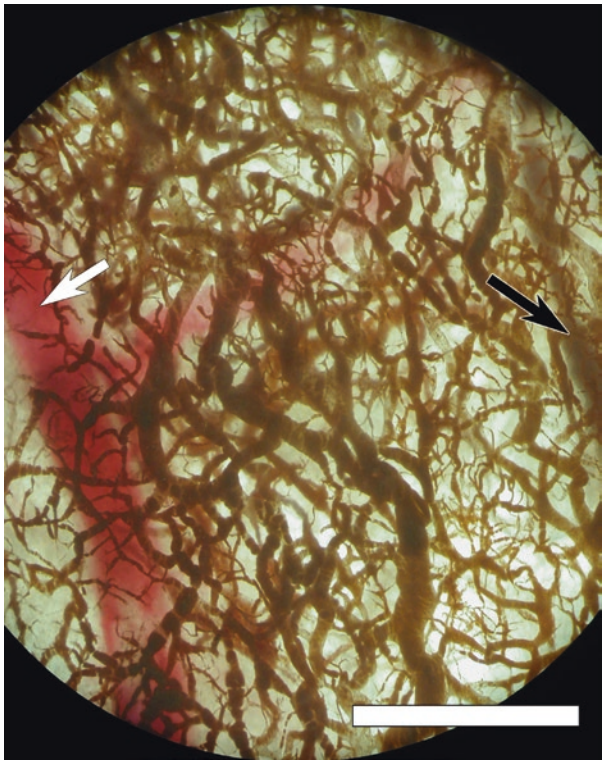
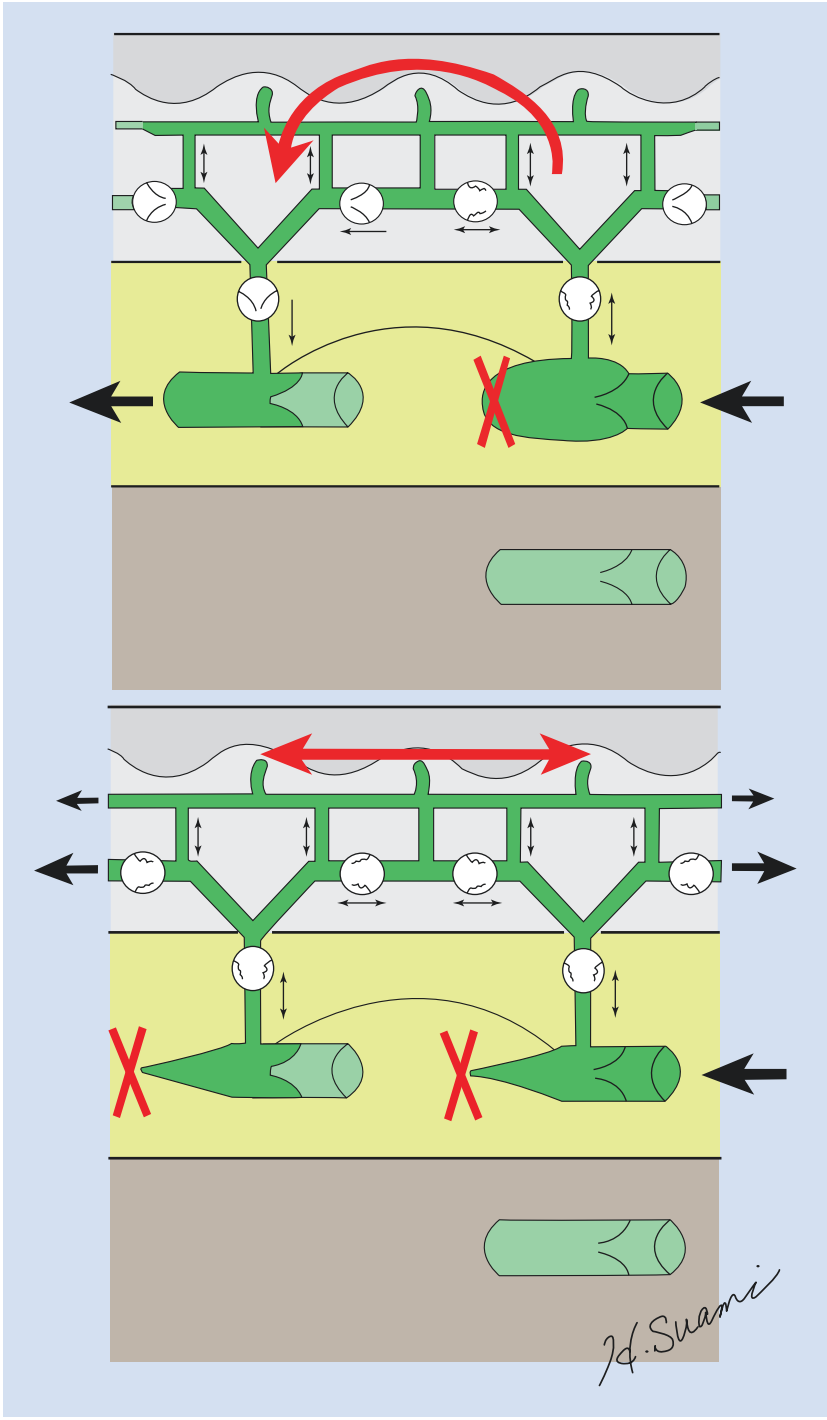


Fig. 5.16 The magnified three-dimensional transilluminated image of the skin lymphatics in the dermal back flow area. The lymph collecting vessel (*black arrow*) and the cutaneous vein (*white arrow*) (Reproduced from Suami et al. [37]) (Scale bar 3 mm)

lymphoedema are prominent in the proximal region close to where the lymph node was dissected; the lymphatic vessels in the distal region are often preserved and patent, even at the moderate stage (ISL stage II). The proportion of dermal backflow in the skin increases as damage to the superficial lymphatic vessels progresses. In advanced lymphoedema (ISL stage III), all superficial lymphatic vessels become atrophic and diminished, and lymphatic transport depends on non-directional dilated capillaries and pre-collectors in the skin (Fig. 5.17 bottom). The linear pattern of lymphatic vessels can no longer be identified by ICG fluorescence lymphography, and the ICG dye spreads through the dilated capillaries and pre-collectors [6, 36] (Fig. 5.18).

Fig. 5.17 Schematic diagrams of structural disorders in lymphoedema. Obstruction of the superficial lymph collecting vessels impedes the function of the valves in the pre-collectors, resulting in lymph reflux (*dermal backflow*). In early lymphoedema, the reflux is absorbed by the nearby patent superficial lymph collecting vessel (*top*). In advanced lymphoedema, lymphatic transport depends on dilated non-directional lymph capillaries and pre-collectors (*bottom*) (Published with kind permission of © Hiroo Suami 2017)


H. Suami

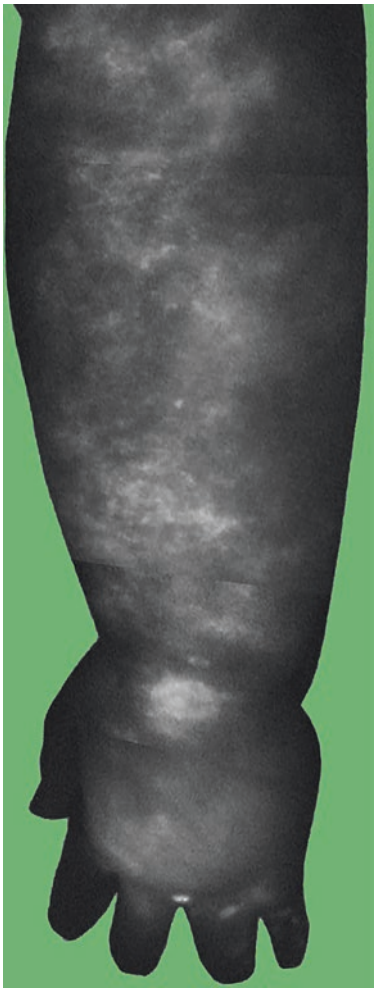


Fig. 5.18 ICG fluorescence lymphography in the posterior forearm of an advanced lymphoedema patient. ICG is spread throughout the dermal backflow (Reproduced from Kato [6])

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Physiology, Pathophysiology, and Lymphodynamics

Contents

General Overview

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B.-B. Lee et al. (eds.), *Lymphedema*, https://doi.org/10.1007/978-3-319-52423-8_6

Summary of Basic Concepts

The principal lymphatic functions include the prevention of edema, immune trafficking, and gastrointestinal lipid absorption. These biological activities are supported by a complex anatomic and functional organization. Failure of adequate lymph transport initiates and sustains lymphedema and likely contributes to the pathological presentation of a wide variety of lymphatic vascular diseases.

- The lymphatic system contributes to the functionality of both the circulatory and the immune systems.
- Lymphatics are found throughout the body, including the central nervous system.
- Lymphatic vasculature and lymphoid tissue are most dense in the compartments that come into direct contact with the external environment (skin, gastrointestinal tract, and respiratory system).
- 100% of the plasma volume exits the blood circulation each 9 h; most of this fluid is returned to the systemic circulation from the interstitial space through lymphatic transport.
- The contractility of the lymphatic vasculature is governed by both extrinsic and intrinsic forces.

The lymphatic system contributes vitally to the functionality of both the circulatory and the immune systems. The principal lymphatic functions include the prevention of edema through the maintenance of physiologic interstitial fluid homeostasis, immune trafficking (transportation of immunocompetent and antigen-presenting cells to the lymph nodes and other lymphoid organs), and lipid absorption from the gastrointestinal tract [6].

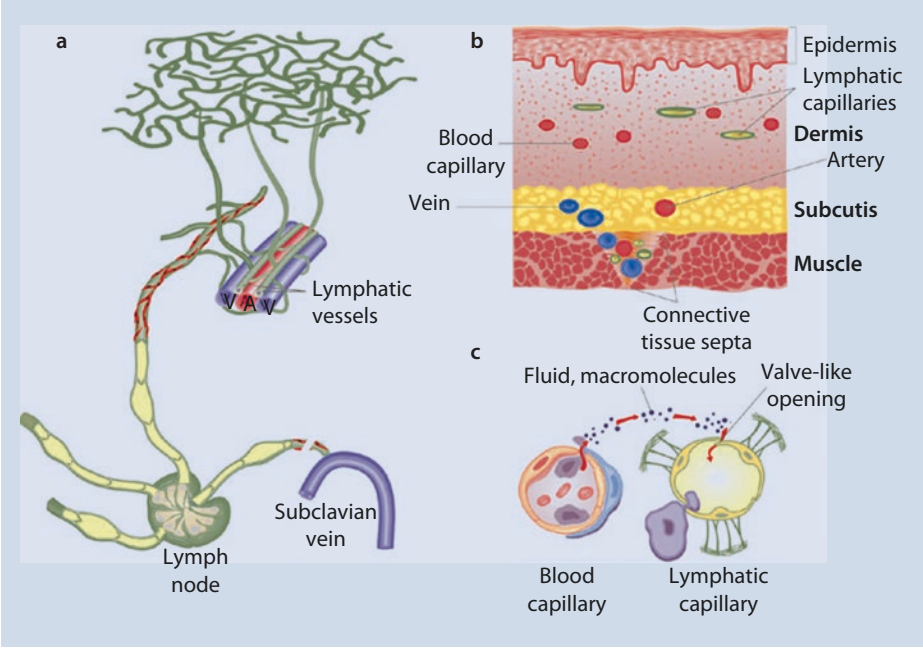
Not surprisingly, this system relies upon a complex intersection of anatomic characteristics and functional specificity to accomplish these goals. Lymphatics are found throughout the body, including within the cranial vault [1, 7]. Lymphatic vasculature and lymphoid tissue are most dense in those bodily components that come into direct contact with the external environment, such as the skin, gastrointestinal tract, and respiratory system [2]. This distribution likely reflects the protective role of the lymphatics against infectious agents and alien particles. Absorption of dietary lipids from the intestine occurs through the lymphatic system, which transports the chylomicron-laden lymph (chyle) to the liver. The lymphatic system also transports cellular debris, metabolic waste products, and excess fluid (edema safety factor) from local sites back to the systemic circulation. It is estimated that 100% of the plasma volume exits the blood circulation each 9 h; most of this fluid is returned to the systemic circulation from the interstitial space through lymphatic transport [3, 8].

In the extremities, the lymphatic system consists of a superficial (epifascial) vasculature that collects lymph from the skin and subcutaneous tissue and a deeper system that drains subfascial structures, such as the muscle, bone, and deep blood vessels. The superficial and deep systems of the lower extremities merge within the pelvis; those of the upper extremity merge in the axilla. The two drainage systems function in an

interdependent fashion, such that the deep lymphatic system participates in lymph transport from the skin during lymphatic obstruction [9].

Lymphatic capillaries are lined by a single layer of overlapping endothelial cells with a discontinuous basement membrane [10]. These vascular structures, which lack both pericytes and smooth muscle cell coverage, begin as blind-ended tubes that interface with the interstitium. Tissue fluid can enter these initial lymphatic vessels between discontinuous button-like cell junctions [10].

Inter-endothelial openings facilitate the entry of cells (macrophages, lymphocytes, erythrocytes) and cellular debris directly into the lymphatic lumen [4, 11, 12]. There is evidence that transendothelial transport of solutes, lipids, and water into the lymphatic lumen also occurs (reviewed in [5]). Fluid transport into the initial lymphatics is observed to occur against a pressure gradient. It is believed that episodic increases in interstitial fluid pressure are created through tissue movement; this effect synergizes with suction forces generated through the periodic contraction of the lymphatic collectors [13]. The general organization of the lymphatic vasculature is schematically illustrated in ◘ Fig. 6.1.



◘ **Fig. 6.1** Organization of the lymphatic vasculature. **a** Interstitial fluid is collected by the initial lymphatic capillary plexus and transported by precollectors to larger collecting lymphatic vessels. Fluid is returned to the circulation through the thoracic duct. Collecting lymphatic vessels have smooth muscle cell coverage (*red*) and luminal valves to propel and maintain unidirectional lymph flow. Deep lymphatic vessels run along arteries and veins. **b** Schematic cross section of the skin, showing the relative positions of blood and lymphatic vessels. **c** Plasma components, cells, and particulate matter, such as bacteria, enter the lymphatic vessels through loose interendothelial openings that function as a primary valve system. Lymphatic vessels are linked to the extracellular matrix by anchoring filaments (Reproduced with permission from [15])

The lymphatic capillary structures («initial lymphatics») coalesce into progressively larger vessels that merge into the lymphatic collectors and, ultimately, the cisterna chyli and thoracic duct. The lymph returns to the blood circulation through lymphaticovenous anastomoses controlled by valvular structures. Since the lymphatics lack a central pump, the lymph progresses through the concerted effects of respiratory motions, skeletal muscle contraction (extrinsic forces), and the autocontractility of the mural smooth muscle of the vasculature itself (intrinsic forces). In the skeletal muscle, lymphatics are usually paired with arterioles, so that arterial pulsation can also contribute to the periodic expansion and compression of initial lymphatics to contribute to the forward propulsion of the lymph [14].

Lymph flow in the collectors depends predominantly on contraction of the smooth muscle layer of the lymphatic vessel. The rate of lymph transport can be augmented substantially by humoral and physical factors that influence the rhythm and amplitude of spontaneous contractions. Lymph flow and lymphatic contractility increase in response to tissue edema, hydrostatic pressure (standing position), mechanical stimulation, and exercise [2].

Failure of adequate lymph transport initiates and sustains lymphedema and likely contributes to the pathological presentation of a wide variety of lymphatic vascular diseases. Accordingly, a detailed understanding of lymphatic anatomy, physiology, and dynamics will certainly contribute to an informed response to diagnosis and therapeutic intervention. Similarly, a detailed understanding of normal lymphatic development should provide biological insights into the pathological lymphatic conditions that lead to inflammation, autoimmunity, cancer, and other forms of human disease [6].

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Lymphodynamics

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Summary of Basic Concepts

As a tributary of the arteriovenous blood circulation, the lymphatic vasculature plays an exquisite, finely modulated role in the regulation of body fluid homeostasis and interstitial fluid balance.

- It is estimated that approximately one-sixth of the body's total volume resides in the interstitial space.
- The lymphatic circulation is responsible for unidirectional fluid transport.
- By definition, without any initial change in composition, the interstitial fluid becomes lymph once it enters the initial lymphatics.
- Under resting conditions, it is estimated that there are 2–3 l/day of lymph formed in the human body.
- Entry of interstitial fluid into the lymphatic capillary is primarily governed by the prevailing interstitial fluid pressure.
- Any physical force that increases interstitial fluid pressure will increase lymph flow.
- Lymph flow becomes maximal when interstitial pressure is slightly higher than the atmospheric pressure.
- The lymphatic circulation relies upon the effects of both intrinsic and extrinsic pumps.
- Cyclical changes in prevailing pressure gradients provide the dynamic forces that favor fluid entry.

As a tributary of the arteriovenous blood circulation, the lymphatic vasculature plays an exquisite, finely modulated role in the regulation of body fluid homeostasis and interstitial fluid balance. An estimated one-sixth of the body's total fluid volume resides in the interstitial compartment [6].

In this context, the lymphatic circulation is responsible for unidirectional fluid transport, moving protein-enriched fluid from the interstitium through a complex vascular network that converges upon the thoracic duct(s) and, ultimately, the great veins [1].

Given the near inaccessibility of the lymphatic vasculature to direct visualization or instrumentation, it is not surprising that insights into the dynamics of this vascular system have been slow to accrue. Remarkably, substantial progress has been made, particularly in the last 20 years.

By definition, without any initial change in composition, the interstitial fluid becomes lymph once it enters the initial lymphatics. The protein content of lymph is determined by the cellular identity of its organ of origin. In most of the body's tissues, interstitial fluid protein concentration approximates 2 g/dl, but mesenteric lymph protein content approaches 3–4 g/dl and that of the liver is even higher. Ultimately, lymph derived from the thoracic duct reflects the relative contributions of these various elements and approximates concentrations of 3–5 g/dl.

Under resting conditions, it is estimated that there are 2–3 l/day of lymph formed in the human body. Thus, it is apparent that in the absence of intact lymphatic transport

mechanisms, circulatory collapse would occur promptly: it has been estimated that the total plasma volume of the human body (≈3 L) extravasates from the blood circulation every 9 h and the vast preponderance of this fluid is transported back to systemic circulation through the lymphatic system [7, 8].

Entry of interstitial fluid into the lymphatic capillary is primarily governed by the prevailing interstitial fluid pressure which, under steady-state conditions, is typically subatmospheric [9]. In situations where the pressure drops below the normal value of −6 mmHg, lymph flow becomes negligible. In contrast, any physical force that increases interstitial fluid pressure will increase lymph flow. Such factors chiefly reflect the influence of Starling forces, such that *increased capillary hydrostatic pressure*, *decreased plasma oncotic pressure*, or *increased interstitial oncotic pressure*, along with *increased capillary permeability*, can all result in an increase in tissue lymph production. Lymph flow becomes maximal when interstitial pressure is slightly higher than the atmospheric pressure. It is somewhat paradoxical that the typical prevailing pressure gradients do not seem to favor fluid entry into the terminal lymphatics [1]. Based upon the available evidence, it has been proposed that *cyclical* changes in prevailing pressure gradients provide the dynamic forces that favor fluid entry [10–12]. Furthermore, there is accruing evidence [2, 13, 14] that active regulation of transendothelial transport of solutes, lipids, and even water across lymphatic capillaries can occur [3]. These active mechanisms are hypothesized to potentiate rapid control over lymph formation rates without altering lymphatic vessel integrity [3].

Beyond hydrodynamics, in order to drive fluid transport through the vasculature, the lymphatic circulation relies upon the effects of both intrinsic and extrinsic pumps [4, 15]. The extrinsic pump mechanism is constituted by the cyclical lymphatic compression and expansion that derives from the operation of extrinsic tissue forces [1]. Extrinsic forces can include the physical movements of parts of the body, contraction of the skeletal musculature, arterial pulsation, and tissue compression by extrinsic forces. Ultimately, normal lymphatic pump function is determined by the intrinsic properties of lymphatic muscle and the regulation of pumping by lymphatic preload, afterload, spontaneous contraction rate, contractility, and neural influences [4].

Historically, the effect of physical activity on lymph flow was deduced from direct measurements after direct thoracic duct cannulation, but previously, there have been no studies of thoracic duct flow as a function of exercise intensity. More recently, it has become feasible to surgically instrument the canine thoracic lymph duct with ultrasonic flow transducers and, after surgical recovery, to determine the effect of exercise intensity [16].

Such experimentally derived insights will be necessary if, in future, we desire to harness the forces of lymphatic physiology for enhanced lymphatic imaging, diagnostics, and therapeutics. Lymphatic contractile dysfunction, barrier dysfunction, and valve defects are observed in disorders that directly involve the lymphatic system, such as inherited and acquired forms of lymphedema, and systemic disorders that indirectly involve the lymphatic system [4]. Just one clinically relevant example resides in the fact that there is growing evidence for constitutive alterations in the lymphatic pumping mechanisms that are thought to contribute to the pathogenesis of breast cancer-associated lymphedema [5, 17].

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Physiology: Lymph Flow

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Summary of Basic Concepts

The specialized structure of the lymphatic vasculature enables it to propel lymph through the body and back into blood circulation. The process starts with the extravasation of fluid from the blood capillaries. This excess fluid is taken up by the initial lymphatics and then propelled by the collective action of the initial and collecting lymphatic vessels back into the blood circulation at the subclavian veins.

- The interstitium is composed of structural proteins and glycosaminoglycans that control its properties.
- Extravasation of fluid into the interstitium occurs from the blood capillaries and is governed by Starling's law.
- The initial lymphatic vessels found throughout interstitial tissue are blind-ended structures composed only of endothelial cells and no basement membrane.
- Fluid entering the lymphatic system is termed «lymph» and is prevented from escaping into the interstitium by the unique morphology of the initial lymphatics which form «primary lymphatic valves.»
- The initial lymphatics play an important role in the uptake of lipid from the intestines and transport of macrophages to the lymph nodes.
- Initial lymphatic function gets disrupted during chronic inflammation and lymphedema.
- Collecting lymphatic vessels are formed of contractile units called lymphangions that actively pump lymph through the lymphatic network.
- Lymphatic valves are present between the lymphangions that prevent the backflow of lymph.
- Production of vasoactive substances, such as neurogenic and hormonal stimuli, allows the body to manipulate lymph flow rates by impacting lymphangion function and structure.
- Mechanical factors, such as intramural pressure, stretch, and shear stress, can modulate and coordinate the function of the lymphatic muscle cells.
- The presence of pacemaking cells has been suggested in collecting lymphatic vessels that might dictate the spontaneous contractility of the lymphangions.
- Extrinsic factors like skeletal muscular contraction, arterial pulsations, and breathing can also contribute to the lymph flow.
- Collecting lymphatic vessels might be compromised during lymphedema due to remodeling of the vessel wall and chronic pathological stimulation.
- The lymph flows into lymph nodes through afferent collecting lymphatic vessels and exits through efferent collecting lymphatic vessels.
- The lymph not only flows through the lymph node, but some of it is reabsorbed into the blood circulation at the lymph nodes.

8.1 Interstitium

8.1.1 Composition of the Interstitium and Maintenance of Interstitial Volume

The source of all lymphatic flow is in the interstitium, where the fluid and soluble interstitial proteins that are not absorbed by the venous circulation are returned to blood circulation by the lymphatic vasculature. The interstitial space is primarily composed of elastic fibers, collagens, and glycosaminoglycans (GAG) that combine to form larger protein complexes called proteoglycans. Proteoglycans are large negatively charged molecules that are essential for the structural properties of the interstitium. Their large negative charge makes them essential for maintaining interstitial volume by providing the interstitium with the capacity to resist compressive forces. Furthermore, the negative charge attracts other diffusible species which helps to maintain osmotic pressure and thus the fluid volume within the tissue. The osmotic pressure of the interstitium plays a significant role in determining the hydration of the tissue and effective porosity of the matrix and hence transport processes like convection, diffusion, etc. The porosity of the matrix and the extent that this porosity can be dynamically altered with mechanical loading depend also on the composition of the interstitium. This in turn dictates the hydraulic conductivity under various physiologic states. Interstitial properties are also highly variable between different parts of the body [6, 7]. Hence, the rates of interstitial fluid formation and drainage, and therefore the local demand on the lymphatic vessels, vary throughout the body.

8.1.2 Physics of Interstitial Fluid Formation

The circulatory system and the lymphatic system form a loop, regulating the amount of interstitial fluid by a continuous process of extravasation and reabsorption [8–10]. This process starts in the blood capillaries. Blood capillaries are composed of a single layer of endothelium with an almost nonexistent basement membrane, which makes it conducive to the exchange of fluid across its walls. The exact mechanism by which fluid is transferred across the blood capillary endothelium was first explained by physiologist Ernest Starling in what has come to be known as «Starling's law».

Starling's law, seen below, is an equation which states that the net rate of fluid transfer across a membrane is the weighted sum of the hydrostatic pressure difference across the membrane and the osmotic pressure of the solutes.

$$J_v = L_p \frac{S}{V}\left(\Delta P + \sigma \Delta \pi\right)$$

where J_v is the fluid flux across the vessel wall (in or out), L_p is the permeability, S is the surface area, V is the volume, ΔP is the hydrostatic pressure difference, $\Delta\pi$ is the osmotic pressure difference, and σ is the capillary osmotic reflection coefficient. In the context of fluid transport across blood capillaries, the blood capillary wall acts as a porous membrane, with blood on one side and interstitial fluid on the other side. There are two opposing forces acting on the blood capillary walls. Hydrostatic pressure drives fluid out of capillaries, while osmotic pressure drives fluid back in.

The rate of uptake of solutes by the blood capillaries is size and charge dependent, and it is found that small molecules and crystalloids are preferentially taken up, while transport of larger proteins is not permitted [11]. This is reflected as an osmotic reflection coefficient that is less than 1 in Starling's law. This value means that there is a higher concentration of proteins within the blood capillaries than the interstitium. As the osmotic pressure is created primarily by the proteins, it is referred to as the oncotic pressure gradient. Fluid moves in the opposite direction of the oncotic pressure gradient, and therefore, the net effect is the movement of fluid from the interstitium into the blood capillaries. The mean capillary hydrostatic pressure is much greater than the mean interstitial hydrostatic pressure, which has the net effect of pushing fluid out of the capillaries [6, 9, 12].

The following example will help to better visualize this continuous exchange process. Let us start with an equilibrium where the contribution due to the hydrostatic pressure difference balances the contribution due to the oncotic pressure difference. Now consider an increase in the hydrostatic pressure in the capillary. This shift will cause movement of fluid out of the capillary. Under physiological conditions, the greater hydrostatic pressure of the capillary would lead to excess fluid flow into the interstitium. Fortunately, any reduction in capillary fluid increases the concentration of protein within the capillary, therefore increasing capillary oncotic pressure. This increase in oncotic pressure will cause movement of fluid into the capillary until an equilibrium is reached again.

In general, the rate at which fluid is squeezed out is slightly greater than the rate at which fluid is pushed back in. Thus, there is a net buildup of fluid in the interstitial space that needs to be drained in order to maintain fluid homeostasis in the interstitium. Additionally, it is essential that the lymphatics drain large proteins from the interstitial space to keep the protein concentration low and thus maintain an effective oncotic pressure gradient that favors fluid retention within the microcirculation. That is where the lymphatic system comes in, acting as a drainage system for the excess fluid or solutes while also serving many other important functions in the body like transportation of lipids from the intestine and the trafficking of immune cells to the lymph nodes [6, 7, 10, 13].

8.2 Initial Lymphatics

8.2.1 Structure

The initial lymphatics, also referred to as lymphatic capillaries, are blind-ended vessels characterized by endothelial cells with an attenuated cytoplasm, discontinuities in the basement lamina, and specialized junctions. The initial lymphatic endothelium is char-

acterized by cells that are apposed to each other, forming valve-like structures that are commonly referred to as «primary lymphatic valves» since functionally they have been observed to allow fluid and large proteins to enter easily when the pressure gradient is favorable for lymphatic uptake and yet provide a large resistance to fluid and molecules leaving the capillary when lymphatic capillary pressure exceeds interstitial fluid pressure [1, 14–18]. This unique functional capacity of the initial lymphatics is thought to occur due to the specialized junctions formed by a unique configuration of VE-cadherin and CD31 commonly referred to as «buttons». The lymphatic endothelial cells form oak leaf-shaped structures that are characterized by discontinuous button-like junctions that form flap-like structures. These are characteristics of mature initial lymphatics, since immature initial lymphatics such as those observed during lymphangiogenesis induced by acute inflammation have zipper-like junctions [1]. The button-like junctions provide enough structural integrity to the initial lymphatics by being anchored at the side of the flaps while also forming points of entry at the tip of the flaps. Thus, the integrity of the initial lymphatic endothelium is maintained while also forming the valves that are necessary for entry of fluid into the lymphatics. While the size of many macromolecules and cells would restrict them from typically entering capillaries, the unique and 'large' entry junctions of the initial lymphatics enable passage into the lymphatics. The primary lymphatic valves are hence involved during the filling up of the lymphatic vessels with interstitial fluid and also prevent backflow into the interstitium. The initial lymphatic endothelial cells are connected to the surrounding connective tissues with anchoring filaments that play an important role in keeping the initial lymphatics from collapsing. Additionally, these filaments help in opening the primary lymphatic valves, leading to the formation of «lymph» [9, 14]. The structure of the initial lymphatic network and anatomy of the initial lymphatic vessels and valves are portrayed in Fig. 8.1.

8.2.2 Functional Role of Initial Lymphatics

Role in Lymph Formation and Transport

The initial lymphatics are the first stage of the lymphatic network that takes up the excess interstitial fluid. The average pressures in the interstitium and the initial lymphatics are similar. In fact, the average pressure in the interstitial space is usually slightly negative, thus being subatmospheric, while the average pressure in the initial lymphatic lumen is slightly positive. These measurements might indicate that the prevailing hydrodynamic forces are not conducive for the flow of interstitial fluid into the initial lymphatics. However, these are average pressures and do not account for the transient fluctuations in the interstitial and initial lymphatic pressures because of extrinsic and intrinsic factors. Extrinsic factors include skeletal muscle contractions, heart contractions, gastrointestinal muscle contractions, respiration, and arterial pulsations; intrinsic factors refer to the spontaneous contractions of the lymphatic network which will be described in greater detail later [13, 20].

During these cyclical pressure fluctuations, when the initial lymphatic pressure is lower than the interstitial pressure, the fluid flows into the initial lymphatics, thereby being referred to as «lymph.» The intrinsic properties of the initial lymphatics, such as anchoring filaments and «primary valves,» play a vital role here. An accumulation of fluid

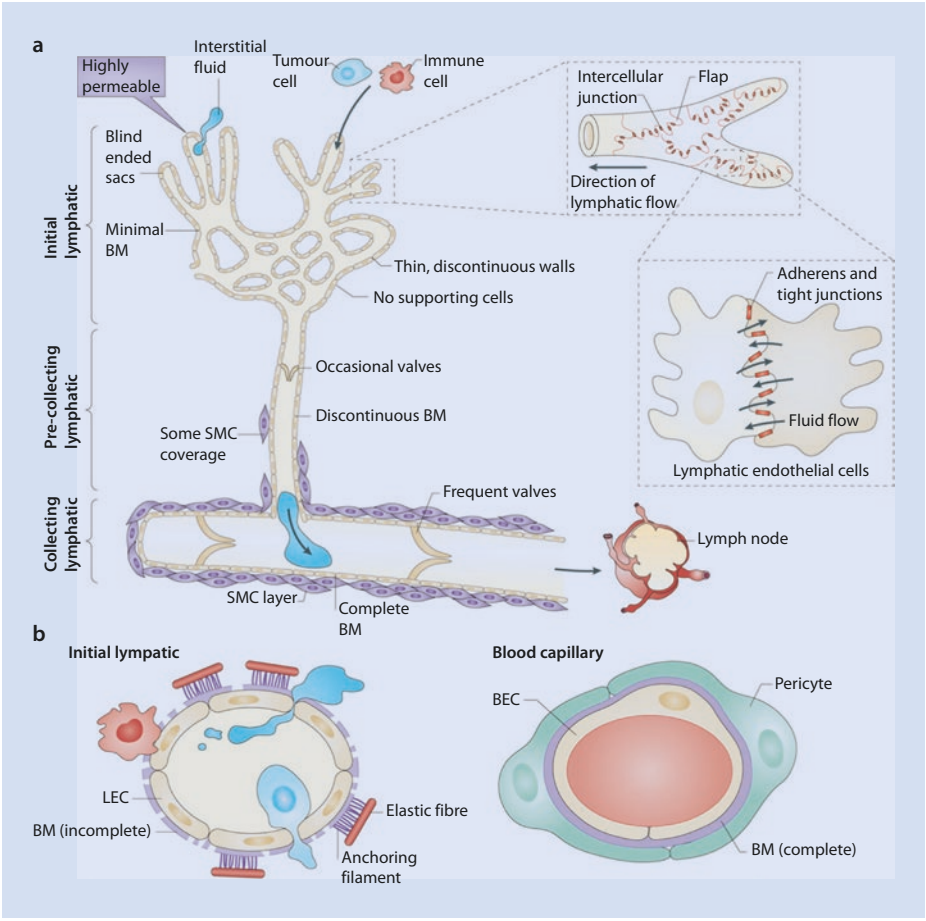

Fig. 8.1 **a** Structure of the initial lymphatic network and how it connects to the collecting lymphatic network is shown. The blowouts show the detailed structure of the initial lymphatic vessels, with the button-like junctions that form the flaps that act like valves. **b** The initial lymphatic vessels exhibit a discontinuous basement membrane and loose endothelial cell junctions, in contrast to blood capillaries that have a continuous basement membrane. This specialized structure of the initial lymphatics allows the paracellular transport of cells and proteins into the initial lymphatic lumen, but transport also happens through transcellular pathways. Anchoring filaments, which are responsible for pulling the initial lymphatic vessel open during the filling up stage, are also shown [19]

in the interstitium leads to swelling, which causes a tension in the anchoring filaments. This tension forces the primary lymphatic valves to open, allowing inflow. Once pressure inside the initial lymphatics is greater than the interstitial pressure, the primary valves in the initial lymphatics close, preventing the backflow of lymph into the interstitium [6, 20–23]. Recent research also suggests that apart from the aforementioned mechanism, transport of solutes can also occur through transcellular pathways which might be important in lymphatic solute transport [24]. Thus, the unique structure of the initial lymphatics coupled with the extrinsic and intrinsic factors leads to the formation of lymph.

Role in Lipid Transport

A special kind of initial lymphatic vessel is the lacteal. Lacteals are the initial lymphatic vessels found in the small intestine at the center of each villus. The main function of the lacteals, apart from the removal of water absorbed across the mucosal membrane [25], is the uptake of absorbed lipids in the form of high-density lipoproteins and chylomicrons from the small intestine. They are also shown to allow the migration of immune cells from the interstitium across the endothelium [26]. The lacteals then act as a conduit toward the mesenteric collecting lymphatic vessels, which then transports this unique, lipid-rich lymph to the systemic circulation [27]. For this reason, the lacteals also serve as an important channel for the uptake of lipophilic drugs that are orally ingested [28]. This uptake of lipoproteins and cells can happen paracellularly across the lymphatic endothelial cell junctions and also through transcellular pathways [29–33].

The lacteals are unique, because they show spontaneous contractility in conjunction with adjacent smooth muscles. This was first discovered by Howard Florey in 1927 [34, 35]. This unique physiology makes them exhibit properties of both the initial lymphatics in that they possess «button-like» junctions and also of the collecting lymphatics in that they possess spontaneous contractility that is regulated by the autonomic nervous system [36]. The function of lacteals, and hence the uptake of chylomicrons, is highly dependent on the prevailing forces in the interstitium, as lacteals have been observed as undergoing morphological changes in response to fasting and feeding and they also show sensitivity to lymph flow [37]. Experiments with mice having abnormal lymphatic lineage commitment due to a heterozygous mutations in the Prox-1 gene develop obesity due to compromised leaky lymphatic vessels [38]. VEGF-C, an important factor in lymphatic endothelial cell growth and proliferation, has been found to be extremely important in the maintenance of the function of the lacteals, as knockout of VEGF-C leads to atrophied intestinal lymphatics and impaired lipid transport [39].

Role in Transport of Immune Cells

The lymphatic vessels play a very important role in immune cell trafficking. However, the transmigration of leukocytes across the initial lymphatic endothelium is a matter of ongoing investigation. In the presence of pro-inflammatory cytokines, cultured lymphatic endothelial cells have been shown to upregulate the expression of leukocyte adhesion molecules [40]. Carbohydrate-binding proteins like galectin have also been implicated in this transmigration. The binding of the leukocytes to the adhesion molecules on the lymphatic endothelial cells causes them to crawl toward the cell junctions, where they interact with other adhesion molecules to promote entry into the initial lymphatic lumen. For example, gradients of the chemokine CCL21 have been implicated in the crawling of dendritic cells (DCs) across the initial lymphatic junctions [41, 42]. The transmigration can occur via both the button-like junctions and through the endothelial cells, although the exact point of entry is unresolved [1]. The amount of lymph drainage through the lymphatic network has also been implicated as a factor in regulating the transmigration of dendritic cells in the initial lymphatics [43]. There is also evidence for bidirectional transmigration of the leukocytes, which might be an important factor in effective immune surveillance [44].

8.2.3 Initial Lymphatic Disruption in Inflammatory Diseases and Lymphedema

Inflammation involves a series of responses initiated by the body in response to harmful stimuli like pathogens or external irritants causing damage to cells. Inflammation has several effects on the circulation, including increased permeability of the blood vasculature, leading to extravasation of fluid and tissue swelling. This increased permeability also allows leukocytes to enter the interstitium by extravasation. In the case of initial lymphatics, the effect of inflammation is similar, with an increase in permeability of the vessels. One probable cause for this increase in permeability might be the opening of the primary lymphatic valves due to the swelling of the tissue, which pulls on the anchoring filaments and holds the valves open. Other reasons proposed include the formation of pores in the lymphatic endothelium and rearrangement and loosening of the tight cell-cell junctions that are occasionally present in the initial lymphatic endothelium [1, 40]. It is hypothesized that there is a reduction in the effective functioning of the lymphatics during chronic inflammation because of compromised initial lymphatic junctions.

Inflammation and lymphedema influence each other in a complex manner, and this can be traced to altered function of the intial lymphatic system. Lymphedema induced in rodent models by artificial lymph stasis has been shown to induce inflammation and fibrosis [45, 46]. There is an overabundance of pro-inflammatory cells like macrophages, dendritic cells, and lymphocytes in the interstitium, leading to chronic inflammation and fibrosis [40, 44, 47]. Fibrosis caused by chronic inflammation can also worsen lymphedemic conditions [48, 49]. Lymphangiogenesis (the formation of new lymphatic vessels from pre-existing ones) induced by inflammation is thought to be involved in lymphedema, although whether the effect is benign or pathological is still a matter of contention [50, 51]. In the context of primary lymphedema, mutations in VEGFR-3 that lead to impaired lymphangiogenesis have been shown to induce lymphedema [52–54]. Hence, the use of lymphangiogenesis as a mean of therapeutics during lymphedema has also been suggested [55, 56]. However, lymphangiogenesis might not always have a benign effect on lymphedema. It has been shown that $CD4^+$ T cells can interact with macrophages to produce VEGF-C which is essential for lymphangiogenesis. Inhibiting the interaction can lead to reduced lymphangiogenesis as well as reduced chances of later onset of secondary lymphedema [51]. The upregulation of VEGF-C during inflammation may also lead to loss of collecting lymphatic pumping function, although there are contradictory reports on the same [57, 58].

8.3 Collecting Lymphatic Vessels

8.3.1 Structure

As initial lymphatics connect downstream, they transition into a region of the lymphatic network known as the pre-collecting lymphatic vessels. Pre-collecting vessels are distinguished from the initial lymphatics by the presence of a basement membrane surrounding the lymphatic endothelial cells and the discontinuous arrangement of lymphatic

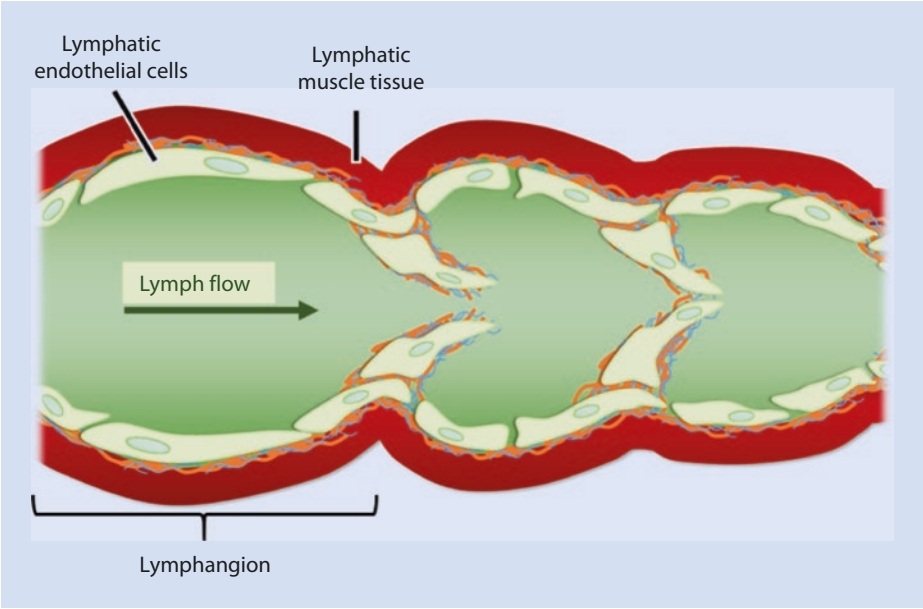

Fig. 8.2 The mature lymphatic collecting vessel. The lymphatic endothelial cells (LECs) are supported by a layer of basement membrane composed primarily of extracellular fibrils of collagen and elastin (seen in *orange* and *blue*). These fibers also provide structural support to the bileaflet valves. The entire collecting vessel is surrounded by a layer of lymphatic muscle cells which contract to propel lymph flow downstream

smooth muscle cells [59, 60]. Pre-collectors have the continued presence of anchoring filaments, presumably to assist in lymph absorption and transport [59].

Pre-collecting lymphatic vessels transition into mature collecting lymphatic vessels. These collecting vessels are characterized by fully developed basement membranes, full coverage by lymphatic smooth muscle cells, and the presence of a second type of lymphatic valve. The basement membrane between the LEC monolayer and the muscle is primarily composed of collagen and elastin fibers which contribute significantly to the mechanical properties of the vessel. These two extracellular protein fibers also provide structural support to the bileaflet, unidirectional valves. The valves separate the collecting vessel into discrete segments known as lymphangions as seen in Fig. 8.2. These valves physically prevent backflow between lymphangions and allow for the directional flow of lymph toward the distal lymph nodes [15, 61]. The smooth muscle cells surrounding the collecting lymphatic vessels are highly specialized and are commonly referred to as lymphatic muscle cells (LMCs). Lymphatic muscle cells are capable of rapid, phasic contractions that are well coordinated with neighboring cells [2].

Unlike blood vasculature, there is no central pump to drive the flow of lymph through the lymphatic system. Lymph transport through the collecting vessels is therefore entirely dependent on the intrinsic contractility of the lymphatic muscle and extrinsic factors such as skeletal muscular contraction, arterial pulsation, passive movement, and respiration.

Lymphatic Valves

Functioning lymphatic valves within the collecting vessels are critical for functional lymph propulsion by either intrinsic or extrinsic factors. In humans, these valves are typically spaced every 1–3 mm [62]. To properly function, these valves must open and close under flow rates and pressure that are relatively low compared to pressure in the blood vasculature. Work with isolated vessels, where the inlet and outlet pressures can be manipulated independently, demonstrated that the pressure gradient across the valve needed for the valve to open is fairly consistent, but closing pressure gradient is dependent on transmural pressure of the adjacent lymphangion. In addition, there appears to be a slight bias in the valve to remain in the open position [3]. This likely explains why a small amount of retrograde flow is typically observed in the contraction cycle before valve closure [4].

While largely efficient, some regurgitation of lymph into an upstream lymphangion may occur before valve fully closes, specifically given their open bias [63]. Eliminating backflow is particularly critical at lymphovenous valves; unique valves present at the intersection of major collecting vessels, known as ducts, and the left or right subclavian vein where lymph is returned to the blood vasculature. At these locations, adverse pressure gradients can be significant, and several studies in mice demonstrate that pathologies of the lymphovenous valves lead to blood flowing into the lymphatic system [64]. Activation of platelets by specific receptors on the surface of lymphatic endothelial cells seems to play a critical role in preventing blood flow into the lymphatics particularly at these locations [65].

8.3.2 Intrinsic Contractility and Active Lymph Propagation

As previously stated, the lymphatic collecting vessel is composed of a chain of lymphangions, separated by unidirectional valves. These lymphangions are considered the contractile units of the vessel, working as a series of pumps to propel lymph. The rapid, phasic nature of this contraction is unique to LMCs and made possible by their unique molecular composition. While the LMCs are nonstriated muscle cells, they share contractile proteins that are otherwise limited to cardiomyocytes, which in part account for their unique pumping phenotype [2, 66]. This pumping mechanism in lymphatics is described using language consistent with the heart. For example, as a heart undergoes systole and diastole, so does the lymphangion. Systolic diameter of a lymphangions describes the minimum diameter in the lymphangion at the peak of a contraction, while the diastolic diameter is the maximal diameter between contractions. Ejection fraction refers to the fraction of end-diastolic volume ejected during lymphatic contraction.

The contractile frequency of a lymphangion is usually on the order of five to ten contractions per minute with amplitudes of up to 50% of the resting diameter for a major collecting vessel, but there is a significant amount of regional variability due to mechanical loading on the vessel [4, 67–69]. These relatively strong, regularly occurring contractions are critical for the collecting vessel to pump fluid against an adverse pressure gradient. In large animal models, experimental work has shown that short segments of isolated lymphatic vessels can overcome adverse pressure gradients of 10–30 cmH_2O [70]. To overcome greater pressure gradients, it is important to remember that collecting

lymphatic vessels work not as individual units, but as chains of pumps arranged in series. The extent that the coordination of the pumping activity of the chains regulates lymph flow is not well established, but computational modeling suggests that coordination could improve pumping [69], and it has also been observed experimentally [71]. Chains of multiple lymphangions are better suited to overcome larger adverse pressure gradients and appear to coordinate contractility to reduce pressure downstream before additional fluid arrives from upstream segments [72]. A chain of lymphatic vessels is able to overcome a rather large pressure gradient, with measurement in vivo reporting pumping pressures in excess of 30 mmHg (~40 cmH_2O) in human legs [73], 40 mm Hg (~54 cmH_2O) in human arms [74], and 35 mmHg (~47.5 cmH_2O) in rats [75].

In addition to executing active phasic contractions, LMCs must modulate the vessel diameter in order to adjust the resistance to lymph flow through the lymphatics. Similar to the blood vasculature, regional changes in the lymphatic vessels' diastolic diameter can locally regulate the quantity and velocity of transported lymph. This is often at odds with the vessels' role as a pump, as relaxing the LMCs often impairs active contractility. Furthermore, active pumping by LMCs may increase the resistance to passive flow by transiently constricting the diameter of the vessel. Therefore, it is important that LMCs react to a variety of environmental cues that regulate their role as either an active pump or a passive conduit to lymph flow [76]. Factors that impact the coordination of these roles are outlined below.

Innervation and Sensitivity to Vasoactive Substances

Collecting lymphatic vessels have long been shown to be responsive to a variety of vasoactive peptides [77]. Noradrenergic, purinergic, cholinergic, and peptidergic neurons can be found throughout collecting vessel walls and manipulate various aspects of contractility [78]. Innervation of the lymphatics leads to altered function in response to a number of neurogenic and humoral stimuli that have been extensively researched [77–83]. Lymphatic regulation through by these vasoactive substances have been shown to influence resistance to flow, ejection rate, rate of formation of lymph, and lymphatic vessel permeability.

Recent work has explored the role of various vasoactive substances on the permeability of collecting vessels. Atrial and brain natriuretic peptides, hormones that are released to reduce stress on the heart, both reduce collecting vessel permeability. This may have the effect of temporarily reducing the reabsorption of lymph into blood circulation [84]. Similarly, immune cells that interact closely with or within the walls of the collecting lymphatic vessel play a significant role in modulating collecting vessel permeability and function [85]. Within adipose deposits, modulation of collecting vessel permeability has been shown to regulate local inflammation [86]. As a whole, the aforementioned studies in combination with others have demonstrated that excessive collecting vessel permeability impairs the ability of lymph, rich in antigens and dendritic cells, to reach downstream lymph nodes, significantly weakening the adaptive immune response [87].

Vasoactive substances released during inflammation appear to play competing roles in regulating lymph flow. Vasoactive substances released by myeloid cells during inflammation, such as nitric oxide and histamine, seem to both dilate collecting vessel walls and reduce frequency of spontaneous contractions. Furthermore, these substances

seem to assist in DC trafficking to lymph nodes [88–90]. Other inflammatory cytokines, such as substance P, actually increase contractile frequency when incubated with isolated vessels [79]. How immune cells coordinate the release of these potentially competing vasoactive substances throughout the progression of inflammation is still poorly characterized.

Mechano-Regulation

As with the blood vasculature, shear stress elevated above a certain threshold due to fluid flow along the lymphatic lumen induces vasodilation of the collecting lymphatic vessels, reducing or fully inhibiting contractility [91]. The mechanism for this response is believed to be largely based on nitric oxide generation by LECs [92, 93], but recent research has implicated other vasodilators, such as histamine [94]. The shear stress magnitude within the lymphatic vasculature is much lower than that seen in blood vasculature and highly oscillatory [4]. A recent study demonstrated that the magnitude of shear needed to inhibit spontaneous contractions is much lower than that seen in the blood vasculature, depends on distention due to transmural pressure [95], and involves Ca2+ release by LEC [96, 97]. It is not clear what the molecular mechanisms are that allow lymphatic endothelial cells to respond to lower shear stresses than blood endothelial cells; however, recent work has suggested that this enhanced sensitivity involves VEGFR3, possibly through a mechanosensory complex formed at the cell junction [98]. Furthermore, shear stress along the wall appears to contribute to the coordination of contractility. Simply put, as lymph ejected from an upstream lymphangion moves into a downstream lymphangion, the increased shear stress along the wall of the downstream lymphangion dilates the diameter, reducing the resistance to the incoming flux of lymph [95, 99].

Contractility of the collecting vessel demonstrates a sensitivity to wall distension in accordance to the Frank-Starling's law [63]. The length-tension relationship of lymphatic muscle cells determines the tension within the LMC at which force generation is maximal. It was determined in human thoracic ducts that average peak active wall tension was 6.24 ± 0.75 N/m at a corresponding transmural pressure of 47.3 ± 4.7 mmHg [100]. Increased transmural pressure increases wall tension, causing greater force generation by the LMCs, leading to an increase in pumping efficiency (e.g., the ejection fraction increases) up until a critical pressure is reached. Beyond this point, pumping efficiency diminishes as the LMCs, presumably, cannot generate more force [101, 102]. An early theory for contraction coordination along the collecting vessel was that the volume increase after a lymphangion takes on a bolus of lymph was the sole trigger for the contraction of locally distended muscle cells. This theory has been shown to be an oversimplification, as lymphangions can contract in the absence of lymph formation [103] and in the absence of apparent intraluminal distending force [104].

Electrophysiology and Pacemaking

Contractility of the collecting lymphatics in the absence of vessel distention indicates that contractile coordination depends, in part, on electrical mechanisms. Multiple ionic channels have been well characterized in LMCs [105–107]. Outward currents include calcium-dependent potassium channels and delayed rectifier potassium channels. Inward currents include fast sodium channels [108] and both L- and T-type calcium channels.

The exact expression of these channels on LMCs seems to be heterogeneous, and it is hypothesized that different channels are responsible for specialized aspects of contractility. For example, work by Roizes and von der Weid demonstrated that the inhibition of L-type calcium channels primarily reduced the force generation during a contraction, while T-type calcium channel inhibition caused irregular contractile frequency [109]. Furthermore, a relationship between the resting membrane potential of LMCs and isometric tension has been established in animal models, further demonstrating the interplay between these regulatory factors [110].

The pacemaking behavior of lymphatic vessels was well demonstrated for decades, but the mechanisms by which this is possible were difficult to elucidate [111]. Are all LMCs capable of pacemaker-like spontaneous depolarization, or are there specialized pacemaker cells embedded within the vessel? More recently, it has been shown that a small population, approximately 5%, of LMCs isolated from sheep lymphatic collecting vessel walls may produce an inward current after hyperpolarization, similar to pacemaker cardiomyocytes. This inward current is similar to the «funny» pacemaker current seen in cardiac pacemaker cells [112]. Interstitial cells of Cajal are a cell type that is known to be responsible for pacemaking in the smooth muscle cells of the gut. Work by Boedtkjer has confirmed the presence of interstitial Cajal-like cells in human thoracic ducts through a variety of imaging modalities, but their exact functional roles need to be further investigated [113]. Earlier work seems to indicate that these pacemaking cells can coordinate over distances of at least 80 mm [114]. The mechanism behind this coordination and the differentiation of these specialized pacemakers within a developing collecting vessel are areas of active research.

8.3.3 Extrinsic Factors that Contribute to Lymph Flow

Under healthy conditions, external factors seem to improve lymph flow and interstitial fluid clearance by the lymphatics. Notably, exercise and manual massaging improve the rate of clearance of tracers injected within the interstitium via the lymphatics and the quantity of lymph flowing through the collecting vessels [115–117]. The exact means by which the extrinsic factors improve these metrics are contested. Amplitudes of pressure changes within subcutaneous lower leg lymphatic collecting vessels (3.2–4.7 mmHg) were unchanged by exercise [118]. In addition, one study demonstrated that muscular contractions did not independently generate flow, but did increase lymph flow during intrinsically generated contractions but muscular contractions did not independently generate flow [119].

Rates of lymph formation and reliance on extrinsic factors vary for collecting vessels found in different regions of the skin, subcutaneous tissue, fascia, or muscle. Lymphatics within highly mobile tissue such as skeletal muscle, lungs, and the heart have undergone special adaptations to adapt to their local environments. A review article by Negrini and Mariondo nicely summarizes some of these adaptations [23]. For instance, their research demonstrates how both the organization and properties of diaphragmatic lymphatics take advantage of the stresses exerted by the muscle fibers. Lymphatic orientation, both perpendicular and parallel to skeletal muscle fibers, allowed lymphatic vessels to exploit the full contractile cycle of lungs for lymph generation and propulsion. In

addition, variations in the stiffness of diaphragmatic lymphatic walls allow compliant regions to act as a reservoir for lymph, while stiffer walled regions better allow local tissue displacement, leading to lymph propulsion [120]. The extent to which lymphatic orientation assists lymph propulsion in other tissue beds (e.g., cardiac tissue) is less known.

8.3.4 Collecting Lymphatics in Lymphedema

During lymphedema, lymph flow through the collectors appears to become increasingly dependent on extrinsic factors. Several studies demonstrate that intraluminal lymphatic pressure increases during lymphedema [121] and becomes more sensitive to contractions of surrounding skeletal muscle. The elevated sensitivity of lymphedemic limbs to manual massaging further highlights the reliance on extrinsic factors for lymph propulsion after the onset of lymphedema. Interstitial tissue pressures can increase to over 100 mmHg after application of manual massaging, creating a favorable pressure gradient for fluid to flow into the lymphatic system [122].

Structurally, it has been shown that the wall thickness of the lymphatic collecting vessel is strongly correlated with lymphedema disease severity. Rapid expansion of smooth muscle actin-positive cells and increased deposition of extracellular matrix elements such as collagen are hallmarks of vessels isolated from lymphedemic regions [123, 124]. While modeling indicates that these changes in vessel mechanics and dimensions would impact contractility [125], there is little work looking at functional pumping metrics of these remodeled vessels in vivo or in vitro. Many animal studies demonstrate that healthy collecting vessels exposed to edematous conditions, such as elevated pressures, have improved pumping metrics and lymph flow [70, 126, 127]. The extent to which these results translate to remodeled collecting vessels is unclear. In addition, it is difficult to determine if the increased lymph flow rates during edematous conditions are due to improved pumping of the collecting vessel or simply elevated rates of lymph formation.

Recent work by Mortimer et al. has shown that women with elevated lymphatic pumping are at a significantly higher risk of developing lymphedema later [74, 128]. They demonstrated that lymphatic pumping pressures before breast cancer surgery were 1.7-fold greater in patients who later developed lymphedema than those who did not. Clearance rates of tracers by the lymphatic system were consistently shown to be elevated by about 2.2-fold in patients who later developed lymphedema. The exact cause of this phenomena is still under investigation.

8.4 Lymph Nodes

8.4.1 Structure

Lymph moving through collecting vessels passes through at least one but often a series of lymph nodes. The human body contains hundreds of lymph nodes, which vary in size from 1 mm to 10 mm. Lymph nodes are vascularized for the exchange of nutrients and

immune cells [5, 6]. Lymph, arriving from multiple afferent collecting vessels, contains a variety of antigen-presenting cells, cytokines, antigens, and exosomes from upstream tissue beds, which play a critical role in the priming and activation of the immune system. Lymph nodes are comprised of multiple «compartments» which house various lymphocytes, and the route and quantity of lymph that arrives in each compartment may potentially impact immune response. Lymph first arrives into the subcapsular sinus and can then be directed through either a «central» or «peripheral» path to the medulla sinus [129]. The path by which solutes travel within the lymph node is dictated in part by hydraulic conductivity, with different conduits within the node having variable densities. Therefore, size alone of arriving solutes can dictate their route through the lymph node [130]. While the peripheral path takes lymph directly to the medulla sinus, the central path has lymph travelling through B cell follicles and the T cell cortex. Within the T cell cortex are high endothelial venules (HEVs) which allow circulating T cells to enter the lymph node.

8.4.2 Lymph Flow and Fluid Exchange

Recent models estimate that about 90% of the fluid that is carried from the afferent collecting vessel into the lymph node flows through paths along the periphery of the lymph node [53, 131, 133]. The remaining fluid that travels along the central path, deeper into the lymph node, is reabsorbed into blood circulation by parenchymal HEVs. While the amount of fluid reabsorbed into circulation at an individual node is relatively small, given the hundreds of lymph nodes within the body, it is estimated that an additional 4 L of fluid is returned to circulation at lymph nodes in basal conditions. This doubles the amount of fluid the lymphatics is responsible for clearing from the interstitial tissue space from previous estimates, which were solely based on the flow rates out of the major lymphatic ducts at lymphovenous junctions. This fluid exchange has been shown to be dictated by Starling's forces and is sensitive to changes in oncotic pressure of lymph or blood pressure at the HEVs [132]. Importantly, this fluid exchange within the node can alter the flow rate of lymph through the node as well as the composition of the efferent lymph. This alteration of lymph composition and flow implicates that the fluid exchange at the node not only regulates fluid recirculation but also activation of adaptive immunity.

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Biomechanics of the Lymphatic Circulation

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Summary of Basic Concepts

- Lymph flow and the associated transport of suspended substances are required for fluid balance and immune function. Timely antigen presentation to immune cells in lymph nodes relies on the flow of lymph in prenodal vessels.
- Lymph is transported centrally by the active contraction of lymphatic vessels, in combination with one-way check valves. Pumping can also be aided by movement of adjacent tissues, resulting in vessel squeezing. The valves open to allow forward flow and close to prevent reverse flow.
- Imaging and measuring lymph flow in vivo is severely limited by the small sizes of the vessels and low flow velocities. The tools developed to measure blood flow are not applicable.
- Understanding lymphatic pumping dynamics and transport thus requires a combination of modeling and experiments. Pumping is highly dependent on the contractile properties of lymphatic muscle cells, proper valve operation, and the passive mechanical properties of the vessel walls. These require carefully tuned behavior at the cellular level and exquisite arrangement of structural proteins.

9.1 Introduction

The ability to transport antigens and antigen-presenting cells quickly to lymph nodes is crucial for adaptive immunity. Indeed, if organisms as large as humans had to rely on active cell migration to transport antigen-presenting cells to nodes, the voyage to the nearest lymph node could take 3–6 months, easily enough time for some antigens to result in death. Instead, the transport ability achieved by lymphatic pumping delivers this information within minutes to hours. Inside lymph nodes, fluid-based transport is required to deliver antigens to the appropriate regions and immune cells; otherwise adaptive immunity would not be possible.

A remarkable feature of the lymphatic system is that it manages to overcome gravity and inherently adverse pressure differences even in normal, healthy conditions to achieve reliable pumping. The gravitational challenge stems from the location of the return point to the venous system being located in the shoulder region. The adverse pressure difference exists because many interstitial tissue beds from which the lymphatic system draws fluid are at subatmospheric pressures (as low as −50 mmHg), whereas veins generally exhibit pressures of +10 to 20 mmHg[1]. A civil engineering analogy for these challenges would be a city that needs to take fluid that drains into its sewer system and pumps it from separate locations distributed around the city to a water treatment plant located on a hill; except in this case, the city is like New Orleans, whose streets are located several meters below the Mississippi River (representing atmospheric pressure).

1 Note that these units of pressure denote the heights of a column of fluid. Any surface area at rest at the bottom of a column of fluid would be subjected to a compressive stress directly proportional to the density of the fluid, the height of the column, and the gravitational acceleration constant.

Lymphatic system pumping is very different from the generation of blood flow through arteries and veins in that there is no centrally located pump. Each individual lymphatic vessel (except initial lymphatics) generates its own pumping through intrinsic, active squeezing and the presence of one-way check valves. In some locations, the squeezing action can be supplied by the movement of adjacent tissues (so-called extrinsic pumping). Along the pathway back to the venous system, all lymph must pass through at least one lymph node. These small, bean-shaped organs are densely packed with structural proteins and immune cells, thus presenting a potentially large resistance to flow[2]. Returning to the sewer system analogy, it would be as if the fluid had to be pumped through a dense bed of rock, and the pumping system must generate enough pressure to maintain the required flow rate.

In approaching the analysis of the lymphatic system from the point of view of an engineer/designer, it is useful to begin with a background in the basic mechanical principles that govern fluid flow and pumping. These are outlined in the next section, which is limited to the concepts required to discuss lymphatic function. We then apply these principles in presenting the current status of the ever-expanding state of the art on lymphatic physiology and biomechanics. The reader is encouraged to refer to additional material for further biomechanics background [5, 9].

9.2 Biomechanics Primers

9.2.1 Fluid Mechanics

A fluid is defined as a substance that flows, or deforms continuously, in response to an applied shearing force. In other words, a fluid will continue to move when forced, whereas a solid would deform to a certain shape and then stop. Imagine placing your hands parallel to one another and then moving them in opposite directions. The air adjacent to your hands would be dragged in each direction, and the fluid in between would provide only viscous resistance to that movement, but otherwise would continue to move. The viscous resistance depends on the viscosity of the fluid, which increases from air to water to maple syrup. Now, imagine that the fluid in between your hands is divided into layers parallel to your hands. If these layers do not mix with one another, the flow of the fluid would be referred to as «laminar.» This would be more likely for maple syrup than air, because of the higher viscosity of the fluid. If, on the other hand, the layers of fluid start to mix with one another, the flow may be referred to as «turbulent,» which is characterized by random or chaotic velocity fluctuations in space and time.

In the late 1800s, a fluid mechanician named Osborne Reynolds established that the likelihood of turbulent flow depends on a dimensionless ratio which now bears his name. The Reynolds number is defined as

$$\mathrm{Re} = \frac{VD}{v},$$

2 There is some evidence that lymph nodes actively contract and thus perhaps aid in propelling lymph [10].

where V is a velocity indicative of the flow situation, D is a length scale (e.g., the space between your hands, or tube diameter), and ν is the fluid's kinematic viscosity. If Re > 2000 in a pipe flow, the flow is likely turbulent; otherwise it is likely laminar. The flow of lymph is clearly in the laminar regime, as we now demonstrate for the thoracic duct.

For thoracic duct:

- *Average flow rate = 5 liters/day*
- *Vessel diameter = 2.5 mm*
- *(Average velocity V = flow rate/cross-sectional area = 1.18 cm/sec)*
- *Kinematic viscosity = 0.01 cm^2/sec*
- *Reynolds number = VD/ν = 29*

The diameter and flow rate through other lymphatic vessels are smaller than the thoracic duct, so this value represents the highest Reynolds number found anywhere in the system. Note that the guideline of Re < 2000 for laminar flow is not a hard rule. There are situations in which turbulence can occur at lesser Reynolds numbers, and there is a «gray zone» of interesting flow patterns in which layers of fluid mix with each other but not in a manner that would be described as random or chaotic. There are many observations of blood flow patterns that fall into this category.

The flow of a fluid in a long, straight, cylindrical tube under laminar conditions is well described by equations derived by Jean Poiseuille in the mid-1800s. These equations allow us to relate the volume flow rate of a fluid Q through a tube of diameter D to the viscosity of the fluid and the difference in pressure P from the upstream to the downstream end,

$$Q = \frac{\pi D^4 \left(P_{upstream} - P_{downstream} \right)}{128 \rho \upsilon \mathrm{L}},$$

where ρ is fluid density and L is tube length. We can also use Poiseuille's analysis to calculate the frictional force exerted on the wall of the tube by the flow of the fluid. This force is related to the wall shear stress, a measure of the internal stress acting parallel to the wall surface area,

$$\tau_{\mathrm{w}} = \frac{32 \rho \upsilon Q}{\pi D^3}.$$

This is a physiologically and biologically important quantity, as it has been demonstrated in numerous studies that cells that line the insides of arteries, veins, and lymphatic vessels respond to different levels of shear stress by changing their morphology, internal structure, and protein expression [11, 15].

A full understanding of flow patterns in any situation is usually obtained by a combination of experimental and theoretical/computational approaches. The equations that govern fluid flow (Navier-Stokes equations) are quite complex. Finding exact solutions

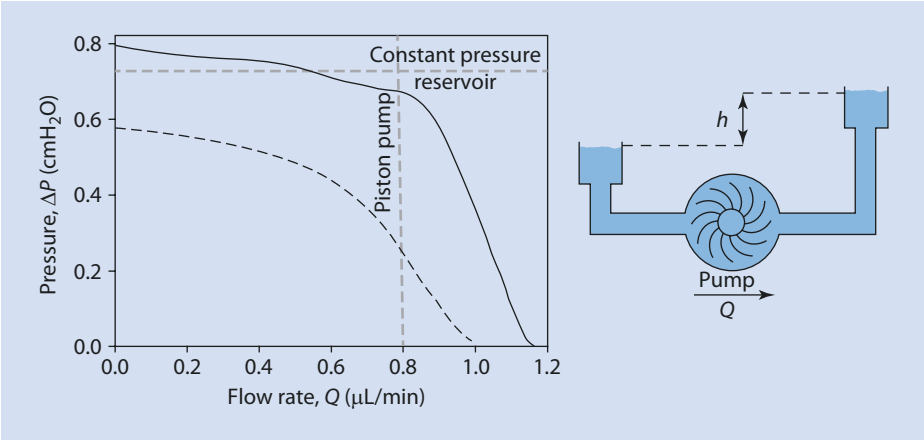

Fig. 9.1 An example pump curve showing the relationship between the pressure difference a pump can overcome and the flow rate it can generate. Pumps can be thought of as moving fluid from one reservoir to another at a height difference h, as shown at the right. The two *gray* lines indicate idealized pump scenarios. The horizontal line represents a constant pressure reservoir, where the height difference never changes and the resulting flow rate depends on the outflow tube diameter. The vertical gray line represents a piston pump, which generates a constant flow, and then the pressure required would be determined by the diameter of the outflow tube. Most other pumps, including lymphatic vessels, fall somewhere in between these two idealized cases, as indicated by the curved lines. If there is no height difference (i.e., $h = 0$ mm), then the pump generates maximal flow. As we increase the height difference, the flow rate decreases. The dashed curve represents the pump curve predicted for a chain of lymphangions in series under baseline conditions. The solid curve results when the tension generated by lymphatic muscle cell contraction is increased by 50% (Based on results from [1])

for these equations can be exceedingly difficult except in the most simplified theoretical exercises (e.g., Poiseuille flow). However, recent advances in computational hardware have made it feasible to obtain highly accurate approximate solutions by breaking the flow domain up into many small pieces. Simplified versions of the governing equations are then solved using techniques that fall into the general category of computational fluid dynamics (CFD), which includes finite difference, finite element, and finite volume techniques.

9.2.2 Fluid Pumping

All pumps, whatever their design, serve to move fluid from a low-pressure reservoir to a high-pressure reservoir at some flow rate. For instance, the aforementioned sewer system needs to move a certain amount of fluid every day from gutters to the treatment plant on the hill. The height difference presents the force that must be overcome. The strength of a pump is then best expressed by the amount of fluid that can be moved in the presence of such a force. If the height difference is large, then the pump will likely only be able to propel a small amount of fluid. If the height difference is reduced, then a greater amount of fluid can be propelled. The relationship between height difference and flow rate is expressed by a pump curve (Fig. 9.1).

9.2.3 Solid Mechanics

Unlike a fluid, a solid has a defined shape at rest and has the ability to resist deformations when loaded. When a volume of solid material is subjected to mechanical loading, it becomes internally stressed and may move and/or deform as a result. If the stress within the material is only a function of the current state of deformation, the material is referred to as elastic. These materials return to their initial shape immediately upon removal of the mechanical load. Many biological materials exhibit viscoelastic behavior, meaning that they require a finite amount of time to relax back to the initial shape.

Deformations are expressed as the strain ε, or change in length divided by the initial (relaxed) length L_0,

$$\frac{\Delta L}{L_0} = \frac{L - L_0}{L_0} = \varepsilon.$$

When strain is calculated in this way, it is known as infinitesimal strain. In some simple situations, the deformation can be measured visually or with a strain gauge. In the general case of 3D deformations, strains depend on direction and can be extremely difficult to measure. In infinitesimal strain theory, the principle of superposition applies, meaning that strain is directly proportional to the change in length. When considering a series of successive motions, one just needs to add the length changes together to calculate the total strain, and the ordering of the deformations does not matter because all length changes are small. However, this only holds as long as changes in length remain small, typically less than 10%. For larger deformations, we must consider finite strain theory, in which the order of successive deformations matters and strain is the result of multiplicative combinations of length changes, rather than additive.

The internal stress σ is defined as the force within the material divided by the area and cannot be directly measured. It is also quite complex in the general 3D case. On a given surface area, there are two types of stress that may be present: normal stresses, which result from a force applied perpendicularly to the surface, and shear stresses, which result from a force applied parallel to the surface. If we can apply the same assumptions as in infinitesimal strain theory (i.e., small displacement gradients and rotations), we can apply linear elasticity in which there is a linear relationship between stress and strain. In linear elasticity, the stress in a material is directly proportional to the strain, scaled by a constant known as Young's modulus E,

$$\sigma = E\varepsilon.$$

Young's modulus can be interpreted as the «stiffness» of the material and varies for different types of material. For example, steel has a much larger Young's modulus than rubber. Linear elasticity concepts remain accurate for most materials under infinitesimal strains, but linear elasticity does not accurately describe the behavior of many materials such as rubbers, elastomers, and biological tissues which can withstand large deformations and exhibit a highly nonlinear relationship between strain and stress (i.e., the

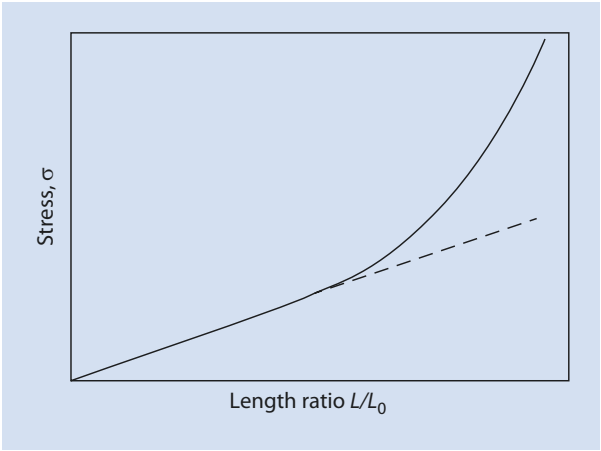

Fig. 9.2 Linear vs. nonlinear elasticity. This plot compares and demonstrates stress from a linear elastic material (*dashed line*) and a strain-stiffening, nonlinear elastic material (*solid line*) for various length changes. The linear and nonlinear material gave similar predictions for small length changes, but as the length ratio continues the increase, the nonlinear material begins to stiffen and requires much more stress to elicit further changes in length compared to the linear material. The walls of lymphatic vessels are made of a strain-stiffening composite of elastin (*inner layer*) and collagen (*outer layer*) [14]. This results in a strongly nonlinear pressure-diameter relationship as shown in Fig. 9.5

modulus changes with the amount of deformation applied) (Fig. 9.2). There are a wide variety of nonlinear elastic models that have been developed to describe this behavior: hypoelasticity, hyperelasticity, plasticity, viscoelasticity/poroelasticity, and more. Each of these models has been designed to replicate certain material behaviors, each based on their own set of assumptions and limitations. Therefore, care should be utilized when selecting an appropriate material model based on the specific problem being studied.

9.3 Lymphatic Biomechanics

9.3.1 Lymphangion-Level Flow Patterns

As demonstrated above, flow in the lymphatic system is clearly laminar. This facilitates estimation of important flow quantities such as flow rate and shear stress based on even the most basic measurements of any flow quantity. For example, measuring the velocities of cells flowing in an exposed rat mesenteric lymphatic vessel, along with the equations above, results in reliable estimates of volume flow rate and wall shear stress (Fig. 9.3).

Such low flow rates in very small (sub-mm) vessels cannot be measured accurately using tools developed for measuring blood flow, such as ultrasound and phase-contrast MRI. This presents a significant challenge in quantifying lymph flow rates noninvasively. Tracer-based techniques such as ICG fluorescence imaging do not provide a measure of flow rate. What they can provide is an estimate of the time required for a tracer to arrive at a downstream point in sufficient concentration to be detectable, and an average tracer «velocity» could be calculated as the ratio of distance over time. Unfortunately, because of

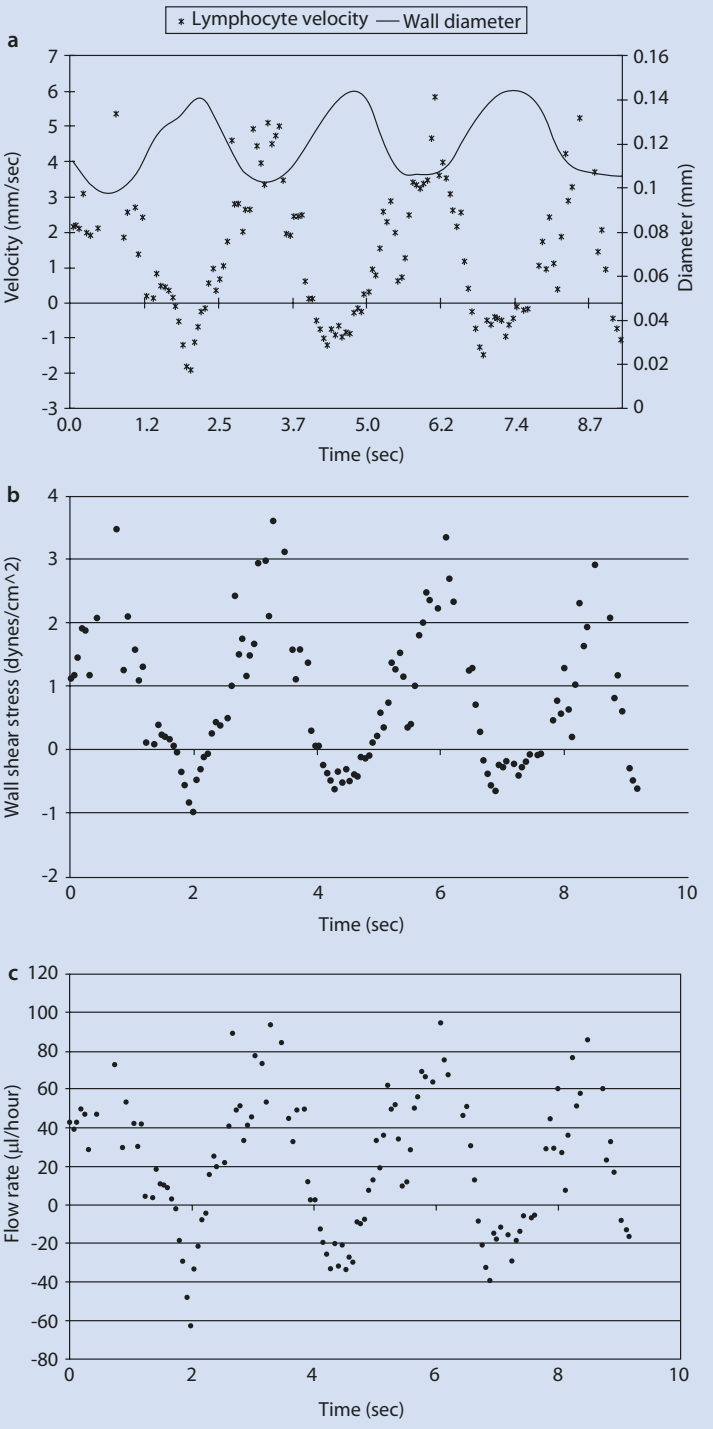
a
Lymphocyte velocity
Wall diameter
Velocity (mm/sec)
Diameter (mm)
Time (sec)
b
Wall shear stress (dynes/cm^2)
Time (sec)
c
Flow rate (µl/hour)
Time (sec)

Fig. 9.3 **a** Measurements of lymphocyte velocities and lymphatic vessel diameter in an in situ rat mesenteric preparation [8]. In this segment, the two waveforms are out of phase, but at other times, they may be uncoupled due to upstream of downstream contractions. Using these measurements, estimates of **b** wall shear stress and **c** volume flow rate may be obtained using Poiseuille flow theory

other effects such as tracer diffusion, this is not equivalent to fluid velocity. Further, lymph velocities are highly time-dependent, as demonstrated above, which the tracer «velocity» would smear out. Finally, a flow rate measurement would require a fluid velocity measurement plus an accurate measurement of vessel diameter, both of which vary dynamically.

9.3.2 Lymphatic Pumping Dynamics

Lymphatic vessels generate pumping through a combination of active or passive squeezing, aided by the action of closely spaced, one-way «check» valves. Each individual lymphangion is bordered by check valves that are spaced at most by about ten vessel diameters. When the lymphangion squeezes, the upstream valve closes, the downstream valve opens, and flow is propelled forward. These lymphangions are arranged in series and in parallel to form a vast network of individual pumping stations. In some cases, the pumping of adjacent lymphangions is coordinated, but this is not always the case. The system apparently does not require tightly coordinated pumping to serve its functions effectively. The reasons for this are currently a mystery.

In the region of lymphatic valves, there are beautiful examples of flow patterns that fall in the gray zone between laminar and turbulent flow (Fig. 9.4). The nature of these

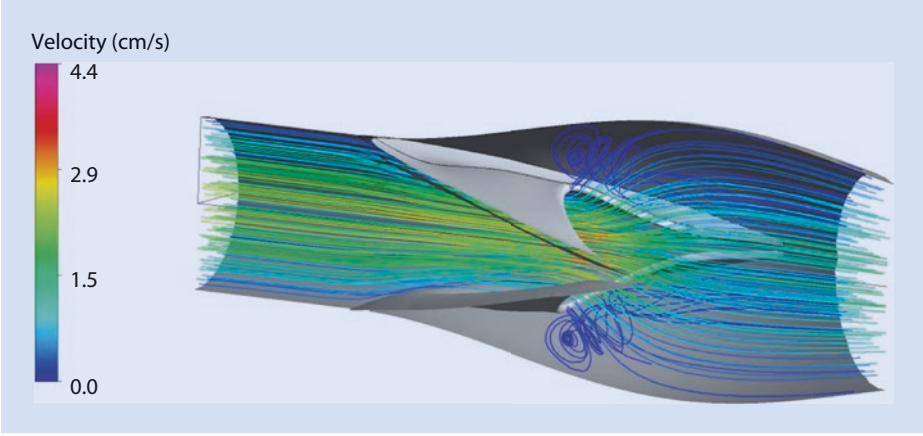

Fig. 9.4 A fluid-structure interaction simulation of idealized geometry of the secondary lymphatic valve. In this model, fluid pressure is used to deform and «open» the valve leaflet. The lines represent streamlines, with velocities ranging from low (*blue*) to high (*red*). For the majority of the fluid domain, the flow is laminar with nonintersecting streamlines. The velocity reaches its maximum value within the narrow valve orifice. However, there are nonparallel flow «eddy» zones near the outer surfaces of the valve leaflets. These eddy zones may facilitate the closing of the valve, as well as affect the transport of solutes such as nitric oxide, an important vasodilator molecule

flow patterns depends on the leaflet and sinus geometries. The primary job of the valves is to close and prevent reverse flow. The leaflets are very thin and made mostly of elastin [14], so closing them requires only a few cmH_2O pressure difference (downstream pressure > upstream pressure). Opening the valves requires less of a pressure difference (upstream pressure > downstream pressure), i.e., the valves are biased in the open position [2]. The pressure differences required to open/close the valves depend on the degree to which the vessel is pressurized. A higher internal pressure pulls the leaflets further apart, increasing the likelihood that they remain open.

Through a series of experimental and modeling studies, we and others have elucidated some of the basic physiological aspects of lymphatic pumping. Some of the findings follow basic common sense, e.g., squeezing with more force produces greater pumping (Fig. 9.1). However, detailed quantitative analysis has revealed that certain system characteristics are more important in determining overall pumping performance. An example is the resistance of valves to forward flow. While the valves exist to arrest reversing flow, they must also open widely when the upstream lymphangion contracts to allow flow to progress. If they do not, pumping performance is greatly compromised [3]. The timing of contractions of lymphangions relative to one another is another important quantity [3, 6]. The triggering of lymphangion contractions depends on biological actions that in turn depend on the details of the local mechanical environment [4, 12, 13].

The ability of lymphatic vessels to modulate their pumping in response to changes in imposed flow is undoubtedly related to the ability of lymphatic endothelial cells to sense shear stress and alter their expression of vasoactive substances such as nitric oxide. For example, forcing fluid to flow through a lymphatic vessel by raising the inlet pressure causes the vessel to cease active pumping. There is also ample evidence that lymphatic pumping is modulated by changes in transmural pressure. Increasing pressure provokes increases in lymphangion contraction frequency and force [4, 7].

The solid mechanics of the lymphatic vessel wall play a subtle but important role in lymphatic pumping. In every case where such measurements have been published, it has been demonstrated that lymphatic vessels exhibit a highly nonlinear pressure-diameter behavior. Note that a pressure is simply a compressive stress that acts equally in all directions (i.e., isotropic or volumetric stress). At low pressures, the vessels are highly compliant. Above some transition pressure (typically <5 cmH_2O), they become suddenly very stiff (Fig. 9.5). Blood vessels also get stiffer at higher pressures, but the transition from low-pressure to high-pressure behavior is much more gradual. The high stiffness presumably prevents the storage of lymph in the very vessels that should be pumping to prevent edema. The highly compliant behavior at low pressures benefits pumping dynamics. Effective lymphatic pumping requires a significant change in diameter to result from lymphatic muscle contraction, i.e., the generation of stroke volume. In the compliant portion of the pressure-diameter curve, there is minimal resistance to reduction in diameter offered by the wall itself, which enhances effectiveness of muscle contraction [3]. The subsequent refilling in diastole is also facilitated by the high compliance of the wall. It is not surprising, therefore, that the transmural pressure «operating point» of most lymphatic vessels corresponds to the pressure at which the vessel transitions from low to high compliance.

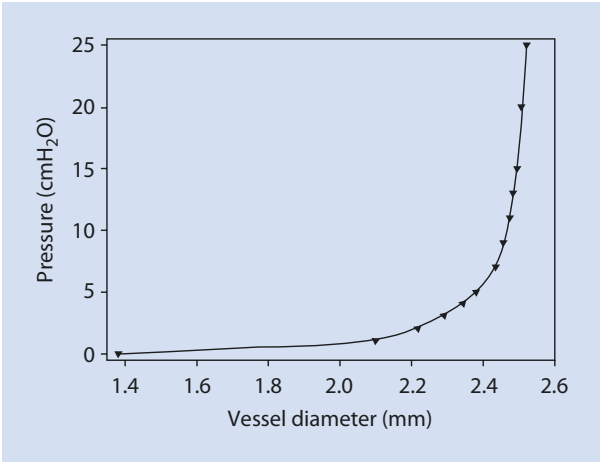

Fig. 9.5 A typical pressure-diameter curve for a lymphatic vessel. At low pressures, diameter increases rapidly with pressure, indicating that the structure is highly compliant. However, the lymphatic wall exhibits highly nonlinear behavior around a pressure of 5 cmH_2O, after which the material stiffens greatly

Concluding Remarks

The physiological functions of the lymphatic system are heavily reliant on proper biomechanical function. The pumping required to move lymph effectively into nodes and eventually back into blood vessels relies on the carefully concerted dynamic behavior of valves, muscle contraction, and passive vessel mechanics. These phenomena, in turn, are driven by biology, beginning with actions the molecular level such as structural protein production and calcium flux. The system is beautifully designed across multiple lengths and time scales. The numerous diseases that result when these mechanisms break down illustrate the importance of a proper understanding of its biomechanical function.

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Pathology and Histochemistry

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Summary of Basic Concepts

Lymphedema develops when the main lymphatic collecting trunks become damaged and obliterated by noxious factors from pathological processes in tissues (infections, trauma) or after surgical removal and irradiation of nodes in cancer.

When the main lymphatic trunks become obstructed, the capillary filtrate called tissue mobile fluid flows toward the skin in the subepidermal plexus (incorrectly called «dermal backflow» instead of «dermal collateral flow»).

Lymphedema is increase in limb volume by accumulation of excess capillary filtrate and hyperplasia of keratinocytes and fibroblasts secreting collagen and adipocytes. Thus, the total mass of the limb is increased with fluid and tissue volume. Fluid can be removed; however, hypertrophied tissues do not undergo involution and remain.

Microorganisms penetrating the skin are retained in lymphedematous tissues because of lack of lymph flow and evoke host chronic immune response.

10.1 Pathology and Histochemistry

10.1.1 Immune Processes in Lymphatics and Nodes

The pathological changes observed in the lymphatics in lymphedema are caused by infection or trauma and include damage of the endothelial and muscular cells, subsequently leading to obliteration of the lumen by fibroblasts. The changes are the price the lymphatic system is paying for its own function in the body. It is devoted to elimination of microbes and own damaged cells and in a feedback fashion to healing of parenchymatous tissues. The inflammatory process is destroying also own cells. The pathological events in the skin and reaction of the regional lymphatic system have been schematically shown in Fig. 10.1. The lymph cells participating in the immune response have been presented in Fig. 10.2 [1, 6, 7].

10.1.2 Classification of Lymphedema of Lower Limbs

Lymphedema is caused by obstruction of the main collecting trunks draining limbs or organs. There is no regeneration (vasculogenesis) of lymphatics with all components of their wall. Only at the level of lymphatic capillaries (initial lymphatics) lymphangiogenesis can be observed. This is most clearly seen during the wound healing process. The pathological changes observed on lymphoscintigrams, MR images, and histolological specimens depend on factors responsible for the development of lymphedema. Today, the sole term lymphedema does not provide enough information on the etiology of the condition. Lymphedema is not a separate entity; it is a symptom. The term «lymphedema» should be preceded by a word informing about the cause (Fig. 10.3). Whereas in Europe and North America mostly early cases of lymphedema of limbs are seen, the bulk of affected population remains in Asia, Africa, and South America. Cases from

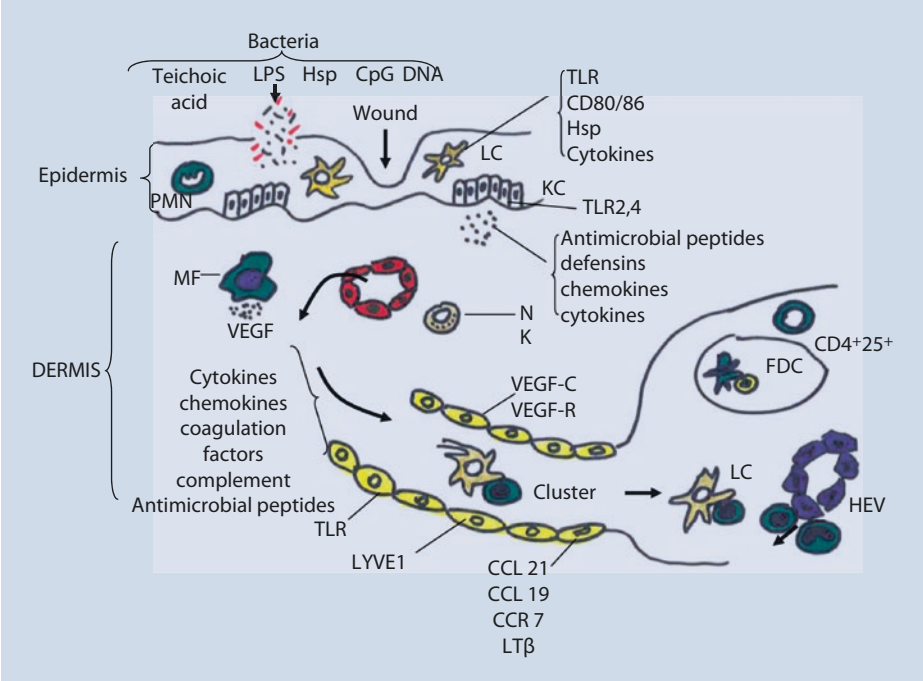


Fig. 10.1 Schematic presentation of immune event in the skin, draining lymphatics and nodes. Bacteria and/or trauma of the epidermis damage the superficial layers of keratinocytes. The bacterial antigen and cellular debris are immediately recognized by Langerhans cells present between keratinocytes. A cascade of natural immune events is initiated. Multiple nonspecific humoral and cellular factors participate in the process. *Yellow cells* line out afferent lymphatics. *LPS* lipopolysaccharide, *hsp* heat shock protein, *CpG DNA* bacterial DNA fragment, *LC* Langerhans cell, *KC* keratinocytes, *TLR* toll-like receptor, *MF* macrophage, *NK* natural killer cell, *VEGF* vascular endothelial growth factor (R, receptor), *LYVE* 1 hyaluronate receptor specific for lymphatic endothelial cells, *CCL* lymphocyte chemoattracting cytokine, *LT* lymphocytotoxin attracting lymphocytes, *FDC* follicular dendritic cells in B-cell follicles, *HEV* high endothelial venule sites of extravasation of blood lymphocytes, CD4 + 25+ regulatory lymphocytes

these geological regions present macro- and microscopical changes fully illustrating the consequences of lymph flow obstruction (Fig. 10.4a–c).

10.1.3 Tissue Changes

Macroscopical changes in limbs include fibrosis of the skin and overgrowth of fibrous and adipose tissue. On the MRI pictures, the distribution of intertissular (edema) fluid and overgrowing tissues is best seen (Fig. 10.5a, b). Specimens of the lymphedematous tissues removed during debulking procedures show in nature what illustrate, MRI pictures (Fig. 10.6a, b). The regional lymph nodes are fibrotic, and there is no lymph flow through their sinuses (Fig. 10.7).

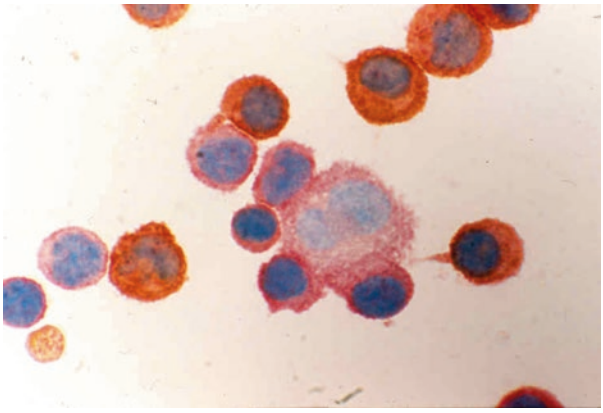


Fig. 10.2 Histological picture of lymph cell smear from a normal human calf lymphatic vessel. The large cell in the middle is a Langerhans cell (dendritic, veiled) with attached CD4 – helper (*rose*) lymphocytes forming the so-called immune cluster. Antigen (bacterial, own tissue-specific) is processed by Langerhans cell and presented to the helper lymphocytes. In close vicinity are the CD8 cytotoxic lymphocytes (*brown*) also participating in the immune processes. The type of cells in lymph is totally different from that of blood. Extravasation of specific cell precursors takes place in the dermal and lymph node blood capillaries. These cells further migrate to the initial lymphatics

10

Fig. 10.3 Classification of lymphedema. Adding the causative term in front of «lymphedema» provides information necessary for proper understanding of the mechanism, establishing treatment protocol, and formulating prognosis

Classification of lymphedema

1. Postinflammatory (dermatitis, lymphangitis, lymphadenitis of various etiologies)
2. Postsurgical (after groin and axillary dissection also including radiotherapy; after arterial reconstructions and saphenous vein harvesting for coronary bypasses)
3. Posttraumatic (closed and open limb injuries with immobilization)
4. Mixed lymphatico-venous type in chronic various
5. Idiopathic (primary)
6. Parasitic (filarial)

10.2 Histology

The histological pictures of lymphatics and tissues differ depending on what was the primary cause of damage [2, 3, 8].

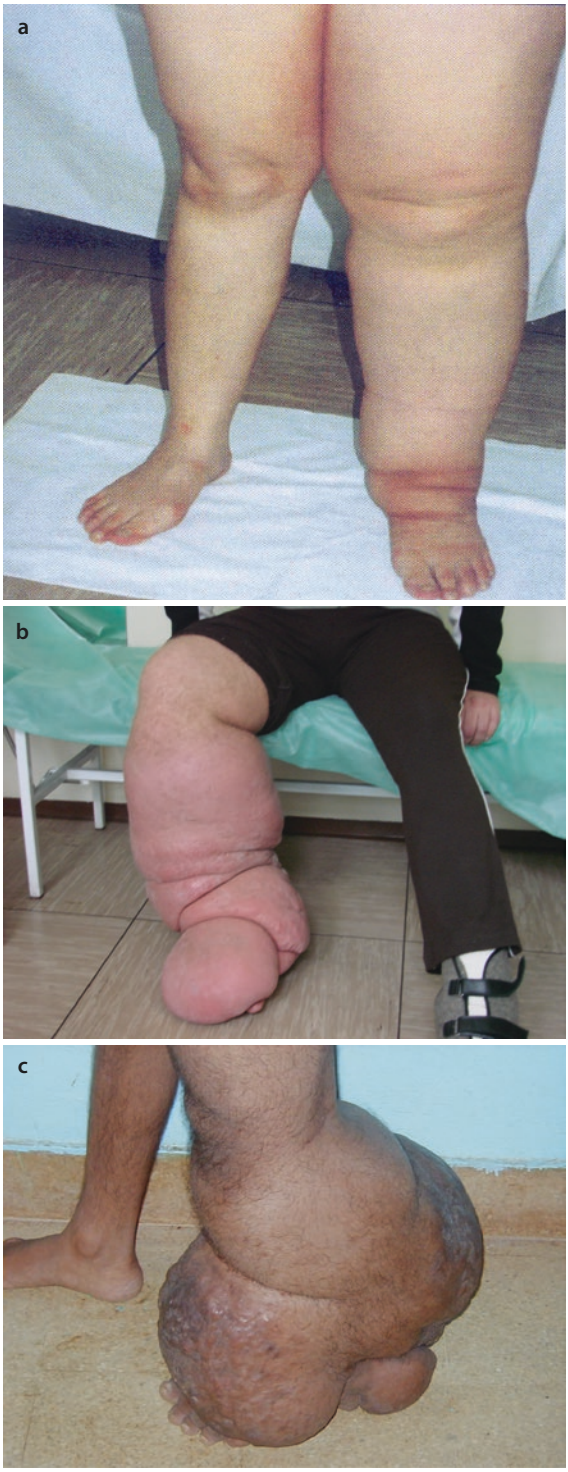


Fig. 10.4 Lymphedema of lower limb stage II **a** III **b** and IV **c** most commonly seen around the world

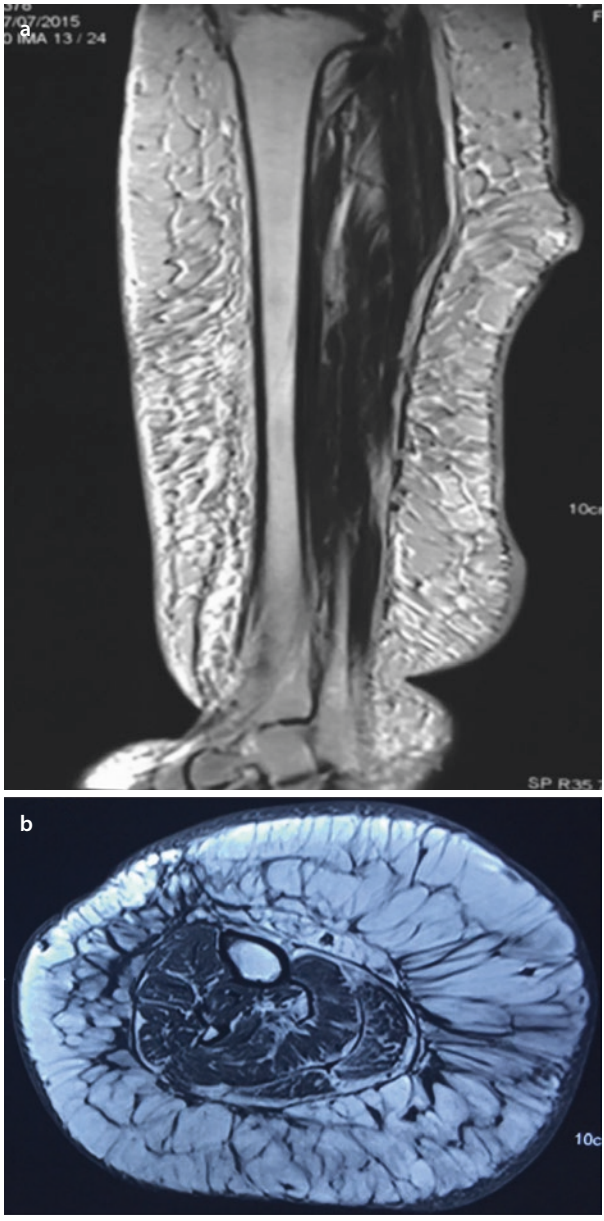


Fig. 10.5 **a, b** The magnetic resonance pictures showing site of accumulation of edema fluid and fibrous and adipose tissues. Note that lymphedema develops mainly in the epifascial compartment leaving the muscular non-swollen

10.2.1 Obstructive Lymphedema

Obstructive lymphedema: (1) obliteration of lymphatic collectors and fibrosis of lymph nodes (Fig. 10.8); (2) hyperkeratosis of the epidermis (Fig. 10.9); (3) immune cell infiltrates of the epidermis, dermis, and subcutaneous tissue

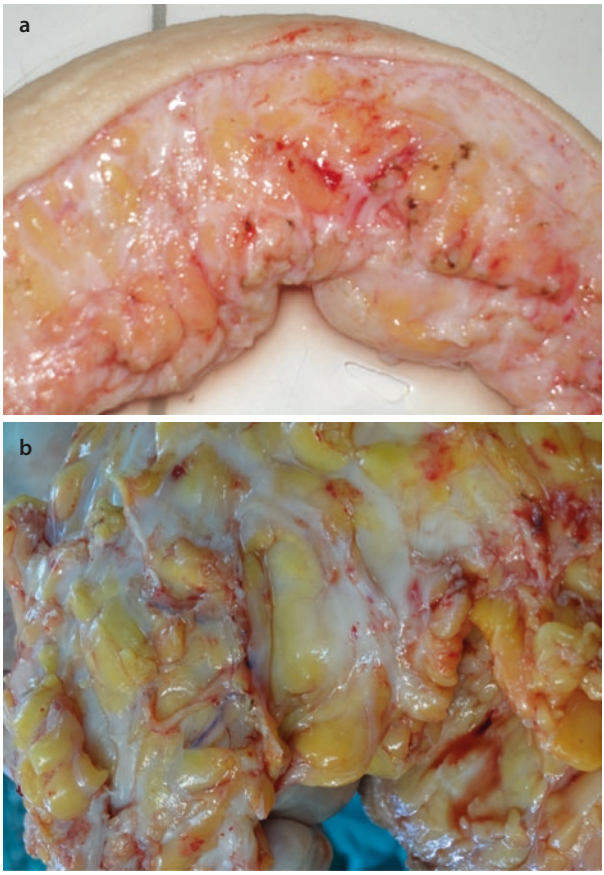


Fig. 10.6 The structure of subcutaneous tissue in lymphedema. **a** Thickness of the epifascial tissues. **b** Fat globules separated by fibrous septa covered by microlayer of fluid

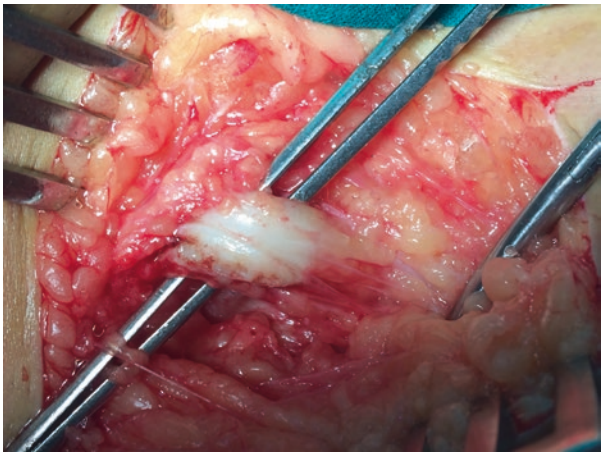


Fig. 10.7 Fibrotic inguinal lymph node in lymphedema. Patient suffered from multiple episodes of dermato-lymphangio-adenitis damaging afferent vessels and depleting lymph node of lymphoid tissue

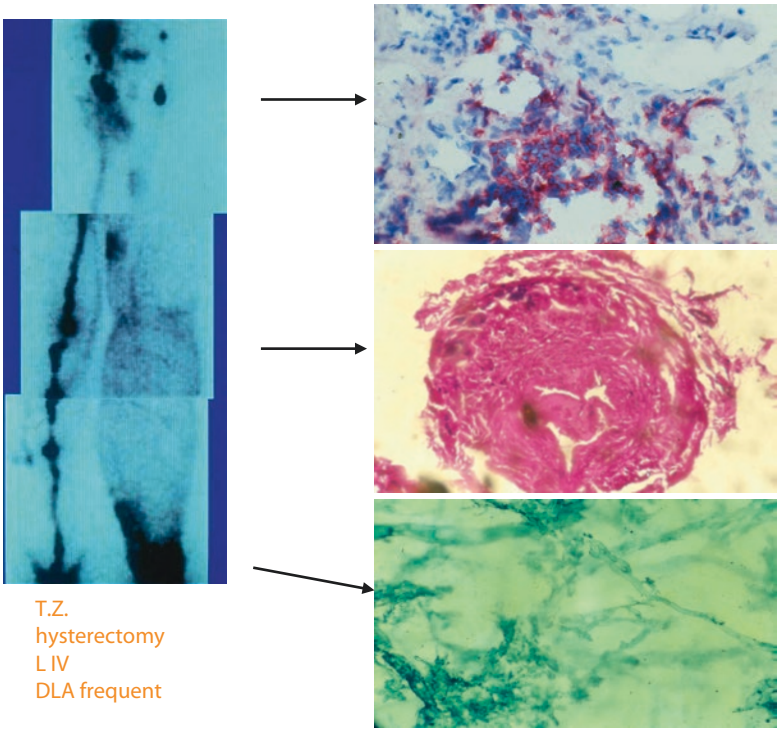
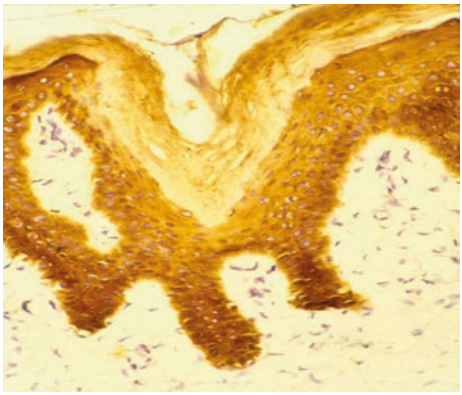
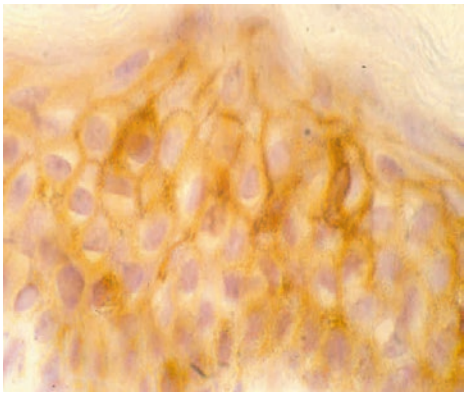


Fig. 10.8 Pathological changes in lymphatics in a case of postsurgical, postradiation lymphedema stage IV. *Left panel* – lymphoscintigram showing lack of lymphatics in the swollen limb. *Right panel* – histological pictures from tissue at levels indicated by arrows. Dilated, irregular structure of subepidermal lymphatic (*lower panel*), obliterated lymphatic collector (*middle panel*), and remnants of an inguinal lymph node (*upper panel*) with few remaining lymphocytes (*red*). This is a typical picture of changes in the lower limb lymphatic system in a long-lasting lymphedema

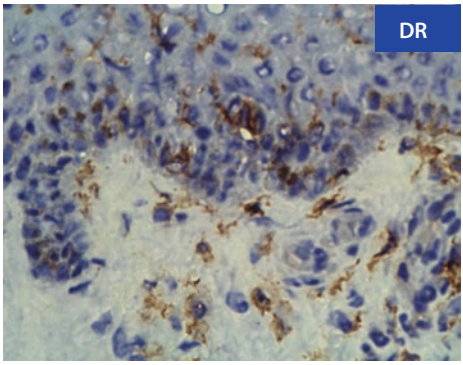
(Fig. 10.9); (4) fibrosis of the dermis (Fig. 10.10), perilymphatic tissues, and muscular fascia (Fig. 10.11); and (5) growth of the skin and fat tissue (fibroblasts secreting collagen, adipocytes). The process of changes in peripheral lymphatics after lymphadenectomy shows first ectasis, followed by contraction, and finally sclerosis. In the ectasis phase, an increase in endolymphatic pressure causes flattening of the lymphatic vessel endothelial cells. In the contraction phase, smooth muscle cells are transformed into synthetic cells and promote formation of collagen fibers. In the sclerosis phase, fibrous elements replace the cellular wall elements, lymphatic vessels lose their transport, and the lumen becomes either narrowed or completely obstructed [8].

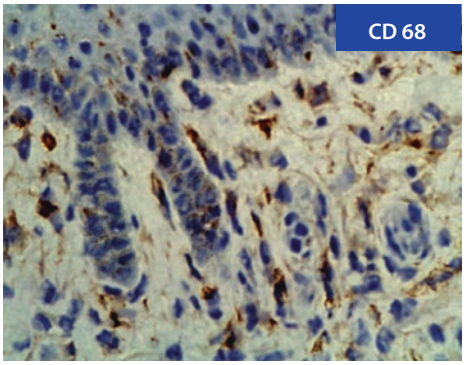


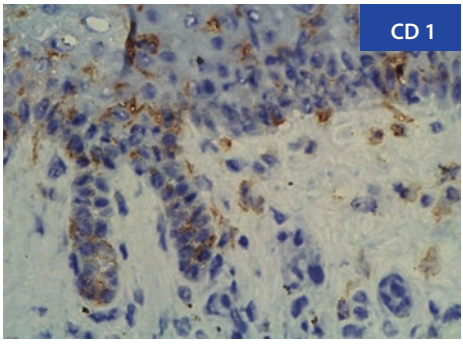
Hyperkeratosis



Activated langerhans' cells







Patient with acute dermato-lymphangio-adenitis

Cellular infiltrates at epidermo-dermal junction

Fig. 10.9 Histopathological pictures of epidermis and subepidermal dermis. Hypertrophy of keratinocytes, accumulation of Langerhans cells; and infiltration by DR-positive, CD68 macrophages and CD1 Langerhans cells

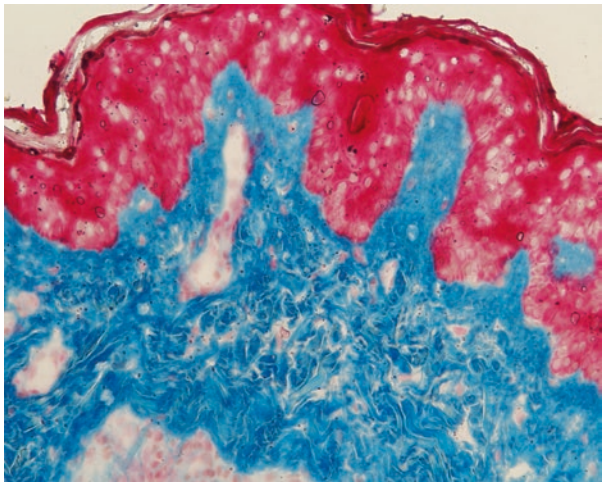


Fig. 10.10 Fibrosis of the dermis in lymphedema. Hyperplasia of epidermal cells (*red*) and excess of immature collagen in the dermis (*blue*)

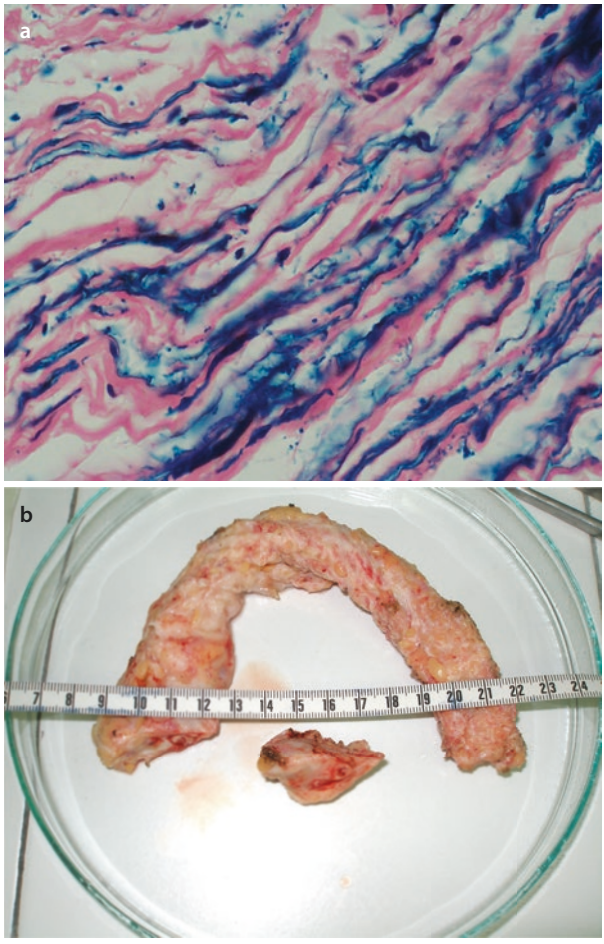
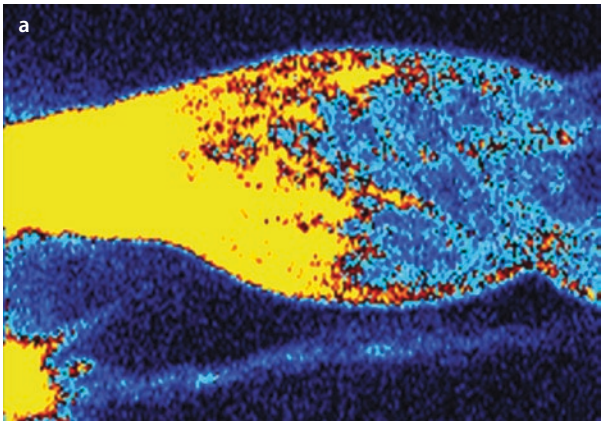


Fig. 10.11 Histological changes in lymphedema involve not only lymphatics and nodes but also dermis, subcutaneous tissue, and fascia. **a** Fibrosis is the main process starting from the most distal parts of the limb and progressing to the knee. The accumulating tissue fluid deforms the subcutaneous tissue creating thousands of lakes and semi-open channels (*blue stained*). **b** In due course, these channels become closed by proliferating fibroblasts. The muscular fascia becomes totally fibrotic reaching thickness of 2–3 cm

Perilymphatic tissue in subcutis and fascia in lymphedema



Tissue fluid channels

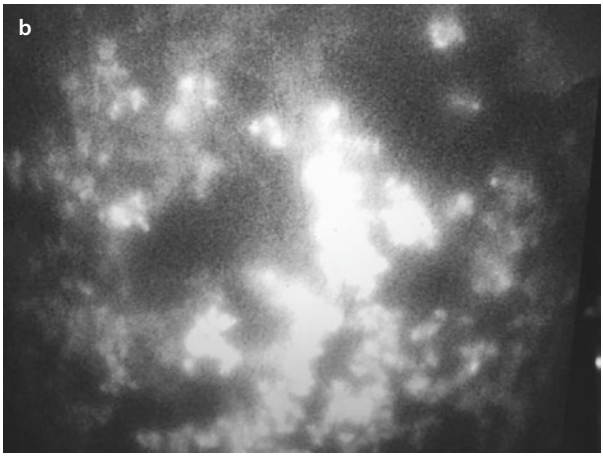


Fig. 10.12 **a** Lymphoscintigraphic picture of the tissue structure showing hundreds of minute spaces filled with isotope forming interconnected fluid channels. No main lymphatics are seen. **b** Indocyanine green fluorescence picture of spaces filled with the dye under the skin

10.2.2 Sites of Fluid Accumulation

Where is edema fluid accumulating? Lymphograms depict most affected regions of limbs (Fig. 10.12a, b). Electron micrographs show fluid between cells and immunohistochemical pictures presence of spontaneously formed tissue channels (Fig. 10.13a, b) [4].

10.2.3 Idiopathic Lymphedema

The so-called idiopathic lymphedema is characterized by (1) normally structured wall of lymphatic collectors, (2) acellular deposits under the endothelium narrowing or fibrotic structures obstructing the lumen (Fig. 10.14), (3) slow fibrotic process in the subcutaneous tissue, and (4) small but normally structured lymph nodes [5].

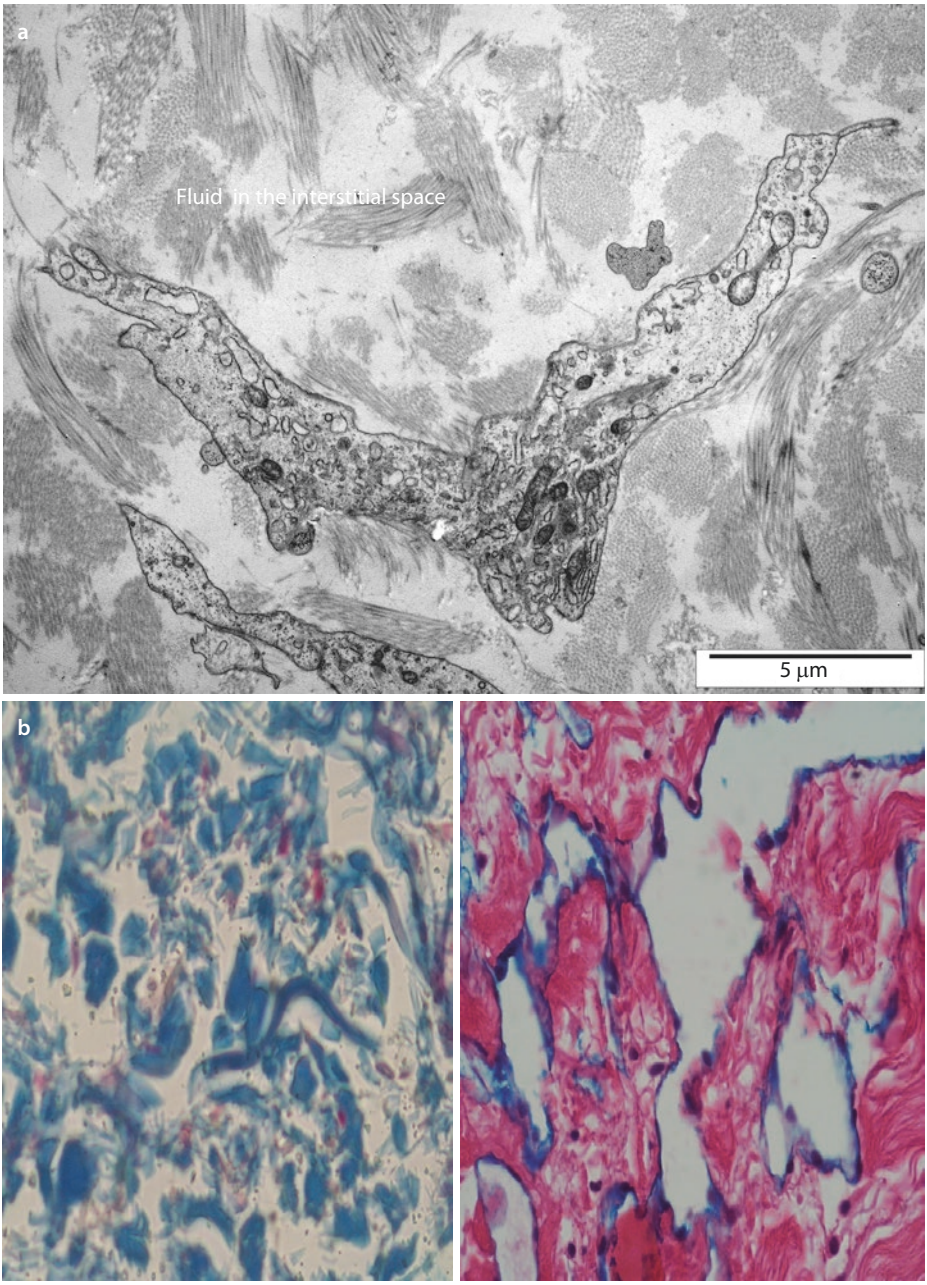


Fig. 10.13 Where does excess tissue fluid accumulate? **a** Collagen bundles (*light blue*) separated by fluid, **b** tissue channels of diameters of 10–100 microns (stained *dark blue*)

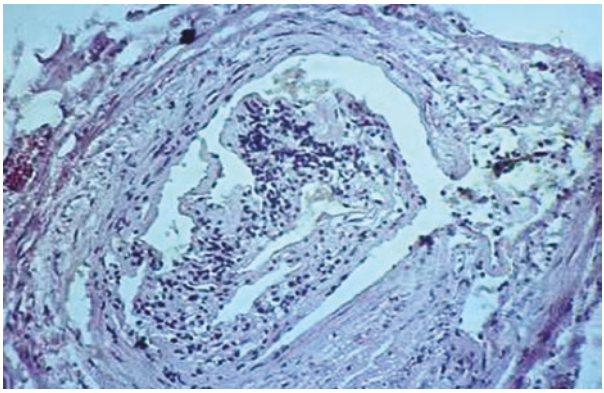


Fig. 10.14 Histological picture of a lower limb lymphatic in the so-called primary lymphedema. All vessel layers are normally developed. In the lumen, fibrotic material with mononuclear infiltrates partly occluding the lumen. The etiology of changes remains unknown; however, the infection factor cannot be excluded

10.3 Remarks

In lymphedema, tissues deprived of tissue fluid and lymph drainage are the site of a continuous inflammatory process. Fluids accumulating in the skin and subcutaneous tissues in lymphedema contain cytokines, chemokines, activated immune cells, and the most important the microorganisms. Microorganisms normally penetrate in a small load the epidermis and are fast eliminated by the circulating immune cells. However, in conditions of lymph stasis, they are not removed and may proliferate evoking host reaction. This is the reason for clinical attacks of dermato-lymphangio-adenitis (DLA) and histolological changes as infiltrates and formation of fibrous tissue.

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Lymph Formation and Composition

Laura Santambrogio

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Summary of Basic Concepts

- The lymphatic fluid is generated by ultrafiltrated plasma proteins and tissue proteome.
- The lymph reflects the molecular and proteomic signature of the parenchymal organ from which it originates.
- The lymph displays the molecular signature of disease processes and overall responses to pathological conditions.
- By transporting the self- and nonself-proteome, the lymphatic fluid has a fundamental role in immune surveillance.

11.1 Introduction

The lymph is a biological fluid produced by the interstitial fluid in combination with products derived from tissue metabolism and catabolism, cellular debris, apoptotic cells, and circulating immune cells. By transporting the tissue proteome to the draining lymph nodes under physiological and pathological conditions, the lymph plays a cardinal role in every immunological process, including maintenance of immunological tolerance, immunity to pathogens, autoimmunity, inflammation, and cancer [6].

Until a few years ago, the composition of the lymphatic fluid was virtually unknown, primarily due to the technical challenge of cannulating lymphatic vessels and the paucity of the collected lymph. These technical issues precluded an in-depth cellular phenotyping of the lymph-bound immune cells as well as any proteomic mapping aimed at analyzing the lymph composition. As many of these issues have been overcome, lymph biology has progressively received more attention. During the last 10 years, advances have been made toward understanding the mechanisms of lymph formation, circulation, and composition. In this chapter, I will summarize developing concepts on the mechanisms of lymph formation and circulation and the progression of the «omic» analysis toward the mapping of the lymph proteome in physiological and pathological conditions.

11.2 Lymph Formation

11.2.1 Protein Ultrafiltration from the Microcirculation into the Interstitial Fluid

The blood that circulates throughout the circulatory system is not directly in contact with the cellular layers of parenchymal tissues; thus proteins, lipids, and other molecules need to move from the intravascular to the extravascular compartment in order to provide cellular nutrients and hydrate tissue cells. This process of ultrafiltration is generated through the intravascular hydrostatic pressure, which moves proteins into the extracellular space to provide nutrients and hydration to parenchymal cells. According to the Starling principle, the ultrafiltration process is controlled by the net balance between hydrostatic and osmotic pressures across the microvascular endothelium which moves

fluid, protein, and macromolecules from the arterial end of the capillary bed into the interstitial space and partially reabsorbs them back from the interstitial space into the venous end of the capillary bed [7, 8]. Indeed, measurements of fluid exchange in the capillary beds have demonstrated that in most tissues the steady-state pressures (hydrostatic and osmotic) provide only a low level of fluid reabsorption back into the capillary bed and there is a net balance that overall favors interstitial fluid formation [1, 9–13]. Thus, fluid and proteins remaining in the interstitial space will generate the interstitial fluid. Under physiological conditions, around 3–4 liters of protein-enriched interstitial fluid are formed every day in the human body. This interstitial fluid, which bathes every parenchymal organ, is the precursor of the prenodal lymph, and through this mechanism, plasma proteins contribute to the overall lymph proteome [1, 8, 9].

11.2.2 The Contribution of Parenchymal Organs to Lymph Composition

A series of proteomic analysis performed in ovine, bovine, rodents, and human lymph, collected under physiological and pathological conditions, have indicated how the lymph fluid collects the «molecular proteomic signature» of the parenchymal organ from which it originates [2, 3, 14–21]. Indeed, although plasma albumin and serum globulins still represent the majority of lymph proteins, tissue-specific antigens are highly represented in the lymph proteome as compared to the plasma proteome. Altogether, major differences can be pointed out between these biological fluids: (i) proteins derived from extracellular matrix (ECM) processing and tissue growth and remodeling which are more abundantly expressed in the lymph compared to the plasma, as well as (ii) proteins derived from ongoing cellular metabolic/catabolic activities and (iii) intracellular proteins released from apoptotic cells [2, 3, 15–21].

On the other hand, proteins required to maintain fluid osmotic pressure (albumin and α1, α2, β globins) as well as coagulation factors are more highly expressed in the plasma than the lymph.

11.3 Lymph Contribution to Body Homeostasis

To prevent tissue edema, the interstitial fluid needs to be returned to the blood circulation for kidney filtration. Thus, an important physiological question is why the interstitial fluid is not directly reabsorbed back at the venule end of the capillary bead but, as lymph, will circulate throughout one or more of the 600–800 draining lymph nodes disseminated throughout the human body, before draining from the thoracic duct into the vena cava.

Overall, there are various important reasons why the interstitial fluid is not directly absorbed into the general blood circulation but is filtrated through the lymph node. In the blood, fluid volume, protein concentration, osmolality, electrolytes, and pH are very tightly controlled, and changes in any of these parameters have severe consequences on the body homeostasis. In contrast, the composition of the lymphatic fluid can range widely in lipid and protein concentration, electrolytes, pH, and overall cellular composition

without harming organ homeostasis. Thus, the lymphatic fluid acts as a buffer, by sustaining changes in its biochemical and cellular composition, according to the metabolic and catabolic needs of each parenchymal organ, as observed in both physiological and pathological conditions, without compromising body homeostasis [6]. A second important function of the lymph is that by draining through the nodes, it ensures that tissue-invading pathogens do not directly enter into the bloodstream but can be captured by macrophages and dendritic cells residing in the lymph nodes. Finally, by transporting products of organ remodeling, cellular secretion/processing, and cellular debris, the lymphatic fluid ensures that nodal immune cells are constantly exposed to each tissue self-proteome for maintenance of peripheral tolerance. Immune cells patrolling the peripheral tissue also use the lymphatic circulation as a fast and direct conduit between lymph nodes and parenchymal organs [6].

Altogether, several important functions can be credited to the lymphatic fluid including the control of bodily fluid homeostasis, transport of the self- and nonself-proteome to the draining lymph nodes, and facilitation of immune cell trafficking [6].

11.4 Lymph Circulation

All parenchymal organs collect the interstitial fluid through a network of open-ended lymphatic capillaries [6]. These capillaries comprise a single layer of lymphatic endothelial cells sustained by a thin and incomplete basement membrane [4]. The endothelial cells are joined by intercellular junctions, containing vascular endothelial cadherin (VE cadherin) and platelet endothelial cell adhesion molecule 1 (PECAM1). These junctions function as one-way valves, which facilitate entry of proteins, fluids, macromolecules, small molecules, and immune cells into the lymphatic vessel [22–26]. The lymphatic capillaries then merge into progressively larger vessels, known as lymphatic collectors, formed by an organized basal membrane which includes lymphatic muscle cells, connective tissue, and fibroblasts that support the lymphatic endothelial cells [4]. The lymphatic muscle cells, which combine characteristics of both smooth and striatal muscles, are important for maintaining a basic vessel tone and propelling the lymph toward the draining lymph node [27, 28]. Among the muscle cells, few of them form the lymphatic pacemakers, which, through Ca^{++} ion-mediated depolarization, initiate the action potential required for muscle contraction.

The directional flow of the lymph is sustained through a series of unidirectional valves placed along the collectors, which open and close in synchrony with the vessel contraction. The valves are bicuspidal in shape and are formed by layers of connective tissue overlaid by lymphatic endothelial cells [29, 30]. The region of the lymphatic collectors comprised between the two sets of valves is referred to as a lymphangion. Contraction initiates from the more distal lymphangion and propagates toward ones closer to the lymph node. By synchronizing the opening and closing of the valves with the lymphangion contractions, the lymph is prevented from backflow and moves unidirectionally toward the lymph node, altogether facilitating the collectors working as pumps [27, 28, 31].

Original studies by Smith et al. reported that under physiological conditions, the lymph flow, both pre- and post-nodal, progresses at about 1–5 ml/h [32]. However, the lymph flux to the regional lymph nodes can increase notably under inflammatory

conditions associated with pathogen-driven inflammation or sterile inflammation. The increased flux is associated with the increased formation of interstitial tissue and formation of tissue edema as well as increased lymphangiogenesis (the formation of new lymphatic vessels from preexisting ones), increased immune cell trafficking to the lymph node, and increased pro-inflammatory mediators, which affect lymphatic contractility [33–35].

Increased lymphangiogenesis has been reported in several pathological conditions, including metastatic and nonmetastatic cancer, acute and chronic inflammation, and primary and secondary lymphedema [36–39]. In all these conditions, the increased lymphangiogenesis is due to an increased production of the vascular endothelial growth factors (VEGF-A, VEGF-C, VEGF-D, and VEGFR-3), which are released by immune and stromal cells [40–43]. Additionally, inflammatory cytokines activate NFκB-dependent pathways which, in turn, promote transcription of Prox1, the master controller of lymphatic endothelial cell proliferation/differentiation [42, 44, 45]. At the present time, it is still uncertain the role that is played by the increased number of lymphatic vessels observed at sites of inflammation. One school of thought proposes that the neo-vessels have a beneficial role since they aid in decreasing tissue edema and clear tissue debris from the site of inflammation. Alternatively, other investigators propose that neo-lymphangiogenesis by increasing trafficking of immune cells and pro-inflammatory cytokines/chemokines can further disseminate the inflammatory process. Less debatable is the role of lymphangiogenesis in cancer where the proliferation of lymphatic vessels has been shown to facilitate metastasis and to be a strong negative prognostic factor [36–39].

11.5 Lymph Proteomics

11.5.1 Lymph Versus Plasma

During the last 15 years, proteomic mapping of lymphatic fluid has exponentially increased with several analyses performed in ovine, bovine, rodents, and human lymphatic fluid. The ultimate goal of these analyses is the finding of protein biomarkers in different pathologies as well as to characterize the molecular proteomic signature of lymphatic fluid collected from different lymphatic sites [14]. Indeed, owing to the close relationship between the parenchymal interstitial fluid and the lymphatic fluid, the lymph proteome has been regarded as an attractive source of protein biomarkers and the organ immunological signature [6].

Because lymph was considered a mere product of blood filtration, its composition was originally thought to overlap with that of the plasma. Additionally, the low sensitivity of the early mass spectrometry instruments gave further credit to this claim since much of the originally mapped lymph proteome sequenced abundantly expressed proteins, such as albumin and globins, as present in both biological fluids [46].

More recently, mapping of human and rodent lymph, both under physiological or pathological conditions, started shedding light on the complexity and unique characteristics of this biological fluid. So far, over 1200 proteins have been compiled from proteomic analyses performed in different species, including humans, rodents, ovine, bovine, and swine.

The first proteomic analysis on lymphatic fluid was performed by Leak and colleagues; the analysis was the first to compare the ovine lymph and plasma proteomes using a 2D PAGE approach combined with MS/MSworkflow [46]. The compositional uniqueness of the lymph proteome was hinted for the first time around 10 years ago (46). Although the low sensitivity of the instrument did not allow for a comprehensive analysis, the authors identified a few proteins, such as glial fibrillary acidic protein and neutrophil cytosol factor-1, as present and much higher in abundance in lymph compared with plasma.

Similarly, another quantitative analysis, performed on the rat mesenteric lymph proteome collected from fed versus fasting animals, reported almost 200 proteins related to innate immunity and tissue protease inhibitors [18, 47].

Our laboratory was the first to perform the analysis of the human lymph proteome. Our proteome coverage confirmed many of the previous findings that the lymph is a biological fluid enriched in tissue-derived proteins [2, 5, 15, 16, 48]. We reported a common lymph plasma proteome, which comprised proteins important to maintain fluid osmolarity, including albumin and α1, α2, and β globulins. Additionally, we reported that the complement system, transporters, metabolism regulators, and protease inhibitors were also shared between the two biological fluids suggestive of a core of conserved functional features between plasma and lymph. However, the proteome also highlighted the presence of lymph-enriched proteins, which included proteins involved in apoptosis and cell catabolism (nucleus, cytosol, and plasma membrane). Several proteins also derived from extracellular matrix tissue remodeling (collagens, cartilage, and other ECM proteins). There are two main reasons why this category was particularly enriched in our analysis: firstly because the lymph was collected from the foot, thus draining the skin, muscle, and subcutaneous tissues, and secondly because the analysis was performed using a less sensitive mass spectrometer compared to the ones available today, thus skewing the mapping toward more abundant proteins [2, 48].

A similar analyses of matched plasma and lymph from trauma patients identified tissue-specific proteins more abundantly expressed in the lymph. Indeed Dzieciatkowska and colleagues reported that in matched lymph vs plasma trauma samples, over 100 proteins could be identified in the lymph but not in the plasma [3, 17]. These proteins included products of cell lysis, mediators of acute phase response and pro-inflammatory responses, and immune modulators. The lymph was also specifically enriched with mediators of vascular function and stimulators of vascular activity, typical of acute adaptation to trauma as well as products of energy/redox metabolism, commonly observed during tissue injury. Finally, products of extracellular matrix remodeling were also enriched in the lymph compared to the plasma [3, 17].

As technical advancements in proteomic technologies facilitated the discovery of increasingly lower abundance proteins in complex biological fluids, many of the proteins formerly identified as unique to the lymphatic fluid have now been included in the nonredundant list of the plasma proteome, as part of the Human Plasma Proteome Project.

As the technology progresses, it is likely that quantitative and not qualitative differences will be reported as distinguishing the two biological fluids [15]. Particularly, the two circulatory systems, although they run independently, will eventually converge and

the lymph, collected into the thoracic and mesenteric ducts, will flow into the superior and inferior vena cava, respectively. More quantitative proteomic approaches that utilize isotope-labeled amino acids will further help mapping the specific composition of the fluids.

11.5.2 Proteins from Intracellular Sources

The mapping of the human lymph proteome has mostly focused on mesenteric and peripheral prenodal lymph, since the former could be collected during surgery and the latter from foot cannulation [2, 49]. Considering that the expression profile of lymph is directly linked to the anatomical region from which it is derived, it is likely that these analyses are far from comprehensive [2, 47]. Indeed, differently from plasma, the lymph is enriched with proteins of cellular origin released from the parenchymal cells. The list comprises proteins of nuclear origin, such as histones, proteins involved in the translation and protein synthesis pathways and splicing, and transcription factors [2]. Many cytosolic and organelle-related proteins were also mapped in the lymph. Besides mitochondrial, ribosomal, and endosomal proteins, proteomic reports have identified several cytosolic enzymes, from different carbohydrate, amino acid, and lipid anabolic and catabolic pathways, as well as membrane and cytoskeletal components. These proteins are likely released following cellular apoptosis, as it occurs in parenchymal organs during physiological conditions or during cellular necrosis as well as during pathological conditions associated with infections, autoimmunity, cancer, and trauma.

Although some components of the subcellular proteome have been mapped in the plasma as well [50, 51], the increase in relative abundance reported in the lymph during physiological [2] or pathological [15] conditions highlights the role of the lymphatic fluid as the major conduit for the tissue proteome [48, 52].

11.5.3 Proteins from Extracellular Sources

Extracellular matrix proteins represent the structural component of each tissue and play a pivotal role in conserving tissue morphological integrity, regulation of tissue growth and remodeling, and cellular division and migration and provide a reservoir of cytokines, chemokines, and growth factors [53]. The extracellular matrix undergoes a continuous physiological turnover and processing to accommodate the needs of parenchymal organs. A low level of matrix turnover is observed in every parenchymal organ, associated with cellular apoptosis and immune cell patrolling. This process of dynamic homeostasis is accelerated following a series of pathological stimuli including tissue injury following trauma, acute and chronic inflammatory events, and cancer [53–56]. The extracellular matrix protein turnover is controlled by the activity of specific matrix proteases, including matrix metalloproteinases (MMPs), a disintegrin and MMPs (ADAMs), ADAMs with thrombospondin motifs (ADAMTs [56]), and released

cathepsins. The amount and activity of these proteases rise under several pathological conditions as indicated above [3].

As such, extracellular matrix proteins and fragments thereof are enriched in the lymph as compared to the plasma [2, 3, 15]. Indeed, several proteins including collagens, laminins, fibrosin-1, aggrecan, mucins, fibronectin, and proteoglycans have been mapped in the lymph [2]. Additionally, a vast array of lymph-circulating peptides, generated by extracellular matrix processing by different MMPs (especially MMP2, MMP8, MMP9, and MMP13), has also been reported [2, 3, 5, 57, 58].

11.5.4 The Lymph Proteome in Pathological Conditions

The lymph proteome does not only report the molecular signature from the anatomical region from where the lymph is collected but also displays the molecular signature of disease processes and overall responses to pathological conditions, such as in the case of infections [20, 59–62], inflammation [47, 61, 62] (e.g., pancreatitis or asthma), or traumatic events (such as trauma/hemorrhagic shock [17, 19, 63]).

Animal models of sepsis, following cecal ligation and puncture, resulted in the mapping of 158 distinct proteins, identified in lymph samples from the sepsis group but not in controls [64]. In particular, five proteins, all involved in lipid metabolism/catabolism (apolipoprotein E (ApoE), annexin A1 (Anxa1), neutrophil gelatinase-associated lipocalin (NGAL), S100a8, and S100a9), were particularly upregulated in the lymphatic fluid, proportional to the gravity of the sepsis. Lymph collected from sheep infected with the parasitic nematode *Teladorsagia circumcincta* presented a significant increase in gelsolin, α-1 β-glycoprotein, and hemopexin as compared to mesenteric lymph collected from control sheep [20]. Popova et al. also reported a lymph proteomic analysis conducted on an animal model of anthrax. Following cutaneous exposure to anthrax, the whole proteome analysis of mouse lymph revealed profound changes in the overall proteome with 297 proteins, identified in a semiquantitative manner as much more abundantly expressed in the lymph of infected mice [60]. Lymph collected from rats exposed to LPS clearly indicated the molecular signature associated with the pro-inflammatory event with increases in the levels of TNF-α, IL-1β, IL-6, IL-10, and ADAMST1, all detected only in response to LPS treatment [61]. Similarly, the lymph proteome was altered during taurocholate-induced acute pancreatitis in rats [47] or in response to asthma-inducing diisocyanates [62].

Similarly, proteomic investigations on mesenteric lymph collected in human, as well as in rat/canine models of trauma followed by hemorrhagic shock, indicated the presence of several soluble components associated with a clinical picture of multiple organ failure, present in the lymph but not in the plasma [49]. Notably, contributions in this field include several proteome analyses of pre-shock vs post-shock lymph samples, in the presence or absence of sham controls to distinguish between the signature of trauma and the one of hemorrhagic shock in rat models [3, 17, 19]. Overall, the analysis indicated that after trauma and hemorrhagic shock, a progressive imbalance between the ratios of serine proteases and antiproteases (SERPINs) was observed. The early decrease in the levels of SERPINs was also accompanied by progressive increases in the levels and activity of MMPs increasing the clotting and the post-hemorrhage responses [3, 17,

19]. Additionally, the release of damage-associated molecular patterns (DAMPs) has been reported in the lymphatic fluid in canine models of trauma and hemorrhagic shock [63]. Finally, studies of human response to trauma and hemorrhagic shock performed on mesenteric lymph have confirmed the previous observations on animal models [15, 16].

Altogether these analyses point to the lymph as the biological fluid that best collects the molecular signature of the ongoing physiological and pathological conditions in parenchymal organs. Indeed these studies indicate that tissue-specific antigens are between 500 and 100 times more concentrated in the prenodal lymph as compared to the plasma, overall confirming what was previously thought that the lymph is a unique biological fluid with great potential for biomarker discovery, yet to be fully benefited.

11.6 The Lymph Peptidome

Similar to plasma, saliva, urine, and other biological fluids, the lymph comprises a rich peptidome [48, 65–68]. Several proteomic analyses sequenced many of these peptides, and as expected, they showed that the peptides derive from intracellular organelles (nuclei, mitochondria, ribosomes, and endosomes) as well as the endoplasmic reticulum, Golgi apparatus, and cytosol. Additionally, peptides from processing of plasma membrane receptors, cytokines, chemokines, immunomodulators, coagulation factors, and ECM proteins have also been mapped [48].

Investigation of the processing enzymes generating the lymph-bound peptides identified a variety of proteases including MMPs, cathepsins, caspases, enzymes involved in the innate immune responses such as angiotensin-converting enzyme, complement factor I, granzymes, and enzymes of the coagulation cascade including thrombin, plasmin, and kallikreins. Altogether these processing pathways underscore the richness of the metabolic/catabolic processes occurring in every tissue such as extracellular matrix degradation, processing/cleavage of surface receptors, endosomal/lysosomal processing, and cellular apoptosis [5, 52].

Few of the lymph-carried peptides have been quantified, but their concentration is estimated to be in the nanomolar to low micromolar range for peptides processed from the most abundant proteins, such as collagens, whereas others derived from less abundant proteins present in the low nanomolar range [5]. Finally, it has been shown that most of the peptides found in biological fluids are not present as free peptides, but are bound to chaperones including albumin, lipoproteins, and transthyretin [69]. These peptides exist in equilibrium between their free and bound forms with half-lives estimated to be approximately 1–20 days [69].

11.7 Immunological Role of the Lymph-Carried Proteome and Peptidome

Lymph-transported proteins and peptides, which carry the molecular signature from the organ where the lymph is drained, will encounter different antigen-presenting cells that include tissue resident dendritic cells (DC) and macrophages, lymphatic endothe-

lial cells (LEC), lymph migratory DC, circulating monocytes and B lymphocytes, and cells from the monocyte-macrophage-DC lineages that are resident in the lymph node. These antigen-presenting cells will phagocytize the lymph proteome by fluid phase and receptor-mediated phagocytosis and transport it through the endolysosomal system for processing and loading by the MHC II processing machinery. On the other hand, pre-processed peptides, also circulating in the lymphatic fluid, will be directly loaded on MHC molecule, either at the cell surface or in early endosomes [70–75]. Importantly, proteins acquired through phagocytosis and processed by the endo−/lysosomal compartments will generate an MHC II peptidome mostly through the activity of cathepsins. On the other hand, lymph-circulating peptides directly loaded on MHC I and MHCII surface molecules derive from a variety of different processing pathways, including MMPs, calpains, caspases, and granzymes [5, 76–78]. Thus, altogether, the endosomal and the non-endosomal processing pathways will generate different sets of peptides from the same protein, increasing, qualitatively and quantitatively, the overall presented peptidome.

The self-proteome and peptidome transported by the lymphatic fluid could be important in the maintenance of central and peripheral tolerance [79–87]. Migratory DC can carry antigens from the circulation to the thymus and contribute to T cell negative selection, as well as transport antigen into the lymph node for maintenance of peripheral tolerance. Similarly, nodal DC can present the incoming proteome to mediate peripheral T cell anergy and Treg differentiation as previously reported [79, 90–92]. However, the lymph-carried self-proteome could also be involved in the development of autoimmunity [88, 89, 93]. Several factors can be involved in skewing the balance from tolerance to autoimmunity including peptide MHC II binding affinity/stability, generation of new peptides by de novo processing pathways, changes in the copy number of the presented epitope, and category of antigen-presenting cells.

Indeed, proteomic analyses have underlined changes in the proteome composition between physiological and pathological conditions. Additionally, it has also been shown that following changes in the makeup of issue proteases, as observed in different pathologies, the lymph peptidome/degradome also changes. Taken together, these changes will affect the local concentration of tissue-specific proteins and processing enzymes and ultimately epitopes available for MHC I and MHC II selection and presentation.

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Clinical Diagnosis

Contents

General Overview

Stanley G. Rockson

B.-B. Lee et al. (eds.), *Lymphedema*, https://doi.org/10.1007/978-3-319-52423-8_12

Summary of Basic Concepts

Edema develops whenever the transport rate of interstitial fluid through the lymphatic vasculature is unable to accommodate the rate of interstitial fluid production. Adequate lymphatic function is central to the avoidance of tissue edema. The clinical diagnosis of lymphedema should be reserved for patients in whom there is objectively documented reduction in lymphatic clearance or in whom the classic cutaneous changes of the lymphedema can be demonstrated.

- In lymphedema, the skin thickens and presents a rough texture. Histologically, lymphedema is characterized by epidermal atrophy, dermal fibrosis, variable degrees of dermal edema, and abundant subcutaneous fat with prominent fibrous septations.
- Clinical signs and symptoms of lymphedema are influenced by the duration and the severity of the disease.
- In early-stage lymphedema, the edema pits easily and remits or resolves with elevation of the affected limb. Later, the attribute of pitting edema diminishes and may disappear entirely: elevation and compression progressively become less effective at reducing the excess limb volume.
- Proliferation of dermal and subdermal connective and adipose tissue creates cutaneous thickening and loss of normal elasticity.
- Most of the features of chronic lymphedema can be identified by inspection and palpation of the skin of the affected limb(s).
- In the lower extremities, thickening of the skin at the base of the digits can produce a positive Stemmer's sign and characteristic involvement of the digits.
- Characteristic physical findings of chronic lymphedema include *peau d'orange* changes, hyperkeratosis, papillomatosis, cobblestone deformities, lymph cysts, and chronic inflammatory changes.
- The differential diagnosis of lymphedema includes any pathological condition that predisposes to edema through distortion of the Starling forces.

Edema develops whenever the transport rate of interstitial fluid through the lymphatic vasculature is unable to accommodate the rate of interstitial fluid production (see ▶ Chap. 6). Overproduction of tissue fluid (an enhanced lymphatic load) or diminished ability to remove fluid from the interstitium (impaired lymphatic transport), or both, can contribute to the appearance of edema in the tissues. Clearly, adequate lymphatic function is central to the avoidance of tissue edema, but the clinical diagnosis of lymphedema should be reserved for those settings in which impaired lymphatic clearance can be demonstrated and/or those in which the classic cutaneous changes of chronic lymphedema are readily demonstrable [1].

12.1 Lymphedema Pathology

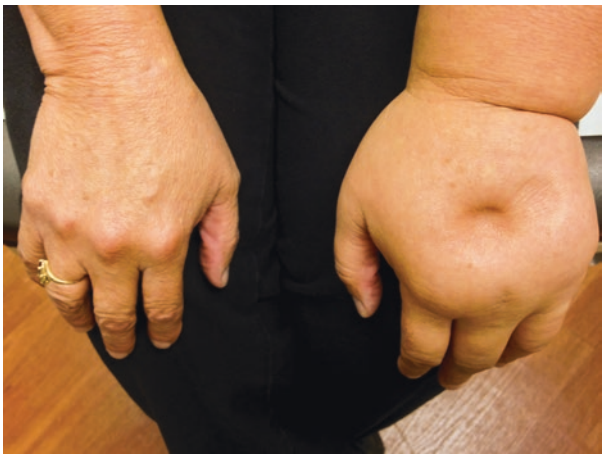
It can be said that any form of tissue edema reflects a relative paucity of lymphatic transport capacity, thereby permitting tissue fluid to accumulate (see ▶ Chap. 17). However, the clinical diagnosis of lymphedema is dependent upon the unique biology that accompanies the edema associated with chronic dysfunction of the lymphatic vasculature [2].

When lymphedema supervenes, the skin quickly thickens and presents a rough texture. Gross examination of cutaneous specimens will disclose the firm, gray appearance of both the dermis and the deep fascia [3]. The layer of subcutaneous fat is exuberant and septated by prominent fibrous strands. Exudation of tissue fluid from the specimen may occur under the influence of externally applied gentle pressure.

Histologic features include epidermal atrophy, dermal fibrosis, and variable degrees of dermal edema [3]. Subcutaneous fat is abundant, with prominent fibrous septa. Perivascular inflammatory reactions are common. When identified, the dermal lymphatics may be observed to be dilated.

12.2 Clinical Presentation

The diagnosis of chronic lymphedema is based primarily upon identification of factors that create the risk for lymphedema; the clinical suspicion can be confirmed by an astute physical examination. Clinical signs and symptoms of lymphedema are influenced, in part, by the duration and the severity of the disease. At the onset of the disease, the physical manifestations will reflect the increasing volume of the interstitial compartment. At this stage, the fluid accumulation is characteristically soft and can be readily displaced (◘ Fig. 12.1) by the external pressure of the examining finger («pitting edema»); in this early stage, the pitting edema will likely decrease or disappear with elevation of the limb.



◘ **Fig. 12.1** Pitting edema in early-stage lymphedema of the upper extremity

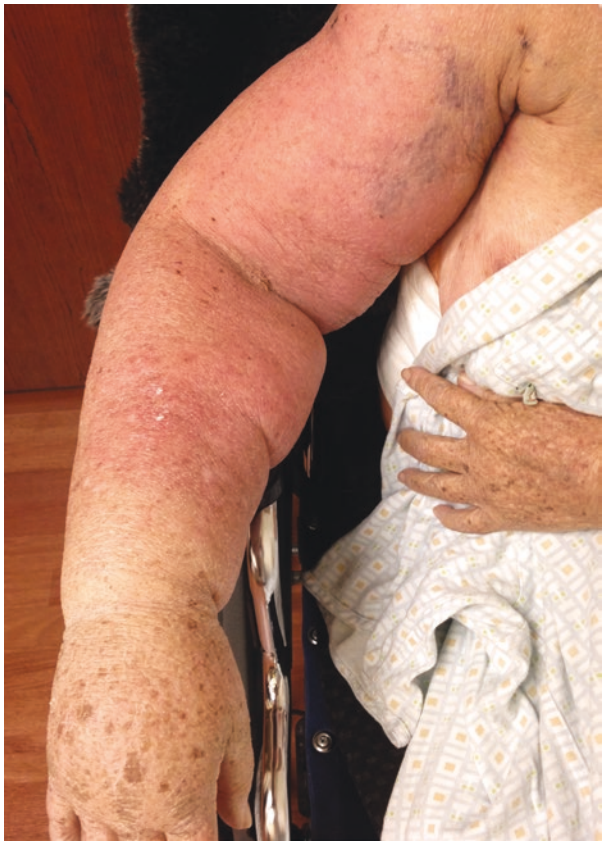


Fig. 12.2 Characteristic changes of malignant lymphedema in metastatic breast cancer

Over the ensuing weeks, months, or years, the lymphedematous limb may acquire a more woody texture as the involved tissues indurate. In these latter stages of lymphedema, the attribute of pitting edema diminishes and may disappear entirely: elevation and compression progressively become less effective at reducing the excess limb volume. Proliferation of dermal and subdermal connective and adipose tissue creates cutaneous thickening and loss of normal elasticity.

Malignant lymphedema (direct, obstructive metastatic spread of cancer to the lymphatic vasculature and nodes) produces a distinct clinical presentation [4]. Here, the development of lymphedema is rapid, and progression is relentless. The malignant form of lymphedema tends to begin centrally, with prominent vascular changes (Fig. 12.2). Often, the tissue is quite firm from the outset, without the soft consistency seen in the early stages of benign lymphedema. Pain is much more prominent than in the benign forms of lymphedema.

Most or all of the attributes of chronic lymphedema can be confirmed through inspection and palpation of the skin. These findings include stretched and prominent cutaneous pores (*peau d'orange*) (Fig. 12.3a), hyperkeratosis (Fig. 12.3b, c), papillomatosis (Fig. 12.3d), cobblestone deformities (Fig. 12.3e, f), and lichenification (Fig. 12.3g), all manifestations of cellular proliferation and fibrosis. Lymph cysts (Fig. 12.3h, i) may be observed, and chronic inflammatory changes may also be present (Fig. 12.3j, k).

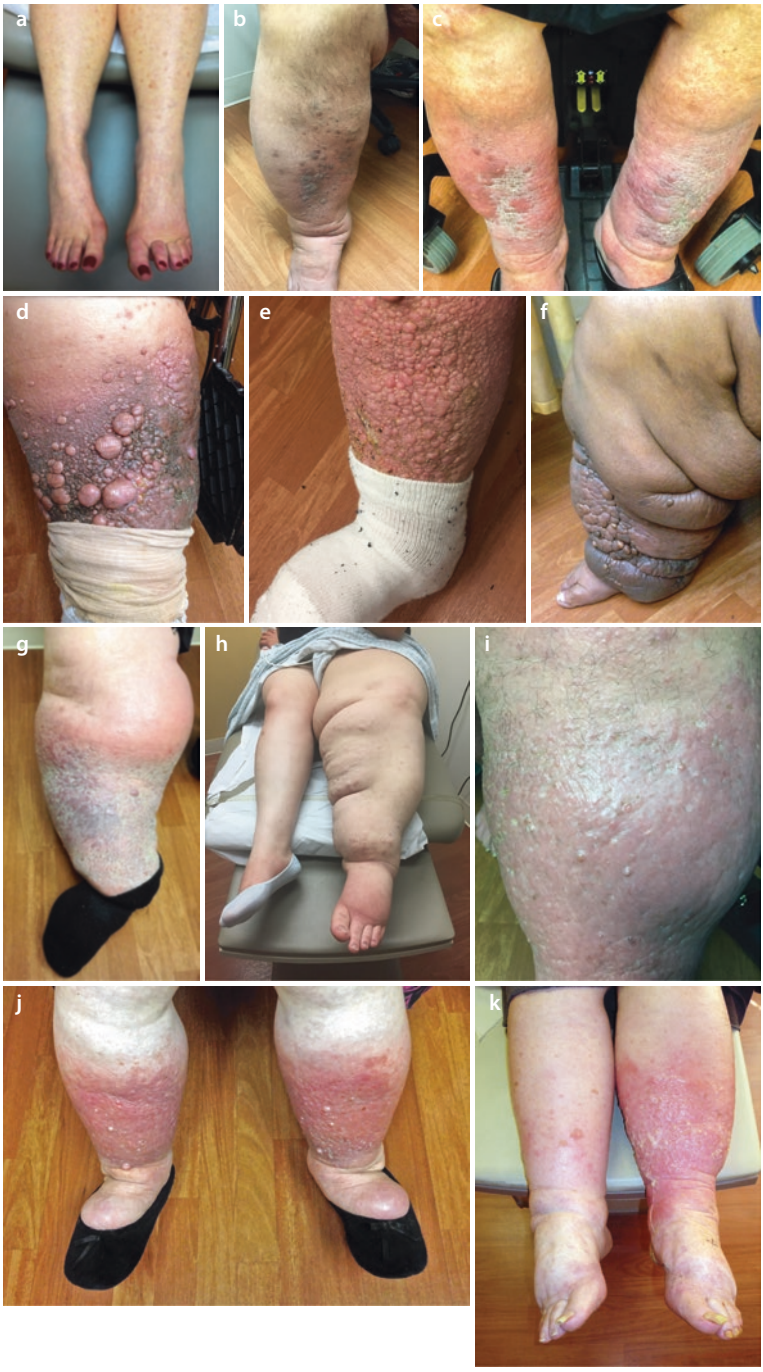


Fig. 12.3 Typical changes of chronic lymphedema include *peau d'orange* **a** hyperkeratosis **b**, **c** papillomatosis **d** cobblestone deformities **e**, **f** and lichenification **g** all manifestations of cellular proliferation and fibrosis. Lymph cysts **h**, **i** may be observed, and chronic inflammatory changes may also be present **j**, **k**

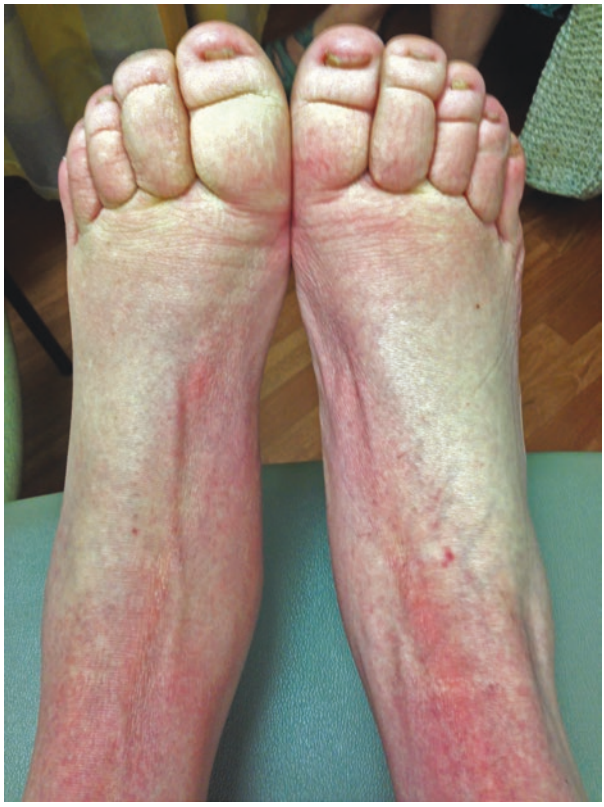


Fig. 12.4 Prominent involvement of digits, with squaring off of the toes, can be characteristic of lower extremity lymphedema

When the lower extremities are involved, additional clinical features may include prominent involvement of the digits, leading to a very characteristic squaring off of these structures (Fig. 12.4). In primary lymphedemas, the integrity of the nail plate itself may be compromised. Thickening of the skin at the base of the digits can produce a positive Stemmer's sign [1, 5, 6]. This physical finding, described as the inability to tent the skin at the base of the digits, is considered to be pathognomonic of lymphedema, but the positive and negative predictive value of this finding has been questioned [2, 3, 7].

Lipedema is a condition that in its most superficial aspects resembles lymphedema of the lower extremities (see ▶ Chap. 18); however, in lipedema, the enlargement of the lower limbs is caused by a pathological accumulation of subcutaneous adipose tissue [1]. The feet are characteristically spared, providing an attribute that readily distinguishes this problem from lymphedema (Fig. 12.5). Patients are almost exclusively female, which strongly suggests a hormonal substrate to this entity.

The differential diagnosis of lymphedema includes any pathological condition that predisposes to edema through distortion of the Starling forces (see ▶ Chap. 17). The

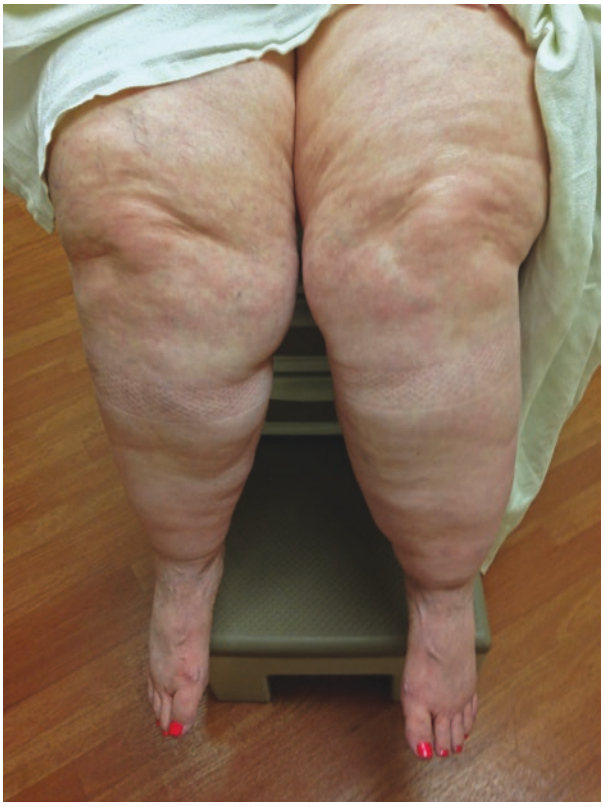


Fig. 12.5 Lipedema superficially resembles lymphedema, but is characterized by sparing of the feet and other typical attributes

list of relevant entities embraces many systemic disorders, including congestive heart failure, hypoproteinemia, chronic liver disease, and others. Pragmatically, the focus of the differential diagnosis most commonly will involve the discrimination of lymphedema from chronic venous disorders (with the recognition that these can also produce lymphedema as a late aftermath). In fact, the hypertrophied limb with the thickened skin of chronic lymphedema has little similarity to the edematous limb of deep venous insufficiency. In the latter case, a soft pitting edema is prominent and seen in association with stasis dermatitis, hemosiderin deposition, and superficial venous varicosities (Fig. 12.6a); dependent rubor is frequently present (Fig. 12.6b). The history and examination should help to easily differentiate chronic lymphedema from the venous disorders that produce swelling of the limb (see ▶ Chap. 17). Of course, early in the presentation of these disorders, it may be more difficult to distinguish lymphedema from venous disease, complex regional pain syndrome, or other nonsystemic causes of limb swelling. In such cases, imaging modalities may become necessary to confirm the presence of lymphatic dysfunction or obstructive anatomy (see ▶ Chaps. 21–27).

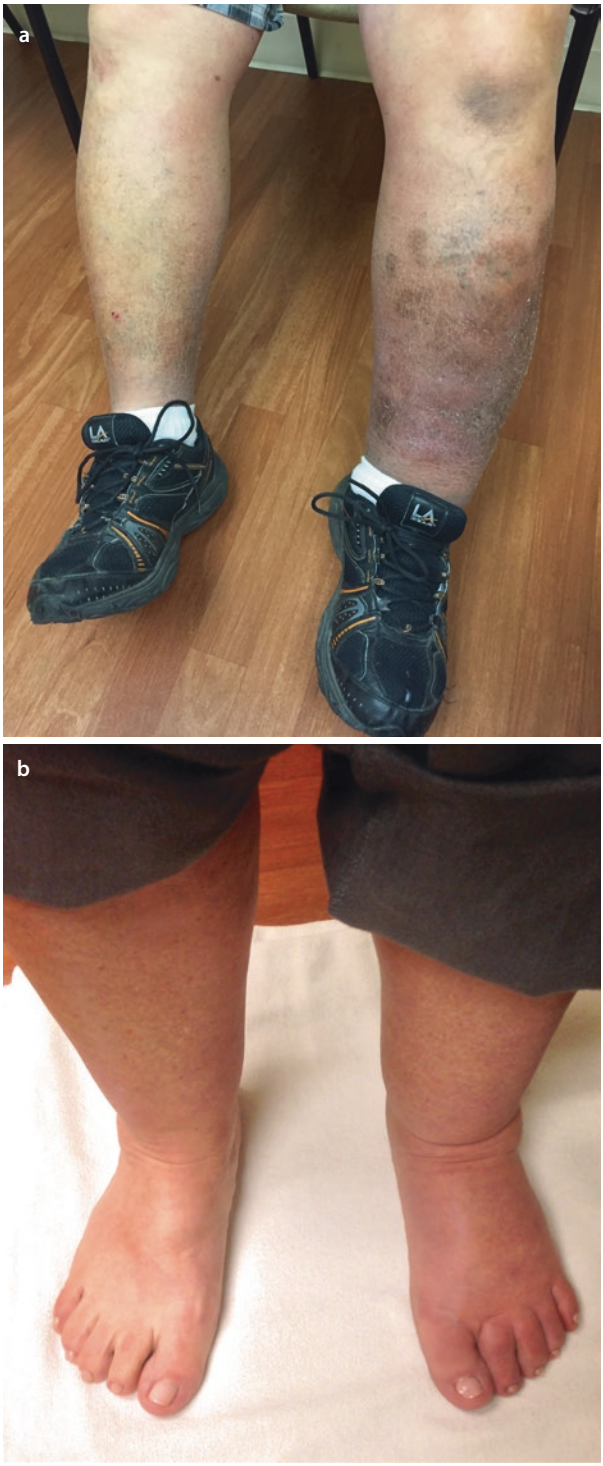


Fig. 12.6 Chronic venous edema is characterized by stasis changes, cutaneous hemosiderin deposits, and dilated superficial veins **a** dependent rubor may be present **b**

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Lymphedema Epidemiology

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Summary of Basic Concepts

- Lymphedema remains an under-recognised and under-resourced aspect of healthcare internationally.
- It is important to measure the prevalence and impact of lymphedema in different populations to be able to quantify the real healthcare needs of people with this condition.
- In prevalence studies, it is important that the population is well defined and a standard definition of the term lymphedema/chronic edema is used.
- Chronic edema is defined as «edema of any body site present for at least 3 months».
- A study carried out in the Midlands of the UK reported a crude prevalence of 3.93/1000. It was higher in those aged over 65 years.

13.1 Background

Lymphedema has been a neglected area of healthcare for a long time. This has largely occurred because it has been considered to be a rare condition, which causes little morbidity, is not fatal and cannot be treated. This has resulted in a lack of investment in both service provision for the diagnosis and management of lymphedema and in research into the causes and treatment of lymphedema.

In recent years, this situation is beginning to change with an increased recognition of the greater prevalence and impact of lymphedema worldwide. In addition, the successful management of this long-term condition has been shown to reduce morbidity and the incidence of complications such as cellulitis.

Despite these developments, there are only a few countries in the world, which have developed a strategic framework for the diagnosis and management of lymphedema, and most countries face difficulties with patchy service provision and a lack of reimbursement for lymphedema treatment.

In many developed countries, the focus of lymphedema management and research has been on that resulting from the treatment of cancer. It is only in recent years that causes of lymphedema other than cancer have been given greater attention, and it is now recognised that cancer-related lymphedema constitutes only a minority of the total cases.

Nevertheless, there is still an urgent need for further data on the prevalence, causes and impact of lymphedema throughout the world. Without these data, it is difficult to persuade governments and health insurance schemes to provide resources to treat this condition and reduce the risk of its development.

This chapter will consider methodologies for determining the prevalence of lymphedema and will describe the results of some UK studies. Details of the incidence and prevalence of lymphedema related to specific conditions such as filariasis and different cancers can be found in other chapters in this book.

13.2 Methodology for Determining Prevalence

The prevalence of a condition in the population at one point in time (point prevalence) is a measure of how common that condition is. Crude prevalence is a measure of all people with the condition at that time point. This does not take into account any variation in prevalence which may occur in the population such as with age or gender. Measuring differences in prevalence in different age groups, for example, allows standardisation of the prevalence calculation. This in turn enables comparisons to be made between prevalence in different populations taking into account different age distributions.

Comparison between prevalence data from different settings is also facilitated by clearly defining the population in which the prevalence was measured and having a consistent definition of the condition concerned.

13.2.1 The Population

To measure how common lymphedema is in a given country, the number of people with lymphedema in the population of that country would need to be determined at a given time point. Population-based studies are difficult to carry out from a practical point of view and are also expensive. Alternative methods can, however, yield useful information. One such method is to measure the number of people with lymphedema known to healthcare professionals in a given population. However, this assumes that all people with lymphedema are known to local health services. Unfortunately, given the lack of awareness of this condition amongst healthcare professionals and the general public, it is likely that many people with lymphedema are not known to health services. Hence, studies using this approach may underestimate the true prevalence.

Furthermore, in an ideal situation, there would be some form of routine health service data collection or a register of those with lymphedema which could then be interrogated to determine the prevalence easily. Unfortunately, although in some countries, e.g. the UK, databases of different diseases/conditions are kept by primary healthcare practitioners, lymphedema is not routinely accurately recorded in these.

Therefore, case ascertainment methodology, which involves carrying out a survey of healthcare professionals in a given population, asking them for details of people known to them with lymphedema, is an appropriate compromise. However, without a routinely kept accurate register, this method relies upon the memories and records of the healthcare professionals involved.

This approach can also be used to determine the prevalence of lymphedema in smaller populations such as those with another clinical condition where chronic swelling is known to occur, e.g. multiple sclerosis (MS) [6]. Such studies require access to a database of those with the other condition, e.g. MS, which is kept accurately and up to date, to define the population (denominator) being investigated.

Prevalence can relatively easily be measured in defined healthcare settings such as hospitals or care homes where the population is fixed over a short time period. In this situation, a visiting team of researchers can determine the number of people with clinically assessed lymphedema and derive an accurate estimation of the prevalence in that setting.

In other clinical areas, e.g. breast cancer treatment, the measurement of the incidence of lymphedema/the risk of developing lymphedema is important. The incidence of a condition is the number of new cases of that condition over a given time period. In the example of breast cancer-related lymphedema, the condition most commonly develops within 2–3 years of the initial cancer treatment, but it is known that some women do not develop lymphedema until many years later even in the absence of recurrent disease. This means that in studies of incidence where the lifelong risk of developing breast cancer-related lymphedema is being determined, the time period of follow-up must be sufficiently long to give the most accurate estimate. Furthermore, when comparing results of different studies aiming to reduce the incidence of lymphedema after breast cancer treatment, the length of follow-up must be taken into account.

13.2.2 The Condition

Whether measuring prevalence or incidence, it is important that the diagnosis of «lymphedema» is defined and used consistently. This has been clearly illustrated in the case of lymphedema following breast cancer treatment where a number of different definitions of lymphedema judged by limb volume changes following surgery compared with preoperative measurements have been used [7].

The incidence of lymphedema at 30 months postoperatively was:

- 67% – if lymphedema was defined by a 200 ml change from baseline
- 45% – if a 10% increase in volume from baseline
- 91% – if >2 cm difference in arm circumference at any one point
- 41% – based on symptoms of heaviness or swelling

13.3 Definition of Lymphedema/Chronic Edema

The term «lymphedema» is defined as edema which develops as a result of failure of lymphatic drainage. When using the term lymphedema, many healthcare professionals think of cancer-related lymphedema and, sometimes, primary lymphedema. Edema arising from venous disease is not always considered to be a secondary type of lymphedema, although there is evidence of lymphatic failure in chronic venous disease with edema and sometimes the term phlebolymphedema is used [8].

In many clinical situations such as in the elderly with multiple comorbidities, a number of factors may contribute to the aetiology of chronic swelling, e.g. immobility, heart failure, chronic venous hypertension, drugs, etc., and not many healthcare professionals would consider this swelling to be lymphedema. However, this type of chronic swelling does involve failure of lymphatic drainage and also causes significant morbidity. It, therefore, should be included in studies of prevalence.

Furthermore, in some types of lymphedema which have previously been considered to be purely due to problems with lymphatic drainage, e.g. breast cancer-related lymphedema and some types of primary lymphedema such as lymphedema-distichiasis, there is growing evidence of a more complex aetiology including a venous component. In breast cancer-related lymphedema, venous flow may be impaired [9], and in lymphedema-distichiasis, there are malfunctioning lymphatic and venous valves [10].

In light of this, the term «chronic edema» was defined for use in a prevalence study carried out in London [1].

«Chronic edema is a broad term used to describe edema which has been present for more than 3 months and involves one or more of the following areas: limbs, hands/feet, upper body (breast/chest wall, shoulder, back), lower body (buttocks, abdomen), genital (scrotum, penis, vulva), head, neck or face».

«Chronic edema» can be considered to be an umbrella term which includes conventional «lymphedema» but also chronic swelling which may have a more complex aetiology.

It therefore includes:

- Lymphedema (primary and secondary)
- Venous edema (phlebolymphedema)
- Chronic swelling due to immobility
- Edema related to advanced cancer
- Chronic swelling associated with lipedema
- Chronic swelling related to obesity
- Chronic swelling due to heart failure
- Chronic swelling associated with rare vascular malformations such as Klippel-Trénaunay syndrome
- Many other types of chronic swelling

Classifying chronic edema into different subtypes can be useful in clinical settings. Table 13.1 shows the breakdown of the predominant cause of chronic edema recorded in patients attending a lymphedema service in Derby, UK. The figures should not be considered representative of the total chronic edema population as they will be dependent upon the types of edema referred to the service. For example, many people with chronic edema associated with venous leg ulcers are managed by specific leg ulcer clinics. Nevertheless, this approach can be used to demonstrate the «case mix» of the service and trends over time.

13.3.1 The Pathophysiology of Chronic Edema

In recent years, our understanding of the physiology of tissue fluid formation and drainage has developed further.

The Starling model proposed that fluid flow out of capillaries into the tissues was governed by the net outcome of opposing pressures across the capillary wall. The pressures concerned are the hydrostatic pressure and the colloid osmotic (oncotic) pressure gradients. The hydrostatic pressure gradient is the physical pressure inside the capillary compared with that outside. The colloid osmotic pressure arises from the attraction of

Table 13.1 Underlying cause of chronic edema in patients attending a specialist outpatient lymphedema service

Classification/underlying cause	Number	Percent
Secondary lymphedema (cancer, infection, inflammation, trauma, etc.)	246	39
Immobility related	169	27
Primary lymphedema	80	13
Venous disease	60	10
Other (not classified elsewhere)	43	7
Edema of advanced cancer	13	2
Lipedema	8	1
Heart failure	7	1
Total	626	

water by proteins, and therefore the pressure gradient is due to the difference in protein concentration between the plasma and the tissue fluid. The flow rate is also governed by the permeability of the capillary wall.

In the original model, estimates of these pressure gradients available at that time suggested that there was an outflow of fluid from the arteriolar end of the capillary and reabsorption of fluid into the venous end of the capillary, with only approximately 10% of the tissue fluid being drained through the lymphatic system.

A more recent, more sophisticated understanding of the ultrastructure of capillaries and more accurate measurements of the various pressures involved have led to a revision of these ideas. It is now thought that in the steady state, in most capillary beds, there is a net outflow of fluid all along the capillary with no reabsorption at the venous end. This means that all of the excess capillary filtrate and macromolecules in the interstitial space is taken up by the lymphatic vessels [2].

This gives the lymphatic system a greater role in tissue fluid homoeostasis than has been previously understood.

Edema arises when capillary filtration exceeds lymphatic drainage. If lymphatic drainage is reduced and capillary filtration is normal, edema develops (conventional lymphedema). If capillary filtration is increased, e.g. in chronic venous hypertension, then the lymphatics drain more fluid to prevent edema formation. In this situation, edema only develops when capillary filtration exceeds the maximum capacity of the lymphatics to drain fluid. A similar situation occurs in hypoalbuminaemia, e.g. in advanced cancer, where capillary filtration is increased. It is clear, therefore, that all edema has a lymphatic component, whether it is due primarily to a lymphatic problem or to other factors, which cause an increase in capillary filtration.

Furthermore, it could be argued that all «chronic edema» should be considered to be «lymphedema». In this case, all of the more complex types of chronic edema, e.g. that due to venous disease, advanced cancer, etc., would be considered to be types of secondary lymphedema.

From a clinical viewpoint, whichever term is used, «chronic edema» or a broader understanding of the term «lymphedema», it is still important to consider the underlying factors which may be causing the swelling as this may influence treatment and risk reduction/prevention.

When considering studies of prevalence, it is again important that the broader meaning of the term «lymphedema» and the term chronic edema are used synonymously to encompass the more complex aetiology of chronic swelling. It is essential that a common definition is used so that the results of prevalence studies are compared. In publications of prevalence studies to date, some use the term «lymphedema», some «chronic edema» and others «chronic edema/lymphedema» [1, 3, 11, 12].

13.4 The Findings of Prevalence Studies

The first study to use the definition of chronic edema was reported in 2003 [1]. The aim of the study was to determine the magnitude of the problem of chronic edema in an urban area of London and to assess the impact of edema on use of health resources, employment and patients' quality of life. The study used a questionnaire-based survey given to health professionals followed by an interview with a random sample of patients. Health professionals from dedicated lymphedema services, specific outpatient clinics, hospital wards and community services (GP clinics and district nurses) were contacted to provide information on patients from within South West London Community Trust known to suffer with chronic edema of greater than 3 months duration. A subset of the identified patients were interviewed and clinically assessed.

Within the catchment area of with a general population of 240,000, 823 patients had chronic edema (crude prevalence 1.33/1000). Prevalence increased with age (5.4/1000 in those aged >65 years) and was higher in women than men (2.15 vs. 0.47/1000). Only 529 (64%) were receiving treatment, despite two specialist lymphedema clinics within the catchment area. Of 228 patients interviewed, 78% had edema lasting >1 year. Over the previous year, 64/218 (29%) had had an acute infection in the affected area, 17/64 (27%) being admitted for intravenous antibiotics. Mean length of stay for this condition was 12 days, with an estimated mean cost of £2300. Edema caused time off work in >80% and affected employment status in 9%. Quality of life was below normal, with 50% experiencing pain or discomfort from their edema. Extrapolating these figures to the national population, it was estimated that at least 100,000 patients were suffering in the UK alone, yet this is a problem poorly recognised by health professionals.

This methodology has been repeated more recently in an urban population of the East Midlands in the UK [4]. This cross-sectional study was carried out in Derby City, which has a population of approximately 247,100. Data were obtained from ten sources, namely, the inpatients of one acute and one community hospital, one specialist and

three non-specialist outpatient clinics (dermatology, plastic surgery and diabetic foot clinic), all community nursing services, general practices ($n = 41$) and nursing/residential homes ($n = 26$) in the Derby City catchment area.

Within the study population of Derby City residents, 971 patients were identified with chronic edema (estimated crude prevalence 3.93 per 1000, 95% CI 3.69–4.19). The prevalence was highest amongst those aged 85 or above (28.75 per 1000) and was higher amongst women (5.37 per 1000) than men (2.48 per 1000). The prevalence amongst hospital inpatients was 28.5%. Only 5 (3%) patients known to community services had edema related to cancer or cancer treatment. Of the 304 patients identified with edema from the Derby hospitals or community health services, 121 (40%) had a concurrent leg ulcer.

Data obtained from this East Midlands study differ greatly from those obtained previously [1] even though the same methods were adopted. In the 2003 London study, the crude prevalence was approximately one third of that reported here. When standardised to the population of England, this difference was reduced to slightly less than three times that observed in London, with adjusted rates for Derby City and South West London of 4.15/1000 and 1.55/1000, respectively. It is unlikely that this difference can be attributed to methodological discrepancies or significant variations in the populations studied, as both samples were derived from an urban community. It is possible that differences in characteristics of the population other than age and gender, such as obesity, may be partially responsible for the higher prevalence. Other findings were comparable to the earlier London study, for example, the prevalence of chronic edema was much higher amongst women than man. It was also more prevalent amongst the obese (Derby study data) and was highest amongst people aged over 85 years.

Analysis of the subsets for which site of swelling was identified (889 patients identified) indicates that the proportion of patients with lower limb edema was much higher in Derby City compared with South West London. This may be a result of a higher awareness of chronic edema in Derby and/or higher rate of referral of patients with lower limb edema to the Derby service compared with that in South West London. If this is the case, some of the difference in overall estimated prevalence could be attributed to greater identification of lower limb edema rather than a true higher overall prevalence.

Nearly a third of the hospital inpatient population had chronic edema, which highlights that a number of other medical conditions are associated with its occurrence and that it can develop through a number of underlying pathophysiological mechanisms. This finding also dispels the commonly held belief that chronic edema is confined to community-based populations and services. Whilst it is well recognised that many community patients have venous leg ulceration, this study highlights that many of these cases have concurrent chronic edema, an association which has received scant attention to date.

The East Midlands data support the hypothesis that obesity is a common problem amongst patients with chronic edema in specialist services. Whilst it is not certain why chronic edema and obesity coexist, a number of mechanisms have been postulated. These include impaired lymphatic flow, chronic inflammation, elevated production of interstitial fluid and reduced mobility. Obesity is also implicated in the development of chronic edema amongst people with cancer and those with other long-term conditions,

particularly those who are wheelchair users. In a case record review of patients with spina bifida, for example, 9.2% had chronic edema. This was estimated to be approximately 100 times higher than in the general population [13].

One limitation of this study is that comprehensive data could not be obtained from general practices as diagnostic codes have not been created for chronic edema in the UK health service. Poor recognition and limited knowledge of chronic edema may have limited the number of patients identified, particularly in nursing/residential home settings where opportunities for continuing education are limited and the proportion of qualified staff is low. Of greater importance is the lack of awareness of chronic edema amongst the general population, as this limits the number of people who present to health services. It is very difficult to estimate the true percentage of the population that have chronic edema, particularly as symptoms can develop at a relatively late stage. A major strength of this study is that patients were surveyed in all public health service settings available to Derby City residents and all nursing/residential homes.

Although it is probable that the true prevalence of chronic edema is even higher than estimated here, the findings of this study clearly illustrate that chronic edema presents a major public health concern which has implications for the delivery of many health and social services.

Other attempts to classify the patient population have been undertaken in specialist services treating lymphedema and chronic wounds, e.g. in the UK and Canada [11, 12].

13.5 LIMPRINT: An International Prevalence Study

An international epidemiological initiative (LIMPRINT) is currently underway and aims to provide further data on the scale of chronic edema in health services in an effort to improve care provision for patients across the world. The strength of this initiative is that it uses an internationally agreed and validated methodology in all participating sites and countries allowing comparison within and between populations.

A recent systematic review has indicated that there is a dearth of population-based epidemiological studies to define the prevalence of chronic edema and little robust evidence of the cost and clinical effectiveness of different models of care [5]. It is therefore difficult for those who commission services, and other healthcare agencies, to determine treatment priorities and to justify the provision of clinical services for people with chronic edema or to reimburse care costs.

Because of these persistent gaps in evidence, LIMPRINT is designed to estimate the prevalence and impact of chronic edema in heterogeneous adult populations in a number of countries in Europe, as well as in North America, Japan and Australia. It also aims to estimate the proportion of patients with chronic edema who also have a wound in the same anatomical region. The countries involved are members of the International Lymphedema Framework (ILF).

The ILF is a UK-based charity, and its aim is to improve the management of chronic edema and related disorders worldwide through the sharing of expertise and resources and by supporting individual countries to develop a long-term strategy for the care and management of chronic edema. The ILF comprises member countries that subscribe to the ideals of the ILF and have developed their own independent National Lymphedema

Framework (NLF). A NLF is a partnership of stakeholders within a given country who are dedicated to improving chronic edema care.

Data are collected using a core tool to determine the prevalence of chronic edema and a set of five module tools to assess the impact of chronic edema on the lives of sufferers. The data are entered into a secure central online database, which will provide reports for each participating country as well as giving an international perspective of the prevalence of chronic edema and its impact.

LIMPRINT is a two-phase project. Phase 1 took place between June 2013 and June 2014 and consisted of the development and validation of the assessment tools followed by piloting them in two countries and the construction of the online database. Phase 2 began in June 2014 with data being collected in eight countries from a variety of settings including hospitals, care homes, local communities and lymphedema services. The final dataset is expected to exceed 15,000 people, and it is planned to report the results in June 2017.

The data from LIMPRINT will be used to inform the case for improved care. Already, preliminary results dispel the myth that chronic edema is rare but instead indicate that it is a growing global healthcare problem affecting many patient populations and is found in all parts of health and social care sectors. Naturally occurring changes in Western populations such as increasing age, obesity, immobility and concurrent chronic illnesses all indicate that this problem will escalate over the coming decades and an appropriate public health response is urgently needed.

Conclusions

Data from well-conducted studies of the prevalence and impact of lymphedema/chronic edema are essential in the process of convincing health service commissioners/funders that this is a common condition which causes significant morbidity and a reduction in quality of life and is, therefore, worthy of investment in service provision and research. It is important to use standard definitions of the condition and clearly define the population studied in order to produce data, which can be compared across different health settings and countries.

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Clinical Staging

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Summary of Basic Concepts

- Although there are guidelines of international scientific societies (ISL, UIP), which show the same clinical staging, in many countries and by many schools, continue to be used classifications of stages «personalized» (tailored).
- The chapter describes the main proposals currently being used by the various operators, emphasizing, however, the opportunity to use a common language, universally shared, which is identified in four stages (from preclinical stage to complicated elephantiasis) of ISL's classification, drafted, and constantly updated by the world's leading experts in the field.
- In addition to International Society of Lymphology staging, described here are the proposals of clinical stagings of German, Italian, Japanese, and Brazilian scientific societies.

The problem of the staging of lymphedema is a perennial topic for discussion at consensus meetings within national and international congresses. First of all, for definitions and scope of pathology to be universally accepted, the requirements of simplicity, recognizability, and worldwide utilization must be met.

Four proposals based on different clinical and instrumental aspects of pathology have been presented at the international level, yet only some of the attributes are common to all. Through the work of a special world commission, a synthesis of the different proposals will provide scientific communication with universally recognized and accepted parameters.

Primary and secondary lymphedemas have different clinical stages of evolution, in part mutually reversible, that influence affected patients differently from the physical, emotional, and psychological points of view.

Achieving common acceptance of stages of lymphedema, as in other diseases, seems to be a problem that cannot be postponed further for reasons of «scientific communication» and for the undoubted medicolegal and social impact. In more advanced clinical stages, the condition takes on the characteristics of a real «social disease,» the costs of which are generated both from medical care and from loss of productive capacity.

The clinical staging, reported in the «consensus document» of the International Society of Lymphology [1], currently includes four clinical stages (Table 14.1); it

Table 14.1 Staging according to the «consensus document» of the International Society of Lymphology

Clinical stage	Evidence
0	Subclinical with possible clinical evolution
I	Edema regressing with treatments with positive pitting test
II	Edema partially regressing with treatments with negative pitting test
III	Elephantiasis with cutaneous complications and recurrent infections

initially included three clinical stages (I, II, and III), but, recently, motivated by our Italian classification [2, 6–8], which underscored the importance of including the «preclinical» aspect of the primary and secondary types of lymphedema, potentially progressive (e.g., mastectomy with coincident limbs), the preclinical stage, defined as stage 0, was included. Stage 0 refers to a latent or subclinical condition, where swelling is not evident despite impaired lymph transport. Stage I represents an early accumulation of fluid relatively high in protein content (in contrast to «venous edema») that subsides with limb elevation. Pitting may occur. Stage II signifies that limb elevation alone rarely reduces tissue swelling and that pitting is manifested. Stage III encompasses lymphostatic elephantiasis where pitting is absent and trophic skin changes, such as acanthosis, fat deposits, and warty overgrowths, develop. The severity of the stages is based on the volume differences: minimal (<20% increase), moderate (20–40% increase), and severe (>40% increase). These stages only refer to the physical condition of the extremities.

Some healthcare workers examining disability utilize the World Health Organization's guidelines for the International Classification of Functioning, Disability, and Health (ICF). Quality of life issues (social, emotional, physical inabilities, etc.) may also be addressed by individual clinicians and can have a favorable impact on therapy and compliance [9].

At the recent XX World Congress of the International Society of Lymphology, held in Brazil, in a Special Consensus session, a special world commission was organized to finalize a new, official staging of the International Society [6].

In Germany, led by Prof. Ethel Foeldi, four clinical stages [4] have been introduced for the first time, adding to those reported in the actual «consensus document» a stage 0, which represents all cases of subclinical lymphedema, but with a significant risk of clinical progression (e.g., lymphoscintigraphy strongly predictive; Table 14.2).

Since 1994 [6], five clinical stages have been recognized in Italy (Table 14.3). This system emphasizes the importance of preclinical cases at risk of evolution (in stage I) and cases of elephantiasis with major chronic inflammatory and infectious complications and risk of neoplastic tissue degeneration (stage V). Depending on the stage, it is also possible to direct the therapeutic treatment toward the corresponding preventive options [10].

In Japan, a team led by Prof. Moriji Ohkuma, a dermatologist with heightened sensitivity to infectious complications in cutaneous and subcutaneous tissues, proposed four-phase staging involving inspection and palpation of the affected areas and of

Table 14.2 Staging according to the German Society of Lymphology (Prof. E. Foeldi)

Clinical stage	Evidence
0	No edema, but evidence of a risk condition for evolution
I	Edema regressing with treatments with positive pitting test
II	Edema partially regressing with treatments with negative pitting test
III	Elephantiasis with cutaneous complications and recurrent infections

Table 14.3 Staging according to the Italian Society of Lymphangiology (Michelini-Campisi)

Clinical stage	Evidence
I	No edema in individuals at risk (preclinical)
II	Edema that regresses spontaneously with elevation and with night rest
III	Edema that does not regress spontaneously, only with treatments and partially
IV	Elephantiasis (abolition of tendon and bone projections)
V	Elephantiasis complicated by cutaneous and recurrent infections and impairment of deep body structures (muscles, joints)

Table 14.4 Staging according to the Japanese Society of Lymphology (Prof. M. Ohkuma)

Clinical stage	Inspection	Palpation	Acute dermo-epidermitis	Prognosis
I	Normal	Pitting ++	Absent	Temporary
II	Thin skin	Increase in thickness, pitting +	Absent	Permanent
III	Cutaneous lichenification	Increase in thickness, pitting –	Present	Worsening
IV	Verrucosis	Pitting absent	Very often	Worsening

assessing the frequency of the infectious episodes and inflammatory complications; based upon the developmental stage, it is possible to obtain prognostic information (Table 14.4). This is obviously a staging with a more strictly dermatological point of view; while clinical, it is conceptually valid, since it considers some clinical and inflammatory aspects, complications that are frequently found in patients with both primary and secondary forms of lymphedema [3, 5, 11].

The staging proposed in South America and, in particular, in Brazil by Prof. Mauro Andrade is of substantial interest because, in addition to taking into account the importance of preclinical cases at risk of development of infectious and degenerative complications, it also analyzes the functional effects of edema on the limb with impairment of one, two, or three major joints (Figs. 14.1, 14.2, 14.3, 14.4, and 14.5). This aspect also permits better definition of the commitments of global functional rehabilitation, the degree of care needed by the patient, and the impairment in «daily living activities» (Table 14.5). This classification thus utilizes both clinical and functional criteria for patient assessment [3].

It should be emphasized, however, that the new Brazilian proposal addresses deficiencies that have been recognized in other stages so far presented.

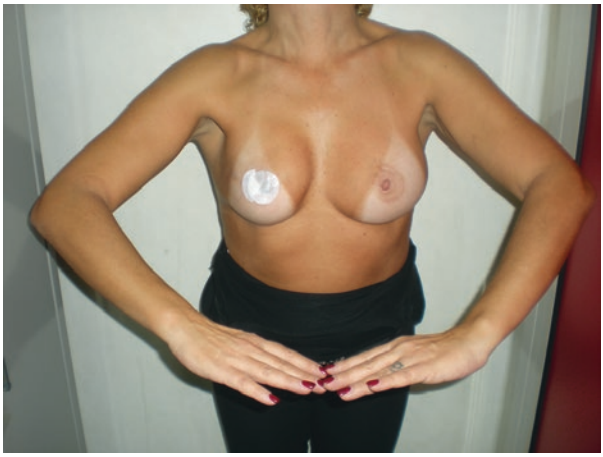

Fig. 14.1 Lymphedema stage 0 (preclinical)

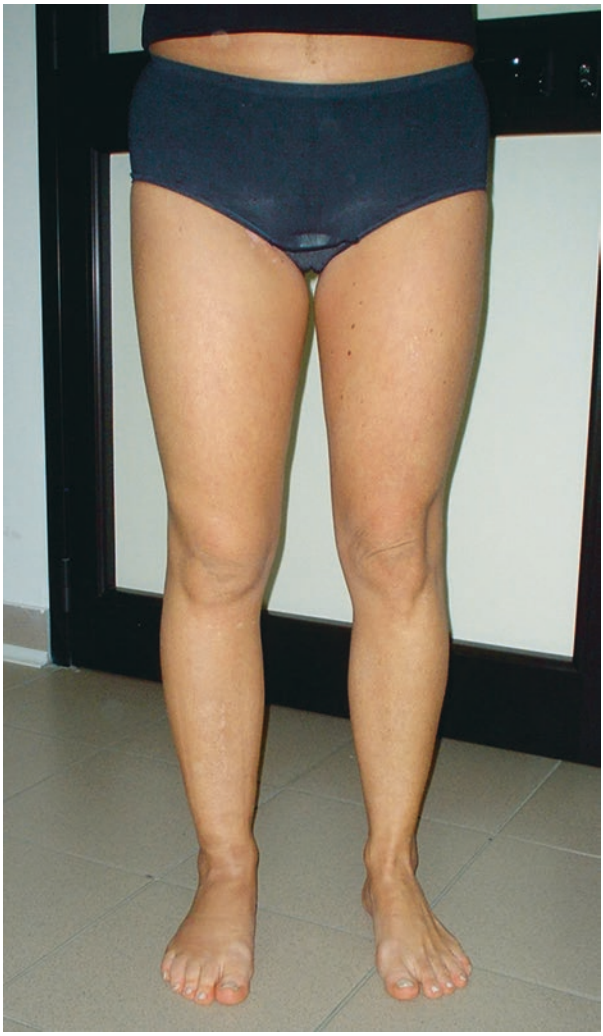

Fig. 14.2 Lymphedema stage I (involvement of one major joint)

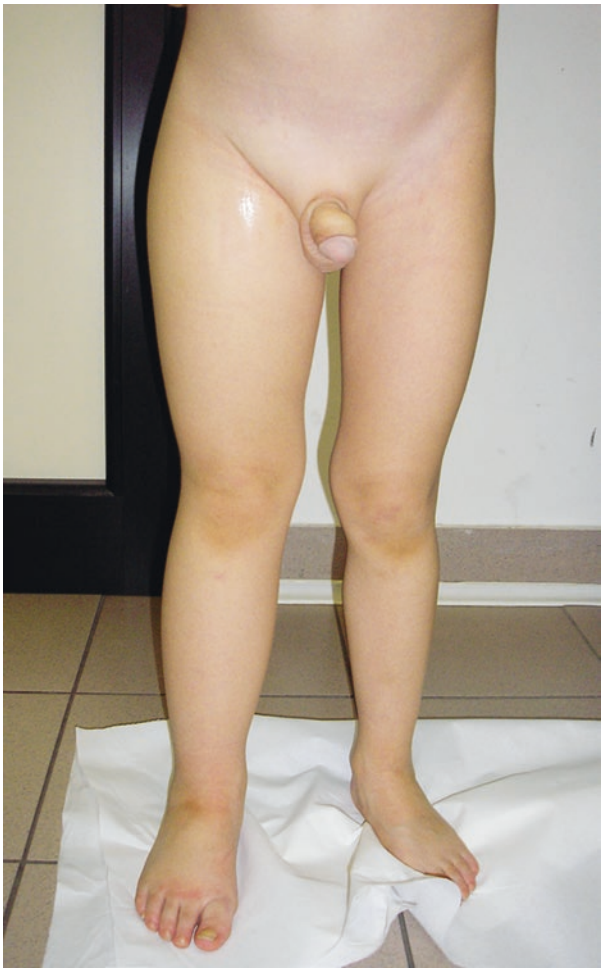

Fig. 14.3 Stage II (involvement of two major joints of the limb)

The respective positions of the «experts» at such a delicate and transitional moment for both public and private health systems in different countries also stem from the need to redefine welfare parameters for these highly prevalent diseases [12]. At more advanced stages of disease, in fact, we can identify the extremes of a true social disease for which the health system must provide incentives and normative facilitations comparable to the other diseases for which such benefits and advantages are provided.

It is pointless to say that, currently, many national healthcare systems provide therapies to patients with both primary and secondary lymphedema in an inequitable manner, with poor distribution of healthcare resources. In most countries, the costs of materials, elastic garments, and phlebo-lymph-active drugs are charged to the patient.

Thus, it is essential to solve these problems in each country at a governmental level. Epidemiological studies are still insufficient and must be updated in order to better define a problem that for too long has been totally ignored, while the number of patients affected is increasing daily.

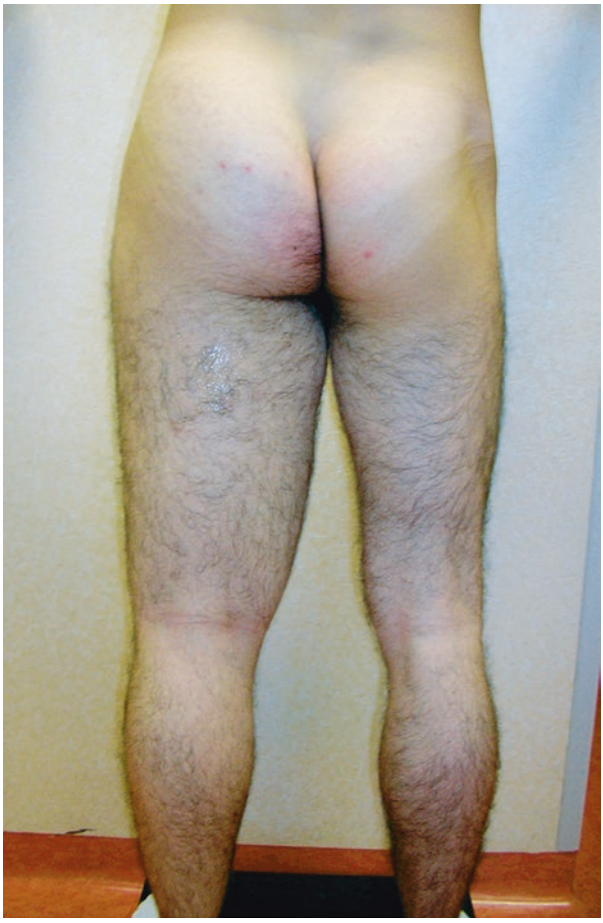

Fig. 14.4 Stage III (involvement of three major joints of the limb)

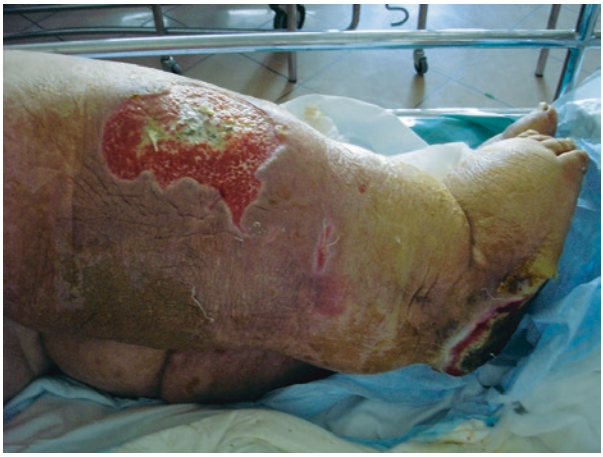

Fig. 14.5 Stage IV (cutaneous infections and inflammatory complications of the limb)

Table 14.5 Staging according to the Brazilian Society of Lymphology (Prof. M. Andrade)

Clinical stage	Evidence
0 (Fig. 14.1)	No edema in individuals at risk (preclinical)
I (Fig. 14.2)	Edema that regresses spontaneously with elevation, pitting ++, Stemmer +, involvement of one major joint of the limb
II (Fig. 14.3)	Edema that does not regress spontaneously, only with treatments, pitting +, Stemmer ++, involvement of at least two major joints of the limb
III (Fig. 14.4)	Edema that does not regress spontaneously, only with treatments, pitting +, Stemmer ++, involvement of three major joints of the limb
IV (Fig. 14.5)	Edema that does not regress spontaneously, only with treatments, pitting +, Stemmer ++, involvement of three major joints of the limb, with cutaneous infections

It should also be noted that the various staging criteria examined take into account only aspects of the organic and physical involvement of the patients; yet, the variable emotional and psychological involvement, in some cases, regardless of the clinical evolution, the age, or the socioeconomic and cultural condition of the patient, assumes greater functional significance. These factors that, over time, have a more profound influence on behavior, personal performance, and social relationships and reinforce the simple physical problem are overlooked in the staging schemes.

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Combined Clinical and Laboratory (Lymphoscintigraphic) Staging

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Summary of Basic Concepts

Lymphedema is a dynamic disease involving the lymphatic system and soft tissue. Staging the disease requires attention to physical exam and clinical and radiographic findings. Accurate staging of patients with chronic lymphedema is essential to provide a reliable method of classifying patients to guide proper treatment and management.

Accurate staging of patients with chronic lymphedema is essential to provide a reliable and objective method of classifying patients to guide proper treatment and management [1, 2]. In particular, staging is critical when reconstructive or ablative surgical therapy is considered as a supplement in a patient who has failed to respond to complex decongestive therapy (CDT) [6, 7]. Appropriate timing of surgical intervention is crucial to avoid irreversible progression of disease [8, 9].

Throughout the last decade, our understanding of chronic lymphedema has undergone significant change. While previously considered a «static» condition of simple lymph fluid stasis, we now understand the condition to be a dynamic, ever-evolving interplay between the lymphatic system and the entire soft tissue [8, 10]. Chronic lymphedema is not a benign process, rather a progressive and degenerative disease which can portend significant disability. Quality of life (QoL) assessment has become an increasingly recognized important factor in the treatment of chronic lymphedema [11, 12]. As such, contemporary management of lymphedema [8, 9] includes the improvement of QoL to facilitate better social interaction and improved functional and psychological well-being.

The radiographic options for diagnosis and treatment of lymphedema have also improved substantially. Various noninvasive to minimally invasive tests have been developed over the last decade to better assess the progression of lymphedema, of which the most commonly utilized is lymphangioscintigraphy (LAS) [13–16]. This study provides detailed images of the lymphatic system following isotope injection. By estimating the uptake of the radiolabeled tracer, useful information about the mechanism and pathophysiology of lymphatic failure can be gleaned [3, 17]. For instance, diagnostic data can be obtained from radiographic delay or absence of lymphatic transport from injection site, asymmetric or absent visualization of regional lymph nodes, and/or the presence of radiotracer uptake in dermal lymphatics called dermal backflow [3]. More recently, indocyanine green lymphography has been explored as a more accurate diagnostic tool, especially in the early diagnostic periods of lymphedema [18]. This method facilitates a real-time examination without radiation exposure that can provide both morphologic and functional data. Utilizing this technique, noninvasive methods of measuring lymphatic pumping have also been explored to provide further functional diagnostic information [19].

Despite the large advancement in our understanding and diagnostic abilities in lymphatic disorders, the staging published in the International Society of Lymphology (ISL) Consensus Document from 2013 utilizes only physical exam to stage lymphedema [4]. Although this society first published in 1995 [20], staging was not described until 2001 [21, 22] with an updated yet still antiquated staging system in 2013. As

Table 15.1 ISL staging of lymphedema [4]

	Clinical characteristics
Stage 0 (or Ia)	Subclinical condition where overt swelling is not present; however, impaired lymph transport exists with subtle changes in tissue fluid/composition with changes in subjective symptoms
Stage I	Early accumulation of fluid high in protein content Pitting may occur
Stage II	Limb elevation alone rarely reduces tissue welling Pitting is present
Stage III	Lymphostatic elephantiasis Pitting absent Trophic skin changes such as acanthosis, wary overgrowth, and deposition of fat and fibrosis

acknowledged by the consensus statement, these stages detail a crude approach to classification with several shortcomings [4]. These staging criteria fail to consider the pathophysiologic mechanisms of lymphedema and underlying genetic contributions as well as QoL factors.

The current system utilizes three stages (Table 15.1). Many clinicians also recognize a stage 0 (or Ia) which refers to a subclinical condition where swelling is not yet evident despite impaired lymph transport (Table 15.1). 2 A functional severity assessment has also been designed to define minimal (<20% increase in limb volume), moderate (20–40% increase), or severe (>40% increase) disease within each stage [4].

In line with the ISL staging, other systems have been developed based on physical descriptors such as the Földi staging system, pitting edema scale, and staging by limb size [2]. Staging by clinical symptoms is also a common methodology particularly in those with lymphedema secondary to parasitic disease. The LVF scale (location, volume fibrosis) method has also been used to collect numerical data for lymphedema grading; however, this method does not comment on the clinical condition of the patient [2].

More recently, volumetry-based staging based on CT, MRI images, and water displacement methods has been used for evaluation. Circumference measurements of the extremity are simple; however, comparison between individuals is difficult as well as the lack of «normal» extremity for comparison in patients with bilateral lymphedema. A more detailed lower extremity lymphedema index (LEL) utilizing cross-sectional area and BMI to stage lymphedema has also been described and validated [23, 24].

Overall, the current staging methods fail to inclusively describe and consider the clinical, radiographic, and pathogenic components of lymphedema [25, 26]. An updated staging system is needed. Recognizing that LAS is not ubiquitously available, we propose two staging systems, one clinical and the other using laboratory (lymphoscintigraphy) data. Together, these two staging systems seek to classify the clinical manifestation and/or progress of the lymphedema more precisely based on two independent criteria (Table 15.2).

Table 15.2 Guideline criteria for the new clinical and laboratory staging system (I–IV)

Laboratory (lymphoscintigraphic) staging		Clinical staging	
Grade I (stage)	Lymph node uptake (LN): decreased (±)	Edema (swelling): mild and/or easily reversible (+)	Stage I
	Dermal backflow (DBF): none (–)	Skin change: none without dermatofibrosclerosis (DFS) (–)	
	Collateral lymphatics (CL): good visualization (+)	Sepsis (systemic and/or local): none (–)	
	Main lymphatics (ML): decreased visualization (±)	Daily activity limitation (DAL): no limitation (–)	
	Clearance of radioisotope from injection site (CR): decreased lymphatic transport (±)	Quality of life (QOL): good with minimal and/or occasional limitation (e.g., exercise, hobby) physically, psychologically, and/or socioeconomically	
Grade II (stage)	LN: decreased to none (–)	Edema: moderate and/or reversible with effort (+)	Stage II
	DBF: visualization (+) [a]IIA – extent of DBF does not exceed half of each limb [a]IIB – exceeds half of each limb	Skin change: none to minimum without DFS (±)	
	CL: decreased visualization (±)	Sepsis: none to occasional (±)	
	ML: poor to no visualization (±)	DAL: occasional and/or moderate limitation (±)	
	CR: more decreased (±)	QOL: fair with moderate limitation physically, psychologically, and/or socioeconomically	
Grade III (stage)	LN: no uptake (–)	Edema: moderate to severe and/or minimally reversible to irreversible (±) to (–)	Stage III
	DBF: visualization (+)	Skin change: moderate with significant DFS (+)	
	CL: poor visualization (–)	Sepsis: common (+) – less than four times a year	
	ML: no visualization (–)	DAL – frequent and significant (+)	
	CR: no clearance (–)	QOL – poor with significant limitation	

Table 15.2 (continued)

Laboratory (lymphoscintigraphic) staging		Clinical staging	
Grade IV (stage)	LN: none (–)	Edema: severe and/or irreversible (–)	Stage IV
	DBF: poor to no visualization (–)	Skin change: severe with advanced DFS (++)	
	CL: no visualization (–)	Sepsis: very frequent (++) – four times or more a year	
	ML: no visualization (–)	DAL: constant and severe (++)	
	CR: no clearance (–)	QOL: bad with severe limitation	

[a]Minimum two or more lymphoscintigraphic findings for laboratory staging and three or more clinical findings for clinical staging

Of note, we initially attempted to incorporate lymphoscintigraphic data of chronic lymphedema patients into the conventional clinical-ISL-staging system. Integrating the clinical findings with those of laboratory findings (e.g., radionuclide lymphoscintigraphy) was too complicated, and in cases in which a significant mismatch between clinical and laboratory findings was observed, more confusion was added to the staging system. We therefore proposed two separate staging systems.

The new clinical staging classifies the clinical manifestation and progression of lymphedema using a four-stage system (clinical stages I through IV). Systemic and local clinical conditions associated with lymphedema are included along with QoL measures. The limitations of the ISL system (three stages) based on clinical data, mostly local factors (edema and skin change), are by and large fully compensated for by the inclusion of various systemic factors including sepsis, daily activity limitation, and QoL parameters – physical, functional, socioeconomic, and psychological [5, 27].

Clinical stage is determined based on a total score of the clinical factors involved: edema (swelling), skin change, sepsis, daily activity limitation, and QoL (Table 15.2). The subjective and objective findings of the local condition of the skin and subcutaneous soft tissue are assessed with the degree of skin change (dermatofibrosclerosis) [10, 28], swelling, and natural reversibility. The presence of local and/or systemic sepsis is assessed along with the presence of erysipelas and cellulitis. Functional limitation of daily activity as a result of the various subjective symptoms is assessed, including pain, uncomfortable sensory complaints (heaviness, tightness, numbness) and skin texture, feeling of the swollen limb, and difficulty wearing clothes because of the swelling The evaluation of daily activity limitation was originally included in the QoL assessment with sepsis; however, this arrangement made interpretation of the clinical status more complicated; therefore, both items were removed from the QoL assessment. Only a limited part of the physical condition was left for the QoL assessment which incorporates the physical factors, including strength, movement, restriction of duties at home and work, and psychological and socioeconomic factors [1, 2, 5, 27].

Table 15.3 Quality of life (QOL)

Excellent	No limitation or difficulty with extra activity (e.g., hobby) physically, psychologically, and/or socioeconomically in addition to daily activity
Good	Some limitation of extra activity, but occasionally, physically, psychologically, and/or socioeconomically, but with no limitation of daily activity
Fair	Significant limitation of extra activity, but no limitation of daily activity physically, psychologically, and/or socioeconomically, or occasionally some limitation of both daily and extra activity
Poor	Significant limitation of both daily activity and extra activity, frequently physically, psychologically, and/or socioeconomically
Bad	Profound limitation of daily activity as well as extra activity or no daily activity feasible without assistance physically, psychologically, and/or socioeconomically

The QoL was evaluated by the impact of the lymphedema on the patient's physical, psychological, and socioeconomic limitations and well-being (Table 15.3). The physical factors for the QoL include strength of the affected limb, restriction of movement compared with the unaffected limb, as well as further additional impact on duties at home and work and recreational activity. The psychological factors included feelings of depression, frustration, anger due to the lymphedema, and difficulty sleeping. The socioeconomic factors included difficulty with intimate relationships and social activities. This new clinical staging system could not separate and exclude the economic factors in the review of the QoL. We learned that patient economic issues have both social and psychological implications for overall patient well-being.

The separate laboratory staging system using four grades (stages) was developed based on lymphoscintigraphic findings of the lymphedema [29–31]. Laboratory stage was determined by the sum total of various normal and abnormal findings on lymphoscintigraphy. These findings include the lymph node (LN) uptake status, the dermal backflow (DB) status, the collateral and main lymphatic visualization status, and the clearance of the radioisotope (CR) from the injection site as a parameter of the lymphatic transport ability [1, 2].

Several revisions of the new staging systems have been made by a multidisciplinary team through the years, in order to make them more user-friendly. This diagnostic tool allows better assessment of the progression of disease thus allowing better treatment and prevention of complications.

15.1 Clinical Experience [1, 2]

Among a total of 840 chronic lymphedema patients, 220 patients (85 primary and 135 secondary (169 female and 51 male, mean age 41.3 years)) were randomly selected during the period 1995 through 2004 to be evaluated using new clinical and laboratory staging systems (Table 15.2).

Table 15.4 Demographic data of the initial clinical and laboratory stage of chronic lymphedema

			Laboratory (L) stage (grades I–IV)				
			I	II	III	IV	Unidentified[b]
Clinical (C) stage[a]	I	77	53	19	1	0	4
	II	98	6	66	24	1	1
	III	29	0	2	15	10	2
	IV	16	0	1	6	9	0
	Total	220	59	88	46	20	7 (total)

220 patients, selected for a 4-year follow-up assessment (1995–2004)
[a]Based on the new four-stage system
[b]Unavailable for the comparison study

Table 15.5 Demographic data of the clinical (C) stage of chronic lymphedema in progress (deterioration or improvement)

			Final (progress) C stage				
			Clinical stage				
			I	II	III	IV	Further deterioration
Initial C stage Clinical stage	I	77	70	6	1	0	0
	II	98	3	81	11	2	1
	III	29		2	14	12	1
	IV	16			1	6	9

The patients underwent various combinations of standard CDT and compression therapy. Periodic clinical evaluation was made with an average interval of 6 months, but no longer than a year's interval. Lymphoscintigraphic study was performed on an annual basis, except in situations where recurrent sepsis was present. In these cases, an additional study was performed whenever feasible.

A comparison of clinical (C) stage and laboratory (L) stage during the initial diagnosis of 220 patients showed a broad overlap between the two different stagings; each group of patients with the same C stage had various L stages, and patients with the same L stage also had a wide range of C stages. In general, a more advanced L stage patient was more likely to have a more advanced C stage (Table 15.4).

Clinical implementation of this new staging system (Table 15.5) demonstrated reliable staging regarding both the progression of lymphedema and improvement of the clinical status following therapy.

Among 220 patients, 49 patients were appropriately classified by this new staging, 43 had deterioration, and 6 showed improvement in their clinical stage. Deterioration of the clinical stage occurred despite adequate therapy in various C stages, but was more frequent among patients with advanced C stage, which was mainly related to decreased compliance.

The majority of patients who deteriorated at the same clinical stage were among the higher L stage accompanying group: 5 out of the 7 in C stage I who progressed had L stage II (4/5) and III (2/5) initially, while 10 out of the 14 in C stage II who progressed also had a higher L stage III (9/10) and IV (1/10) from the beginning. Another 11 out of the 13 in C stage III, who progressed, had L stage IV or higher before treatment.

Maintenance of the initial clinical stage throughout the 4-year follow-up period was achieved in the majority of patients (171/220) with good to excellent compliance. Further improvement in the C stage was observed in a limited number of patients, particularly among the excellent compliance group with a good motivation, reversing the C stage (Table 15.4). Two out of the three converted from C stage II to I and showed a concomitant improvement in the L stage from II to I.

This limited experience with a new, combined, clinical and laboratory staging system appears to be useful in guiding surgical therapy. Using the staging system allowed earlier determination of treatment failure in patients with minimal clinical improvement with CDT and allowed optimal timing of various surgical therapies during the appropriate stage of chronic lymphedema as a supplement to failed CDT.

Patients experiencing progression of lymphedema by C stage, despite maximum CDT, benefited from reconstructive surgery [8, 9, 32] when surgery was added during an earlier C stage, before a minimum of 2 years in order to become a surgical candidate when C stage patients were also classified as having advanced L stage. The excisional surgery [32–35] was also added to the lymphedema in C stage III and IV, based on the same principle.

The addition of laboratory staging in the development of this new clinical staging system has improved the overall predictability of treatment outcome with regard to clinical response to various therapies and progression of the lymphedema. A patient with an advanced L stage, compared with lymphedema patients in the same C stage, demonstrated a tendency to progress faster in this study. L stage has therefore been used to help determine which lymphedema patients would benefit from different treatment modalities, particularly surgical therapy in order to prevent further disease deterioration.

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Four-year follow-up evaluation of the complex decongestive physiotherapy (CDP)-based therapy results among 220 patients.

Conclusion

Current staging systems are inadequate to describe the clinical and radiographic factors affecting patients with lymphedema. We propose two separate staging systems that can be utilized in combination that may be useful in establishing guidelines for the treatment of chronic lymphedema and in the decision-making process for supplemental surgical therapy. Further clinical implementation of the staging systems and new radiographic techniques is still needed to prove its clinical efficacy, especially in defining the role of surgical therapy.

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Early Diagnosis in Latent Phase

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Summary of Basic Concepts

The latent phase of lymphedema is prior to the presence of visible swelling. Sensitive objective yet practical diagnostic tools are required to detect lymphedema at this very early stage. Two approaches have been developed to a stage of practical clinical utility: bioelectrical impedance spectroscopy (BIS) and tissue dielectric constant (TDC). Both are based on measurement of electrical properties of tissue water. The methods should be viewed as complimentary; BIS is best suited for whole limb assessment, while TDC is ideal for focal or localized lymphedema assessment. Both devices are simple to use; relatively inexpensive; show high sensitivity, specificity, and reproducibility; and represent practical alternatives to reference methods such as lymphoscintigraphy.

Lymphedema is typically characterized by the time of onset (staging) and the severity of the symptoms (grading). Various staging schemes have been proposed, but increasingly most use a four-stage scale: stage 0, a latent or subclinical phase when swelling is not evident, although lymphatic insufficiency is presumed; stage I, accumulation of tissue fluid that generally resolves with elevation of the affected limb with minimal swelling (<20% increase); stage II, when elevation fails to reduce a moderate amount of swelling (20–40% increase) and pitting edema is present; and stage III, irreversible, severe (>40% increase) swelling is present and the tissue is fibrotic [6]. Despite the absence of outward clinical signs of lymphedema in the latent stage, lymphoscintigraphy or lymphangiography shows disrupted lymphatic function [7]. Detection of patients in the latent phase has been recognized as important for identification of those in whom advanced lymphedema may occur [8]. This enables therapeutic intervention at the earliest opportunity, which has been shown to be more effective than intervention after lymphedema has become established, [1] but this approach is predicated on the ability to detect lymphedema in the latent phase.

A wide variety of objective methods, other than clinical examination, are available for the detection of lymphedema [9]. However, many are either technologically complex (e.g., magnetic resonance imaging [MRI], laser scanning, or dual-energy X-ray absorptiometry [DXA]) and invasive and involve a radiation hazard (e.g., isotopic lymphoscintigraphy) or are otherwise not suitable for routine clinical use because of cost, e.g., computed tomography (CT). The most commonly used techniques for lymphedema detection are those based on detecting an increase in volume due to the presence of edema and include water displacement, opto-electrical perometry, bioelectrical impedance, and circumferential measurements. Unfortunately, because, by definition, the latent phase of lymphedema is that prior to *detectable* swelling, the utility of such techniques is questionable. Nevertheless, such methods are currently accepted as the best measurement options to detect preclinical lymphedema [10]. O'Toole et al. [2] have described a standardized lymphedema screening protocol based on a ≥ 5% change in volume, measured by perometry, at two consecutive assessments. Alternatively, Stout Gergich [1] and colleagues defined a more conservative 3% change in volume from a baseline or preoperative measurement in the case of secondary lymphedema as a diagnostic criterion for subclinical lymphedema. They further suggested that, in the absence of perometry, (which was used in their study), other tools that assess swelling, such as

Table 16.1 Accuracy and precision of methods for assessment of lymphedema of the limbs

Method	Accuracy (%)	Precision and reproducibility[a]	References
Impedance	<±1	ICC > 0.94 (15 Ω, ~4%)	[11, 12]
Water displacement	±0.5	ICC > 0.94 (81 mL, ~4%)	[13–15]
Perometry	±2	ICC > 0.99 (81 mL, ~ 4%)	[11, 13, 16]
Tape measurement	±1	ICC > 0.95 (85 mL, ~4%)	[11, 15, 16]
Tissue dielectric constant	<±5[b]	ICC 0.50–0.92 TEM 10.5–13.3%[c]	[23, 24]

ICC intra-class correlation coefficient
[a]Absolute values and approximate percentage of measured value
[b]Accuracy estimated on tissue phantoms
[c]Technical error of measurement

water displacement, bioimpedance, or girth measurements, may be equally useful. Other than assessment of volume, simple practical methods for early detection of lymphedema are few. Determination of localized skin water by measuring tissue dielectric constant shows early promise, particularly for assessment of localized or focal lymphedema [3].

Unfortunately, there are no universally recognized diagnostic criteria for each of these methods, and equivalence between methods has not been defined. Furthermore, assessment of lymphedema lags behind many other branches of science where standardization of measurement has long been recognized as the key to quality control and assurance. Preference should be given to methods of assessment that meet accepted standards for accuracy, precision, sensitivity, and specificity of measurement and that are practical and applicable for routine clinical use [4].

Accuracy can be difficult to assess because the «true» value, i.e., the smallest change in the measured parameter (volume, impedance, or girth) presumptive of lymphedema, is unknown. It is necessary to resort to using «phantoms» of precisely known characteristics, such as cylinders of known volume or electronic circuits of known impedance. Precision or reproducibility of measurement is more easily determined from repeated measurements, using either phantoms or human subjects. Published data, summarized in Table 16.1, suggests that the various methods used to assess early-stage lymphedema perform similarly with an accuracy of about ±1% and reproducibility of approximately ±4% standard error of measurement.

Of greater importance for the detection of subclinical lymphedema than absolute accuracy or precision is the limit of detection, the magnitude of difference for a given measurement parameter that can be reliably detected. This is calculated as the minimal detectable change (MDC) and is given by 1.96 ± 2 SEM (standard error of measurement). The MDC for volume measurements is approximately 140 mL, assuming a typical SEM of 50 mL for volumetric measurement. This can be compared with the generally

accepted inter-limb difference of 200 mL used as a detection threshold for breast cancer-related lymphedema (BCRL). Czernieic et al. [11] have shown that a minimum of a 120 mL change is required to account for normal fluctuation in limb volume in the absence of lymphedema to be confident of an effect, while Stout Gergich and colleagues [1] have recommended a 3% change in perometrically measured volume from a pre-lymphedema baseline measurement as a threshold for lymphedema treatment intervention. With respect to impedance measurements, similar calculations suggest a detection limit of approximately 40 Ω or an inter-limb ratio difference of 0.04 in BCRL [11]. Again, larger change is required (a ratio of 0.08) to account for normal fluctuation of approximately 4.8% [11]. We should, however, question the relevance of this to the detection of preclinical lymphedema. By definition, lymphedema in the latent phase is *prior to* a detectable change in volume. On this basis, simple volumetric measurements, irrespective of how small the limit of detection, can never be used for lymphedema assessment at this early stage. Equally, bioimpedance techniques are not suitable either, since the magnitude of changes in impedance equates to changes of comparable magnitude in volume.

A more pragmatic approach is to assess promising technologies on the basis of their practicality in use and sensitivity and specificity for detection at the earliest opportunity. Surprisingly, relatively few studies have been undertaken. Despite detection thresholds such as a 200 mL volume difference being widely promulgated, the evidence base for their validity is sparse, and sensitivity and specificity analyses are few in number [4]. Box et al. [17] demonstrated a 100% confirmation of BCRL in women when using a 200 mL detection threshold, but this cannot be classed as latent phase lymphedema. Hayes et al. [18] showed, again in women with BCRL, that compared with bioimpedance, set at 100%, circumferential measurements of the arm had good specificity (88–100%), but much worse sensitivity (35%). More recent analyses have questioned the impedance thresholds used to define lymphedema. Adopting a more liberal threshold of an inter-limb impedance ratio for detection of breast cancer-related lymphedema of two standard deviations (SD) above the population normative mean than the accepted cut-off of three SD improved specificity to 90% with a slight reduction in sensitivity (80%) [19]. Improvement in performance has also been confirmed using two SD thresholds when impedance has been used to assess localized lymphedema [5].

The data of Cornish et al. [20] are perhaps most persuasive that bioimpedance, at least, may be capable of detecting changes indicative of impending lymphedema at an early stage. In a prospective study, BCRL was detectable by bioimpedance up to 10 months prior to clinical confirmation. This study has yet to be confirmed and extended to other forms of lymphedema, but provides encouragement that using relatively simple noninvasive technology lymphedema may be detectable in the latent phase or at least prior to observable changes in volume. The sensitivity of impedance assessment over other diagnostic modalities is supported by the theory on which the technology is based. The impedance that is measured is solely that of the extracellular fluid, which includes the lymph [21]. In contrast, simple volume measurement, be it by water displacement, perometry, or tape measure, is that of the total tissue and may be confounded by changes in tissue compartments other than the lymph, e.g., adipose tissue mass.

Table 16.2 Comparison of potential technologies for the early detection of lymphedema

	Cost	Portability	Ease of use	Time involved	Patient convenience	Operator skills
Impedance	Low to high	High	High	Low	High	Low
Perometry	Very high	None to medium	High	Low	High	Low
Tape	Very low	High	High	High	Medium to high	Low
Water displacement	Very low	Low	Medium to high	Medium	Low	Low
Tissue dielectric constant	Medium	High	High	Low	High	Low

Notwithstanding the relative merits of individual assessment methods, no single simple objective method uniquely diagnoses early stage lymphedema. It is likely that a combination of tools provides greater power for early detection. This view is supported by the work of Dylke et al. [5] who have defined likelihood ratios for lymphedema, positively diagnosed by lymphoscintigraphy, based upon normatively determined inter-limb circumference differences and impedance ratios. Using these likelihood ratios, they have developed a nomogram that combines single-site circumference measurements with whole-arm impedance measurements that improves the likelihood of correct diagnosis of lymphedema.

Detection of latent phase lymphedema implies screening of at-risk individuals. It is therefore important that the instruments adopted for assessment are fit for this purpose. Ease of use and cost are important considerations in the uptake of technologies into routine clinical practice. All of the methods referred to above have their advantages and disadvantages (Table 16.2). A tape measure is inexpensive to purchase and is, undoubtedly, easy to use, but its use is time-consuming. Perometry is also easy to use and rapid to perform, but initial equipment costs are high. Water displacement is inexpensive, but may not always be suitable, for example, where there are infections or wounds. Impedance is rapid to perform, with modest cost (dependent upon instrumentation), but its utility for all forms of lymphedema has yet to be established.

In conclusion, detection of lymphedema in the latent phase poses significant challenges. The definition of latent phase or subclinical lymphedema that it is prior to appearance of swelling appears to preclude many of the methods currently used to detect lymphedema. Other than technologies that measure lymphatic function, such as lymphoscintigraphy, covered elsewhere in this volume, tools in current use without exception measure volume either directly or indirectly as in the case of impedance. Nonetheless, the routine use of these techniques is of clinical value, particularly where

change compared with baseline measures is available, as shown by the work of Stout Gergich et al. [1] and O'Toole et al. [2] Maximum benefit will be gained by routine surveillance of those at risk of developing lymphedema. At present, the tool most suited for this purpose appears to be impedance in that it is suitable for home use by those at risk of or with incipient lymphedema [22]. It would be remiss, however, not to additionally acknowledge the importance of self-report by those with lymphedema. Objective assessments in current use may simply not be measuring the correct parameters that characterize the subtle early changes in tissue morphology and physiology that occur in the latent phase. These may, however, be apparent to the patient. Much additional research into the biology of the development of early-stage lymphedema is required to allow us to determine the optimal detection strategy.

Statement of Conflict of Interest

L.C. Ward has consulted for ImpediMed Ltd. ImpediMed Ltd. had no involvement, financial or otherwise, in the conception and execution of this study or in the preparation of the manuscript.

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Cutaneous Manifestations of Edema

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Summary of Basic Concepts

- Edema always represents a failure of lymph drainage, either lymph flow is inadequate or lymph load overwhelms lymph drainage capacity.
- Venous edema indicates relative lymph drainage failure.
- Kaposi-Stemmer sign is pathognomonic of lymphedema.
- Elephantiasis refers to severe skin changes in any lymphedema irrespective of cause.
- Lipodermatosclerosis is commonly mistaken for infection (cellulitis/erysipelas).

17.1 Swelling May Not Always Be Fluid

It is important to determine if edema (Greek oídēma, swelling) is due to fluid or another tissue component. Overgrowth syndromes, such as Klippel-Trenaunay syndrome, may have excessive growth of the bone, fat, or muscle (with or without additional fluid). A plexiform neurofibroma (neurofibromatosis) may cause tissue swelling from both the neural tumor and lymphedema (Fig. 17.1).

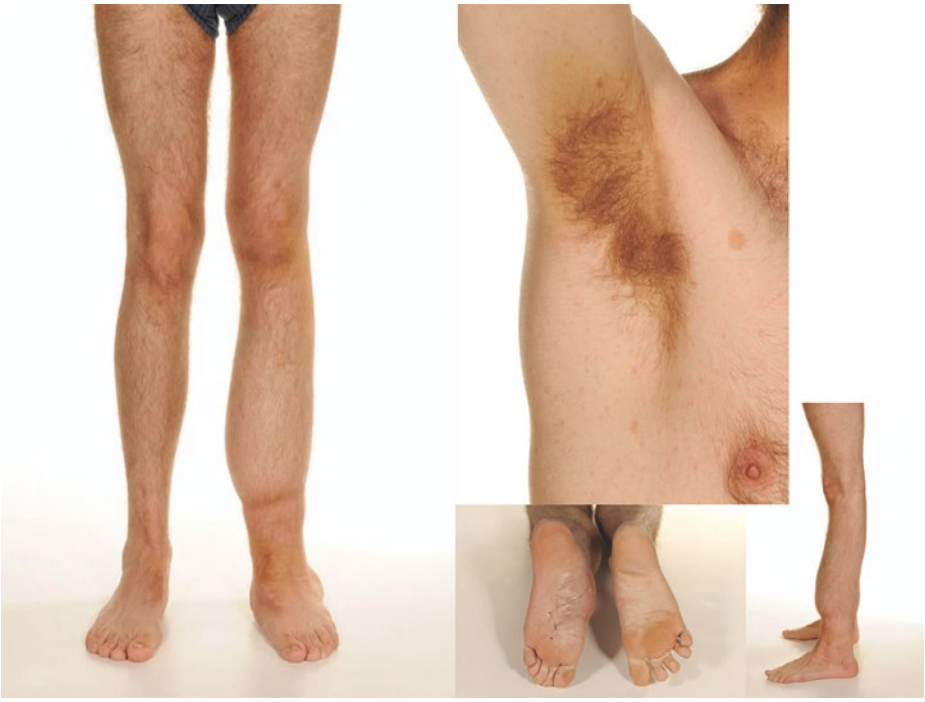


Fig. 17.1 Lymphedema arising from a plexiform neurofibroma in neurofibromatosis

17.2 Lymph, Not Venous Reabsorption, Drains Interstitial Fluid

Lymph transport, not venous reabsorption, is the main process responsible for interstitial fluid drainage. Any edema, whatever the cause, is due to capillary filtration overwhelming the lymph drainage for a sufficient period of time [5]. Contrary to popular belief, venous reabsorption of interstitial fluid cannot be maintained for any length of time except in certain vascular beds, for example, that of the kidney [1].

As peripheral interstitial fluid is reabsorbed almost entirely by the lymphatic system, with only transient absorption by the blood vessels, all peripheral edemas represent lymphatic failure. Edema arising principally from a failure in lymph drainage is lymphedema (absolute lymphatic failure). Most chronic edemas, however, arise from increased microvascular fluid filtration overwhelming the lymph drainage, i.e., high lymph load (relative lymphatic failure). Examples are heart failure, venous disease, and nephrotic syndrome.

It is not unusual in circumstances following a sustained and prolonged increase in microvascular filtration for the lymph vessels to become «exhausted,» and then absolute lymph drainage capacity is permanently reduced. This means that even if microvascular fluid filtration is corrected, such as treatment of heart failure, edema may persist. This is then lymphedema.

17.3 Think Lymphatic when Confronted with Edema in the Clinic

It is best not to approach a lower limb chronic edema clinically by trying to pigeonhole the diagnosis into «heart failure,» «venous edema,» «lymphedema,» etc. A far better approach is to consider if the edema is due simply to a failure of lymph drainage or high lymph load overwhelming lymph drainage or perhaps a combination of the two. Indeed there may be a range of dynamic physiological factors contributing to chronic edema. Here is an example to illustrate the physiology.

17.4 Venous Edema

Phlebolymphedema or mixed lymphovenous disease is swelling of the lower limb due a mixture of chronic venous insufficiency and lymphatic insufficiency. Phlebolymphedema refers to chronic edema arising from chronic venous hypertension causing increased microvascular fluid filtration overwhelming lymph drainage.

Edema is a common complication of venous insufficiency. It is assumed that venous edema is the sole consequence of increased capillary filtration from venous hypertension. As lymph drainage is the main buffer against edema, it is in fact the failure of local lymphatic drainage to compensate for the increased lymph load from filtration that leads to edema. Over time the lymphatic vessels become compromised and start to fail permanently, so full-blown lymphedema results.

17.5 Clinical Signs from Edema

The major clinical changes of edema take place in the skin and subcutaneous tissues; such changes are of value in diagnosis.

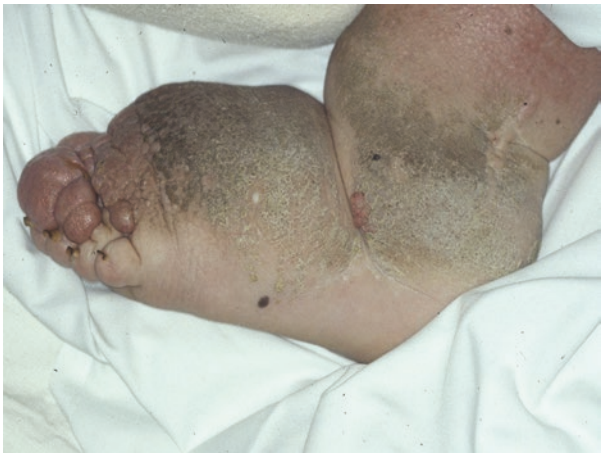
Skin Edema The skin consists of an outer layer, the epidermis, which is devoid of blood or lymph vessels, and a dermis, which is the underlying supporting layer rich in blood and lymph vessels, nerves, and glands, e.g., sweat and sebaceous glands. The epidermis is compact and does not develop intercellular edema except through inflammation.

Edema does develop in the underlying dermis. When lymph drainage is impaired, the epidermis becomes much thicker in depth and surface keratin increases. As lymphedema becomes chronic, so this epidermal thickening becomes visible clinically as a warty change known as elephantiasis. Elephantiasis is not unique to filariasis but can occur in any lymphedema when severe (◘ Fig. 17.2).

Edema in the dermis manifests as «peau d'orange» due to expansion of the dermis between the hair follicles, whereas subcutaneous edema gives rise to pitting. Expansion of the dermis from fluid bulges the surface of the skin, but the follicle pore remains tethered to deeper structures, hence the orange peel appearance. Peau d'orange is most often seen in breast skin that is edematous (◘ Fig. 17.3).

Subcutaneous Edema The subcutaneous layer consists primarily of fat. The connective tissue, containing blood and vessels, encircles the fat to form lobules. The subcutaneous tissue is relatively loose and not firm in texture such as the skin. Consequently it has higher stretchiness, known as compliance, and can swell with fluid to a much greater extent than the skin.

Pitting is a sign, which results from displacement of subcutaneous fluid by pressure (◘ Fig. 17.4). In edema of high microvascular filtration, swelling is almost entirely fluid. This fluid can easily be pushed aside by pressure to leave a temporary indentation. This is pitting. Once pressure is released, fluid re-equilibrates, and fluid flows back within the interstitial spaces.



◘ **Fig. 17.2** Elephantiasis with hyperkeratosis and papillomatosis from lymphedema

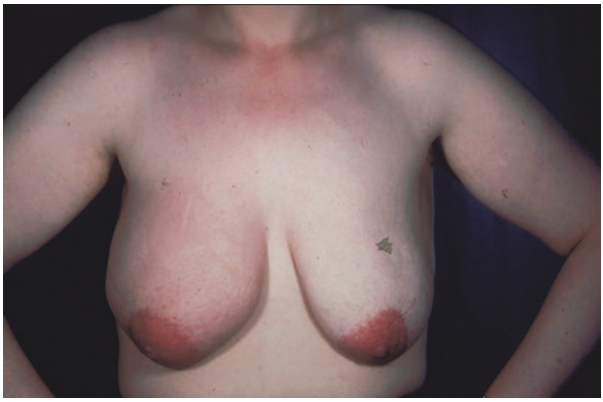


Fig. 17.3 Peau d'orange skin change with breast lymphedema

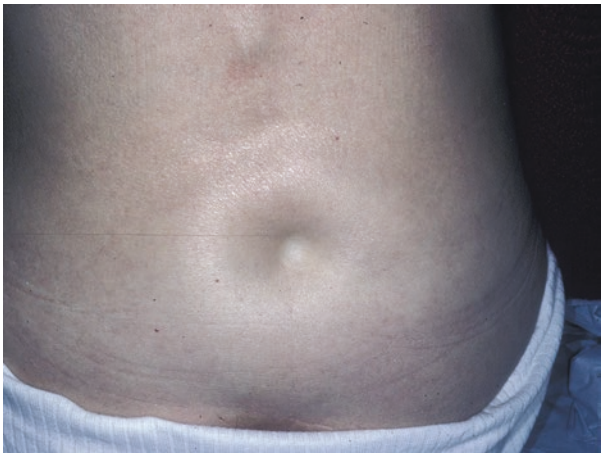


Fig. 17.4 Pitting from sacral edema

In lymphedema, however, the edema is not just fluid. Other components such as proteins fat and cells also accumulate because the lymph is not draining them either. These other tissue components convey a more «solid» texture to the edema, and pitting is not quite so easy to demonstrate. Therefore, it is important to press with the thumb over a bony prominence for at least 10 s before deciding if edema is present or not.

17.6 Skin Signs from Lymphedema

Kaposi-Stemmer sign Although swelling occurs most in the subcutaneous layer, the skin exhibits most changes. In 1976 Robert Stemmer published a clinical sign usable for early and differential diagnosis of lymphedema, the so-called Stemmer's sign [6]. Stemmer's sign is defined as enlargement of the skinfold above the second toe. This makes it difficult to pinch and pick up a fold of skin at the base of the second toe (Fig. 17.5). It reflects the thicker epidermis and is pathognomonic of lymphedema. Why the second toe exhibits

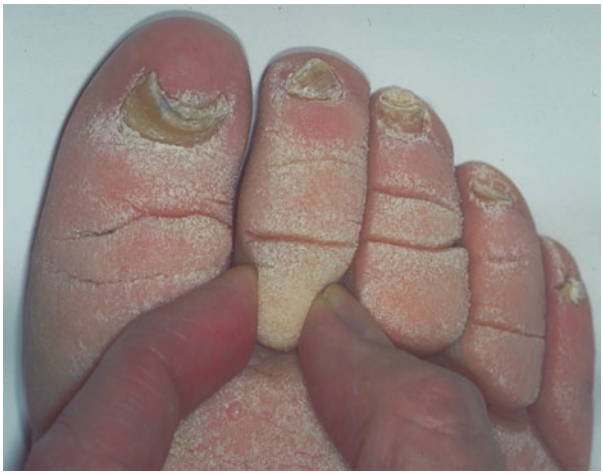


Fig. 17.5 The skin thickens – as demonstrated clinically by the Kaposi-Stemmer sign-a thickened skin fold on the top of the second toe

most skin change with foot edema is not known. Földi stated that Stemmer's sign is never false positive for lymphedema, but it can be false negative [7].

It is thought that Moritz Kaposi described a similar sign some time before Stemmer in his famous book *Pathologie und Therapie der Hautkrankheiten in Vorlesungen für praktische Ärzte und Studierende* (Pathology and Therapy of the Skin Diseases in Lectures for Practical Physicians and Students), published in 1880, but the exact reference is hard to find. Nevertheless some refer to the sign as the Kaposi-Stemmer sign.

Papillomatosis Papillomatosis manifests as a cobblestone change to the skin surface due to the multiple papillomas that develop with chronic lymphedema (Fig. 17.2). Papillomatosis is a skin surface elevation caused by hyperplasia and enlargement of the dermal papillae and dilated lymphatic capillaries [8].

Skinfolds Skinfolds are a striking feature of severe lymphedema. They form from bulging skin and subcutaneous tissue and can become pendulous under the influence of gravity particularly in the very obese. If excessive in size, they are referred to as massive localized lymphedema (Fig. 17.6). MR imaging typically demonstrates a sharply demarcated, pedunculated mass consisting of fat partitioned by fibrous septae surrounded by a thickened dermis [9]. Histologically, dermal fibrosis, expansion of the fibrous septa between fat lobules with increased numbers of stromal fibroblasts, lymphatic proliferation, and lymphangiectasia, is observed [10]. Alternatively named pseudotumors, they can easily be mistaken for soft tissue sarcomas.

Elephantiasis Skin creases become enhanced and hyperkeratosis develops. As dermal lymph stasis progresses, so skin changes become more marked and are referred to as elephantiasis, because the skin resembles elephant hide. As tissue fibrosis and thickening of skin and subcutaneous tissues become marked, so pitting disappears.

Elephantiasis tropica refers to lymphatic filariasis; non-filarial elephantiasis is podoconiosis; and elephantiasis nostras verrucosa refers to the skin changes seen in Western society (our type of lymphedema).

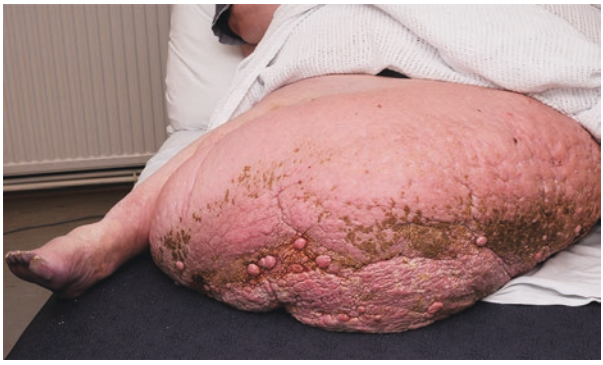


Fig. 17.6 Massive localised lymphedema (elephantiasis nostras verrucosis)

Thickening of the skin causes pseudoscleroderma. Scleroderma is an autoimmune condition, giving rise to hard skin (from Greek *skleros* «hard» + *derma* «skin»). Pseudoscleroderma means hard skin arising for other reasons such as lymphedema. Elephantiasis makes the skin more vulnerable to trauma, and hard skin surrounding a joint will limit joint mobility.

Verrucosis Verrucosis (from Latin *verruca* «a wart») refers to the warty change to the skin surface with elephantiasis/lymphedema. The appearance is that of multiple warts. Indeed in many cases of lymphedema with marked verrucosis, it can be very difficult to distinguish from a human papilloma wart virus infection. This probably reflects a similar pathological mechanism, which gives rise to a hyperplasia of epidermal keratinocytes and increased production of surface keratin.

Lymphangiectasia Expansion or dilatation of dermal lymphatic vessels is called lymphangiectasia («angeion» means vessel, and «ektasis» means a stretching out, extension, or dilatation). If the lymphatic vessels are engorged with the lymph and markedly enlarged, the lymphangiectasia(s) can be seen as «lymph blisters» on the skin surface, giving a «frog-spawn» appearance. With time lymphangiectasia can become more wart-like.

Lymphangiectasia(s) may arise from an underlying lymphatic malformation. Dermatologists frequently use the term «lymphangioma circumscriptum,» but the lesion is not usually progressive and growth is from expansion, not cellular proliferation. Lymphangiectasia(s) also occurs secondary to damage to deeper lymph drainage channels, and the back pressure to the dermal lymphatic capillaries results in engorgement and their expansion on the skin surface. Lymphangiectasia(s) is more common in the genital region, i.e., scrotum and vulva post radiation (Fig. 17.7).

Lymphorrhea Leakage of the lymph through the skin (lymphorrhea) may occur from engorged dermal lymphatics (lymphangiectasia). These engorged dermal initial lymphatics may be visible or not. If not then the patient will simply be aware of a fluid leak from the skin but not be able to identify a source. This is particularly troublesome in the genital region where lymphangiectasia is more common.

On occasions the lymphorrhea can contain chyle (white or milky lymph originating from the gut) (Fig. 17.8).

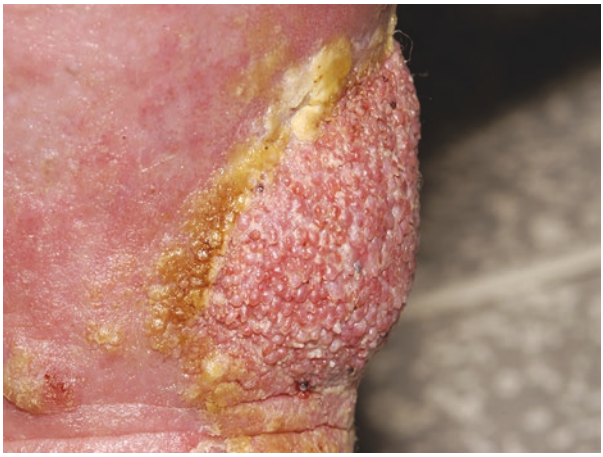


Fig. 17.7 Genital lymphangiectasia from radiation for anorectal cancer

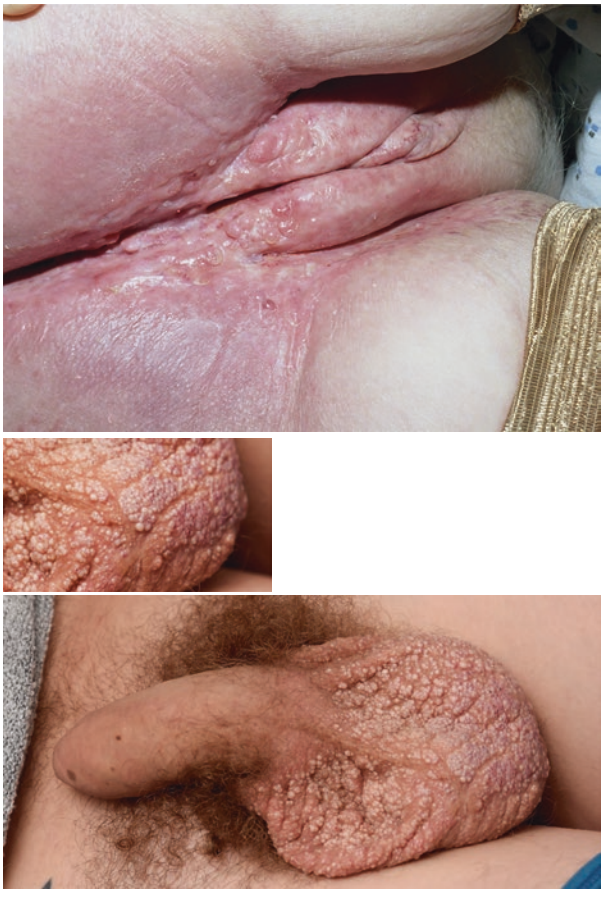


Fig. 17.8 Chylous reflux

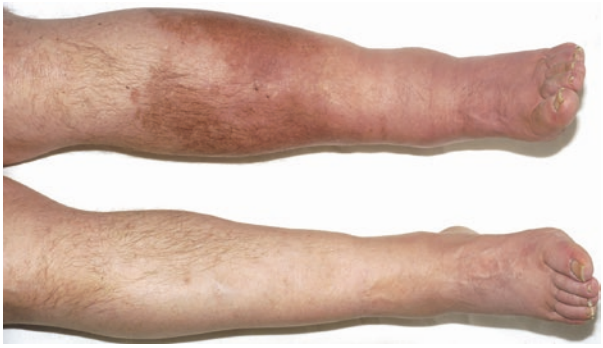


Fig. 17.9 In venous hypertension purpura arises from extravasation of red cells into the skin. Breakdown of red cells leads to haemosiderin staining

17.7 Signs of Venous Disease

Chronic venous disease frequently accompanies lymphedema for a number of reasons. First, veins and lymphatics have similar embryological origins, so if one is genetically faulty, so may be the other. Second, venous hypertension results in excessive fluid filtration into the tissues of the lower limb, and with time this exhausts the lymph drainage capacity. The resulting damage to lymphatic vessels results in permanent lymphedema.

Venous disease may result in symptoms such as heaviness, aching, itching (from varicose dermatitis), skin pigmentation, as well as visible varicose veins. Physical signs indicating venous hypertension, apart from edema and the veins, are purpura, stasis dermatitis, atrophie blanche, lipodermatosclerosis, and ulceration [11]. The *purpura* arises from extravasation of red cells into the skin. They then degrade leaving a stain from hemosiderin (Fig. 17.9). *Varicose eczema*, stasis dermatitis, and varicose dermatitis are all one of the same. They will produce itching and so signs of scratching. There may be oozing from the skin surface. The inflammation generated will also add to the edema. *Atrophie blanche* represents ivory-colored, smooth depressed scars surrounded by telangiectasia. It can be very painful and readily ulcerate. *Lipodermatosclerosis* is considered unique to venous disease but not so (see below). *Venous ulceration* is the severest complication of venous hypertension but can be made much worse by accompanying lymphedema. Weeping lymph fluid is very corrosive to an ulcer edge and will contribute to the ulcer extension and poor healing.

17.8 Lipodermatosclerosis

The chronically swollen red leg is a common sight in medical practice. Often wrongly mistaken for bacterial cellulitis, it is frequently mismanaged. Lipodermatosclerosis (LDS) is an inflammatory condition of the skin and subcutaneous tissues affecting the lower third of the leg and is commonly called chronic cellulitis. It is due to sustained «congestion» – that is, high interstitial fluid and lymphatic and venous pressures. It is most usually described with chronic venous disease, but the common denominator is chronic edema, and it can frequently be seen in lymphedema without any venous reflux.

While it resembles bacterial cellulitis, there are no systemic symptoms or signs of infection. Bacterial infection (true cellulitis) can, however, frequently complicate LDS,

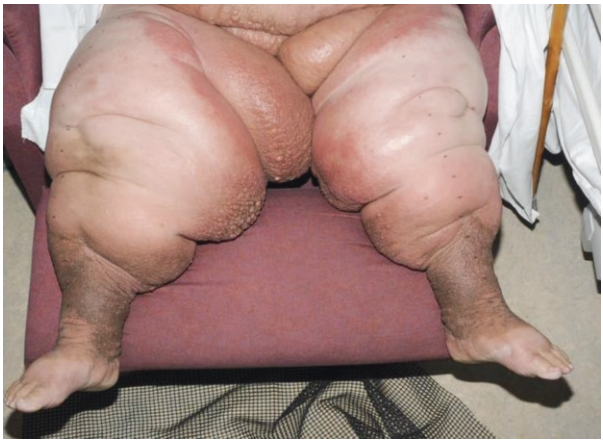


Fig. 17.10 Acute and chronic lipodermatosclerosis; the bright red skin (acute) could be mistaken for bacterial cellulitis but it is an inflammatory response to the skin fluid congestion; the more chronic form of lipodermatosclerosis results in darker pigmented skin in the gaiter region plus fat sclerosis and indrawing of skin. The treatment is decongestive lymphatic therapy with or without antibiotic cover

but antibiotics alone do not resolve it, and the only proven treatment is compression therapy to «decongest» the tissues [12].

Lipodermatosclerosis is usually bilateral. While redness and edema are always present, warmth is usually, but not always, present. Induration indicates that the underlying subcutaneous tissues are involved with the inflammatory process (sclerosing panniculitis). Pain and tenderness are ever present but not itch; if itch occurs, varicose/stasis eczema probably coexists.

There are two forms of LDS: acute and chronic. Acute LDS simulates acute cellulitis with a flare of local redness and pain. With time the chronic form supervenes. The skin becomes «bound down» and retracted as the subcutaneous tissues become more fibrotic and contracted (Fig. 17.10). Eventually redness gives rise to brown pigmentation, and the leg contour takes on an «inverted champagne bottle» shape. Pitting edema will continue to exist both above and below the area of LDS and is a common feature (and common denominator) throughout.

Compression therapy is the only proven therapy. Compression bandaging will achieve quicker results than compression hosiery but may not be tolerated if the affected tissues are very inflamed and tender. In such circumstances it may be necessary to start with bed rest or even topical steroids before introducing gentle compression. In more chronic cases, where shape change exists, multilayer lymphedema compression bandaging works better [2]. Bandaging may have to be continued until a more normal contour shape is obtained. Only then will compression hosiery fit and work satisfactorily.

17

17.9 Infection

Infection is a particular risk with lymphedema because of the important role lymph drainage plays in tissue immunosurveillance. Impaired lymph drainage can predispose to any type of infection, but cellulitis (erysipelas) is the most challenging.

In some forms of genetic lymphedema, e.g., Emberger syndrome due to a mutation in the GATA2 gene, infection may result from the systemic insufficiency independent of the lymphedema.

Cellulitis (Erysipelas) Cellulitis occurs irrespective of the cause of the lymphedema. Cellulitis is a sudden, noncontagious infection of the skin, characterized by redness, swelling, and heat, accompanied by pain and tenderness (Fig. 17.11).

In filarial lymphedema, recurrent episodes of acute dermatolymphangioadenitis (ADLA), equivalent to cellulitis, are characterized by diffuse inflammation and swelling often associated with an ascending lymphangitis and adenitis. Secondary bacterial infections appear to be important for the progression of the elephantiasis [13]. Therefore, not only does bacterial infection result from lymphedema, but also infection can progress lymphedema, resulting in a vicious cycle. Interdigital entry points between the toes appear associated with bacterial entry, precipitating ADLA. These «acute attacks» can be prevented with long-term penicillin and improvements in skin hygiene thus reaffirming the bacterial etiology as opposed to the acute attacks of fever from the microfilariae.

In primary and cancer-related lymphedema, recurrent cellulitis can be as common as in filariasis. Most episodes are believed to be caused by *Group A Streptococci*. However, microbiologists consider *Staphylococcus aureus* to be the cause in some patients [14]. Some episodes are accompanied by severe systemic upset, with high fever and rigors; others are milder, with minimal or no fever. Inflammatory markers (CRP, ESR) may, or may not, be raised. Cellulitis can be difficult to diagnose and to distinguish from other causes of inflammation particularly in the legs, e.g., lipodermatosclerosis (Fig. 17.10). Cellulitis most commonly affects one leg only, whereas lipodermatosclerosis more commonly affects both legs.

Antibiotic prophylaxis should be considered in patients who have two or more attacks of cellulitis per year. Penicillin V 250 mg bid should be the first choice [3]. Prophylaxis may need to be lifelong if relapse occurs when antibiotics are discontinued after a 2-year period of successful prophylaxis [► www.lymphoedema.org/Menu3/Cellulitis%20Consensus.pdf].

Fungal Infections Tinea pedis, a ringworm fungal foot infection, may be difficult to avoid because of web-space skin maceration from swollen toes (Fig. 17.12).

Viral Infections Viral infections are more common in lymphedema because of the immune dysfunction. Human papilloma wart virus infections can be difficult to resolve without effective tissue immunity (Fig. 17.13). Recurrent herpes simplex lymphangitis can be another problem caused by a viral infection (Fig. 17.14).

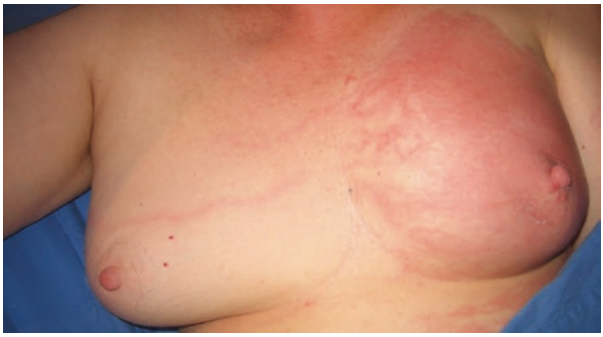


Fig. 17.11 Acute cellulitis with lymphedema of the breast. Lymphangitis can be seen tracking to the contralateral lymph drainage basin

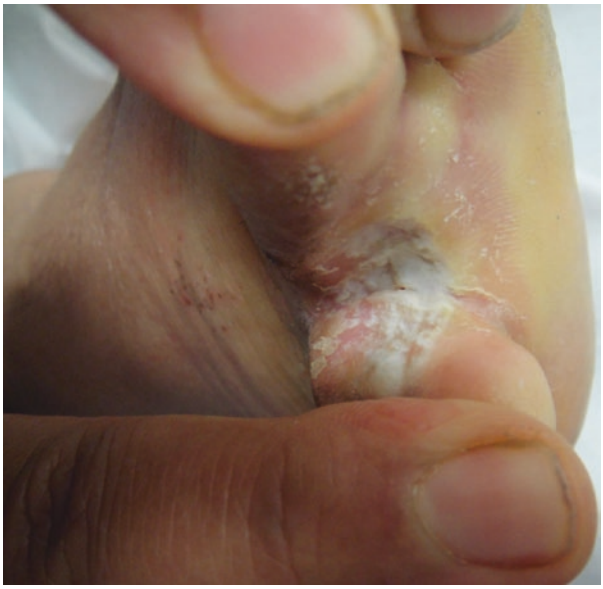


Fig. 17.12 Maceration between the toes is common entry point for bacteria and may be complicated by fungal infection

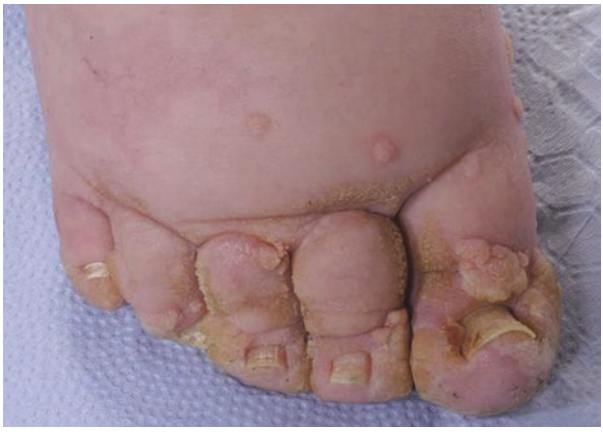


Fig. 17.13 HPV warts and «warty» change from lymphedema. It can be difficult to distinguish one from the other

17.10 Cutaneous Malignancy

17

A rare but important complication of chronic lymphedema is the development of cutaneous malignancy. Although the best known associated malignancy is lymphangiosarcoma (Fig. 17.15). Other tumors have been recorded and include basal cell carcinoma, squamous cell carcinoma, lymphoma, melanoma, malignant fibrous histiocytoma, and Kaposi's sarcoma.

The Stewart-Treves syndrome describes lymphangiosarcoma developing from well-established postmastectomy edema. However, lymphangiosarcoma is now described as occurring with lymphedema of any cause. The favored theory for the development of

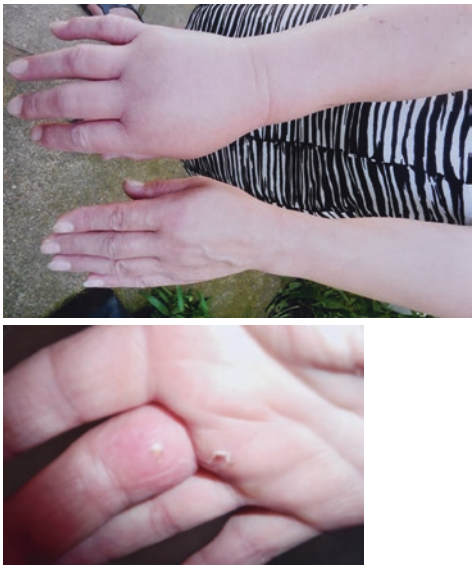


Fig. 17.14 Herpes simplex as a cause or recurrent lymphangitis/cellulitis

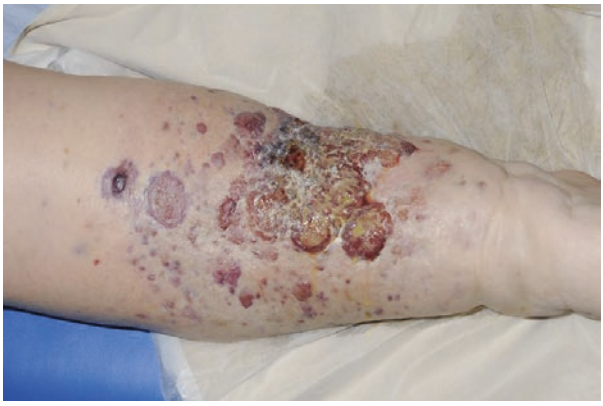


Fig. 17.15 Lymphangiosarcoma in primary lymphedema

malignancy in lymphedema is altered immune surveillance within the lymphedematous region [15].

Kaposi's sarcoma has an interesting relationship with lymphedema because it can both cause and result from lymphedema. Herpes virus 8, by infecting endothelial cells, causes KS.

17.11 Cutaneous Birthmarks

Cutaneous vascular birthmarks are not a manifestation of lymphedema but frequently coexist hence the reason for including them here. Vascular malformations (or nevi) usually arise because of a somatic mutation within the affected tissue region. Those

birthmarks associated with lymphedema are usually capillary malformations, but epidermal nevi also occur. Examples are the port-wine stain associated with Klippel-Trenaunay syndrome.

Many of these birthmarks are associated with overgrowth and caused by somatic mutations in the phosphatidylinositol/AKT/mTOR pathway. The spectrum of disorders caused by a PIK3CA mutation includes fibroadipose overgrowth, hemihyperplasia-multiple lipomatosis, congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal (CLOVES) syndrome, macrodactyly, and the megalencephaly syndrome [4].

Proteus syndrome is caused by a mutation in the AKT pathway. Also, overgrowth, lymphedema, and cutaneous malformations occur (Fig. 17.16). Skin biopsy reveals these can be cutaneous lymphatic malformations.

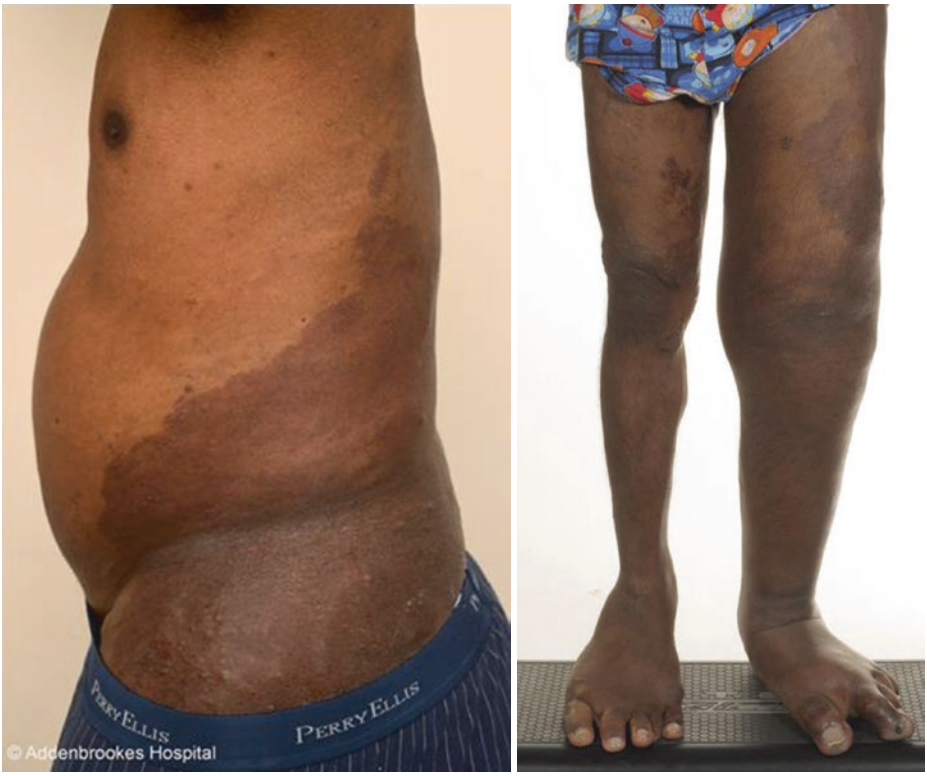


Fig. 17.16 Proteus syndrome caused by a somatic mutation in the AKT1 pathway and resulting in overgrowth and lymphedema in the left leg. Skin biopsy revealed the birthmark to be a lymphatic capillary malformation

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The Diagnosis of Edema and Its Pathogenesis

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Summary of Basic Concepts

Edema is the presence of an excess of interstitial fluid and is an important sign of ill health in clinical medicine. It is most common within the peripheral subcutaneous space. The differential diagnosis of edema comprises four broad categories: elevated hydrostatic pressure, pathological sodium retention, reduced plasma oncotic pressure, inflammation, and intrinsic malfunction of the lymphatic circulation.

- The presence of edema signals a failure of body fluid homeostasis.
- This homeostasis is governed by the Starling forces, namely, the hydrostatic and oncotic pressures that prevail in the plasma and in the interstitium, respectively.
- The modern view of the Starling forces suggests that there is a net, ever-diminishing filtration that occurs along the entire length of the capillary, with no venous reabsorption.
- Lymphatic homeostasis requires an equilibrium between the lymphatic load and the lymphatic transport capacity.

Edema is, of course, the hallmark presenting feature of lymphedema, yet it is self-evident that not every edematous patient should necessarily be assigned the diagnosis of lymphedema. Edema is the presence of an excess of interstitial fluid and is an important sign of ill health in clinical medicine. It may occur in the lungs (pulmonary edema), the abdominal cavity (ascites), and other body cavities (synovial, pericardial, and pleural effusions), but the most common site is within the peripheral subcutaneous space [1].

In the differential diagnostic evaluation for lymphedema, the clinician must understand, and have the capacity to distinguish, the various clinical categories of edema (Table 18.1). There are four broad pathophysiological categories to be considered: elevated hydrostatic pressure, pathological sodium retention, reduced plasma oncotic pressure, inflammation, and intrinsic malfunction of the lymphatic circulation.

In principle, the presence of edema signals a failure of body fluid homeostasis. The normal, continuous circulation of body water necessitates the appropriate contribution of multiple functions: normal cardiac pump function maintains cardiac filling pressures within normal limits; an intact vasculature ensures appropriate delivery of plasma water and its diffusion at the capillary level; exchange of extracellular and intracellular water and solutes; a functioning lymphatic system; balanced solutes within the body water, in order to maintain appropriate osmotic pressure equilibrium between intravascular and interstitial spaces and between interstitial and intracellular spaces; and normal renal excretory mechanisms for the elimination of excess water, solutes, and other products of metabolism.

The forces that govern this process were first related to one another in the work of Frank Starling [3]. While the fundamental relationships among plasma hydrostatic pressure,

Table 18.1 Categories of edema

Elevated hydrostatic pressure
Arteriolar dilatation
Neurohumoral mediation
Increased ambient or body temperature
Impaired venous return
Congestive heart failure
Pericardial constriction
Hepatic disease (ascites)
Sodium retention
Renal hypoperfusion
Renal insufficiency
Hyperaldosteronism
Reduced oncotic pressure
Cirrhosis
Malnutrition
Protein-losing enteropathy
Proteinuria
Inflammation
Acute inflammation
Chronic inflammation
Angiogenic
Lymphatic malfunction
Postsurgical
Postirradiation
Inflammatory
Neoplastic
Primary lymphatic insufficiency

interstitial hydrostatic pressure, plasma oncotic pressure, and interstitial oncotic pressure expounded by Starling continue to describe the fundamental functional relationships, these have more recently been reconsidered and partially modified (Fig. 18.1) [2, 4].

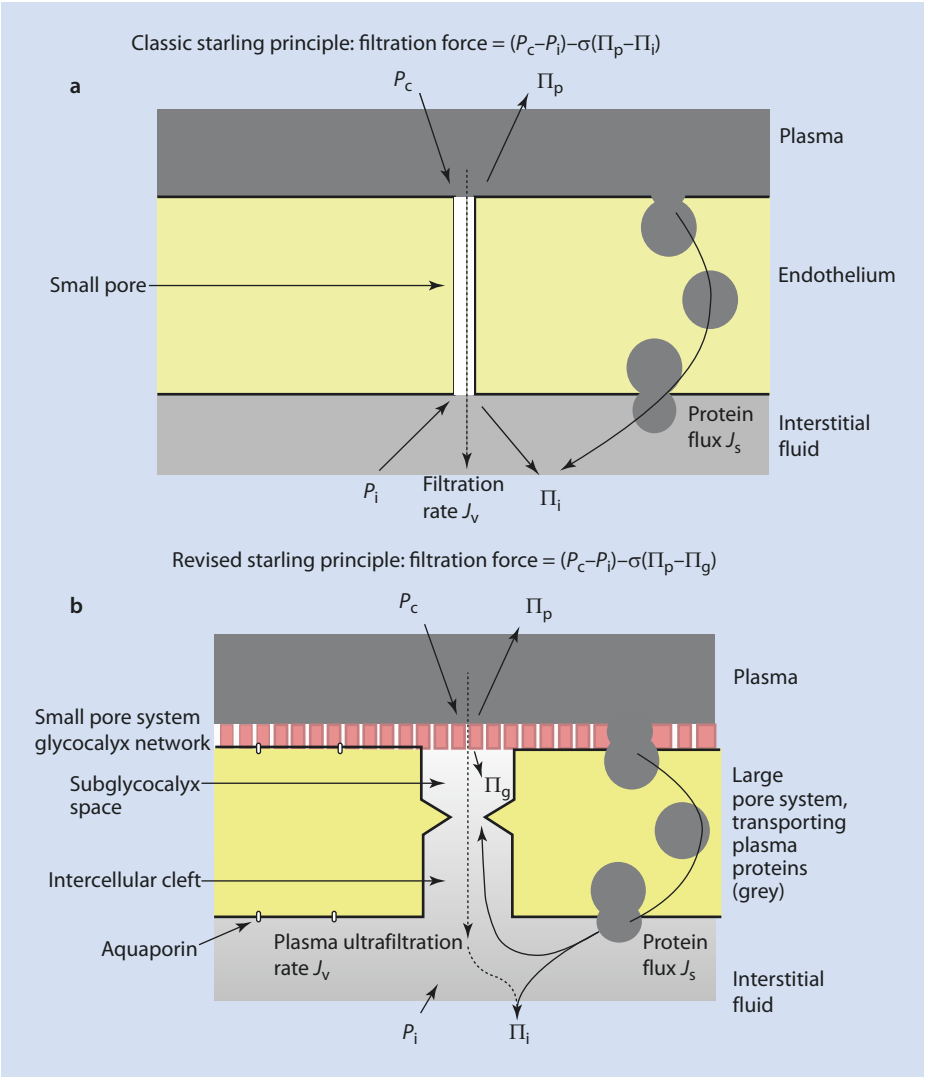

Fig. 18.1 Comparison of traditional and modified models of the endothelial semipermeable membrane and the operative forces. **a** Traditional view of continuous endothelium as a semipermeable membrane. **b** The glycocalyx-cleft model identifies glycocalyx as a semipermeable layer. Its underside is subjected to the colloid osmotic pressure of fluid high inside the intercellular cleft rather than interstitial fluid, with important functional consequences. *Gray shade* denotes concentration of plasma protein. P_c plasma hydrostatic pressure, P_i interstitial hydrostatic pressure, Π_c capillary colloid osmotic pressure, Πi interstitial colloid osmotic pressure, P_g glycocalyx hydrostatic pressure, Π_g glycocalyx colloid osmotic pressure, σ = osmotic reflection coefficient (Reprinted with permission [4])

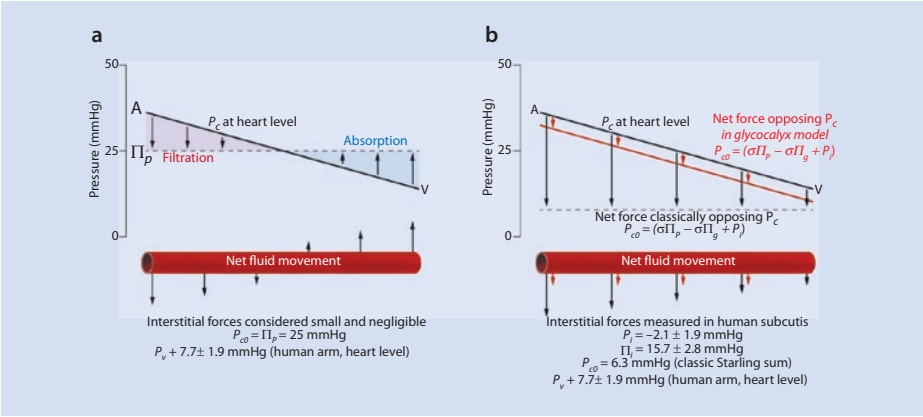

Fig. 18.2 **a** In the traditional view, interstitial forces are deemed negligible (the sum of Starling forces opposing filtration [P_0] = 25 mmHg, P_V = 7.7 mmHg). **b** However, interstitial forces are taken into account when using direct measurements (P_i = –2.1 mmHg, π_i = 15.7 mmHg, P_0 = 6.3 mmHg, P_V = 7.7 mmHg) (Reprinted with permission from Journal of Clinical Investigation [1])

If one relies upon the traditional view of these microvascular forces, as initially expounded by Starling, an interpretation can be elaborated that predicts net filtration of fluid at the arteriolar end of the capillary and net filtration at the venular end (Fig. 18.2a) [1]. However, if all Starling forces are considered, including interstitial colloid osmotic and hydraulic pressures, there is a net, ever-diminishing filtration along the entire length of the capillary, with no venous reabsorption (Fig. 18.2b).

In relationship to the pathogenesis of lymphedema, the central driving force can be considered to be the capillary hydrostatic pressure. This is the pressure that drives fluid out of the capillary by filtration and is highest at the arteriolar end of the capillary and lowest at the venular end. The mean capillary hydrostatic pressure is determined by the arterial and venous pressures (PA and PV) and by the ratio of postcapillary to precapillary resistance (RV/RA). Capillary pressure will change in proportion to a change in either arterial or venous pressure, but an absolute change in venous pressure is 5X more effective in changing capillary pressure than any given change in arterial pressure. This is because venous resistance is relatively low, and, therefore, changes in venous pressures are readily transmitted back to the capillary; in contrast, because arterial resistance is relatively high, changes in arterial pressure are more negligibly transmitted to influence the capillary pressure.

These concepts can be readily applied to a mechanistic approach to diagnosis and treatment of edema. Since it is the circulatory responsibility of the lymphatic vasculature to assure interstitial fluid homeostasis, the presence of edema, regardless of pathogenesis, can be regarded as a relative failure of optimal lymphatic function. This lymphatic «responsibility» for the presence of edema can, in turn, be interpreted as either an increase in lymphatic load, based on an inappropriate excess component of hydrostatic filtration, or as an inappropriate reduction in the lymphatic transport capacity, reflecting an insufficient function or structural integrity of the lymphatic

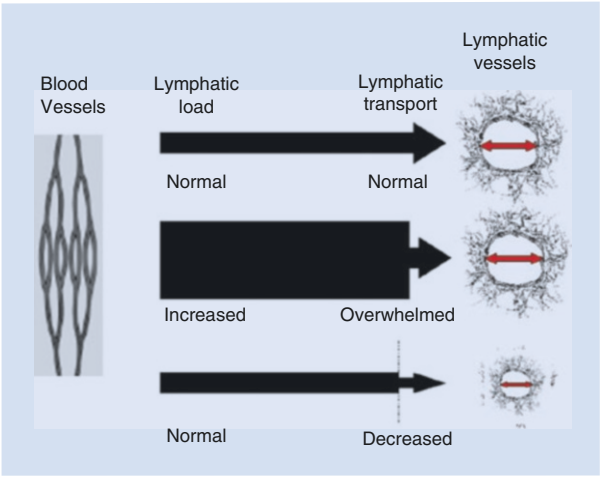

Fig. 18.3 The role of the lymphatic vasculature in the pathogenesis of edema can be interpreted as either an increase in lymphatic load, based on an inappropriate excess component of hydrostatic filtration, or as an inappropriate reduction in the lymphatic transport capacity, reflecting an insufficient function or structural integrity of the lymphatic vasculature, or any combination of the two

vasculature, or any combination of the two (Fig. 18.3). Increased lymphatic load might occur in the pathogenesis of congestive heart failure, where the elevated right heart pressures are communicated through the relatively low-resistance pathway of the veins to the capillary bed, where the capillary hydrostatic pressure is elevated, leading to increased filtration. Conversely, in obstructive or hereditary forms of lymphatic vascular insufficiency, even when lymphatic load is normal, the regional lymphatic transport capacity becomes sufficiently impaired to allow for interstitial edema accumulation. In any of these circumstances, attendant activation of the renin-angiotensin system and other neurohumoral responses can further exacerbate the propensity to edema formation and accumulation (Fig. 18.4) [5, 6].

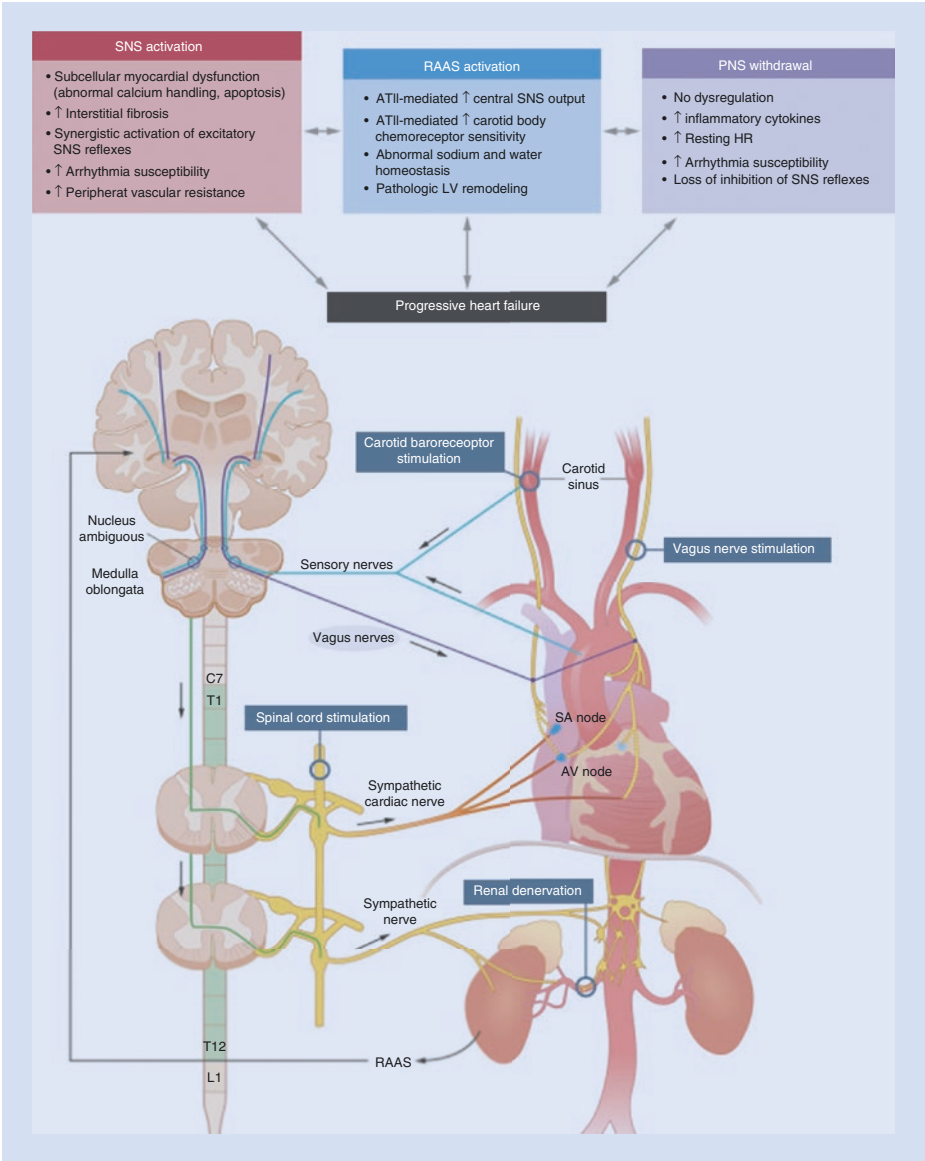

Fig. 18.4 Schematic demonstrating the synergistic relationships between autonomic imbalance, neurohormonal activation, and the pathogenesis of heart failure. (*Lower right*) Schematic highlighting the interactions between the central nervous system, heart, and kidneys. Anatomic sites of autonomic modulation are highlighted. *ATII* angiotensin II, *AV* atrioventricular, *HR* heart rate, *LV* left ventricular, *NO* nitric oxide, *PNS* parasympathetic nervous system, *RAAS* renin-angiotensin-aldosterone system, *SA* sinoatrial, *SNS* sympathetic nervous system (Reprinted with permission from [6])

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Differential Diagnosis: Venous Edema

Eri Fukaya

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Summary of Basic Concepts

- The lymph system and the venous system are intricately entwined, and symptoms of edema can occur independently or concurrently as phlebolymphedema [1].
- The pathophysiology of chronic venous insufficiency is prolonged venous hypertension.
- Careful physical examination is most useful for diagnosis of both lymphedema and venous edema.
- Duplex ultrasound examination is used to diagnose venous reflux and obstruction.

19.1 Lower Extremity Venous Anatomy

The venous system functions not only as a conduit to return blood to the heart but also as a blood reservoir of the circulatory system. The vein is made of three layers which are the intima, media, and adventitia. Compared to the artery, the muscular tunica media is much thinner in the vein which allows for the significant distensibility in maintaining a low-pressure system. The veins of the lower extremity start at the capillaries and become larger in size as they eventually reach the vena cava. The veins are divided into the deep veins, superficial veins, and perforator veins based on anatomical location and function [6]. The deep veins course deep to the muscle fascia, whereas the superficial veins course between the muscle fascia and dermis. The perforating veins connect the superficial veins to the deep veins by perforating the muscle fascia. Other non-named veins include the tributary veins which are the branch veins from the superficial veins and the communicating veins which connect the veins in the same compartment.

19.2 Pathophysiology of Venous Insufficiency

Venous insufficiency is the result of increased venous hydrostatic pressures. Since venous return depends on both the proper functioning of valves within the vein and the calf muscle pump function, valvular incompetence, obstruction, and calf muscle pump dysfunction will lead to venous insufficiency. Valvular incompetence can occur both within the deep and superficial veins [7]. This can be a primary or secondary incompetence following an injury such as deep vein thrombosis (DVT) or other causes including mass effect compressing the proximal veins, pregnancy, obesity, congenital anomalies, and lymphedema.

Prolonged venous hypertension causes inflammation around the vessel walls and causes venous wall injury and migration of inflammatory cells into the interstitial tissue, which lead to clinical changes seen with varicose veins and chronic venous disease. Increased venous pressure produces altered shear stress and mechanical pressure on the endothelial cells and promotes the production of E-selection, inflammatory molecules, chemokines, and prothrombotic precursors [8] (Fig. 19.1). The low shear stress and mechanical forces on the endothelium sensed by the intercellular adhesion molecule 1 (ICAM-1) also activate the recruitment of leukocytes. The glycocalyx in the endothelium works to prevent leukocyte adhesion, inflammation, and thrombosis. However, the

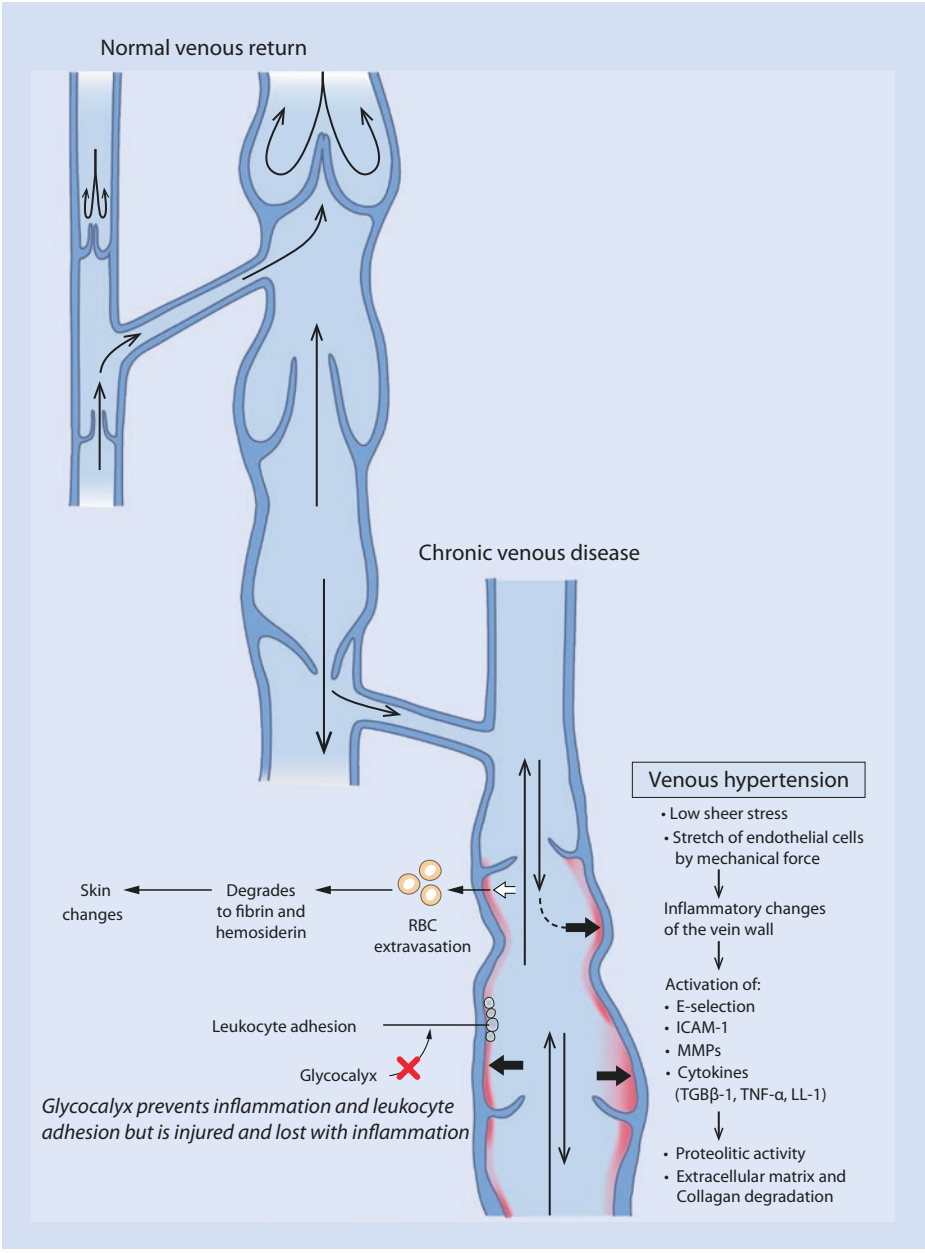

Fig. 19.1 Pathophysiology of venous insufficiency

inflammation caused by the venous hypertension leads to the injury and loss of the glycocalyx. In addition, changes in mechanical forces on the endothelium lead to nitric oxide production, release of vasoactive substance, and extravagation of erythrocytes into the surrounding tissue, which eventually degrades in to fibrin and hemosiderin. During this inflammatory process and increased mechanical pressure, matrix metalloproteinases (MMPs) and cytokines including TGF β-1, TNF- α, and IL-1 are produced [9]. MMPs are endopeptidases that cleave most of the constituents of the extracellular matrix, and out of the 23 found in humans, 14 have been localized in the vascular tissue. MMPs can affect the endothelium and smooth muscle in the vein wall causing changes in the venous constriction and relaxation properties. The examination of smooth muscle and dermal fibroblasts from varicose veins showed a decrease in collagen type III and an increase in collagen type I. Type III collagen is important for blood vessel elasticity and extensibility, while type I collagen is related to the rigidity. Interestingly, it appears that various MMPs play a role in the regulation of these collagen depositions, which can effect structural vein wall changes [2].

19.3 Physical Findings and Symptoms of Venous Insufficiency

In addition to obtaining history and inquiring about symptoms, physical examination is most important in the diagnosis for venous insufficiency. Common findings include telangiectasia, varicose veins, edema, brawny skin, hemosiderin staining (Fig. 19.2), tapering of legs above the ankles forming a constricting band resembling an inverted

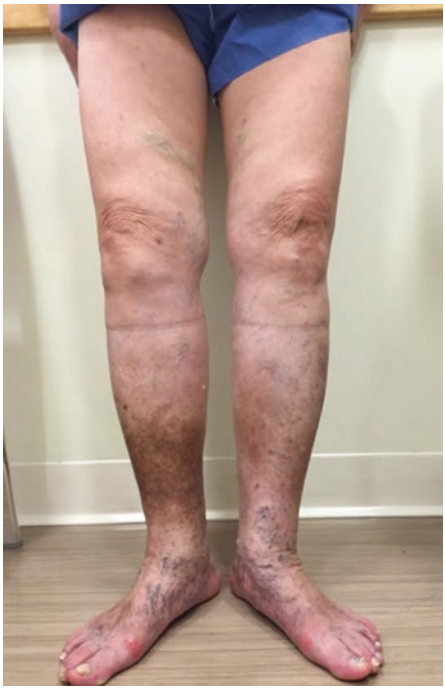

Fig. 19.2 Venous edema with hemosiderin deposits, varicose veins, reticular veins, and spider veins

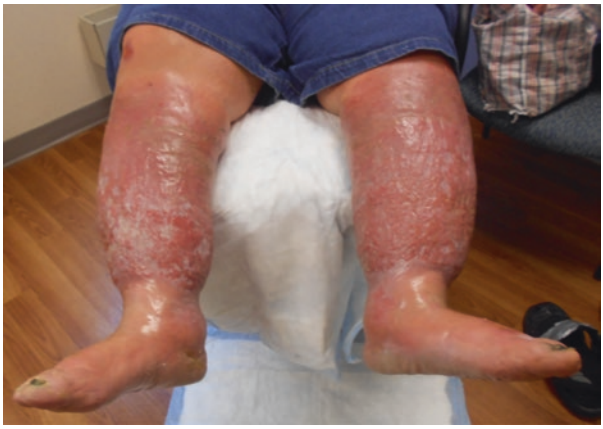

Fig. 19.3 Lipodermatosclerosis with ankle tapering

Table 19.1 CEAP classification

Clinical C0: No visible evidence of venous disease C1: Superficial spider veins (telangiectasia or reticular vein) C2: Simple varicose vein only C3: Ankle edema of venous origin C4: Skin pigmentation in the gaiter area C5: Healed venous ulcer C6: Active venous ulcer A: Asymptomatic S: symptomatic		
Etiology	*Anatomy*	*Pathophysiology*
EC: Congenital	AS: Superficial veins	PR: Reflux
EP: Primary	AD: Deep veins	PO: Obstruction
ES: Secondary	AP: Perforator veins	

champagne bottle (lipodermatosclerosis) (Fig. 19.3), polyangular ivory-white depressed atrophic plaques with prominent red dots within the scar (atrophie blanche), mottled discoloration (livedo reticularis), red/scaly/crusty/cracked occasionally oozing frequently itchy skin (stasis dermatitis), recurrent cellulitis, and ulcers. Venous ulcers usually have a distinct margin and can be highly draining. These lesions are distributed medially over the ankle and lower leg, especially just above the medial malleolus. The Clinical-Etiology-Anatomy-Pathophysiology (CEAP) classification (Table 19.1) is commonly used to describe the degrees of venous insufficiency [3, 10]. In addition to changes in appearance, venous insufficiency will result in symptoms of leg discomfort often described as heaviness, cramping, or aching after prolonged standing and relieved by leg elevation. There may also be tenderness along the dilated veins. Severe cases of venous obstruction may cause claudication symptoms or

severe pain with cyanosis and edema of the affected limb (phlegmasia cerulea dolens). Although this does not occur frequently, it requires urgent attention if noted as it can lead to venous gangrene.

19.4 Duplex Ultrasound Examination

Duplex ultrasound examination is the most useful noninvasive testing to examine valvular incompetence and obstruction and to map venous anatomy. The duplex ultrasound examination examines vein compressibility, venous compliance, vein wall changes, and valvular incompetence and is able to directly map venous patterns. Venous obstruction is diagnosed by non-compressibility and loss of flow by color Doppler in the examined vein. Valvular incompetence is assessed using compression maneuvers such as leg compression or Valsalva. The venous reflux time following a venous compression maneuver is used to determine valvular incompetence. A venous reflux time of greater than 1 s in the above-knee deep veins (femoral and popliteal vein) and 0.5 s in the superficial veins, perforator, and the below-knee deep veins (posterior tibial, peroneal veins) is determined as incompetent and useful for diagnosis of axial reflux. Although duplex ultrasound examination is the gold standard for detecting venous valvular incompetence and obstruction, it is important to note that the absence of these findings does not rule out venous insufficiency since chronic venous insufficiency as a result of increased venous pressures can be present without significant ultrasound findings [4].

19.5 Other Diagnostic Examinations

When venous obstruction is suspected proximal to the inguinal ligament, duplex ultrasound examination may have insufficient penetration to sufficiently evaluate the veins depending on the patient's body habitus. In such cases, anatomical studies with MR or CT venogram are necessary to evaluate patterns of obstruction and venous compression.

Although not commonly used, physiologic testing with plethysmography is a useful noninvasive test that measures limb volume changes to detect venous insufficiency.

19.6 Lymphedema Versus Venous Insufficiency Versus Phlebolymphedema

Lymphedema and venous insufficiency can often be difficult to differentiate especially in mild disease with minimal other symptoms outside of edema. In addition, the vascular and lymph system are interdependent; thus, venous and lymph disease can occur concurrently and present as phlebolymphedema [5]. An increase in lymphatic load can occur with chronic venous insufficiency causing increased pressure in the venous end of the capillary. This will impact the lymph system by increasing the volume load on the

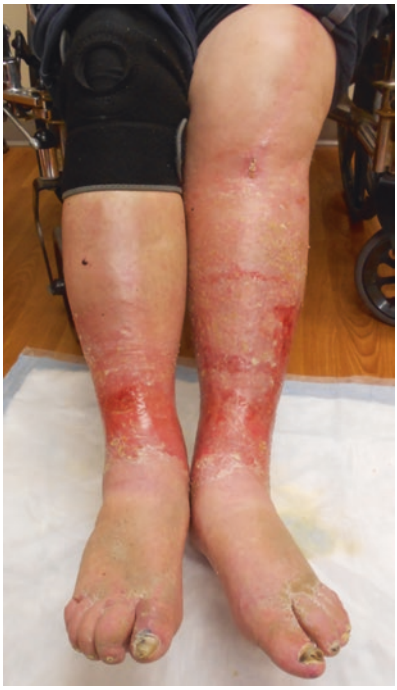

Fig. 19.4 Phlebolymphedema with positive Stemmer sign

system. Thus, long-standing chronic venous insufficiency can cause lymph drainage problems and become a phlebolymphedema (Fig. 19.4). This is commonly observed, especially in obese patients.

A thorough physical examination to evaluate specific findings for each disease is very valuable. Differentiating findings include varicose, spider, and reticular veins, brown discoloration secondary to hemosiderin deposits in venous insufficiency, dorsal foot swelling with squared-off appearance, up-sloped «ski-jump» nail changes, positive Stemmer sign, limb skin temperature, thickened skin with increased hyperkeratosis, hyperpigmentation, and papillomatous or verrucous skin in lymphedema (Fig. 19.5).

19.7 Clinical Management

Venous disease presents as a spectrum of disease starting from small spider veins which may be aesthetically unpleasing but otherwise irrelevant to severe disease with significant swelling and/or recurrent non-healing highly exudative ulcers. Thus, strategies for clinical management vary depending on disease severity.

In general, conservative treatments for venous insufficiency include weight loss, exercises using calf muscle pump function, leg elevation, and use of compression stockings. If sufficient symptomatic relief cannot be achieved with conservative treatment,

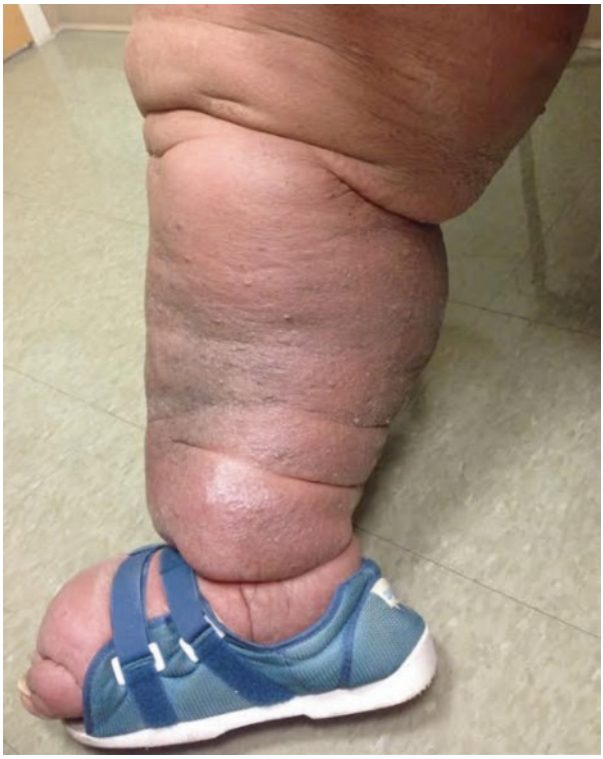

Fig. 19.5 Lymphedema with papillomatous skin

venous procedures including sclerotherapy, phlebectomy, stripping, ablation, thrombolytic therapy, endovascular stenting, and such can be performed; however, the details of these procedures will be another topic.

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Differential Diagnosis: Lipedema

Győző Szolnoky

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20

Summary of Basic Concepts

Lipedema, the disproportionate, symmetrical adipose swelling characterized by spontaneous or mild trauma-induced pain and bruising, is a common feminine disease.

The pathomechanism is nearly unknown; however, the role of estrogen is presumable, and the familial accumulation is fairly common.

Treatment comprises weight control and noninvasive (decongestive lymphatic therapy) and invasive (liposuction) interventions, while the maintenance therapy usually includes elastic compression.

Early diagnosis and treatment are of outmost importance so as to prevent impaired mobility, arthrosis, and lymphatic insufficiency.

20.1 Introduction

Lipedema is an infrequently recognized and often neglected clinical entity that nearly always affects women. It poses a significant importance as being one of the most common disorder to be mistaken with lymphedema [1, 6–8].

20.2 Definition

Lipedema is a disproportional obesity characterized by bilateral, symmetrical, biker's hosiery-shaped fatty swelling of the legs, whereas arms are also commonly involved [1, 6–8]. Different synonyms are found in the literature (adiposalgia, adiposis dolorosa, adipositas spongiosa, adiposis edematosa, thick leg of healthy woman, fat leg, fatty edema, lipidosis, lipomatosis dolorosa, rider's hosiery disorder, column leg, stove pipe leg, jelly leg, areal adiposity, lipohypertrophia corporis inferioris, segmental adiposity, inferior obesity), and this abundance of the terminology and unclear definitions has partially resulted in confusion about lipedema, causing underdiagnosis and mistreatment [9].

This is a feminine disease, and males usually develop lipedema on the basis of hormonal disturbance; however, there is one published case report where a healthy man was diagnosed with lipedema [10]. The general incidence of lipedema among women is supposed to be around 11% [7]. 10–18% of all patients referred to lymphedema clinics are diagnosed to have lipedema. It has been suggested that in all women with increased fat deposits of the lower extremities, 60% is caused by obesity, 20% by lipedema, and 20% by a combination of both [1].

Manifestation of lipedema usually starts after puberty [1, 7, 8]. According to the current knowledge, lipedema is likely an estrogen-regulated polygenetic disease which manifests in parallel with feminine hormonal changes and leads to blood and lymphatic angiopathy. The presumed inflammation of peripheral nerves and sympathetic innervation abnormalities of the subcutaneous adipose tissue involving estrogen may be responsible for the neuropathy-like feature. Adipocyte hyperproliferation is supposed to be a secondary phenomenon [2, 7, 11, 12]. Two leading hallmarks are the frequent hematoma formation by even minor traumatic injuries and spontaneous or palpation-induced pain [1, 6–8]. Lipedema, especially in advanced stages, is quite frequently combined

with lymphatic or venous insufficiency that may strongly modify the original limb shape resembling the features of identical vascular abnormality [1, 7, 8].

20.3 Clinical Diagnosis

In most cases the diagnosis of lipedema can be established by patient history and clinical examination [1, 7, 8]. There is no absolutely unambiguous pathognomonic diagnostic test for lipedema.

20.4 Classification

In stage I, the skin looks flat, but the subcutis is already enlarged and on palpation feels like «Styrofoam balls in a plastic bag» (see Fig. 20.1). In stage II (see Fig. 20.2), walnut- to apple-sized indurations develop, and the overlying skin has an irregular surface

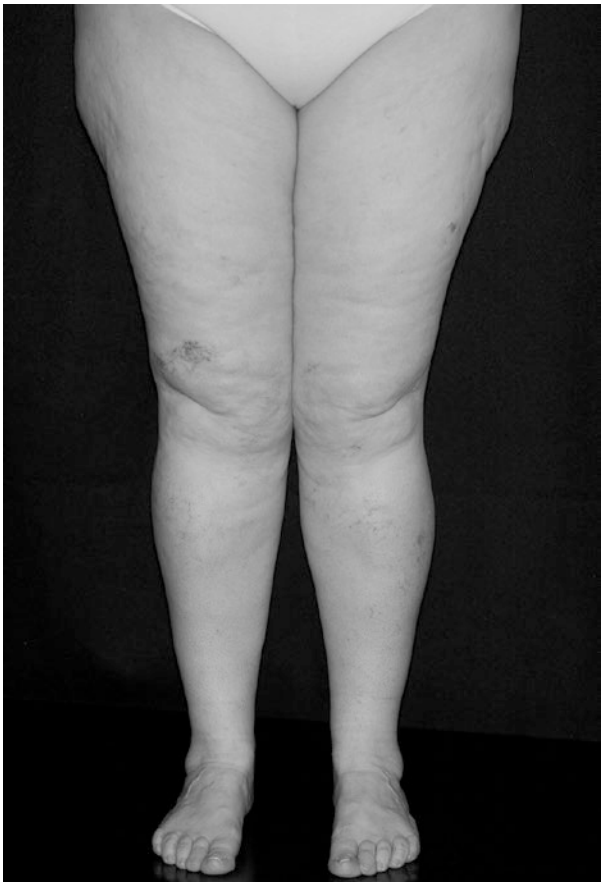

Fig. 20.1 Stage I lipedema

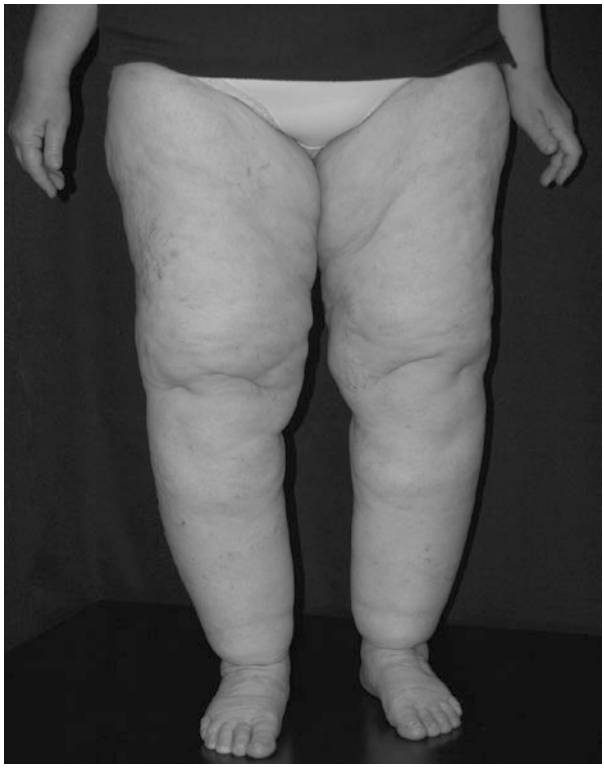

Fig. 20.2 Stage II lipedema

(«mattress phenomenon»). Stage III shows larger indurations and deformations, even lobular fat deposits (see Fig. 20.3).

The same working group suggested a classification concurring with the location of the fat deposits: mainly buttocks (type I), buttocks to knees (type II), buttocks to ankles (type III), arms (type IV), and lower legs (type V) [2].

20.5 Differential Diagnosis

The most notable differential diagnosis of lipedema (see Tables 20.1, 20.2, and 20.3) embraces obesity and various forms of lipohypertrophy and phleb- or lymphedema. Further elaboration of the causes of calf edema (idiopathic cyclic, internal disease-associated, and orthostatic edema) concerns pitting edema.

Uni- or bilateral phlebedema is a hallmark of chronic venous insufficiency. Pitting edema usually disappears or is minimal after bed rest. In contrast to lymphedema, Stemmer's sign is mostly negative [2].

In obesity, the distribution of subcutaneous fat deposits is mostly generalized. Simple obesity may equally affect males and females. Furthermore, the typical sparing of the feet and the pain of lipedema are lacking. Unlike lipedema, simple obesity efficiently

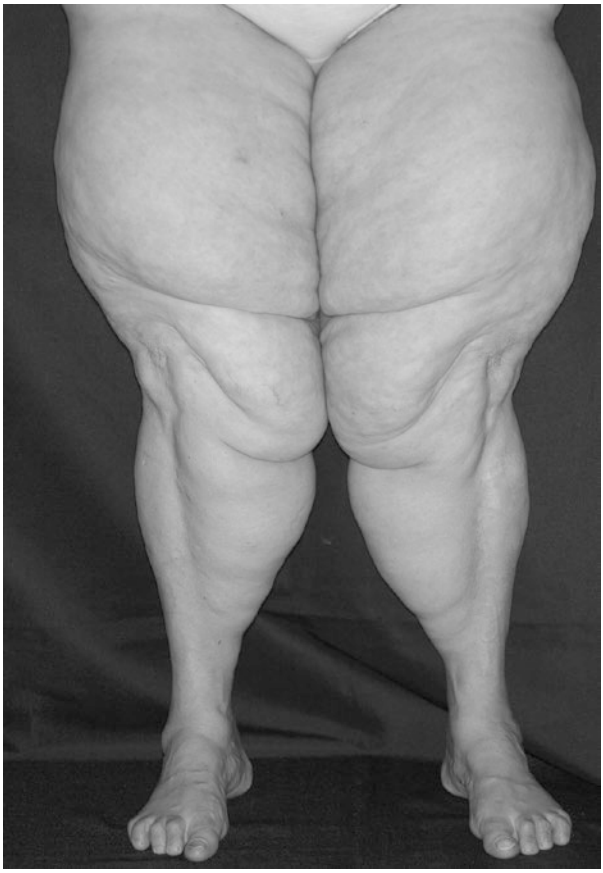

Fig. 20.3 Stage III lipedema

responds to restricted diet and increased exercise. Lipedema is frequently combined with obesity, and altered body structure may misdirect examiner resulting in false diagnosis. Early lipedema may associate normal weight [7, 13].

Lipohypertrophy is described as increased symmetrical subcutaneous fat deposits, mostly on the legs and arms in women [14]. Lipedema is preceded by lipohypertrophy. The basic difference between lipohypertrophy and lipedema is found in the absence of edema and pain in lipohypertrophy; however, there are also painful lipohypertrophy subtypes. The widely used substratification talks about lipomatosis indolens simplex (multiple lipomas without relevant symptoms), lipomatosis dolorosa (painful fat deposition), lipomatosis atrophicans (accompanying fat atrophy), and lipomatosis gigantea (overgrowing fatty parts).

The term «lipodystrophy» is usually reserved for local damaged subcutaneous fat [15]. Acquired partial lipodystrophy unequivocally refers to Barraquer-Simons syndrome where adipose tissue loss is noted primarily in the neck, face, arms, thorax, and upper abdomen. The clinical onset commences the childhood or adolescence of mostly females. Women are frequently subjected to hirsutism, amenorrhea, or polycystic ovary syndrome.

Table 20.1 Differential diagnosis

	Gender	Family history	Onset	Location	Symmetry	Excess fat	Pain at pressure
Lipedema	Female	Possible	Puberty	Leg, arm	Yes	Yes	Yes
Lipohypertrophy	Female	Possible	Convalescent, adult	Hip	Yes	Yes	Rarely
Primary lymphedema	Female > male	Yes	From birth to third decade	Buttock, leg, arm	Uni- or bilateral	Possible	No
Phlebedema	Both	No	Adult	Leg	Uni- or bilateral	No	No
Morbus Dercum	Female	No	Menopause	Neck	Yes	Yes	Yes
Morbus Madelung	Male	No	Adult	Arm, trunk, leg	Yes	Yes	No
Obesity	Both	No	Adult	General	Yes	Yes	No

Table 20.2 Differential diagnosis

	Edema	Foot affection	Arm affection	Dietary effect	Effect of elevation	Stemmer's sign
Lipedema	Yes	No	Yes	No	Minimal	No
Lipohypertrophy	No	No	Yes	No	No	No
Primary lymphedema	Yes	Yes	Possible	No	Minimal	Yes
Phlebedema	Yes	Possible	No	No	Efficient	No
Morbus Dercum	No	No	No	No	No	No
Morbus Madelung	No	No	Possible	No	No	No
Obesity	Rarely	No	Yes	Yes	No	No

Dercum's disease (lipomatosis dolorosa) is a rare, symmetrical disorder involving the inner side of the upper arms, elbows, stomach wall, buttocks, inner and outer surfaces of thighs, and knees with painful subcutaneous adipose tissue deposits [16, 17]. Severe hyperalgesia is triggered even by light pressure. It is 5–30 times more frequent in women than in men and usually results in a number of psychosocial problems that may partially

Table 20.3 Differential diagnosis

	Ankle fat pad	Consistency	Pitting edema	History of cellulitis	Progression	Hereditary factor
Lipedema	Yes	Soft-to-firm	No	No	Yes	Probable
Lipohypertrophy	No	Soft	No	No	No	No
Primary lymphedema	No	Firm	Yes	Yes	Yes	Yes
Phlebedema	No	Soft-to-firm	No	No	Yes	Possible
Morbus Dercum	No	Soft-to-firm	No	No	Yes	No
Morbus Madelung	No	Soft-to-firm	No	No	Yes	No
Obesity	No	Soft	No	No	Yes	No

be attributed to the context of chronic pain syndrome. Other characteristic symptoms are swollen hands and fingers with accompanying paresthesias, numbness, joint stiffness, dryness of eyes and mouth, and telangiectasia with increased fragility of vessels causing ecchymoses. It may first occur in the menopausa and associates no edema.

Benign symmetric lipomatosis (Madelung's disease or Launois-Bensaude syndrome) is a rare, benign disorder of unknown etiology [18, 19]. This syndrome is characterized by multiple, symmetric, nonencapsulated fatty accumulation diffusely involving neck and upper trunk areas. It uncommonly involves the lower limbs and lower trunk. Madelung's disease can be divided into three major forms according to localization: type I (neck), type II (shoulders, interscapular region, and upper arms), and type III (lower trunk). In other stratifications, there are proximal (neck, shoulders, scapular region), central (backs, thighs), and distal forms (knees, hands, and feet). Postulated etiologies include abnormal proliferation of brown fat cells and mitochondrial mutations. It predominantly affects middle-aged men of Mediterranean origin with a history of alcohol abuse. It is usually asymptomatic; however, in advanced forms dysphagia, diminished cervical range of motion, hoarseness, and respiratory complications may appear. Glucose intolerance and increased serum insulin level are commonly found. There are signs of primary neuropathy and neurogenic muscular atrophy.

Steatopygia is characterized by protrusion and excessive fatness localized solely to the buttock region [20].

Fibro-fatty syndrome (juxta-articular adiposis dolorosa) shares some similarities with lipedema as having enlarged fatty mass on thighs and the inner side of knee joints; however, some experts consider this disorder as the early form of Dercum's disease [21]. In half of the cases, there are additional foot deformity and varicosity. Compromised lymphatic and venous circulation are believed to play a significant role in the maintenance and further progression of this disorder. It is sometimes combined with arterial hypertension.

20.6 Laboratory Diagnosis

20.6.1 Waist-to-Height Ratio

Of the anthropometric measurements, waist-to-height ratio may give the most reasonable results in lipedema [13].

20.6.2 Capillary Fragility Assessment

Bruising is attributed to increased capillary fragility in lipedema [1, 7, 8, 22]. Capillary fragility measurement is accomplished with a vacuum suction chamber (Parrot's angiosterrometer) exerting an adjustable suction to the skin. Determination of capillary fragility is based on the count of viable petechiae. Non-complicated simple obesity was compared with non-complicated lipedema from the perspective of capillary fragility (unreported study). The vacuum suction method revealed that the number of viable petechiae was significantly higher in the lipedema group emphasizing the possible role of angiosterrometry or other methods of capillary fragility measurement as a possible tool for discrimination.

20.6.3 Assessment of Aortic Distensibility [23] and Stiffness [23] in Lipedema

In a recent trial where women with non-complicated lipedema were compared with healthy age- and BMI-matched individuals, lipedema associated notably higher aortic stiffness and lower distensibility.

20.6.4 Pain Perception Assessment

Pinch test is the simplest method for pain detection [7]. Lipedematous pain is complicated to describe; therefore, a 30-item questionnaire was designed to characterize the most typical adjunctives [24]. A four-grade scale was assigned to each item, and adjunctives with the highest grades referred to the most characteristic descriptions. In a comparative clinical trial, the top ten fitting items as well as a special numerical analogue scale (from 0 to 10) called pain rating scale [25] and Wong-Baker FACES scale were applied for pain assessment [26].

20.6.5 Dual-Energy X-ray Absorptiometry

Dual-energy X-ray absorptiometry (DEXA) is capable of measuring regional body composition including the extension of adipose tissue. DEXA is, of course, a useful tool helping clinicians in differential diagnosis and also in the assessment of the efficacy of various invasive or noninvasive interventions [27].

20.6.6 Ultrasound Examination

High-resolution duplex sonography is a method that can distinguish lipedema from phleb- or lymphedema with a high level of sensitivity [28, 29].

Lipedematous subcutaneous tissue is definitely enlarged and has substantially higher echogenicity («snowfall sign») without echo-losing spaces or channels. Subcutaneous septa are thickened having increased echogenicity. Lymphedema has thickened subcutaneous tissue with enhanced echogenicity associating small, <1 mm echo-losing spaces as initial dilated lymphatic vessels and larger, longer echo-losing spaces and channels with echo-rich margins as lymphatic collectors under congestion. Beyond venous stasis and dilated, often varicose veins, no specific duplex ultrasound feature is described in phlebedema.

20.6.7 CT and MRI Examination

CT [30] and MRI [31] are rather indicated for scientific purposes or subtle cases and show that the real edema is minimal and that limb swelling can mostly be attributed to bilateral homogeneous enlargement of the subcutaneous compartment in the early stages of lipedema.

These examinations are capable of volumetry, the evaluation of various tissue components and simultaneous display of blood or lymphatic vessels with high precision [32].

20.6.8 Lymphoscintigraphy and Fluorescent Microlymphography

The peculiar enlargement of subcutaneous fat is presumably linked with microangiopathy and altered microcirculation leading to increased permeability and protein-rich fluid extravasation that further enhances the amount of interstitial fluid. Therefore, in less advanced forms of lipedema, increased lymph flow may be visualized by lymphoscintigraphy. Lymph vessels must raise their transport capacity, because of augmented capillary filtration and increasing volume of interstitial fluid. In later stages, the lymphatics may become exhausted [33, 34]. Fluorescent microlymphography displays lymphatic microaneurysms and dilated vessels of the uppermost lymphatic network, indicating that lymph vessels are also involved [35].

20.7 Clinical Management

However, lipedema is believed to be fairly recalcitrant to dietary approaches, and anecdotic reports have been able to show some benefit of various diets, but none of them have been confirmed by controlled trials. Nevertheless, weight control is of outmost importance in preventing or slowing down the progression of lipedema. The conservative approach corresponds to complex decongestive physiotherapy (CDP) consisting of manual lymph drainage (MLD) and optionally intermittent pneumatic compression (IPC) physical exercise, multilayered compression bandaging, and meticulous skin care

[7]. The first observational study on the effect of CDP in lipedema showed that the maximally achieved reduction was nearly 10% of the original leg girth [36]. In a clinical study, MLD-based CDP was compared with MLD plus IPC-based CDP. Each treatment modality resulted in significant limb volume reduction; however, no significant difference was proven between the two regimens [3]. In other controlled trials, MLD + IPC-based CDP drastically decreased capillary fragility and pain perception of lipedema patients [4].

Various forms of liposuction as an invasive intervention give reliable and durable benefit (improvement in spontaneous pain; sensitivity to pressure, edema, and bruising; and restriction of movement) to lipedema patients without proven damage of lymphatics [5, 37].

20.8 Prognosis

Early diagnosis and treatment are mandatory for this disorder; otherwise gradual enlargement of fatty deposition causes impaired mobility, debilitating condition, and further comorbidities like arthrosis and lymphatic insufficiency. Interlobar areas may become susceptible for fungal and especially bacterial infections that may further progress to cellulitis or septicemia especially when coexisting with lymphedema is present. Lipedema has remarkable psychological impact ranging from mild upset to severe anxiety, depression, or even anorexia [1, 7, 8].

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Laboratory/Imaging Diagnosis

Contents

General Guidelines

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21

Summary of Basic Concepts

- Indications for diagnostic tests in extremity edema.
- Purpose of diagnostic procedures.
- Description of basic tests and imaging methods.
- What novel tests can we anticipate in the future.

21.1 Why?

In majority of patients diagnosis of lymphedema is straightforward and does not require specialist investigations; however, some basic tests are recommended to rule out concomitant diseases and other causes of edema.

21.2 When?

In every patient with suspected lymphatic disorder at the time of initial evaluation, basic panel of blood tests and imaging should be done. Genetic testing is not routine and should be considered in patients with family history of lymphedema and with syndromic lymphedema. Testing for lymphatic filariasis is mandatory in all patients at risk (coming from areas endemic for lymphatic filariasis).

21.3 What for?

The primary goal of testing is screening for coexisting systemic disorders (congestive heart failure, liver and kidney insufficiency, hypothyroidism, autoimmune diseases, etc.). It is also necessary to confirm the presence of lymphatic pathology and to visualize in detail lymphatic anatomy in selected patients planned for surgical procedures. In patients with familial lymphedema, genetic testing is available, and some specific gene mutations and chromosome abnormalities can be identified.

21.4 What Methods?

Basic blood and urine tests should be considered in every patient at the first-time visit. The blood test should include full blood count, urea and electrolytes, thyroid function tests, liver function tests, plasma total protein and albumin, erythrocyte sedimentation rate, C-reactive protein, B-natriuretic peptide, and antinuclear antibody screen in selected patients. In patients with suspected filarial lymphedema, test for circulating filarial antigen or demonstration of microfilariae or filarial DNA in the blood is necessary to rule out or confirm lymphatic filariasis.

Several gene mutations were identified in patients with familial lymphedema: VEGFR3 (Milroy disease), FOXC2 (distichiasis-lymphedema), SOX18 (hypotrichosis-lymphedema-telangiectasia), CCBE1 (generalized lymphatic dysplasia-Hennekam syndrome), GJC2

(inherited lymphedema type 1C), PTPN14 (lymphedema-choanal atresia), GATA2 (Emberger syndrome), VEGFC (Milroy-like lymphedema), GJA1 (oculodentodigital syndrome), KIF11 (microcephaly – lymphedema and chorioretinopathy), and others. Also genetic and chromosomal defects were identified in syndromic lymphedema, e.g., Turner syndrome (45X0); Klinefelter syndrome (47XXY); trisomies 21, 13, and 18; Noonan syndrome (PTPN11, KRAS, SOS1); neurofibromatosis type 1 (NF1); and others.

21.4.1 Imaging Methods

Discovery of mesenteric lymphatic vessels by Gaspare Aselli was possible because mesenteric lymphatics were filled with white chyle. Subsequently using various contrast media like mercury and black ink, researchers were able to study the lymphatic system in animals and humans. All these studies were possible in cadavers. Since 1933 Patent Blue V was used to visualize skin lymphatics in humans. Patent Blue injection enabled visualization of small lymphatics in the skin and lymphatic trunks after skin incision. Maurice Servelle in 1943 performed first contrast lymphangiography [1].

X-ray contrast lymphangiography was further developed by Kinmonth and others [2]. For the first time images of lymphatic anatomy in healthy persons and patients with lymphatic disorders like lymphedema were seen. Visualization of lymphatics and possibility of precise description of anatomical defects in patients with lymphedema led to attempts to surgical correction of lymphatic defects. In patients with chylous reflux and enlarged, valveless lymphatic trunks, surgical ligation was performed. In patients with obstruction of the lymphatic trunks, lymphaticovenous anastomoses were introduced. Therefore lymphatic microsurgery followed development of new imaging methods [3].

Lymphoscintigraphy (lymphangioscintigraphy) uses various radiotracers (isotope-labeled colloids) to depict lymphatic vessels and assess lymphatic function. Introduced in the 1950s, it practically replaced lymphangiography in the diagnosis of lymphatic disorders. Lymphoscintigraphy is a safer and easier procedure than oil contrast lymphangiography which is nowadays reserved for selected cases of chylous reflux and thoracic duct abnormalities.

All current guidelines recommend radionuclide lymphoscintigraphy as the basic diagnostic method in lymphedema and disorders of the lymphatic system.

The radionuclide lymphoscintigraphy remains the gold standard of lymphedema diagnosis. It allows to depict lymphatic anatomy as well as function. It is also safe and minimally invasive [4].

Near-infrared fluorescence imaging is a relatively new emerging diagnostic method proved useful in early lymphedema diagnosis. It is minimally invasive but however has some limitations like cost of the camera and ability to visualize only the superficial lymphatics.

Oil contrast lymphography remains reserved for selected patients with lymphatic abnormalities planned for microsurgical repair.

Ultrasound evaluation of venous system is obligatory in the initial evaluation of patient with swollen extremity. It allows to exclude venous pathology especially deep venous thrombosis in patients with lymphedema. Assessment of subcutaneous tissue allows to measure skin and subcutaneous tissue thickness and fluid accumulation.

CT and MR imaging helps to diagnose complex vascular malformations with lymphatic involvement. It helps to diagnose underlying or concomitant pathologies like malignancies.

To monitor lymphedema treatment traditionally, circumference measurements are used; however, bioimpedance and ultrasound are proven to be useful.

21.5 Future?

Future research will bring us biomarkers of lymphostasis; broader utilization of proteomics, metabolomics, and lipidomics for a better characterization of patients; identification of patients at risk; and monitoring therapy. Functional genomics will help to identify and characterize individual risk and course of lymphedema. Improved imaging methods with broader utilization of novel lymphography methods like ICG lymphography and MR lymphography will allow to better understand pathology and pathophysiology of lymphedema and accelerate development of new therapies.

21.6 ISL/ILF Guidelines

Current guidelines of ISL, ILF, and IUP unanimously agree that careful history and physical examination followed by lymphoscintigraphy, venous ultrasound, and basic blood tests should be performed in all patients suspected for lymphatic pathology [5–7].

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Radionuclide Lymphoscintigraphies

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Summary of Basic Concepts

The principle of lymphoscintigraphies has to be kept in mind by the nonspecialists in imaging. This principle in its application can be formulated as follows: if of adequate size (usually under 100 nM) and if labeled with a gamma-emitting radioisotope (usually Technetium (Tc)-99 m), these radiolabeled particles (also called the «tracer» in this chapter) and using scintigraphic techniques will allow:

- Study and quantification of their removal by the initial lymphatics from the tissue where they are injected.
- Study and visualization of the lymphatic vessels efferent from the injected site and where they will be transported and will transit.
- Demonstration of the lymph nodes that are part of these lymphatic pathways and where these particles, if colloidal, will be partly trapped by the reticuloendothelial cells during their intra-nodal transit.
- When they reach the systemic circulation (after their transit in the thoracic duct when the tracer is injected in the lower limbs), study of their accumulation in the liver (and sometimes the spleen and bone marrow), where their uptake is finally representative of the lymphatic load extracted from the limb or organ studied.

22.1 The Physicians, the Edemas of Lymphatic Origin, and Their Imaging Techniques?

Physicians currently face three main problems when imaging lymphedema. The first issue is related to the clinical symptom – the edema, which can be observed anywhere on the body. The term «lymphedema» can be used only if the edema has been demonstrated as caused (either partly or totally) by an abnormality involving the lymphatic system. This causality can be obvious in the case of secondary edema related to prior events, such as surgery with removal of lymph nodes, radiotherapy on diseased lymph nodes, trauma or surgery that damages the lymphatic vessels, and infections that damage the lymphatic vessels or lymph nodes; however, the causality can frequently be less clear with other types of edema. Some clinical presentations may directly suggest a diagnosis of primary lymphedema, as is the case in the familial setting (i.e., with other members of the family presenting with an edematous limb, the true familial hereditary lymphedemas), in association with other symptoms (i.e., part of a syndrome that includes lymphedema), and when they are either present at birth («congenital» lymphedemas) or arise typically within the first decades of life (lymphedema «praecox»). However, most of these primary lymphedemas frequently affect a single individual in one family and may be clinically apparent only later in the patient's life (i.e., lymphedema «tarda»). Additionally, clinicians more frequently face edematous situations that are associated with other symptoms and for which lymphatic system involvement represents only one of the pathogenic factors (e.g., phlebo-lymphedema, lipo-lymphedema, cyclic edemas).

The second problem for the clinician is which questions to ask and which answers to seek for the purposes of establishing a diagnosis, ruling out differential diagnoses, and selecting the appropriate treatment for the patient (◘ Table 22.1). Along with symptoms,

Table 22.1 Reasons to perform a lymphoscintigraphy in patients with lymphedema

To establish:
In edemas clinically staged 0, 1, or 2: to establish the diagnosis of lymphedema In edemas clinically staged 1, 2, 3, or 4: as a pre-therapeutic «inventory» of the lymphatic system
An investigation useful for the physical therapist:
To be reimbursed by the Health Insurance System for the physical treatment (in Belgium) [5] To show where and which (with which pressure) manual lymphatic drainage maneuvers have to be applied To show the lymphatic collateralization pathways present in the patient
One way to select the surgical procedure(s)?
«If no lymph node present, one indication for lymph node grafting?» «If no lymphatic vessels present, one indication for liposuction?» «If good lymphatic vessels are present, one indication for lymphatic-to-vein anastomosis?» «If lymph nodes are present, one indication for lymph node-to-vein anastomosis?»
For prevention:
In case of unilateral lower limb lymphedema, to confirm that the other limb is not affected To investigate other family members (if clinical questions raise the possibility of familial hereditary lymphedema) Before any operation with damage to the lymphatic system, especially in patients with a familial history and/or mild symptoms of edema

these questions and the answers being sought will guide the imaging technique to be used and the methodological approach to take.

The third problem clinicians will encounter is related to the imaging technique itself [6–8]. Many imaging approaches of the lymphatic system are available (Table 22.2). Scintigraphic investigations of the lymphatic system using the injection of a radiolabeled pharmaceutical, known as lymphoscintigraphies, are now the best established techniques to investigate edema in which the lymphatic system is either involved or its involvement is suspected [9–12]; however, lymphoscintigraphies, like other imaging techniques of the lymphatic system, carry both advantages and limitations (Table 22.3).

The first key message of this chapter is as follows:

Key Point

Edema is one clinical symptom. The symptom becomes a lymphedema when morphological and/or functional abnormalities affecting the lymphatic system can be demonstrated. But the lymphedematous problem must always be placed in its overall context and presented with the (eventually) associated symptoms and with the specific patient's history. The clinician has then to formulate well the question(s) to be answered. These questions will determine not only the technique to be proposed to the patient but also the methodology that will be applied by the specialist who will perform the investigation.

Table 22.2 The imaging techniques of the lymphatic system in 2014: can lymph nodes and/or lymph vessels be directly viewed and can lymph node and/or lymph vessel morphology and/or function be evaluated?

Imaging technique	Direct?	Indirect?	Lymph nodes		Lymph vessels		Comments
			Morphology	Function	Morphology	Function	
Vital dyes	*Yes*		Yes	No	*Yes*	*Yes*	Sentinel node
Fatty meal!	*Yes*		No	No	*Yes*	«No»	Chyliferous!
Radiocolloids							
Lymphoscintigraphy		*Yes*	Yes	No****	*Yes*	*Yes**	*Need dedicated protocols of investigation!
Plus vital dyes	*Yes*	*Yes*					
Lympho-SPECT-CT		*Yes*	*Yes*	Yes****	yes	Yes*	****See text
Positron-emitting molecules		*Yes*	Yes	No	No	No	See footnote (a)
Ultrasound		*Yes*	*Yes*	No	*Yes***	*Yes***	**High frequency and/or injection of microbubbles
X-rays							
Lymphangiography		*Yes*	*Yes*	Yes	*Yes*	*Yes*	No longer performed?
CT		*Yes*	*Yes*	No	*Yes****	No	*** Only if enlarged!
MRI							
Hydrography		*Yes*	No	No	*Yes*	No	

Lymphangiography		*Yes*	*Yes*	No	*Yes*	*Yes?*	
Lymphadenography		*Yes*	*Yes*	No	No	No	
Fluorescent molecules		*Yes*	Yes	Yes	*Yes*	*Yes*	To date, not registered by FDA and/or EMA

SPECT single-photon emission computed tomography
CT computed tomography
MRI magnetic resonance imaging
(a) Only for the demonstration of primary and/or secondary tumoral process involving the lymphatic system

Table 22.3 Respective contributions of the various imaging techniques in the management of the lymphedematous diseases

		Lymphoscintigraphies		Lympho-SPECT-CT		CT		Lympho-fluoroscopies		MRI	
		Diagnosis	Treatments	Diagnosis	Treatments	Diagnosis	Treatments	Diagnosis	Treatments	Diagnosis	Treatments
Upper limb edemas (ULEs)											
Primary		++++	++++[b]	++++	++++[b]			?	?	++[a]	<
Secondary	Oncologic	++	++++[b]	+++	++++[b]	+/++	+	GP +++	GP +++	++[a]	++++[a]
	Others	++++	++	++++	<	+++	<	?	?		
Lower limb edemas (LLEs)											
Primary	Congenital	++	++++[b]	+	++++[b]	+		?	?	+[a]	++++[a]
	Praecox	+++	++++[b]	++	++++[b]	++	+	P +++?	P +++?	++[a]	++++[a]
	Tarda	++++	++++[b]	+++	++++[b]	+++	++	GP ++	GP +++	+++[a]	++++[a]
Secondary	Oncologic	++	++++[b]	++	++++[b]	+/++	+	GP ++	GP ++	?	++++[a]
	Others	+++	++	++++	<	+++	<	?	?		
Lipoedema/ lymphedema		++	+/++	+++	+	++		?	?	?	?
Phlebo-lymphedemas		+++	+/++	++	+?	++		P ++?	?	?	?

Lymphangioma		+		++		++++	<	?	?	++++[a]	+++[a]
Lymphangiomatosis		+		+		++++	<	?	?	++++[a]	+++[a]
Chylous reflux disorders		++	+/++	‘++++	+++	++		?	?	++++[a]	++++[a]
Genital LE	Males	++	+/++	‘++++	‘++	+		?	?	++[a]	++++[a]
	Females	++	+/++	‘++++	‘++	+		?	?	++[a]	++++[a]

[a]With injection of contrast; [b]with additional injections at the root of the limbs; in some indications («lymphedematous diseases»), data are lacking for the «lympho-fluoroscopies,» and the technique (its contribution) has been classified as «?» (undetermined). In other indications, the contributions of the «lympho-fluoroscopies» have been classified – on the basis of the existing literature – as «GP» («of great potential») and/or «P» («of potential» to be established)
SPECT single-photon emission computed tomography, *CT* computed tomography, *MRI* magnetic resonance imaging, *LE* lymphedema

22.2 «Chaos» or «Ordo Ab Chaos» in Lymphoscintigraphies?

Although lymphoscintigraphic investigation can be considered the gold standard for evaluating and managing edematous situations, clinicians and specialists who analyze the international lymphoscintigraphy literature may be left with the impression to be facing a «chaos». Indeed, many different methodological and analytical protocols are proposed. This chapter addresses hereafter the numerous problems facing the field today. It is the author's hope that readers will develop a clear (better) understanding of the current lymphoscintigraphic investigations and be left with the impression that «ordo» is emerging «ab chaos.»

22.3 The Problem of the «Tracer»

For readers who are not imaging specialists, the first thing to address is the «tracer» that is used to image the lymphatic system. The tracers used for lymphoscintigraphy have two distinct components: the gamma-emitting radioisotope and the radiolabeled carrier.

The physical characteristics of the radioisotope, i.e., its physical half-life and the energy(ies) of the emitted gamma ray(s), will determine some of the technical aspects of the exam and will also influence some of the parameters that can be studied and how long they can be studied.

- Radioiodine (131I), for example, has a long physical half-life of 8 days that allows one to study slow and long-lasting biological phenomena. The emission of electrons by I-131 implies, however, the injection of low activity and the use of gamma probe (no possible imaging).
- Indium-111 (111In; physical half-life = 2.8 days) is used by the English team headed by Mortimer PS and Peters AM for the labeling of human immunoglobulin G. The «medium» energy of 111In gamma rays limits, however, its use.
- Technetium-99 m (99mTc) is finally the best-suited radioisotope for gamma camera imagings. The physical half-life of 99mTc is «however» 6.0 h «only» (after 24 h, the activity of 99mTc is divided by a factor 16, and at that point, usually only the injected sites and the lymph nodes are visible).

The characteristics of the carrier are, however, the main determinants that influence the results of lymphoscintigraphy. The following characteristics are useful to know and to understand for each tracer for comparison purposes:

- The tracer size. This is the most important characteristic to consider. Particles that are smaller than a few nanometers will mostly penetrate the capillary membranes, whereas larger particles, i.e., those up to 100 nm, will enter the lymphatic capillaries and be transported to lymph nodes. Particles larger than 100 nm will, however, be trapped in the interstitial space for a long time [38, 39].

- The electric charge of the carrier and its interactions with the salts and plasma proteins in the interstitial fluid and with the proteins and glucosaminoglycans of the extracellular matrix. Negatively charged tracers move with higher average velocity through the interstitium than neutral and positively charged particles.
- The molecular weight (MW) of the tracer: as its MW increases, a tracer has a decreased ability to penetrate blood capillaries and, consequently, is more likely to enter lymphatic vessels.

Table 22.4 is a non-exhaustive list of the 99mTc-labeled tracers that have been used or are currently used along with some of their characteristics and their «areas of use» (the availability of these tracers varies in different continents and sometimes even within countries, depending on whether they are approved as radiopharmaceuticals and also depending on their commercial «marketing»).

Table 22.4 The 99mTc-labeled tracers used for lymphoscintigraphy

Antimony sulfide (Sb2S3) colloids [64]
Particle size ranging 2–15 nm
pH 5–6 → burning sensation when injected!
«Area»: Australia
Phytate (calcium phytate) colloids: [53]
Particle size ranging 200–1000 nm (depends on Ca^{2}+ concentration)
«Area»: Japan, Asia
Stannous sulfur colloids
Unfiltered: particle size ranging 30–1000 nm
Filtered: particle size ranging 38 nm?
pH 5–6 → burning sensation when injected!
«Area»: North America
Absorbed dose for 2.5 mCi 99mTc = 1–5 rad (depending on the volume administered)
Rhenium sulfide colloids
Particle size ranging 50–500 nm (but 8–68 nm using dynamic light scattering)
«Area»: Europe (France)
HSA «micro-sized» colloids (Lymphoscint®: no more available): particle size 10 nm

Table 22.4 (continued)

HSA «nanosized» colloids (Nanocoll®): frequently referred as HSA nanocolloids
Particle size <80 nm (obtained by filtering human serum albumin denatured by heating)
pH 7
«Area»: Europe
Dextrans ([40]; [66]):
Particle «size»: will depend of their molecular weights
«Area»: South America, Asia
Liposomes ([67]; [68]); no clinical development
Mannosyl dextran derivative or tilmanocept: [69]
MW: 36,000 g/mol
«Area»: USA (approved under the name of Lymphoseek® since 2013) and Europe (approved by the European Medicines Agency) but for use restricted to patients with breast cancer and melanoma who will undergo SLN surgical procedure
Human serum albumin (HSA)
Particle size: 2–3 nm (but 3–23 nm using dynamic light scattering).
pH ranging from 2.0 to 6.5 → burning sensation when injected!
When injected in the skin, one part of the 99mTc-HSA is colloidal and is trapped in the LN, but the part directly entering back to the blood through the capillary membrane and/or reaching the systemic circulation shows the vascular spaces (the heart, for instance).

If the injection of these 99mTc-labeled tracers is used to obtain qualitative images of the lymphatic vessels and lymph nodes, one must be aware that certain of their characteristics can limit the imaging results. Therefore, optimized/adapted protocols must be developed for each of these tracers enabling the comparison of their images. In addition, their different characteristics require the definition of «standards» for each of them, especially when different results are presented in quantitative terms (transport speed, amount extracted at the injection site over time, accumulation/uptake in the lymph nodes, etc.) (see ▶ Sect. 22.6). For instance, the normal values obtained for the transport index developed by Kleinhans et al. in 1985 [22] with the subcutaneous injection of 99mTc-labeled HSA nanosized colloids cannot be used with other tracers. A diagnostic interpretation of a lymphoscintigraphic

examination using a given tracer cannot therefore use the standards of another tracer.

Personally, we have selected the 99mTc-labeled human serum albumin (HSA) nanosized colloids on the following grounds:

- The pH is not acid.
- The sizes of the particles are well standardized.
- Their sizes are between 10 and 100 nm.
- Albeit heat denatured, these particles are «proteins,» more «physiologically» representative of the interstitial equilibrium than nonproteinic tracers.
- These colloids are taken up by the reticuloendothelial cells in the lymph nodes, but also, when they have reached the systemic circulation, they are taken up (and seen) in the liver (also in the spleen and, sometimes, in the bone marrow).

22.4 Scintigraphic Materials and Qualitative Imaging of the Lymphatic System

The evolution and the current state of the art of scintigraphic techniques when applied to the evaluation of the lymphatic system must be emphasized. These images can be centered on one part of the lymphatic system (i.e., «spot» pictures) but can also cover the entire body [from the injected sites; for instance, from the level of the feet up to the level of the head, including the transit of the tracer in the thorax, i.e., whole-body scanning (WBS)]. Most gamma camera systems are now dual-headed, which allow simultaneous acquisition of anterior and posterior views of the lymphatic system and which also, by acquiring images when rotating around the patient [as with the single-photon emission computed tomography (or SPECT) devices], allow three-dimensional images of the lymphatic structures. Using adequate software, it is now possible to merge the acquired transverse, sagittal, and coronal lymphoscintigraphic slices with the corresponding pure anatomic slices showing the structures surrounding the lymph vessels and/or nodes and obtained using classical x-ray computed tomographic (CT) systems or, less (but more and more) widely available, magnetic resonance imaging (MRI) systems. Finally, more nuclear medicine facilities are now equipped with hybrid devices combining SPECT and CT (SPECT-CT) in a single system, which yields direct images of the lymphatic structures within their anatomical surroundings. Thus, lymphoscintigraphies can yield morphological images of the lymphatic system (normal or abnormal at each of its parts; ◘ Table 22.5), with a definition that might be considered «limited» when compared to other imaging techniques but, when applied with the most advanced approaches (lymphoscintigraphic SPECT-CT), are still very informative [13].

22

Table 22.5 What can be seen on lymphoscintigraphic imaging? [13]

From one injected site, the «normal» lymphatic (superficial and/or deep) vessel pathways expected on the basis of the historical anatomical data (Rouvière remains the «must»), including sometimes (and in case of lower limb lymphoscintigraphies) the ductus thoracicus (and sometimes abnormalities of this great intrathoracic lymphatic vessel; see Fig. 22.1)
The radiocolloidal activities transiting («in transit») in these lymphatic vessels
The lymph nodes that are «normal» part of these lymphatic pathways, where these radiocolloids remained trapped and as expected on the basis of the historical anatomical data (Rouvière also remains the «must»)
The liver (and sometimes the spleen and bone marrow) where the radiocolloids (when they reach the systemic circulation) are taken up
Sometimes (varying with the characteristics of the injected radiocolloids), activities in the «great» systemic circulation, in the kidneys, in the bladder
From the injected site, one (abnormal) progression of the radiocolloidal tracer (not in well-delineated lymphatic vessel(s) but) diffuse, in and through the superficial lymphatic collateralization network without visualization of lymph nodes and/or lymphatic vessels
From the injected site, one (abnormal) progression of the radiocolloidal tracer (not in well-delineated lymphatic vessel(s) but) diffuse, in and through the superficial lymphatic collateralization network (sometimes limited to one small area and sometimes extended to the whole limb) with visualization of (superficial and/or deep) lymphatic vessels draining the corresponding area
On any part of these lymphatic pathways, (abnormal) «blockade» of the lymph flows with lymphatic vascular reflux (see Figs. 22.2, 22.3, 22.5, and 22.6) into the (surrounding) superficial lymphatic collateralization network (the «dermal backflow(s),» sometimes limited to one small area (see Figs. 22.2, 22.3, and 22.5) and sometimes extensive (see Fig. 22.6)) and/or into, with visualization of (superficial and/or deep) lymphatic vessels draining the corresponding area (see Fig. 22.5) and/or of the lymph nodes that are «normal» and/or abnormal part of these lymphatic pathways and where these radiocolloids remained trapped (see Fig. 22.5, arrow 4)
(Usually in secondary lower limb lymphedema(s)), lymph nodes «absent» in one limited and/or extended anatomical area:
From «normal» lymph nodes, reflux of the lymph (coming in the nodes from «large» collecting lymphatic vessels) in the «smaller» lymphatic vessels connected to these nodes (see Fig. 22.4, arrow 2, and Fig. 22.1, arrow 1) with lymphatic «vascular» reflux that may reach the (surrounding) superficial lymphatic collateralization network (the «dermal backflow(s),» sometimes limited to one small area (see Fig. 22.1: arrows 2 and 3) and sometimes extensive (see Fig. 22.4: arrow 7)) and/or into, with visualization of (superficial and/or deep) lymphatic vessels draining the corresponding area and/or of the lymph nodes that are «normal» and/or abnormal part of these lymphatic pathways and where these radiocolloids remained trapped.
Sometimes, collection of lymphatic activities (that does not correspond on single-photon emission computed tomography–computed tomography (SPECT-CT)) to a lymph node but to a «true» lymphocele and, in case of lower limb investigations, sometimes to reflux of lymph into the digestive tract (see Figs. 22.4, 22.16, and 22.1).
Sometimes, in cases of secondary upper limb edema, one «effusion» of lymphatic activities in one axilla and/or at the level of the thoracic wall, one «lymphorrhea,» and the lymphatic drainages of this area (see Figs. 22.2, 22.19, and 22.20).
Sometimes, direct and/or indirect signs of (spontaneously opened) lymph-to-vein anastomosis.
Sometimes, in cases of ascitis and/or or chylothorax and/or chyloperitoneum, it is possible using dedicated protocols to show and to precise the level of one lymphatic leakage.

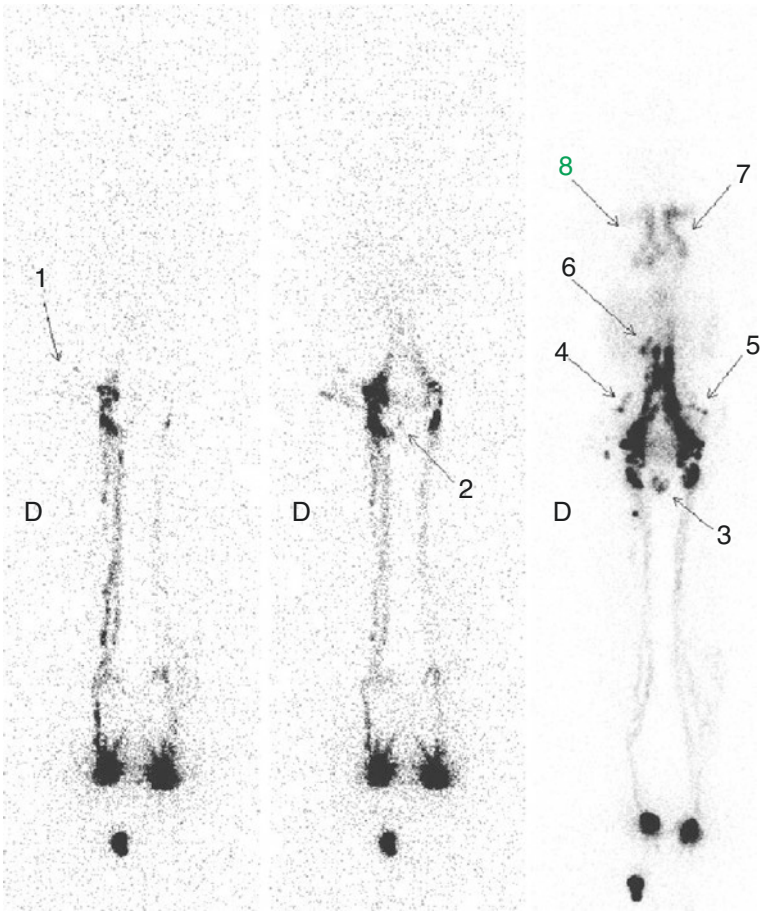


Fig. 22.1 Anterior WBS obtained (after one subcutaneous injection of 99mTc-labeled HSA nanosized colloid in the first interdigital space of each foot, the patient lying on the examination table), from right to left, after 30 min without movement, after 5 min of tiptoeing, and after 1 h of walking. This young woman did not complain of lower limb edema, but was referred for evaluation of intermittent lymph leakage at the level of her right labium majorum. After 30 min without movement, the tracer reached the first inferior inguinal node on the left side and all the inguinal nodes on the right side but with lymphatic collaterals appearing from the inguinal nodes toward the external part of the buttock *(arrow 1)*. After 5 min of tiptoeing, infradiaphragmatic lymph nodes are now seen on both sides (and right collaterals are confirmed); the beginning of lymphatic reflux in the right labium majorum can also be observed *(arrow 2)*. After 1 h of walking, the reflux of lymph in the right magna labia is now obvious *(see arrow 3)*, but abnormal zones of activity are also demonstrated in the right and left lateral part of the abdomen *(arrows 4 and 5)* as well as at least two right pararenal lymph nodes *(arrow 6)*, and, at the supradiaphragmatic level, there is a completely abnormal presentation of the great lymphatic thoracic duct with right and left components persisting *(arrows 7 and 8). With permission from Bourgeois P. Combined Role of Lymphoscintigraphy, X-Ray Computed Tomography, Magnetic Resonance Imaging, and Positron Emission Tomography in the Management of Lymphedematous Disease. In: Lee BB, Bergan J, Rockson SG, eds. Lymphedema: A concise compendium of theory and practice © Springer 2011*

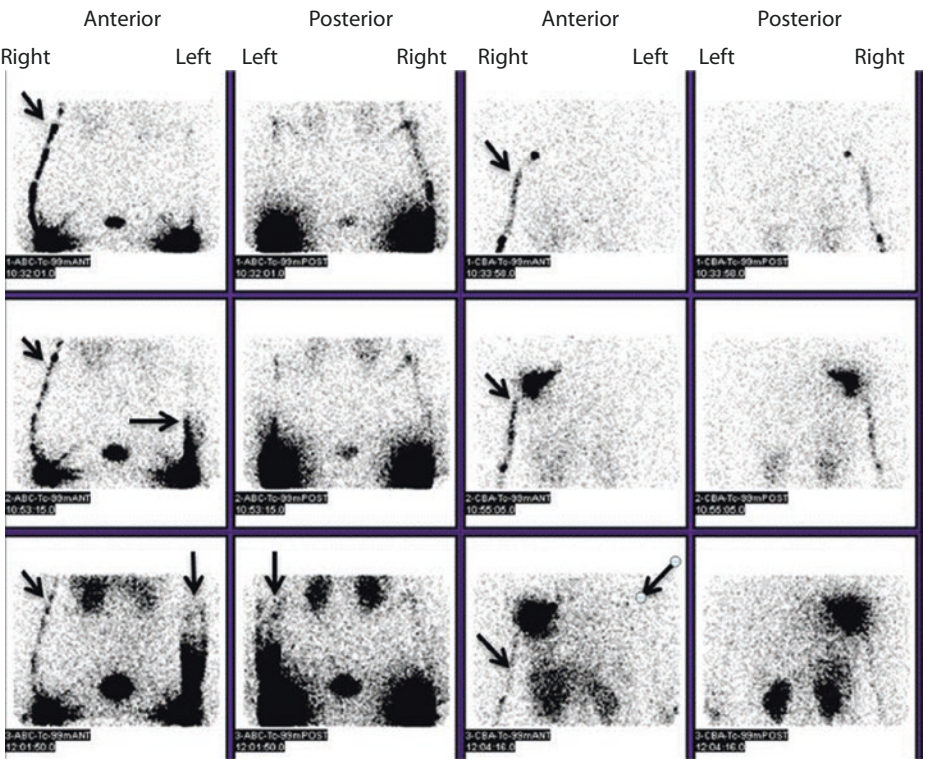


Fig. 22.2 Pictures (*anterior and posterior views*) centered on the hands, wrists, forearms, and elbows (*on the left-sided part of the figure*) and on the elbows, arms, and axillas (*on the right-sided part of the figure*) obtained (from up to down after 30 min without movements, after 15 min of handgripping, and after 1 h of normal activities) in one woman with edema limited at the level of her left forearm after one radical mastectomy with complete axillary node dissection. The left to right oblique arrows from up to down) show the normal lymphatic vascular drainage of the right interdigital injection reaching the right axillary lymph nodes. On the left side, one limited lymphatic reflux toward the superficial network at the level of the wrist is observed after 15 min of exercise (*horizontal arrow from left to right*). After 1 h of normal activities, the tracer has progressed through and in the superficial collateralization lymphatic network up to the elbow at the level of the forearm (*vertical arrows*). At the level of the left axilla, two lymph axillary lymph nodes are faintly seen (*from right to left oblique arrow*). These two lymph nodes are better seen on spect-ct imaging (see fig Fig. 22.19)

22.5 Scintigraphic Acquisitions and Quantitative–Functional Imagings of the Lymphatic System

It must be reminded (for the nonspecialist in imagings) that these images, even if static, always contain useful quantitative information (each «pixel» of these images represents a number of «counts,» i.e., the number of gamma rays emitted by the radioelement and that is registered by the gamma camera system). Additionally, the acquisitions can be «dynamic.» So, these acquisitions allow the study and quantification of, for instance, the

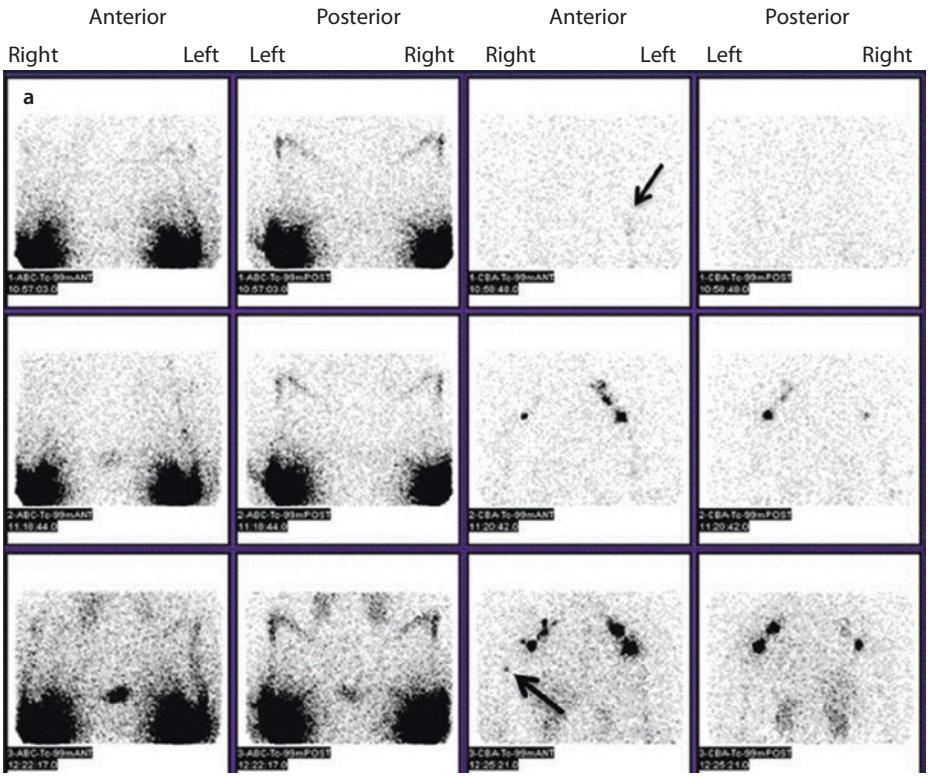


Fig. 22.3 **a** Pictures (*anterior and posterior views*) centered on the hands, wrists, forearms, and elbows (*on the left-sided part of the figure*) and on the elbows, arms, and axillas (*on the right-sided part of the figure*) obtained (from up to down after 30 min without movements, after 15 min of handgripping, and after 1 h of normal activities) in one woman with edema limited at the level of her right arm after one radical mastectomy with complete axillary node dissection. On the right side, no lymphatic drainage is seen after 30 min without movement (**1**) (lymphatic vessels can be seen at the level of the forearm after one hour of normal activities). After 15 min of handgripping, the activity in the right axillary lymph nodes is lower than the activity in the left axillary lymph nodes (**2**). One lymph node is also seen (*see from down to up oblique arrow*) inter-calated at the level of the mid part of the right arm (**3**). Key point 1 for Fig. 22.3a: These 3 observations (1, 2 and 3) are representative for one "functional" lymphedema, for one functional insufficiency of the superficial lymphatic system with one intercalated lymph node corresponding to one "collateral" drainage in the deep lymphatic system. On the left side, the tracer has progressed up to the mid part of the arm (*see oblique arrow from up to down*). Key point 2 for Fig. 22.3a: The tracer has not reached the left axillary lymph nodes after 30 min without movements (*see oblique arrow from up to down*). This is observed in more than 90% of the women referred for the investigation of one secondary upper limb lymphedema and supports the hypothesis that these women who are developing such lymphedema had one preexisting latent lymphatic functional insufficiency. **b** Transversal (*on your left side*) and frontal (*on your right side*) SPECT-CT slices showing that one of the right axillary lymph nodes (*vertical arrows*) is in fact «superficial» «pre-pectoral and that the lymph node seen at the level of the mid part of the right arm is superficial (*oblique arrow*) and intercalated on Mascagni's pathways

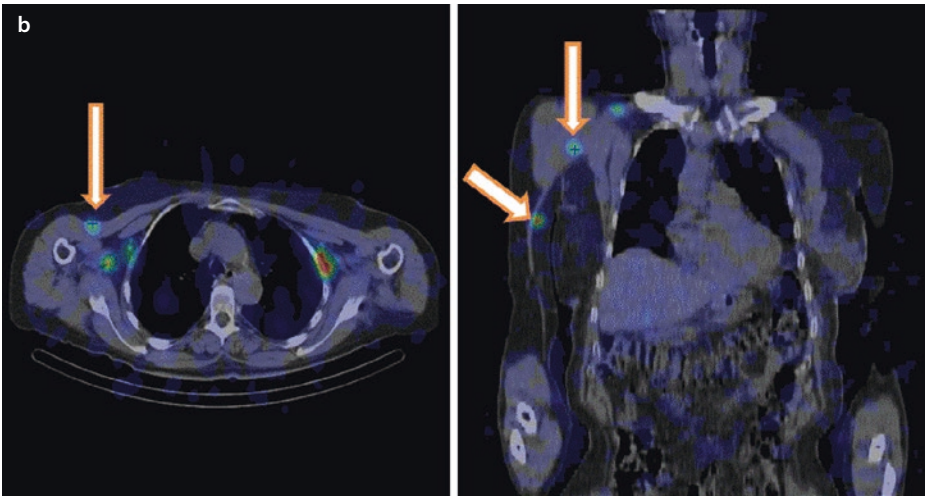


Fig. 22.3 (continued)

transit of the tracer in the lymphatic vessels (the lymphatic «speed» and «flows») and/or the accumulation of the tracer in the lymph nodes (and/or in the liver) under various conditions and during various periods. Lymphoscintigraphies thus not only allow acquisition of morphologic–qualitative information about the lymphatic system but also provide information about the functional parameters describing the lymphatic system of the studied edematous structures.

The functional parameters that can be obtained using this method (with radiocolloids) are listed in Table 22.6. Each of the parameters listed in Table 22.6 and followed by (a) is usually expressed in percentages of the activities injected. They provide quantitative information about the ability of the lymphatic system to transport the radiolabeled colloids; they (obtained in any patient) can be compared to (those – when available – obtained in) a normal population and, in case of lateralized edema, between the edematous and «healthy» areas.

The most refined quantitative approaches for studying the lymphatic system have been developed by one English team [1, 2, 14–16].

22.6 The «Clinical» Conditions When to Perform and Acquire Lymphoscintigraphic Images?

If any tracer can be used in an optimized protocol to perform morphological imaging of the lymphatic system of a patient at a particular time (any time after the injection of the tracer), the resulting images will always represent a qualitative result and should be viewed as a snapshot of the anatomy (either normal or abnormal) of the lymphatic system at that time.

It is important to be kept in mind because some edemas may be in fact a manifestation of a functional insufficiency of the lymphatic system of the limb, but, in precise condition. An edema may be just manifest in a person when he/she is at rest and disappear with

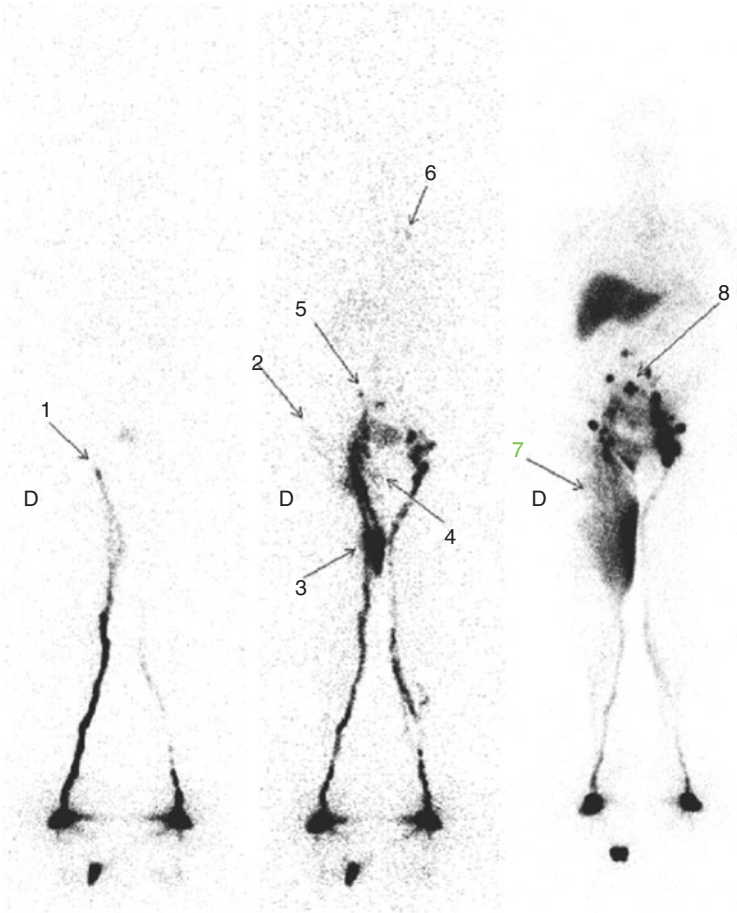


Fig. 22.4 Anterior whole-body scanning (WBS) obtained (after one subcutaneous injection of 99mTc-labeled HSA nanosized colloid in the first interdigital space of each foot, the patient lying on the examination table), from right to left, after 30 min without movement, after 5 min of tiptoeing, and after 1 h of walking. This man was sent for evaluation of right lower limb lymphedema (he also had prepubic edema on clinical examination) secondary to surgery and radiotherapy for prostatic carcinoma. After 30 min without movement, the tracer has reached the first inferior inguinal node on the right side (*arrow 1*), but progressed only to the level of the knee on the left side. After 5 min of tiptoeing, lymphatic reflux is seen in collaterals toward the external part of the right buttock (*arrow 2*), up to and in the mid internal part of the thigh (*arrow 3*), and in the right prepubic area (*arrow 4*). One right common iliac node is observed (arrow 5), as well as – faintly – two left retroclavicular lymph nodes (*arrow 6*) proving that the thoracic duct is pervious. After 1 h of walking, the reflux of lymph in the superficial collateralization lymphatics extends to the upper and inner half of the right thigh (*arrow 7*), but one abnormal zone of activity is also demonstrated in the mid suprapubic part of the abdomen (arrow 8: see also Fig 22.16!). With permission from Bourgeois P. Combined Role of Lymphoscintigraphy, X-Ray Computed Tomography, Magnetic Resonance Imaging, and Positron Emission Tomography in the Management of Lymphedematous Disease. In: Lee BB, Bergan J, Rockson SG, eds. Lymphedema: A concise compendium of theory and practice © Springer 2011. Key points for Fig 22.4: Lymph can normally flow from the right foot up and into the first inguinal lymph node (*arrow 1*) in resting conditions (→«good indication for one lymph node-to-vein anastomosis?»). True lymphatic vascular reflux can (sometimes) be seen (only) with exercise (*see arrow 2*). «Dermal backflows may mask the normally functioning lymphatic vessels (*arrow 1 versus arrow 7*)

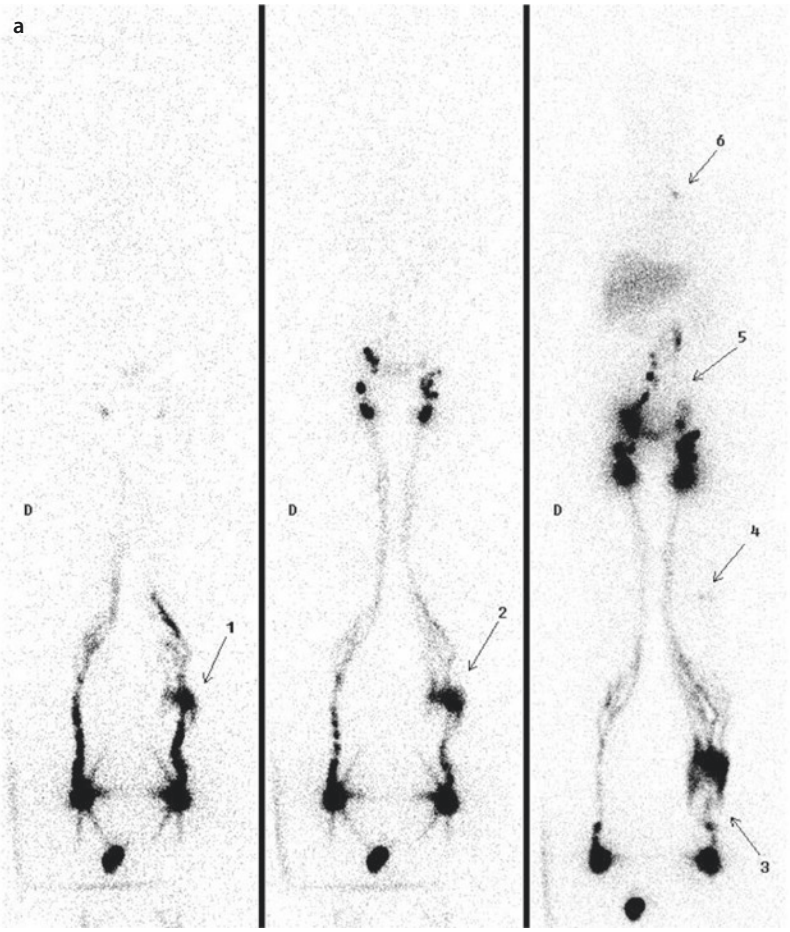


Fig. 22.5 **a** Anterior whole-body scanning (WBS) obtained (after one subcutaneous injection of 99mTc-labeled HSA nanosized colloid in the first interdigital space of each foot, the patient lying on the table of examination), from right to left, after 30 min without movement, after 5 min of tiptoeing, and after 1 h of walking. This woman was sent for evaluation of left lower limb lymphedema. After 30 min without movement, the tracer has reached the first inferior inguinal node on both sides, but the beginning of lymphatic reflux is seen at the level of the distal part of the left calf (*arrow 1*). After 5 min of tiptoeing, lymphatic reflux in the left calf is more obvious (*arrow 2*). After 1 h of walking, the reflux of lymph in the superficial collateralization lymphatics is obviously extended to the left ankle (*arrow 3*), one left popliteal lymph node (*arrow 4*), and one left retroclavicular lymph node (*arrow 6*) but not the left common iliac nodes (*arrow 5*). On the basis of this lymphoscintigraphic examination, the diagnosis of primary lymphedema tarda was proposed. With permission from Bourgeois P. Combined Role of Lymphoscintigraphy, X-Ray Computed Tomography, Magnetic Resonance Imaging, and Positron Emission Tomography in the Management of Lymphedematous Disease. In: Lee BB, Bergan J, Rockson SG, eds. Lymphedema: A concise compendium of theory and practice © Springer 2011. **b** The patient later developed left sciatica, and blockage of the common iliac vein was suspected. PET-CT after IV injection of 18F–DG was performed and demonstrated (on the selected transverse PET-CT slides) a hypermetabolic process later histologically proven to represent metastatic tumor of uterine cervix origin. *With permission from Bourgeois P. Combined Role of Lymphoscintigraphy, X-Ray Computed Tomography, Magnetic Resonance Imaging, and Positron Emission Tomography in the Management of Lymphedematous Disease. In: Lee BB, Bergan J, Rockson SG, eds. Lymphedema: A concise compendium of theory and practice © Springer 2011*. Key points for Fig 22.5a and 22.5b: -False diagnosis of primary lymphedema tarda and/or a mixed situation (benign and malignant)? The persistence of «sciatica» led to the diagnosis of the malignant disease. – Even specialized, we remain doctors inmedicine

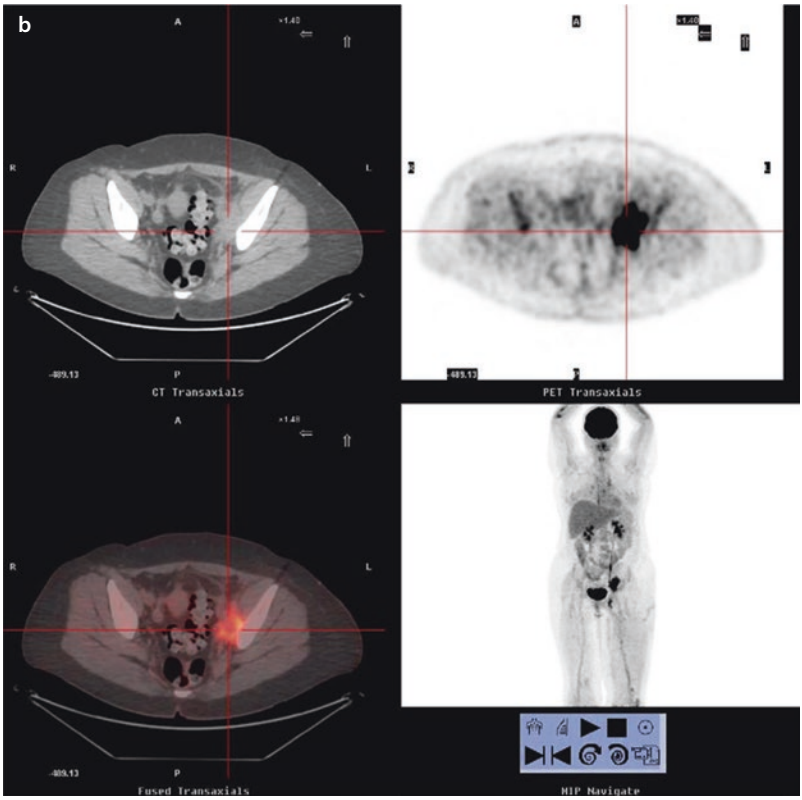


Fig. 22.5 (continued)

exercise or on the other hand just be noticeable at the end of the journey after a normal activity. The edema can be «cyclic» (and if the patient is investigated after her menstruations) or/and can have been treated and no longer be residual with, as consequence, one scintigraphic investigation of the lymphatic system appearing morphologically and/or functionally normal. In the lymphoscintigraphic protocol investigation of any edema, the circumstances of appearance of this edema have to be reproduced.

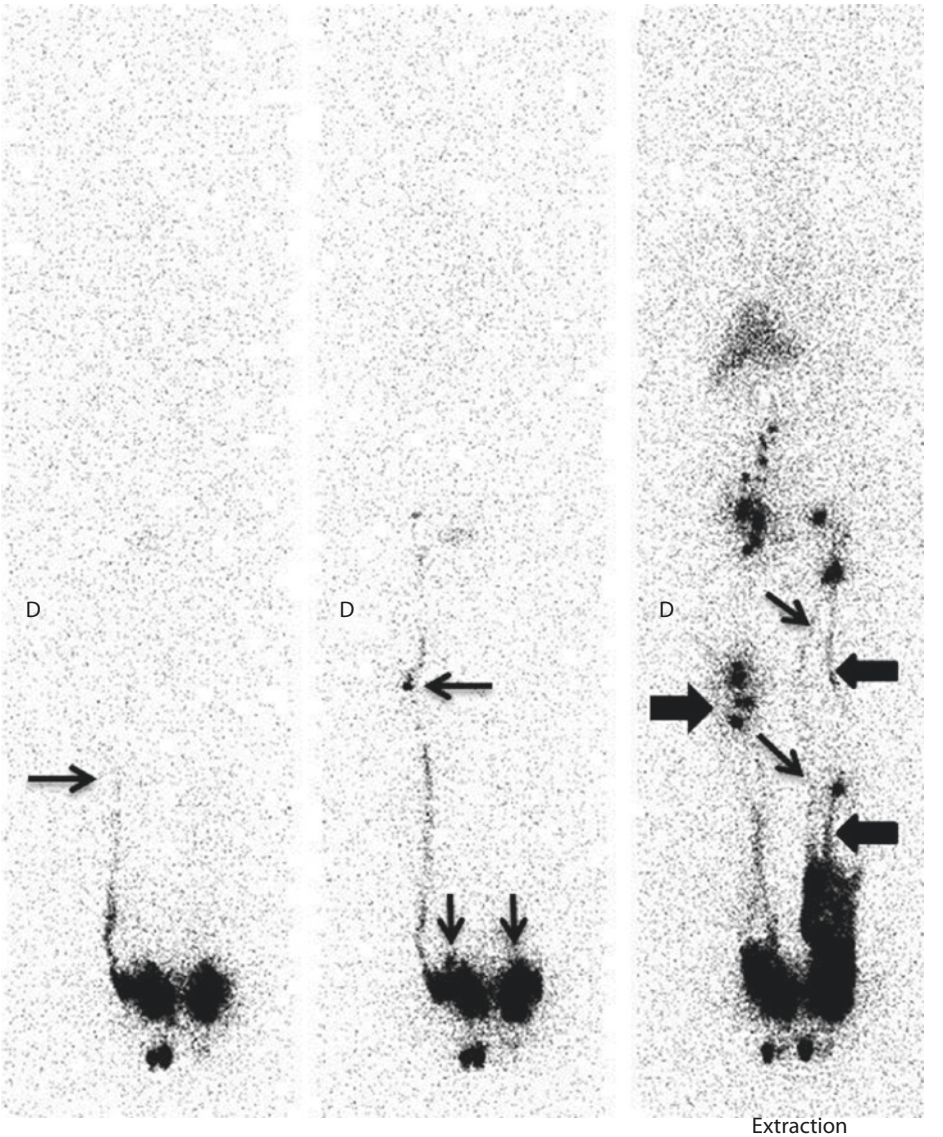
Key Point
This may be a truism, but *the lymphoscintigraphic imaging of one edematous patient has to be performed when the edema is present* (see ▶ Sect. 22.15).

22.7 The Scintigraphic Methodological Approaches

As noted, either static or dynamic lymphoscintigraphic images can be obtained under various conditions.

Based on the clinical conditions of edema occurrence, the images must be obtained in at least two conditions:

22



	Extraction
Gauche	4 %
Droite	8 %

Fig. 22.6 Woman sent for the evaluation of one left lower limb lymphedema but who presenred clinically with bilateral edema left > right and Stemmer's sign positive on both sides. From the left to the right, anterior Whole Body Lympho-Scintigrams obtained after 30 minutes in resting conditions ("Phase 1"), after 5 minutes tip-toeing ("Phase 2") and one hour of walking ("Phase 3"). On the left side, there is no lymphatic flow in resting conditions and on the right side, the tracer has spontaneously progressed in one lymphatic vessel up to mid external part of the calf (*from left to right horizontal thin arrow*). After tiptoeing, the tracer has reached the inguinal lymph nodes on the right side but with one "intercalated" lymph node (*from right to left horizontal thin arrow*) and on both side, dermal progression of the tracer begins to be seen (*vertical arrows*). After one hour of walking: (**i**) On the right side, dermal progression of the tracer is confirmed at the level of the foot with at least two lymphatic vessels observed at the level of the calf, additional lymph nodes in the femoro-popliteal area (*from left to right thick arrow*) and quite normal visualization of the inguinal and iliac lymph nodes. (**ii**) On the left side, the tracer has progressed in the superficial collateralization lymphatic network at the level of the foot, the ankle and the distal part of the calf. One deep lymphatic vessel (*from right to left thick arrows*) with one intercalated lymph node at the level of the calf and one superficial ("internal") lymphatic vessel (*from left to right and up to down oblique arrow*) are seen. The intra-abdominal lymph nodes are not seen but only two inguinal lymph nodes, one inferior and one at the level of the inguino-iliac junction)

- In resting conditions, because lower limb edema, for instance, will appear only after the patient sits for several hours without moving or with limited movement
- After a period of normal activity in cases in which edema only appears after several hours of normal activity

In practice, however, these two conditions can result in insufficiently detailed or in incomplete images of the studied lymphatic system, particularly considering the potential implications for treatment. Fig. 22.1 and subsequent images illustrate such situations. In many cases, the solution is to obtain an intermediate image after a short period of standardized exercises.

22.7.1 Our Three-Phase Protocol for Lymphoscintigraphic Investigation of Limb Edemas

In the 1980s, these previous considerations prompted us to develop a three-phase protocol of lymphoscintigraphic investigation of the limb edemas. The protocol was then refined over time. These three phases correspond to image acquisitions as follows [17–19]:

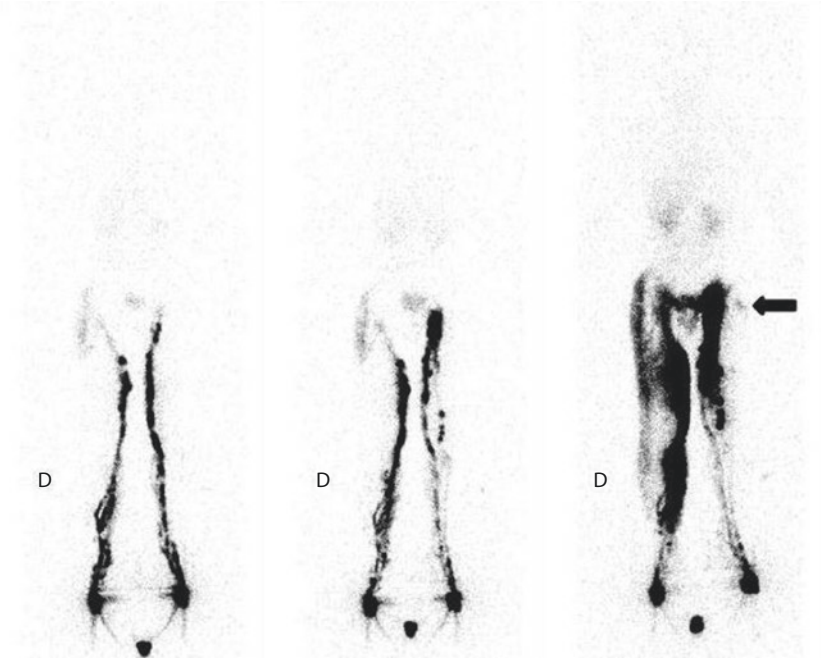
1. Phase 1. Images are acquired during and after a resting period, with the patient lying on the examination table for 30 min.
2. Phase 2. With the patient lying on the examination table, the images are acquired during and after performing a standardized exercise (5 min of tiptoeing or 15 min of hand gripping).
3. Phase 3. Images are acquired after the patient performs normal activities for 1 h. In cases with lower limb edema, the images should be acquired after walking, making sure that the patient does not remain sitting in the waiting room prior to imaging. In cases with upper limb edema, the images should be acquired after the patient performs movements with the fingers, hands, and limbs in ways that would be part

22

Phase I
WBS après 30 min au repos

Phase II
WBS après 5 min d'exercice

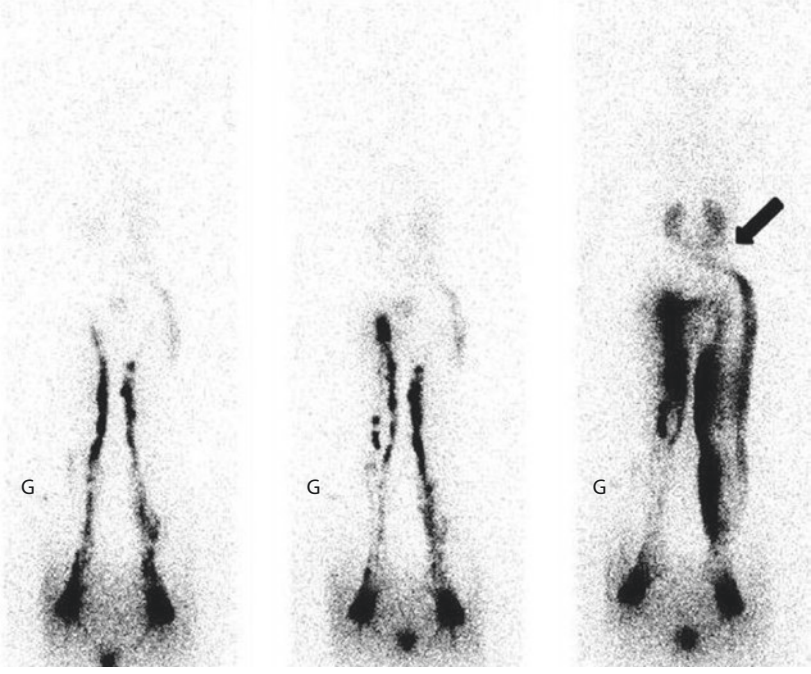
Phase III
WBS après 1 heure de narche



Phase I
WBS après 30 min au repos

Phase II
WBS après 5 min d'exercice

Phase III
WBS après 1 heure de narche



Figs. 22.7 and 22.8 Anterior (upper pannel: Fig 22.7) and posterior (lower panel: Fig 22.8) WBS (see also the SPECT-CT slides: Fig 22.17) obtained in one young boy referred with the diagnosis of lymphangiomatosis (and with one planar lymphangiomatous lesion clinically obvious in his right posterior costo-lumbar area), who had edema limited to the right thigh but who showed the recent extension of the right swelling up to the ankle and the appearance of one edema limited to the inner part of the left thigh. After phase 1 (30 min in resting conditions), normal lymphatic vascular drainage is observed on the left up and into the first inguinal LN. On the right side, the lymphatic vessels reach the mid-part of the inner thigh, and, from there, one lymphatic drainage is observed toward the external part of the buttock. After phase 2 (5 min of tiptoeing), the situation is not changed on the right side, but one deep lymphatic vascular drainage with intercalated popliteal LN is now seen on the left side. After phase 3 (1h of walking), we observe: - On the left side, lymphatic reflux at the level of the inner part of the thigh but also at the level of the external part of the left buttock (*from right to left horizontal arrow*). - On the right side, lymphatic reflux at the level of buttock, the thigh, and the calf, popliteal LN (posterior WBS), dermal backflow in the prepubic area and in the scrotum. - On the posterior WBS, one lymphatic activity extending from the left buttock toward the posterior abdominal area wall under the (shadow of the) kidneys. This activity corresponds to the tracer in the lymphangiomatous lesion of the patient (see Fig. 22.17a). - No clear right inguinal LN and (bilaterally) intra-abdominal LN. - One very faint hepatic (colloidal) activity. Key points from these pictures: Lymph is normally drained up from the feet toward the root of the limbs in resting conditions. Lymphatic reflux «appear» with walking and lymphatic vessels are seen worse than after phases 1 and 2. Accumulation of lymph (from the right lower limb) in the lymphangiomatous lesion may be suspected on the basis of the planar WBS imagings but is clearly demonstrated on the SPECT-CT slices (see Fig. 22.17). The very faint hepatic activity suggests that the colloidal tracer has not reached the systemic circulation even after 1 h of walking. The intra-abdominal LNs are also not seen. These two factors suggest that the patient also presents one «lymphadenodysplasia». This information turns toward a surgical solution approach.

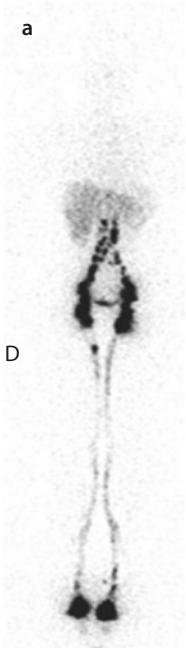
of his/her normal daily activity. The images can be obtained after longer periods of normal activity, but normal values for the extractions of the tracer (see below) will have to be obtained. Note that 1 h is usually convenient both for patients and for imaging scheduling at a nuclear medicine service. The images and the information they contain will then be representative of the response of the lymphatic system to the patient's lifestyle activities that precede the appearance of edema.

Such images are thus both morphological–qualitative and also morphological–functional (see Figs. 22.1, 22.2, 22.3, 22.4, 22.5, 22.6, and 22.7).

22.7.2 The Interpretation of the Imagings After These Three Phases

1. Phase 1
   After its subcutaneous injection in the first interdigital space of each limb with the patient at rest, the tracer should normally penetrate the initial lymphatic vessels and their collectors and be transported from the injection site by the superficial lymphatic vessels due to their normal intrinsic contractility to reach (at least) the first lymph nodes at the limb's root 30 min after injection.

   These images (the anterior and posterior whole-body images from the head to the toes for the lower limbs or the anterior and posterior views of the upper limbs including the axillas) that are obtained after 30 min of rest give us morphological information about the status of the lymphatic system. All the images that show deviations from this expected result indicate an abnormal situation.



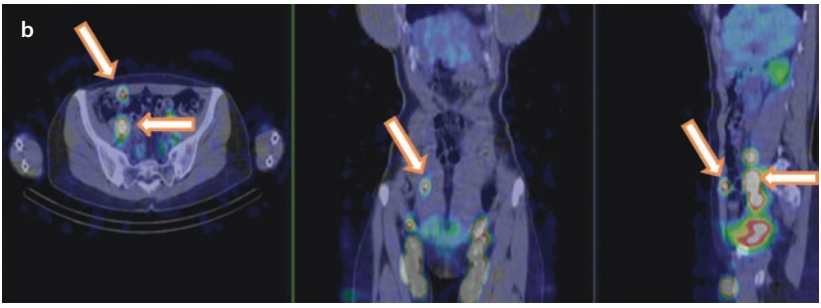
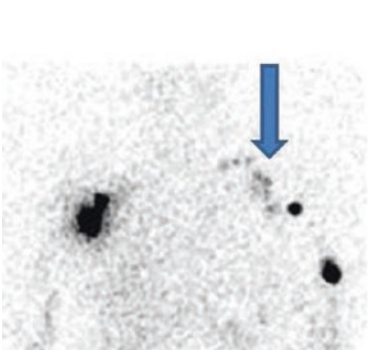
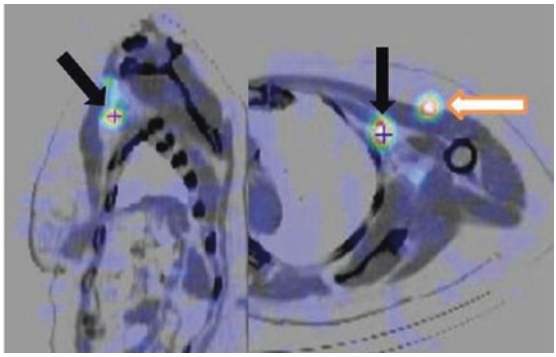


Fig. 22.9 Anterior WBS (Fig 22.9a) obtained in one young woman with stage 1 bilateral lower limb Edema. The SPECT-CT slices (Fig 22.9b) show one unsuspected LN (*see oblique arrows*) in the right rectus major muscle just in front of deep iliac LN (*horizontal arrows*)





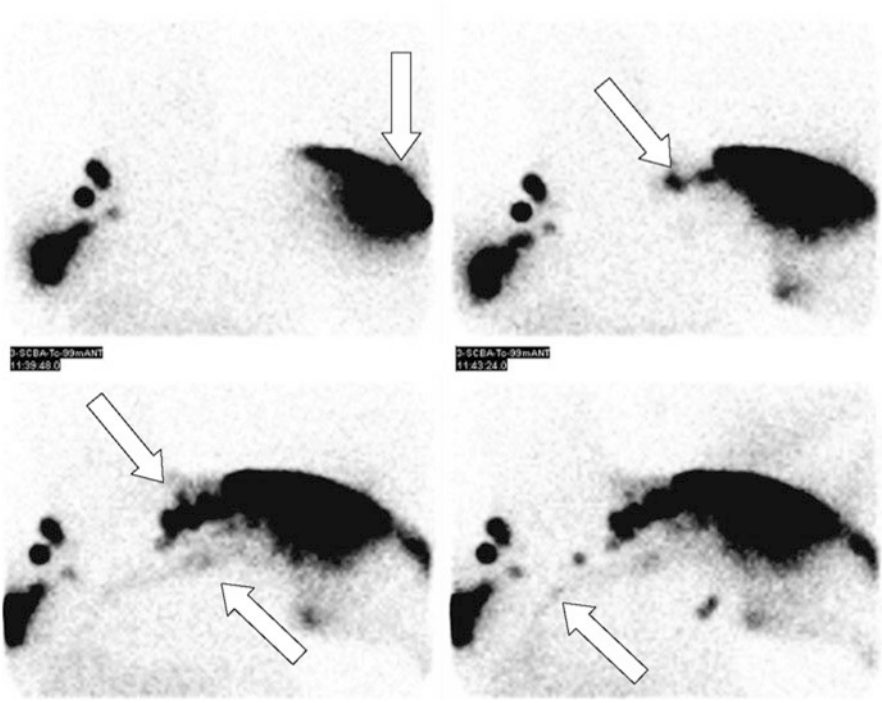


Fig. 22.11 From left to right and from top to bottom, anterior views centered on the axilla in a woman with post-therapeutic left upper limb lymphedema where the subcutaneous injection of 99mTc-HSA nanocolloid in the first interdigital space of the hands showed normal right axillary nodes, but no node in the left axilla. Intradermal injection was then performed at the level of the upper and external part of the left arm *(vertical arrow)*, and the tracer was shown to spontaneously flow toward the retroclavicular lymph nodes *(left to right oblique arrows)* and also toward the left anterior chest wall, to cross the midline to reach the opposite axillary lymph nodes *(right to left oblique arrows)*. *(With permission from Bourgeois P. Combined Role of Lymphoscintigraphy, X-Ray Computed Tomography, Magnetic Resonance Imaging, and Positron Emission Tomography in the Management of Lymphedematous Disease. In: Lee BB, Bergan J, Rockson SG, eds. Lymphedema: A concise compendium of theory and practice © Springer 2011)* (■ Fig. 15.3 from my chapter «Lymphoscintigraphy and other imaging methods» in «Lymphedema: presentation, diagnosis and treatment» A.K. Greene et al. (eds) ▶ https://doi.org/10.1007/978–3–319-14,493-1_15, © Springer international publishing Switzerland 2015)

Fig. 22.10 Anterior planar view (of the axillas in one woman with left secondary ULE) showing «intercalated» LN at the level of the arm and numerous LN «in» the left axilla (*blue arrow*). Sagittal and transversal SPECT-CT slices showing that some LNs are indeed «deep» and «in» the axilla (*black arrows*) but that one LN is in fact «superficial» «pre-pectoral» (*white arrow*) and is intercalated on Mascagni's pathways. (*from left to right*)

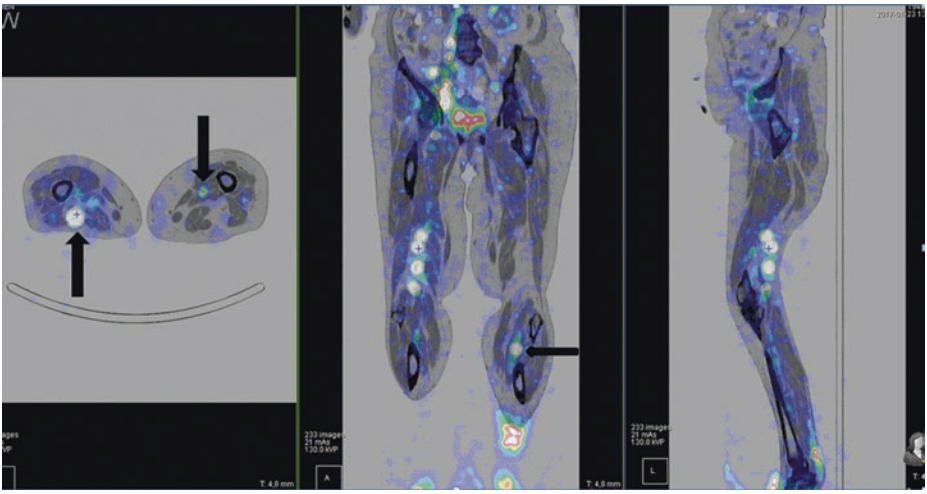


Fig. 22.12 From left to right, selected transverse, sagittal, and coronal/frontal fused slides from the SPECT-CT across the abdomen and pelvis (*obtained in the patient described in* Fig. 22.6) showing from left to right one of the right popliteal lymph nodes (*from down to up vertical arrow*), activity "in transit" in one intramuscular lymphatic vessel in the left calf (*form up to down vertical arrow*) and one sural lymph node in the left calf (*from right to left horizontal arrow*)

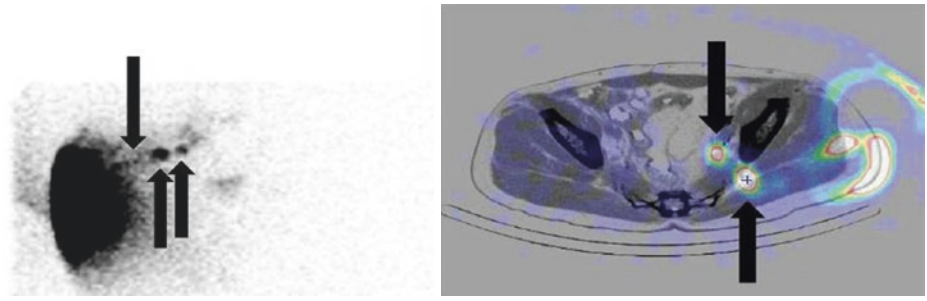


Fig. 22.13 Posterior planar view (*on the left*) obtained after one intradermal injection in the left buttock in front of the great trochanter showing one lymphatic vascular drainage (*from up to down black arrow*) in two LNs (*from down to up vertical black arrows*) which are shown on the SPECT-CT slice at this level (*on the right*) to be located for the first most external one between the muscles deep in the buttock (*from down to up black arrow*) and for the second in the iliac area in the pelvis (*from up to down black arrow*)

Specifically, studying the arrival of the tracer at the first nodes allows one to:

- Identify lymphatic system insufficiency in resting conditions (when the tracer has not reached the first lymph node at the root of the limb).
- When the tracer has reached the first lymph nodes at the root of the limb on both sides, analyze the (time–activity curves derived from the area of interest drawn on) dynamic imaging acquired on the lymph nodes at the root of the limb which may (also) show functional asymmetry in lymphatic function between the edematous limb site and its normal contralateral part

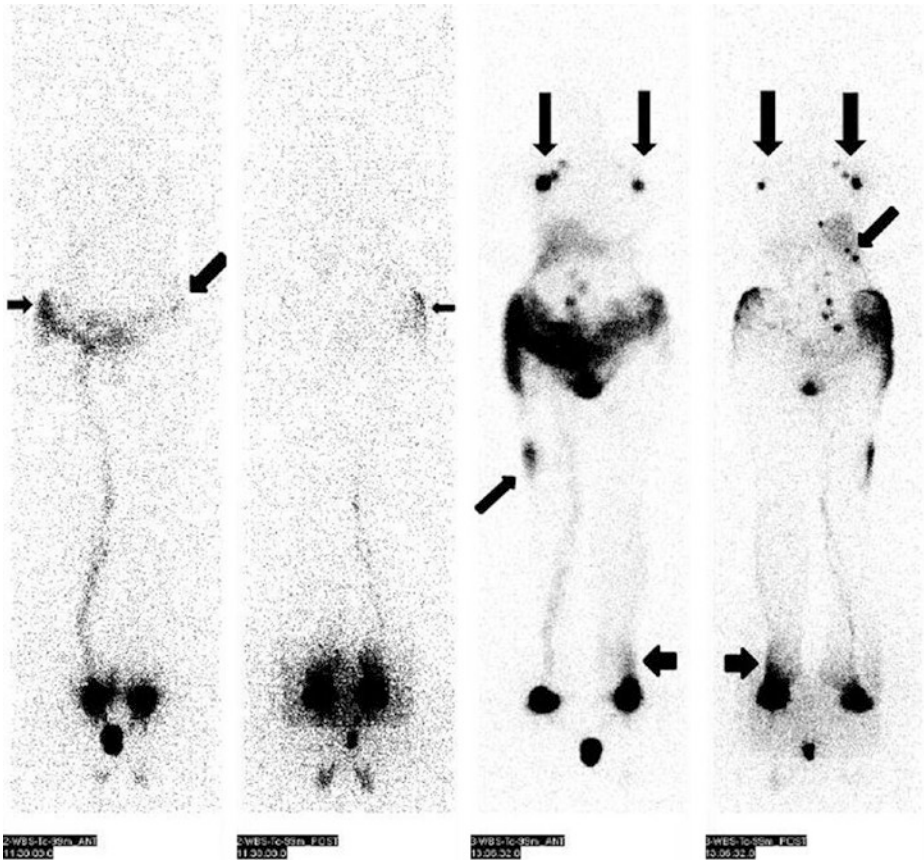


Fig. 22.14 From left to right, whole-body scanning (WBS) imagings (*anterior and posterior*) obtained after phase 1 and phase 3 with bilateral lower limb lymphedema (left > right) after LN dissection for ovarian cancer 10 years before our investigation. On the left side, progression of the tracer (limited to foot), either in the superficial collateralization lymphatic network or in the tissues, is only seen after 1 h of walking (*thick horizontal arrows*) without clear vascular lymphatic drainage at the level of the calf and thigh and without lymph nodes at the root of the limb. On the right side and after phase 1 (30 min in resting conditions: left-sided WBS), the tracer was normally drained in lymphatic vessels from the foot to reach the first right inguinal lymph nodes. Lymphatic reflux (and dermal backflows) are observed from these LN toward the external and upper part of the ipsilateral buttock (*small horizontal arrows*) and through the prepubic area toward the external and upper part of the contralateral buttock (*from up to down and right to left oblique arrow*). After phase 3 (after 1 h of walking: right-sided WBS), the lymphatic reflux have reached the superficial dermal collateralization network («dermal backflows») of the whole anterior and inferior abdominal wall (including the genital area), but also on the right side the tracer is observed descending (flowing back in the superficial lymphatic network) up to the distal and lateral part of the thigh (*from down to up oblique arrow*). Axillary lymph nodes are seen on both sides (*from up to down vertical arrows*), testimonies of vascular lymphatic drainages collecting the tracer from the upper limits of the dermal backflows areas toward these nodes. On the posterior WBS, two LNs (*from up to down and right to left oblique arrow*) are also seen in the left flank intercalated between the left buttock and in the direction of one paravertebral left-sided LN. Intra-abdominal right-sided iliac and lumbo-aortic LNs are also seen but no left-sided ones

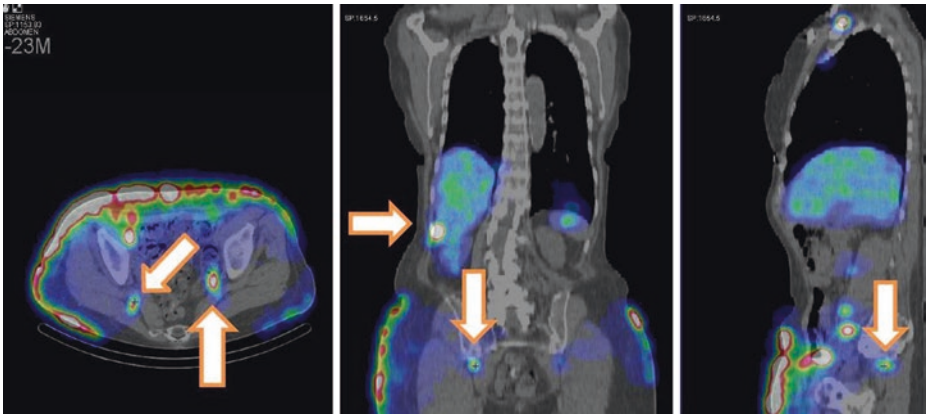


Fig. 22.15 From left to right, selected transverse, sagittal, and coronal/frontal fused slides from the SPECT-CT across the abdomen and pelvis (obtained in the patient described in Fig. 22.14) showing: The extension of the tracer in the superficial lymphatic collateralization network of the anterior abdominal wall, of the lateral parts, and (right > left) of the posterior parts of the buttocks. One of the two lymph nodes in the right flank (horizontal arrow). Unsuspected on the planar imagings, one lymph node under the arch of right iliac bone (*from up to down vertical arrows*), and intercalated between the muscles (*from down to up vertical arrow*). Also unsuspected on the planar imagings, one iliac common left-sided lymph node (*from down to up vertical arrow*)

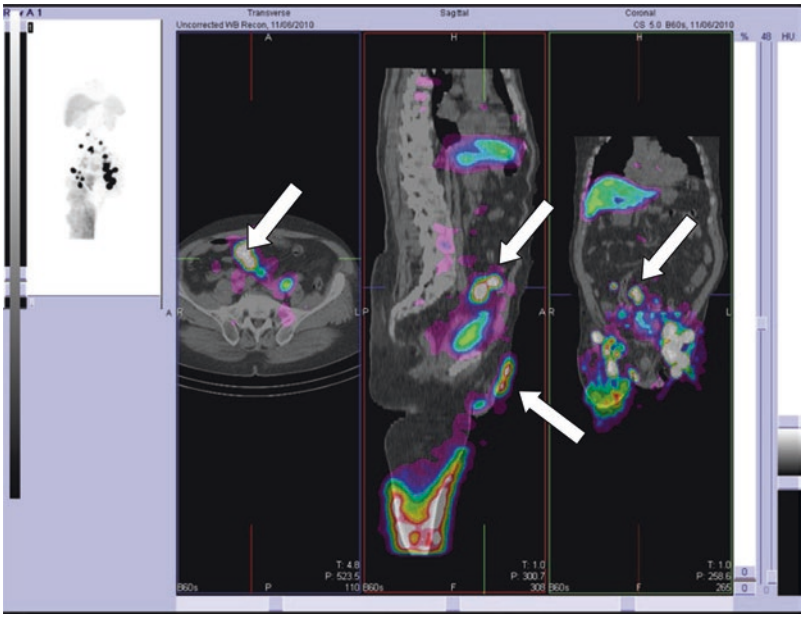


Fig. 22.16 From left to right, selected transverse, sagittal, and coronal/frontal fused slides from the SPECT-CT across the abdomen and pelvis showing nicely (1) *(top to bottom oblique arrows)* that the abnormal zone of activity seen on the planar WBS image in the mid suprapubic part of the abdomen corresponds, in fact, to lymph flowing back from lumbo-aortic nodes in the digestive tract and (2) *(bottom to top oblique arrow)* dermal back flow in the right prepubic area. *With permission from Bourgeois P. Combined Role of Lymphoscintigraphy, X-Ray Computed Tomography, Magnetic Resonance Imaging, and Positron Emission Tomography in the Management of Lymphedematous Disease. In: Lee BB, Bergan J, Rockson SG, eds. Lymphedema: A concise compendium of theory and practice © Springer 2011.* Key point for Figs. 22.4 and 22.16: When subsequently questioning the patient, he also complained of intermittent diarrhea

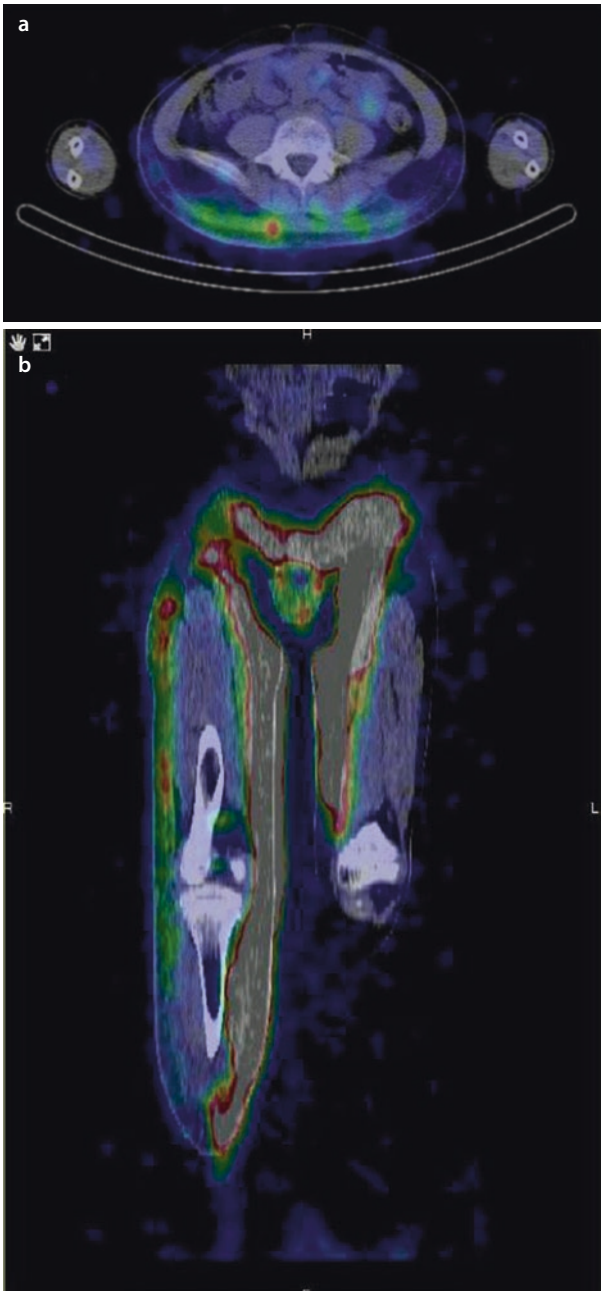


Fig. 22.17 **a** Transversal SPECT-CT slide across the posterior lymphangion showing the radiocolloidal tracer in the lesion. **b** Coronal–frontal SPECT-CT slide across the anterior abdominal wall, the scrotum, and the lower limbs showing the lymphatic reflux (dermal «backflows») of the tracer in these areas

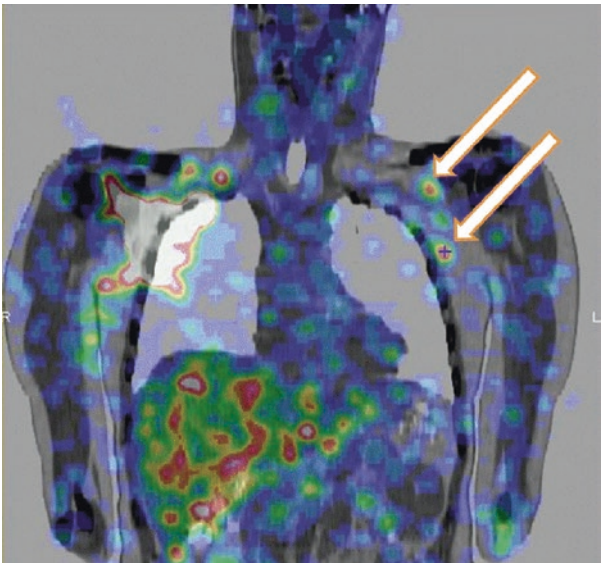


Fig. 22.18 Frontal slides from the SPECT-CT obtained in the woman (described in Fig. 22.2) and showing the right axillary nodes (*vertical arrow up to down on* Fig. 22.2)

Table 22.6 The quantitative and functional parameters that can be obtained in the framework of lymphoscintigraphic investigations

Extraction of the tracer by the lymphatic system at the level of the injected site(s)
The speed of the lymphatic flows in the lymphatic vessels (a)
The activities remaining in the lymphatic vascular structures (a)
The time of the tracer to reach the first lymph nodes (for instance, from the foot to the first inguinal lymph nodes)
The activities in the lymph nodes (a)
The ratio of the activities in the lymph nodes (right/left, edematous versus non-edematous)
The time to reach the half of the maximal activity in these lymph nodes
The activity in the liver (a)
The ratio of the activities in the lymph nodes versus the activity in the liver

2. Phase 2
   Either anterior and posterior whole-body imagings from head to toes or anterior and posterior views of the upper limbs (including the axillas) are obtained after the patient (always lying on the table of exam) has been tiptoeing for 5 min (for lower limb edema) or after 15 min of finger and hand movements (for upper limb edema).

These exercises improve the penetration of the tracer in the initial lymphatics and collectors, and they also activate and stimulate the lymphatic vessels. The result should be a perfect image of the lymphatic vessels and increasing filling of the ending nodes.

This second phase is important. At rest (after phase 1), the amount of extracted tracer may in certain cases be insufficient to produce an acceptable image of the lymphatic vessels, and, in other pathological cases that have important reflux, the normal lymphatic vessels can (after phase 3) be masked by the reflux. These phase 2 images may also show localized lymphatic lesions or suspended lymphatic reflux that may arise at any level in an early stage (that may be masked after phase 3 imaging).

The analysis of (time–activity curves derived from the area of interest drawn on) dynamic imaging acquired on the lymph nodes at the root of the limb during exercise may show (as for phase 1) functional asymmetries.

3. Phase 3

Either anterior and posterior whole-body imagings from head to toes or anterior and posterior views of the upper limbs (including the axillas) are obtained after an hour of normal activity, i.e., a 1-h walk (for lower limb edema) or an hour of normal activity using the upper limbs (for upper limb edema).

At this point, we should have (1) minimal extraction of the tracer out of the injection site; (2) an image of variable quality of the superficial lymphatic vessels of the limb plus the complete visualization of the lympho-nodal axis at the ends of the limb; (3) visualization of colloidal activity in the liver (and sometimes in the spleen and bone marrow); and (4), after one lymphoscintigraphy of the lower limbs, visualization (in one-third of patients) of retro-supraclavicular left-sided lymph nodes (that normally end the ductus thoracicus). Here, too, images that are not as expected indicate an abnormal situation.

The specialist in nuclear medicine, however, will have to keep in mind that the dynamic and/or static acquisitions (and their consecutive results) will have sometimes to be adapted to answer specific questions as listed, but not limited to, in ◘ Table 22.7.

◘ Table 22.7 Reasons for adapting the methodological approach

To study the ductus thoracicus, the thoracic duct
To precisely determine the level of one lymphatic leakage (in the abdomen, in the thorax)
To demonstrate the patency–functionality of the lymphaticovenous anastomoses, of the node-to-vein anastomoses, and of grafted lymphatic vessels (or veins; used to «bridge» the lymphatic «gap,» to reconstruct the lymphatic pathway, to switch the lymph flow from one side to the other), so that grafted lymph nodes remain functional and/or viable
To study the effects of specific manual lymphatic drainage maneuvers, of pressotherapy systems, of wearing specific bandaging and/or elastic stockings, of drugs
To investigate edema at the level of the face (see ◘ Fig. 22.19), of the breast, (limited to part) of the genitals, etc.

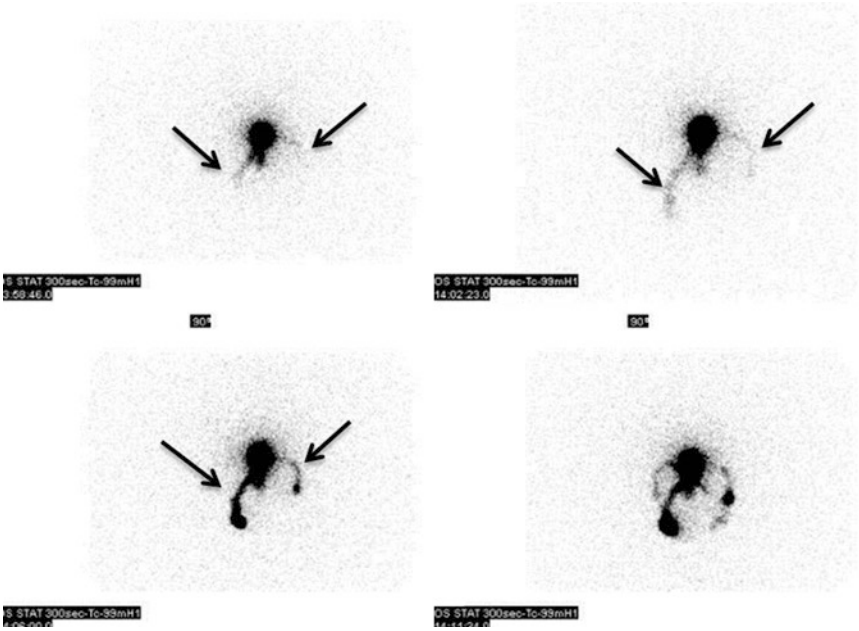


Fig. 22.19 Patient with one edema affecting the left side of the face. One intradermal injection of the tracer above the nose medially shows normal right lymphatic vascular drainages but one absent drainage above the left eye (*oblique arrow*) and one decreased lymphatic flow in the left lateral part of the nose (*horizontal arrow*) (Fig. 15.13 from my chapter «Lymphoscintigraphy and other imaging methods» in «Lymphedema: presentation, diagnosis and treatment» A.K. Greene et al. (eds) ▶ https://doi.org/10.1007/978–3–319-14,493-1_15, © Springer international publishing Switzerland 2015)

Anyway and in conclusion of (and as key point for) this subchapter, any imaging protocol of the lymphatic system, once the injections are made, should always specify:

- The clinical condition of the acquisitions: at rest, during or after a standardized exercise, after a period of «normal» activity for the patient, etc.
- The duration of the different clinical conditions imposed on the patient.

22.8 The Type of Injection («Intradermal» or «Subcutaneous») and Their Implications

How the tracer is injected is of great importance [3]. In case of edema at the level of the skin, two kinds of injections can be performed: either subcutaneous or intradermal. The latter will usually allow rapid entry of the tracer into the initial lymphatics, fast transport into the lymphatic vessels, and rapid arrival in the lymph nodes. The former is, however, more «physiological» and sensitive to the pathophysiological parameters underlying the observed edema. Removal of the injected tracer will indeed depend on the characteristics of the injected interstitial tissue and, more precisely, on the local density of the lymphatic vessels' network, but more importantly on the local

hydrostatic and oncotic pressures [4]. Once in the lymphatic vessels, transport of the tracer will depend (in addition to some of the characteristics of the tracer itself) on the normal or abnormal contractility of these vessels and on the forces that eventually oppose the lymph flows. The choice of injection will depend on the type of information desired.

In practice, this means that both injections will allow the clinician to obtain morphological images of the studied lymphatic system, albeit in different ways. However, with intradermal injections, the observations may not be physiologically relevant. This might explain why Kafejian-Haddad et al. [40] found that manual lymphatic drainage had no significant effect on the transport of 99mTc-labeled dextran in patients with lower limb lymphedema.

22.9 The Importance of Standardization of Subcutaneous Injections

When performing subcutaneous injection of radiocolloids, it is important to work with standardized products, especially in the framework of a protocol with quantitative parameters. The amount of the labeled particles and the volume of injection in which they are diluted clearly influence the quantitative results obtained in terms of both what is removed by the lymphatic system and what will be found in the lymph nodes [4].

22.10 Where Should the Tracer Be Injected?

In cases with limb edema, the anatomical site where the tracer is injected should also be taken into consideration. The injected site will define and show the expected normal and anatomically well-described effering lymphatic vessels and the lymph nodes that will be finally demonstrated (but with also their normal variants). Most of the literature about scintigraphic investigation of the lymphatic system focuses on the superficial lymphatic system, while relatively few reports focus on the deep lymphatic system.

Unfortunately, the superficial lymphatic system and the deep lymphatic system are not as independent from each other as we would hope in terms of simplifying the diagnostic workup. For instance, Caplan [41] conducted anatomical studies by injecting a modified Gerota mass into one of the toes of 183 normal cases (177 fetuses). That report showed the presence of lymphatic connections between the superficial and deep lymphatic system, with perforating vessels in 12% of the cases and communicating vessels in 2% of the cases. It remains unclear, at least to the author, whether the latter variants are normal or whether they in fact represent abnormal development of the lymphatic system.

With regard to clinical situations, Malek et al. addressed the problem of the possible relationships between the superficial and deep lymphatic systems in normal and pathological conditions. By injecting radiological contrast medium into the lymphatic system behind the outer malleolus, they regularly found such connections in patients with progressive chronic polyarthritis and with arterial sclerosis as well as at the site of healing fractures [42].

22.10.1 To Investigate the Superficial Lymphatic System… but…

Most of the protocols used to investigate the superficial lymphatic system propose using one subcutaneous injection in the first *interdigital* space of the feet or hands. The anatomical lymphatic drainage of this site is well established. Consequently, in the case of lower limb edema, it is not normal to see popliteal lymph nodes [43], which are related to the deep lymphatic system. Visualization of the popliteal lymph nodes is a sign of functional insufficiency and/or overload of the superficial lymphatic system. On the other hand, a subcutaneous injection in a more external interdigital space, i.e., in the *fourth interdigital* space, normally leads to lymphatic drainage toward and into the popliteal lymph nodes. At the level of the upper limbs, it is not normal to see interosseous antebrachial or humeral lymph nodes after a single injection in the first interdigital space.

Two or more injections in different interdigital spaces will certainly give a more representative view of the entire edematous area compared to a single injection in the first interdigital space. However, multiple injections can lead to misdiagnoses of some pathological conditions that affect the superficial lymphatic system that would be diagnosed correctly if a single injection was made in the first interdigital space.

Technical note: the term «interdigital» merits further precision. Intradermal or subcutaneous interdigital injections do not have to be performed on the dorsum of the hands in the inter-metacarpal spaces, even those that are distal, or «into the dorsum of the feet» in the inter-metatarsal spaces [44–46]. Rather, the injections should be made in the skin between either the metacarpophalangeal articulations or the metatarsophalangeal articulations and in the upper and dorsal rather than the ventral–palmar half of these cutaneous areas (► see further section 22.15.1).

22.10.2 To Investigate the Deep Lymphatic System

Various sites of injection have been proposed and are used to study the deep lymphatic system of the limbs, each of which has advantages and disadvantages. At the level of the lower limbs, these sites include the calf muscles, the medial part of the tissular space between the Achilles heel and the distal part of the tibia (our choice), and the periosteum of the calcaneum, deep in the sole of the foot.

In 1987, Clement et al. [48] injected 99mTc rhenium colloid behind the outer malleolus in 18 arteritic patients with femoropopliteal obstruction and severe (stage III or IV) ischemia (in 16 operated limbs and 20 non-operated limbs). They reported external saphenous drainage in 86% of the limbs, including 94% of the non-operated limbs; popliteal lymph nodes in 44% of the limbs, including 66% of the non-operated limbs; deep femoral drainage in 85% of the limbs, including 94% of the non-operated limbs; internal saphenous drainage in half of the cases; and communication between the external saphenous vein and the internal saphenous vein and deep pathways toward the internal saphenous vein in one-fourth of the cases. Interestingly (although unfortunately they did not describe their technical approach), they found that the lymphatic flow was normal in 15 of the 16 non-operated limbs.

Partsch and Mosbeck [47] injected a tracer (colloidal gold, 99mT-HSA nanosized colloids) intramuscularly into the distal third of the calf and quantified nodal uptake after a standardized exercise using either a probe system or a gamma camera. They observed that among 155 patients (204 limbs) with post-thrombotic syndrome, the lymph nodes in relation with the deep lymphatic system either were not visualized (49% of the cases) or showed decreased global activity (41% of the cases).

22.10.3 Why and/or for Which Patients Do We Have to Investigate the Deep Lymphatic System?

To date, relatively few scintigraphic studies have investigated the deep lymphatic system [20, 49, 50], although as early as quiet 50 years ago, Tosatti [51, 52] noted that «one attempt of the deep lymphatic system has to be searched when the edema is exclusively located to the foot and the retro-malleolar area or when exist one big foot tough to the touch.» In our clinical practice, mounting evidence indicates that some edemas are not related to morphological or functional issues of the superficial lymphatic system; rather, they are related to the deep lymphatic system. More and more frequently, women are presenting who complain of edema of the ankle and associated pain and tension in the calves («heavy limbs»). Sometimes the edema extends to the dorsum of the foot, but usually it does not involve the toes. In fact, this matches the symptoms of the patients described by Tosatti. Investigation of the superficial lymphatic system after subcutaneous injection of the tracer into the first interdigital space of such patients frequently shows normal findings. However, when there is unilateral edema, the investigation may also show a paradoxical functional asymmetry in which the superficial lymphatic system of the affected limb seems to work better than that on the non-edematous side. Investigation of the deep lymphatic system of both limbs in these women show that the deep lymphatic system of the edematous side is either absent or functionally insufficient compared to the normal side (for the methodology, the readers are invited to contact us).

We recently reviewed our data. Such a review has several scientific limitations, since it is necessarily a retrospective analysis of work performed at a single center, with the additional problem that there is no gold standard. However, we think that the strength of this review is that it helped us identify trends in the patient population and in edema presentation that clinicians and imaging specialists will have to address in the future. The analyzed patients in the review were included based on the following characteristics: (a) they presented with clinical symptoms of edema (swelling of the calf or the ankle, or a heavy limb, or tension or pain in the calf) that affected either just one limb or that affected both limbs but showed asymmetric clinical presentation; (b) they presented with no major criteria after scintigraphic investigation of the superficial lymphatic system according to our protocol (some patients presented with a paradoxical functional response in resting or in exercising conditions); (c) we did not observe popliteal or sural lymph nodes after scintigraphic investigation of the superficial lymphatic system (when there was unilateral limb edema) at the level of their edematous limb or (when there was bilateral asymmetric edema) at the level of their most affected limb.

Eight patients had unilateral edema symptoms and no past signs of venous problems, such as superficial or deep phlebitis, venous thrombosis, varicose veins, or varicosities. Their results are the following:

- Two patients with paradoxical superficial lymphatic system function (increased function compared to the normal contralateral limb) either lacked a deep lymphatic system or showed decreased deep lymphatic system function.
- Four patients with decreased function of the superficial lymphatic system compared to the normal contralateral limb either lacked a deep lymphatic system or showed decreased function of the deep lymphatic system.

Seven patients had unilateral edema symptoms but also had signs of current or past venous problems, such as superficial or deep phlebitis, venous thrombosis, varicose veins, or varicosities. Six of the seven patients had paradoxical superficial lymphatic system function (increased function compared to the normal contralateral limb). Two of these six patients had paradoxical deep lymphatic system function, while the other four either lacked a deep lymphatic system or showed decreased deep lymphatic system function. In these last four patients, it is possible that the issues with their deep lymphatic system function were the result of lesions due to venous disease. Alternatively, the issues might result from unsuspected primary disease that only affected their deep lymphatic system.

The final 22 patients had bilateralized but asymmetric edema symptoms. Some had signs of venous problems, such as superficial or deep phlebitis, venous thrombosis, varicose veins, or varicosities. Their results are the following:

- Half of the patients had paradoxical superficial lymphatic function (increased function compared with the contralateral limb), and seven of these 11 patients either lacked a deep lymphatic system or showed decreased deep lymphatic system function. The last four patients also had paradoxically increased deep lymphatic system function.
- The other 11 patients had decreased function of the superficial lymphatic system compared to the contralateral limb, and all but one either lacked a deep lymphatic system or had decreased deep lymphatic system function.

These results, even with their limitations, allow us to consider discussing the following with patients:

- We found paradoxical (increased) function of the deep lymphatic system in only 2 of 17 patients along with decreased function of the superficial lymphatic system. These results suggest the uselessness of such deep lymphatic system investigations in these last patients.
- In contrast, we found that 13 of 19 patients had paradoxical function of the superficial lymphatic system. If they have no present or past signs of venous problems, such as superficial or deep phlebitis, venous thrombosis, varicose veins, or varicosities, investigating the deep lymphatic system could explain the paradoxical response in the superficial lymphatic system. Such an investigation could reveal decreased function of the deep lymphatic system. Clearly this should be validated in a larger series. For the other patients, paradoxical function at the level of the

deep lymphatic system might suggest a simple venous problem. For others, abnormal findings during investigation of the deep lymphatic system might reveal that their issues result from lesion in the deep lymphatic system within the framework of venous disease. Another possibility is that an unsuspected primary disease is affecting their deep lymphatic system.

In practice, these preliminary results may have implications for patient management. In addition to instructing patients to wear sleeves or stockings, some patients that currently only have decreased function of their deep lymphatic system should be encouraged to perform additional muscular exercises. Other patients who lack a deep lymphatic system might benefit from additional stimulation of their superficial lymphatic system.

Apart from their interest in the diagnosis and evaluation of some edemas, these injections to visualize the deep lymphatic vessels are also used by some surgeons who seek other less superficial lymphatic vessels to use for lymphaticovenous anastomoses.

22.11 For Additional Injections!

In our clinical experience, one-third of the patients (with upper and/or lower limb lymphedema) show none of the lymph nodes expected to be seen at the root of the limb, either in the axillary area or in the inguinal and/or iliac area. This outcome raised two possibilities: either the tracer injected peripherally was not transported up and into these lymph nodes (which are in fact present) or these lymph nodes are absent as either a normal variant or a symptom of a lymphatic disease. This question can be addressed by the use of an additional injection.

In three-fourths of upper limb lymphedemas, intradermal injection of 99mTc-labeled human serum albumin (HSA) nanocolloids (twice what is injected into the hands) in the lateral part of the arm under the shoulder led either spontaneously or after massage to the lymphatic drainage of the tracer toward the homolateral axillary lymph nodes. In some cases, collateralization lymphatic pathways reaching lymph nodes in the ipsilateral supra- and/or retroclavicular area were also demonstrated (the Caplan and Mascagni pathways; see Fig. 22.10), as were the ipsilateral posterior scapular and/or cervical lymph nodes, the ipsilateral internal mammary, the ipsilateral posterior intercostal and/or paravertebral lymph nodes, and the contralateral parasternal and/or axillary lymph nodes (see Fig. 22.11).

In cases of lower limb lymphedemas, an intradermal injection at the level of the lateral part of the thigh in front of the great trochanter led (spontaneously or after massage) to direct lymphatic drainage of the tracer toward the homolateral inguinal lymph nodes and/or to the demonstration of collateralization lymphatic pathways reaching lymph nodes in the ipsilateral inguinal and/or iliac area in 90% of cases. Ipsilateral or contralateral posterior lumbo-aortic nodes were also demonstrated, as well as the opposite–contralateral inguinal lymph nodes (through lymphatic collaterals transiting in the prepubic area and/or through the genitals and rarely by transiting in the back of the patients; see Figs. 22.14, 22.15, 22.16, and 22.17b) and, more rarely, the ipsilateral axillary lymph nodes. Deep intergluteal lymphatic drainages and nodes could also be identified (see Fig. 22.13).

The results of additional injections are interesting in many respects:

- In case of lower limb lymphedemas, the demonstration of the presence of normal inguino-iliac lymph nodes (not reached by the tracer) excludes lymphadenodysplasia (associated with peripheral lymphangiodysplasia), which is associated with a worse prognosis for the lymphedema according to Kinmonth [21].
- These inguinal lymph nodes that we are able to visualize with the help of the injection may be used by surgeons to perform lymph node-to-vein anastomoses.
- For physical therapists, these additional injections also show the collateralization pathways present in their patients, pathways that the therapists can target for pushing the fluid of the edema. This practice could be an improvement on attempting all of the possible collateralization pathways that physical therapists have learned but that are not systematically present in the treated patient.

22.12 Lymphoscintigraphies of the Superficial Lymphatic System and Diagnosis of Lymphedema in Terms of Sensitivity and Specificity

From the previous paragraphs, it will be obvious for the readers that establishing the diagnosis of lymphedema («edema of lymphatic origin») will depend on many factors (the tracer, the kind of injection, the materials (one single-headed gamma camera, one dual-headed camera, one simple SPECT device, one SPECT-CT), the methodological protocol, the clinical approach or not) but, also, on the analytical criteria applied to the acquired imaging, and all these factors will define the «sensitivity» and «specificity» of the lymphoscintigraphic examination to diagnose lymphedema.

Table 22.8 shows the analysis made of the criteria proposed in 2003 in the literature [9, 19] and to which we added the data from another presentation in 2012 and can be summarized as:

- Based on the presence of morphological lymphoscintigraphic abnormalities, the sensitivity will range only from 70% to 78%.
- Sensitivity of the functional parameters (considered solely) will range from 50% to 100%. In fact, the sensitivity of a functional parameter will depend on the population studied (Table 22.8 shows the difference in the sensitivities of extraction in our first series with primary and secondary lower limb edema (LLE) and in our second series with only primary LLE).
- Finally, optimal sensitivity is obtained using a «multi-parametric» approach combining morphological and functional criteria, as in the transport index proposed by Kleinhans et al., [22] ranging from 82% to 100%. We should point out that the low value obtained by Nawaz et al. [23] is due to the fact that these authors were performing their investigations with intradermal injections of radiocolloids and thus did not acquire physiological information but only morphological.
- With regard to the term «specificity,» morphological abnormalities will usually not yield false positives (when they are observed at the level of the non-edematous limb, an explanatory cause can be found in the majority of the patients).

Table 22.8 Sensitivities and specificities of lymphoscintigraphies for the diagnosis of ULE and LLE [17]

		Sensitivity based on:				Specificity based on:			
Authors	**Year**	**N patients or limbs**	**Morphology**	**Function**	**Both**	**N patients**	**Morphology**	**Function**	**Both**
Franco et al. [31]	1980	12 primary LLE		100%[a]		48 limbs		92%[a]	
		8 secondary LLE		75%[a]					
Carena et al. [32]	1988	77 with LLE and 15 with ULE		90%[b]		16 limbs		87%[b]	
				98.2%[c]				100%[c]	
Golucke et al. [33]	1989	17	70–73%						
Ter et al. [34]	1993	17				17	100%		
Weissleider et al. [35]	1988	238 patients but 256 LLE	70% ($n = 219$)		100%				
Nawaz et al. [23]	1992	164 LLE			66%				
Cambria et al. [36]	1993	124 LLE			82%	79 limbs			83.5–100%
Bourgeois et al. [17]	1997	47 unilateral LLE	78%	50%[b]	98%	47 opposite limbs	94%	66%	
		(primary and secondary)		68%[a]		97 normal limbs	100%	100%[b]	99%

(continued)

Table 22.8 (continued)

		Sensitivity based on:				Specificity based on:			
Authors	**Year**	**N patients or limbs**	**Morphology**	**Function**	**Both**	**N patients**	**Morphology**	**Function**	**Both**
Bourgeois et al. (personal oral presentation)	2012	58 primary praecox LLE	71%	91.4%[b]	100%	<35 years of age	100%		
						Right LLE		96%[b]	
						Left LLE		94%[b]	
						Bilateral LLE		97.6%[b]	

[a]Time to node, [b]extraction, [c]nodal uptake

- Well-defined functional parameters also present high values of specificity.
- The 66% value that is shown in ◘ Table 22.8 is not an error; rather it illustrates that, when reporting the results of 47 unilateral primary or secondary LLEs, in one-third of cases, the opposite limb showed functional and/or morphological abnormality that simply traduced the presence of a «clinically latent» (stage 0) lymphedematous situation at the level of the «normal» contralateral limb (which can be observed in up to half of the patients under 26 years of age with primary praecox unilateralized clinical lower limb lymphedema). Burnand et al. [2] reported results that were similar to ours. Specifically, they reported that 32% of their patients in whom clinical lymphedema appeared to be unilateral showed abnormal scintigraphic result in the clinically normal limb.

Additional points should be kept in mind:
- These results were based only on planar images.
- These results need to be redefined as the use of SPECT-CT grows (please see ▶ Sect. 22.14) [55–62].
- These values only apply to the investigation of the superficial lymphatic system. They need to be reviewed and analyzed to take into account the growing evidence that the function and findings of the deep lymphatic system can affect the results of scintigraphic investigations of the superficial lymphatic system.

22.13 For «Lympho-SPECT-CT» Investigations?

It is now quite standard for nuclear medicine services to be equipped with hybrid devices that combine SPECT and CT in a single system, termed the SPECT-CT. The use of SPECT-CT has proven to be valuable for sentinel lymph node mapping in many cancers [55–62]. In terms of the management of patients with edema, interest in lympho-SPECT-CT was first raised by Pecking et al. [63], and its use is now well documented [13, 53, 54]. The contributions of SPECT-CT to investigations of the lymphatic system are the same as for other systems. That is, SPECT-CT can better define lymphatic-related activities, especially those of the deep lymphatic system, after the signals are corrected and enhanced. It can also correlate lymphatic-related activities with the corresponding and surrounding anatomical structures that are seen on the CT slices. These contributions are described in greater detail below:
- SPECT-CT allows better definition of the anatomical extent of dermal backflow than on planar images.
- Although some deep lymphatic structures may be recognized as such at the level of the limbs, such as the sural, popliteal, femoral, interosseous antebrachial, and humeral lymph nodes, a SPECT-CT approach allows definitive assessment of the deep (intermuscular) structures versus superficial localization of these lymphatic structures.
- In the popliteal areas, at the roots of limbs, in the abdomen, and in the thorax, SPECT-CT can better identify the deep lymphatic structures, which can sometimes be superimposed on superficial structures on planar images (see ◘ Figs. 22.9, 22.14, 22.15 and 22.17b).

- In patients with extensive dermal backflow which is better seen on delayed images, SPECT-CT highlights the activities of the underlying deep structures or normal lymphatic vessels and nodes, which can be masked by superficial signals on planar images and which may sometimes be missed when an ad hoc approach is not used.

We recently reviewed the results of abdominal and pelvic SPECT-CT imaging of 53 patients with secondary lower limb lymphedema and compared them to the results of their planar images. SPECT-CT imaging showed or confirmed lymph node localization, indicating the presence of collateral lymphatic pathways, in the following areas: intergluteal (12%; none were seen on planar images) (Fig. 22.15), anterior abdominal wall (8%; none were seen on planar images) (Fig. 22.9a, b), suprailiac (11%; in half of the cases, these lymph nodes could not be seen on planar images) (Fig. 22.15), and thoracovertebral (11%; these were seen on planar images, but SPECT-CT allowed more precise localization). Thus, in one-fourth of the patients, SPECT-CT showed lymphatic drainage pathways that could not be seen on the planar images.

22.13.1 For Lympho-SPECT-CT Definitions!

Based on SPECT-CT images, Baulieu et al. [13] proposed the following definitions for the lymphatic lesions and abnormalities seen during lymphoscintigraphic investigations:

- Lymphatic varicosis: tortuous lymphatic vessels.
- Lymphangiectasia: saccular dilatation of the main lymphatic vessels.
- Localized or diffuse lymphangioma: circumscribed dermal lesions with a cluster of large interconnected multiple spots or large lymph spaces that might extend into the dermis, muscles, and bones.
- Lymphatic saccular aneurysms: lymphatic collection connected to the surface of a lymphatic vessel by a thin neck.
- Lymphocele: accumulation of lymph outside the lymphatic system, resulting from an injury.
- Lymphorrhea: leakage of lymph from the skin due to communication between the lymphatic vessels and the epidermis.
- Lymph nodes: foci of activity that are usually spherical and that are found along the vascular pathways.
- Lymphatic dermal backflow: when the imaging agent flows back from the lymphatic nodes or vessels toward the superficial dermal collateralization lymphatic network or when it has reached this network. In lymphoscintigraphy, the imaging agents are radiolabeled molecules, but in other imaging techniques, the agents may be radiological contrast, gadolinium, free ICG, or ICG that is bound to fluorophores. Such dermal backflow is the result of either limited or extensive blockade of the lymphatic flow, with backflow of the tracer in collateral and smaller lymphatic vessels in which the propulsive pressure is lower than in the great vessels and in which, due to their dilatation, the valves become incompetent. The agent can then flow up to and into the superficial dermal collateralization lymphatic network. This is what I personally describe as vascular lymphatic backflow that results

in rerouting of the lymph. Blockade of the lymphatic flow can be due to lymphatic vessel thrombosis, to massive lymph node invasion, or to lymph node aplasia, among other possibilities. In the framework of lymphoscintigraphic investigations, we have observed that this sometimes limited dermal backflow can finally collect in normal lymphatic vessels.
- Dermal collateralization of lymphatic flow or dermal lymphatic progression: from an injected site, the tracer is no longer collected in lymphatic vessels but rather flows only in the superficial dermal collateralization lymphatic network. In very severe cases, sometimes only diffusion of the signal in the subcutaneous tissues is observed, i.e., lymphatic structures are no longer visible.

SPECT-CT sometimes allows the clinician to recognize that activities that appear on planar images are non-lymphatic. Two such situations (apart from their accumulation in the bone marrow) can be identified when 99mTc-labeled colloids are used:
- Activity in the urinary tract or superficial contamination by the urinary tract, which should not be confused with true lymphatic dermal backflow in the magna labia of women. Notably, backflow is usually more active. This is related to the presence of unlabeled reduced (non-anionic) technetium that is excreted by the kidneys. It is usually observed in the bladder within 30 min after the injection of the 99mTc-labeled HSA nanocolloids, even in patients in whom no lymphatic vascular drainage is seen.
- Activity in muscles that may be related to necrosis.

22.13.2 SPECT-CT in the Therapeutic Management of Lymphedematous Patients?

In general, SPECT-CT is of particular interest for the following situations:
- In patients with a past history of cancerous disease, SPECT-CT may allow the detection of a mass or lymph nodes, especially when the structures are not taking up the colloids. Sometimes the mass or lymph nodes may be unexpected at the time that the edema develops or worsens. This may suggest evolution of the cancerous disease, and this must then be confirmed or excluded.
- For the microsurgical treatment of lymphedema or for planning surgical liposuction–lymphosuction [54], SPECT-CT allows the precise localization of superficial or deep functional lymphatic vessels or lymph nodes that can be used for lymphatic-to-vein anastomosis. SPECT-CT can also show their relationships with the surrounding structures (as can also be seen on MRI).
- SPECT-CT visualization and localization of the superficial lymphatic vessels and collaterals can help guide physical therapists who perform manual maneuvers to stimulate the lymphatic vessels or to flush the contents of the lymphatic vessels or nodes. When superficial lymphatic vessels or nodes are shown to be deep at the root of the limbs within the fatty tissues of overweight patients, the manual maneuvers might have to be performed using higher pressure than that used on very superficial structures (which could be damaged with high pressure manoeuvers). When the

lymphatic draining structures are demonstrated to be deep, i.e., intramuscular or subaponeurotic, for example, the physical therapist should question the use of light/soft superficial manual maneuvers and should consider using muscular exercises as a way to stimulate these lymphatic structures.
- For the patients themselves, SPECT-CT can demonstrate that some lymphatic draining vascular structures are very superficial. The images can show the patients that they should avoid positions that press on or that collapse these structures and that they should avoid wearing clothes that have localized elastic that might also collapse the draining lymphatic vessels or collaterals.
- As noted in the previous point, visualization of very superficial lymphatic draining vascular structures can guide physicians or bandagists to direct the patient to wear elastic stockings. For instance, sometimes pantyhose or elastic stockings that extend to the buttock and are fixed at the level of the abdomen should be worn rather than stockings that only extend to the root of the limb and are held up by elastic at that level.

SPECT-CT is also useful in these specific situations:
- In the patients with oozing ulcers and in whom SPECT-CT identified lymphorrhea, the localization of the lymph escape from the lymphatic vessel is a relevant abnormality that could guide local therapy.
- In patients with activity that is seen on planar images in unusual areas that are outside the classical lymphatic pathways (see Figs. 22.4 and 22.16).
- When the diagnosis of lymphangioma circumscriptum or extensive lymphangioma allows treatment options to be discussed.
- In patients with Gorham's disease, SPECT-CT clearly shows the lymph spaces, allowing the patients to avoid invasive biopsy.

22.13.3 Indications for Lympho-SPECT-CT?

Where SPECT-CT devices are available, lympho-SPECT-CT investigations should systematically plan for the following situations:
- Patients with limb lymphedema in whom the edema originates (descends) from the root of the limb or extends up to the root of the limb or involves the root of the limb and the neighboring areas
- Patients with a past history of cancer in whom edema either appears suddenly or worsens despite appropriate physical treatment
- Patients with proven or suspected evolution of cancer
- Patients in whom lymphangiomatosis (see Figs. 22.7, 22.8, and 22.17) or lymphangiectasia or loss of lymph (chylothorax, chyloperitoneum, or protein-losing enteropathy, among others) is known or suspected
- Patients with lymphedema that does not respond to appropriate physical treatment
- Patients with syndromic lymphedema

22.14 «The Devil is in the Detail(s)»

Based on my analysis of our own data and also of data from lymphoscintigraphies at other institutions, this subchapter will review situations that can lead to erroneous conclusions and possible responses that can help avoid such situations. This list of situations and responses is not exhaustive, and specialists must remain critically alert.

22.14.1 The Technical «Details»

15.1. Doctors do not process the acquired pictures themselves and analyze images taken by technicians → activity in the lymphatic vessels or lymph nodes may be present but faint and hard to recognize.
Response: Review the original data yourself using higher contrast.

15.2. Low activity is injected (i.e., lower than what is generally used) → activity is faint in lymphatic vessels or in lymph nodes (popliteal, humeral, or mediastinal), so these lymphatic structures can be missed.
Response 1: Increase the time per frame for the acquisitions (this response is however not perfect, because the background activity will also increase).
Response 2: Increase the injected activities.
Response 3: Perform SPECT-CT so that the activity in these lymphatic structures can be corrected for attenuation.

15.3. The patient is obese, and the attenuation is problematic in addition to possible decreased lymphatic drainage → activity in the lymphatic vessels or in lymph nodes is present but faint.
Response: See 15.2 response 3 (or responses 1 or 2 if you have no SPECT-CT).

15.4. If you wish to quantify the signals, before the first exam, you should control for the linearity of the response by the camera to punctual sources, especially for the high signals.

15.5. When there is high activity at the site of the injections and possibly also in the lymph nodes, some gamma camera systems make it possible to observe a stardust artifact that masks some structures (see below).
Response: Choose your best camera and the best collimator to avoid or to minimize this problem.

15.6. If you are aware of the problem described in 15.5 and think that it is not important, you cover your injection sites with a lead shield → you may miss some problems or diagnoses.
Response: See response 15.5 above.

15.7. If there is high activity at the injection site and after SPECT-CT acquisition, you may sometimes observe a ring artifact (see SPECT-CT slice of Fig. 22.13).
Response 1: The ring artifact can be recognized as such, and sometimes, true nodal structures can be identified despite the confusing image.

Response 2: Being aware of this risk, perform SPECT-CT acquisitions so to minimize the problem. Specifically, make sure the injection site is at the limit of or outside the acquisition field, but stay aware that you may then miss parts of the drainage.

15.8. You see foci of activity in unusual locations or you cannot differentiate between deep and superficial structures on the anterior and posterior planar images, and you have no SPECT-CT machine or do not have time to perform a SPECT-CT.
Response: Obtain lateral or oblique planar views with anatomical markings.

15.9. Despite 1 h of normal activity, you see no lymph drainage.

Response 1: This is rare, but first make sure that the technician who prepared the product is not inexperienced and is well aware of the problem raised in point 10.

Response 2: Make sure the technician has not given you or injected activity that is correct but that corresponds to an amount of tracer (i.e., labeled proteins) that is so low as to be insufficient. In this case, the patient's lymphatic system has nothing to drain (see also 15.19).

Response 3: It is possible that there is severe edema (during chemotherapy, for instance) → in this case, perform additional injection(s) (see ▶ Sect. 22.12).

15.10. In addition to the stardust phenomenon, you should also avoid or be aware of shine-through effects, i.e., diffused activity. Do not confuse diffuse activity with true dermal backflow.

Response 1: True dermal backflow is usually not isolated; rather, it is usually continuous with lymphatic vessels.

Response 2: Diffuse activity can be related to external activity → remove the external source that may be responsible for the artifact and control your image.

Response 3: During lower limb investigation, put the feet in Charlot's position for whole-body scanning.

22.14.2 The Patient's «Details»

15.11. Even with very compliant patients, one has to consider his or her abilities. Some may not be able to tiptoe or perform handgripping exercises or will only be able to perform limited movements with their distal limbs. In these patients, the function of the lymphatic system will «normally» be decreased (but in fact, it explains some edemas).

15.12. In contrast, some patients will present, even in resting conditions, with spasmodic contractions of the muscles of their limbs. In such cases, the observed lymphatic system function is not representative of what happens in true resting conditions.

15.13. The same problem can occur when patients get off of the examination table after performing the two first parts of our protocol. We have to be very clear about what we ask them to do. For patients with lower limb edema, we ask them to walk for 1 h, and we ask that they do not remain sitting in the waiting room. For patients with upper limb edema, we ask them to perform movements with their fingers, hands, and arm that are truly representative of the daily activities that usually trigger their edema. We ask that these patients do not remain sitting or simply relax and read a magazine or book.

15.14. Sometimes, at the end of an examination, we have either normal or abnormal results that we do not understand or that appear to contradict the patient's clinical data. In patients with localized morphological abnormalities, after we exclude technical problems, it is frequently sufficient to call the patient's attention to the abnormal area, and this will remind them of a past causal event. Sometimes we can carefully reexamine the part of the limb that shows abnormal lymphoscintigraphy results and observe a lesion that explains the situation. When there are functional abnormalities or discrepancies with the clinical situation, it is frequently the case that we had to ask some more questions, e.g., «Is the edema cyclic or generalized?» or «Have you been treated for your edema (how and when?) or do you take medications?» Sometimes this helps explain the contradiction or it helps us realize that the patient originally did not understand the question. Alternatively, additional questions sometimes show that the clinical examination had not been complete and further examination reveals the problem. However, sometimes we are faced with latent edema, or, when investigating the superficial lymphatic system, the explanation is instead found in the deep lymphatic system.

22.14.3 The «Problematic» Interpretations («When, Sometimes, I Cannot Agree with Some Colleagues' Interpretation of Their Lymphoscintigraphies…» [65])

15.15. A true lymph node appears as a single focal structure in which the colloids are trapped. That is, the colloidal activity either increases over time, or it is stable after saturation is reached. Such lymph nodes should not be confused with simple vascular spaces and vice versa.

Response 1: First make sure that what appears to be one focal activity is not located on the lateral part of the patient and does not correspond to activity in a vessel that is perpendicular to the field of the camera.

Response 2: An isolated focus of activity (without incoming and outcoming lymphatic vascular activity) must be first confronted with Rouvière's anatomical data.

Response 3: Vigorously massage the area that shows focal activity, and flush rather than fill the space. If the activity either decreases or disappears, it is not a lymph node but is a lymphatic vascular space.

Response 3′: Vigorous massage does not work well with very deep structures, but if the problematic foci are present on several phases, the answer will be clear.

Response 4: On the CT slices, verify that the foci of activity correspond to lymph node(s). However, also make sure that the patient has not moved between the SPECT scan and the CT.

Response 5: If there are no clear lymph nodes on the CT slices, for example, because the resolution is not optimal or there are very small lymph nodes, go back to response 2.

Response 6: As a technical note, regarding the SPECT-CT slices, if the answer is unclear after steps 1–5 above, be aware that some foci, usually faint foci, may be artifacts, so compare their activity to true artifactual spots.

15.16. Some apparent dermal backflow is not dermal backflow.

Response 1: Please refer to technical note 15.8 for patients who are identified by response 3. After response 3 is excluded, the problem of a diffuse signal can be minimized by performing additional imaging with the limbs in such a position that the high activity sources are farther from the genital area, such as putting the limbs in a gynecological position. In addition, or alternatively, use lead to cover these high activity sources.

Response 2: In the (pre)pubic area, especially when there is lymphatic reflux from inguinal lymph nodes toward the superficial lymphatic collateralization network, do not confuse bladder activity with dermal backflow.

Response 3: In some women, reflux in the genital magna labia can be confused with urinary contamination. Similarly, in some men, scrotal reflux can cause this confusion.

Response 4: See response 3 to point 15.2.

15.17. Some lymphatic vessels may not be lymphatic vessels, so be careful not to confuse collateral pathways with bladder activity in the prepubic area.

Response 1: Lymphatic vessels are usually linear, while underlying bladder activity is irregular and fainter.

Response 2: Perform a SPECT-CT, keeping the limitations of SPECT-CT in mind.

15.18. In the intra-abdominal areas, do not confuse collateral pathways with activity in transit in the ureters.

Response: Repeat the imaging in the hope that the urinary activity will disappear.

15.19. In any part of the body, and for example when using 99mTc-HSA, do not confuse lymphatic pathways with venous or arterial pathways, especially if activity is seen in the heart.

15.20. Include the supradiaphragmatic lymph nodes when investigating lower limb edema.

Response 1: Demonstration of lymph nodes in the left supra-retroclavicular area is a strong argument in favor of normal ductus thoracicus.

Response 2: In contrast, when investigating lower limb edema, the presence of lymph nodes in other areas is a strong indication of abnormal ductus thoracicus and of congenital-malformative lymphatic disease.

Response 3: Keeping in mind the two previous responses, avoid investigating the upper limbs at the same time as the lower limbs, since this can cause you to miss some information.

15.21. Recently, I viewed the images obtained 15 min after subcutaneous injection of a tracer in the first interdigital space of the hands, and I was somewhat surprised to see not only internal–radial lymphatic vascular drainage on both sides, which in my experience is normal when I myself perform the injections, but also external cubital lymphatic vascular drainage. The nurse who performed the injections explained that the injections were made at the junction between the dorsal and palmar areas of the interdigital space. This explained the observed drainage, since the palm area of the hand can drain into cubitally running lymphatic vessels.

22.15 Lymphoscintigraphies and Irradiation?

Regarding lymphoscintigraphy, the injection of radionuclides, of a radiolabeled tracer, and the related irradiations are a frequent concern raised in many articles in the literature and by patients.

In the case of secondary edemas (after one cancer), it must be considered that the patients, as part of their treatment and diagnostic workup, have been frequently irradiated, with exposures that largely exceed the absorbed doses arising from radionuclide investigations. For instance, it has been calculated that the dose absorbed by one theoretical volume of distribution equal to 1 mL after the injection of 111 MBq (or 3 mCi) of 99mTc-labeled HSA nanosized colloids in the cutaneous tissue is equal to 1.23 Gy (or 1230 mJ per gram of tissue). Such a value has to be compared to the dose absorbed in the framework of classical irradiation, either of the chest wall or of the breast, that the patient will have experienced after a mastectomy or a tumorectomy and that is at least equal to 50 Gy.

Even for patients with edema who have not been irradiated as a (necessary) part of their treatment(s), the irradiation risks must be placed in context. In ◘ Table 22.9, we provide some facts and compare the absorbed doses attributable to some other classical radiological investigations (that are more frequently used than lymphoscintigraphies) to the corresponding data related to radionuclide-based investigations of the lymphatic system.

◘ **Table 22.9** Cancer risk related to effective dose leading to one death per 100,000 persons in comparison with the corresponding effective doses related to other classical investigations (either of nuclear medicine or of radiology) and the risks of death related to other causes

	Effective dose (mSv)	Death per 100,000 persons
Lymphoscintigraphy	0.511	2.8[a]
CT chest [25]	6	33.3[a]
CT abdomen [25]	7.2	40[a]
CT head [25]	2.4	13.3[a]
CT pelvis [26]	6.8	37.7[a]
PET scan [26]	15	83.3[a]
Background per year [27]	2.4	13.3[a]
Cancer risk probability for a population of all ages [24]	0.18	1.0
Accident (unintentional injuries) [28]		39.4
Taxi drivers and chauffeurs (USA 2013) [29]		15.7
Deaths from road traffic accidents USA (2004) [30]		12.5–20

[a]Adapted from [24]
CT computed tomography, *PET* positron emission tomography

Finally, it has to be emphasized that, to our knowledge and since the introduction of 99mTc-labeled pharmaceuticals for such investigations, no cutaneous radionecrosis has been reported.

The irradiation problem cannot be ignored, but it also must not be exaggerated. Nevertheless, it has to lead the specialist in nuclear medicine to perform this exam in the best and most complete way.

Thus, the second key message from this chapter for nuclear medicine specialists is as follows:

Key Point

Our materials that enable us to perform whole-body and/or three-dimensional imaging(s) of the lymphatic system in relation to their surrounding anatomical structures, our acquisition techniques, and our ability to quantify and dynamically analyze lymphatic system functions and the applications of clinically based protocol(s) for investigation place our specialty at the center of the diagnosis and management of the edematous presentations. The physiological basis and limitations of our examinations have to be well known and understood. Especially with our lymphoscintigraphically based functional and morphological analysis of the lymphatic system, our results must be interpreted by taking into account the patient's clinical symptoms (*see* Figs. 22.4 and 22.16) *and history and also the results of other examinations* (*see* Figs. 22.5 and 22.18). *These investigations may seem time-consuming in terms of equipment needs and human investment (they are certainly not «fast-food» medicine), but they are no more so than many other investigations now performed. These investigations must also be planned and adapted to answer clinician's questions and meet patient's expectations. If these considerations are explained to the clinicians and to the patients, you will be surprised by their adherence to and acceptance of what you propose.*

Conclusions and Final Key Messages

Lymphoscintigraphies have, until now, occupied a central place in the management of edema of suspected lymphatic origin. These imaging approaches have to be well understood by the clinicians who request these exams, specialists who perform them, and patients for whom they are proposed. Lymphoscintigraphy must be performed with care and thought, using available materials in the most appropriate ways, with the best applied methodological approaches, and always analyzed and interpreted taking into account the specific patient's situation and expectations and the clinician's demands. The specialist in nuclear medicine who performs lymphoscintigraphy also must integrate lymphoscintigraphic investigations into the growing field of other imaging techniques now proposed for investigating patients with edema while never forgetting that the primary duty of a doctor of medicine is service to the patients.

Key Points

- Edema is one clinical symptom. The symptom becomes a lymphedema when morphological and/or functional abnormalities affecting the lymphatic system can be demonstrated. *But* the lymphedematous problem must always be placed in its overall context and presented with the (eventually) associated symptoms and with the specific patient's history. The clinician has to then formulate the question(s) to be answered. These questions will determine not only the technique to be proposed to the patient but also the methodology that will be applied by the specialist who will perform the investigation.
- Materials that allow whole-body and/or three-dimensional imaging(s) of the lymphatic system in relation to their surrounding anatomical structures, acquisition techniques, and the ability to quantify and dynamically analyze lymphatic system functions and the applications of clinically based protocol(s) for investigation place the specialists in nuclear medicine at the center in the diagnosis and management of edematous presentations.
- The physiological basis and limitations of current examinations should be well known and understood. Especially with lymphoscintigraphically based functional and morphological analysis of the lymphatic system, results must be interpreted by taking into account the patient's clinical symptoms and history as well as the results of other examinations. These investigations may seem time-consuming in terms of equipment needs and human investment (they are certainly not «fast-food» medicine) but no more so than many other currently available investigations. These investigations must also be planned and adapted to answer clinician's questions and meet patient's expectations. If these considerations are explained to both the patient and the referring clinicians, they will be more acceptable and tolerated.
- The specialists who perform these investigations have always (when reporting their results and especially in their publications) to precise and detail their methodology!
- Lymphoscintigraphies have, until now, occupied a central place in the management of edema of suspected lymphatic origin. These imaging approaches must be well understood by the clinicians requesting these exams, specialists who perform them, and patients for in whom they are proposed.
  Lymphoscintigraphies must be performed with care and thought, using available materials in the most appropriate ways, with the best applied methodological approaches, and always analyzed and interpreted taking into account the specific patient's situation and expectations and the clinician's demands. The specialist in nuclear medicine who performs lymphoscintigraphy also must integrate lymphoscintigraphic investigations into the growing field of other imaging techniques now proposed for investigating patients with edema while never forgetting that the primary duty of a doctor of medicine is service to the patient.

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22

■■ Declaration of Conflict of Interest

The author declares no conflict of interest (except may be in the «regard» of some, to be specialist in nuclear medicine).

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Duplex Ultrasonography

Attilio Cavezzi

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Summary of Basic Concepts

- Color-duplex ultrasound has become the reference diagnostic tool in venous and arterial diseases; in the last 20 years, this technology has been employed in lymphology as well.
- Ultrasound imaging has been extensively used both to diagnose lymph node and tissue changes in lymphedematous limbs/areas and to target and monitor treatments along the time. The possibility to combine CDU with other diagnostic techniques, such as bioimpedance analysis, elastography, and indocyanine green, has permitted to target ultrasound scanning and to assess its accuracy while possibly potentiating its usage.
- Correlation between CDU images and clinical stages of LYM has been object of some research, though all the provided data on ultrasound imaging in LYM generally present some operator-/technique-depending variability.
- A preliminary experience with visualization of lymph vessels, possibly with ultrasound contrast agents, has been proposed as well.
- As overall ultrasound imaging in LYM has definitely conquered a place in the armamentarium of the vascular specialist who has to diagnose and treat patients affected by lymph stasis; possibilities and limitations of CDU in LYM are to be elucidated more comprehensively yet.

Diagnosis of lymphedema (LYM) of the upper and lower limbs currently relies upon the clinical assessment and upon lymphoscintigraphy in most cases. Color-duplex ultrasound (CDU) is an extremely reliable diagnostic technology for arterial and venous investigation, and the application of ultrasound investigation in LYM diagnostics has been reported since 1986 [6, 7], to complement the aforementioned imaging modalities. The exploitation of this safe, easily repeatable, quite reproducible, and relatively inexpensive technology for lymphatic diseases has resulted in the possibility of collecting some useful information before, during, and after LYM treatment.

High-frequency (10–20 MHz) ultrasound probes allow a fine study of the more superficial tissues [8], including the LYM sites, with regard to both qualitative and quantitative findings on the accumulation of fluid in supra- and subfascial planes, and elucidating the architecture. Similarly, ectatic lymphatic vessels [3, 4, 9, 10], with some degree of complexity, alterations in lymph node morphology/vascularization in particular, and venous or arterial hemodynamics may be visualized (Fig. 23.1); any concomitant anatomical abnormality, such as nodules or cysts that appear in a lymphedematous limb, will be easily imaged with CDU as well. Since the early 1990s [1, 11–14], an ultrasound semiology has been proposed to exploit the CDU diagnostic proprieties in this new field. More recently, comparison of ultrasound imaging, magnetic resonance imaging, computed tomography, spectroscopy, and histology in LYM cases has revealed a good intercorrelation of the diagnostic findings [15, 16], confirming the usefulness of this inexpensive technology.

By means of repeatable measurements, it is possible to monitor the LYM evolution and the therapeutic results. CDU examination may equally detect any venous concomi-

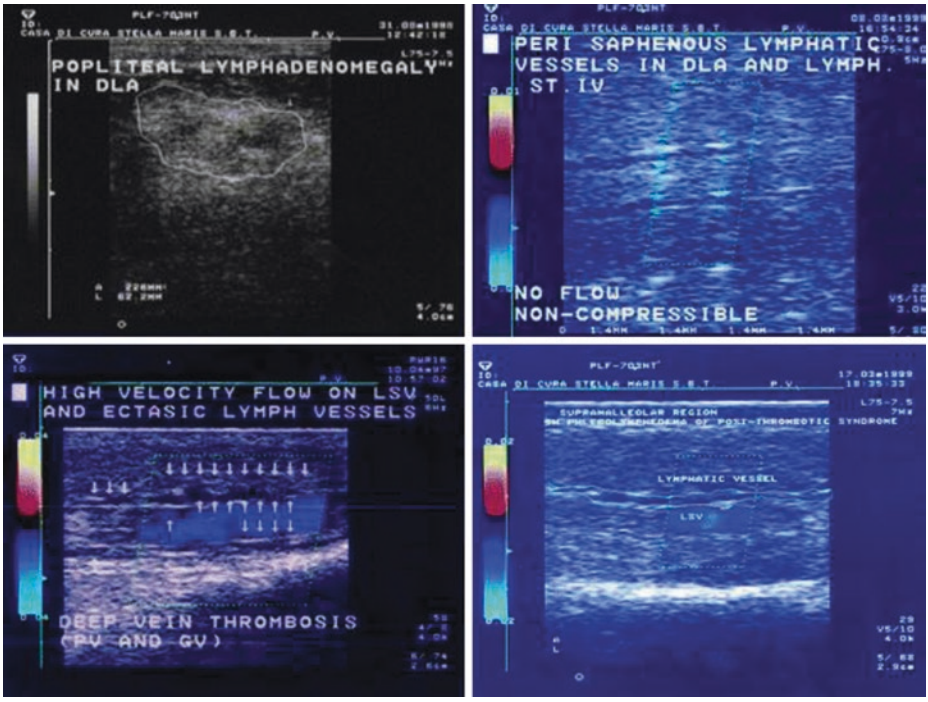

Fig. 23.1 Multiple images of color-duplex ultrasound (CDU) imaging of lymph vessels and nodes

tant disorder with great accuracy and is necessary and sufficient for most of the differential diagnoses of the swollen limb (e.g., deep venous thrombosis [DVT], angiodysplasia, post-thrombotic syndrome [PTS]). In consideration of the possible role of CDU in identifying venous changes in lymphedematous limbs, a few authors [17] have described the possible dilation of the major deep and superficial venous structures as a consequence of the impaired lymphatic drainage in lymphedematous limbs, with or without acute dermatolymphangioadenitis. In contrast, several publications have highlighted the possible participation of reduced venous drainage in many cases of «apparently» pure LYM. In fact, impaired subclavian–axillary venous drainage is often present in the edematous arm after mastectomy (in up to 31% of the cases) [18], and some degree of obstruction, or occlusion, of the deep veins has been demonstrated in upper limb LYM [19, 20]. The phlebolymphedema, which may characterize these patients with breast cancer-related arm edema, results in an aggregate of the typical ultrasound findings of LYM (e.g., the so-called lymphatic «lakes,» edematous/fibrotic tissues, etc.) and of CDU signs of a PTS and pathological patterns within the subclavian–axillary veins (Fig. 23.2).

The lower limb PTS may, of course, represent a concomitant disease in any case of LYM of the lower extremity as well, and the CDU investigation of deep, superficial, and perforating veins in these mixed cases of phlebolymphedema of the lower limbs is commonly undertaken and is of great benefit for a more precise diagnostic and therapeutic approach.

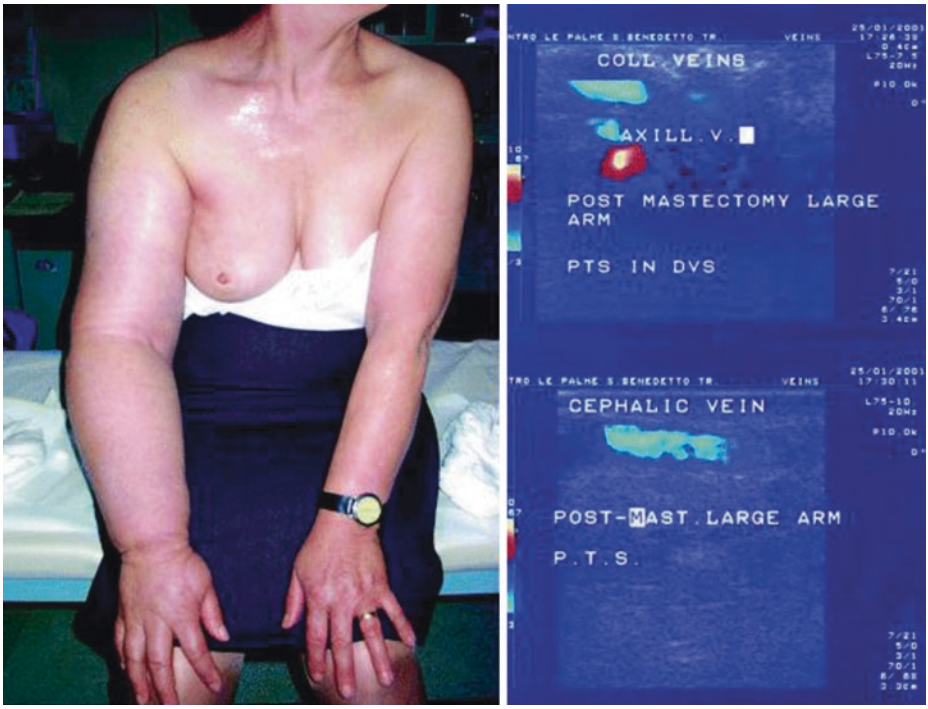

Fig. 23.2 Clinical and CDU pictures of post-mastectomy phlebolymphedema (lymphedema and post-thrombotic syndrome of the upper extremity)

On the arterial side, in 1994, Svensson et al. [21] used CDU to demonstrate increased arterial inflow in arm edema after mastectomy, possibly as a result of altered vasoconstrictor innervations.

Another CDU application relates to vascular malformations involving the lymphatic system. In fact, most «apparently» pure venous angiodysplasias exhibit a relevant lymphatic dysplastic component, and the opposite is also true. Safe and accurate use of CDU in vascular malformations has been proposed by most experts as first-line diagnostic technology, and detection of lymphatic abnormalities may be of help to focus on a proper treatment for these complex diseases.

In cases of posttraumatic or postoperative lymph stasis, CDU once more plays a decisive role, in order to screen for deep venous thrombosis and to image any serum and blood accumulation and other pathological findings.

With reference to the use of CDU in the investigation of lymphadenomegalias (dilated lymph node[s]) in the groin or, more rarely, in the popliteal or axillary area, b-mode imaging is usually complemented by color-flow Doppler to highlight possible altered vascularization of the nodes, which usually represent a negative prognostic sign because of its association with neoplasms/metastases [22].

Other possible, quite common findings in CDU imaging of lymphedematous limbs include the ruptured or intact popliteal cyst and/or fluid collection in the knee joint.

The use of CDU investigation was proposed several years ago in specific LYM cases related to filariasis, and a few specific diagnostic markers (such as «the worm dance sign») have been reported [2, 23, 24]. Ultrasound imaging may help address local/regional pharmaco-mechanical treatment for filiariae removal. Monitoring of the infection is facilitated through repeated ultrasound scanning.

It can be argued that the complexity of differential diagnosis and of the therapeutic options available in cases of a swollen limb fully justifies extensive and systematic use of CDU, especially in expert hands [25].

23.1 Specific Details in Ultrasound Investigation of Lymphedema

Ultrasound anatomy of normal skin and deeper layers is generally characterized by:

1. A first, superficial hyperechogenic layer (the epidermis).
2. The usually low-echogenicity layer of «papillary» dermis and hyperechogenicity of the deeper reticular dermis.
3. The mixed echogenicity of the subcutaneous layer, which is characterized by connective bands and nodule-like (adipose component) images.
4. At greater depths, the hyperechogenic muscular fascia is quite easily recognized, and the muscular layer ultrasound image is well defined.

In the case of LYM of the lower or upper limb, several possible modifications may occur in the architecture, echogenicity, and imaging characteristics within the epifascial and subfascial layers. Strict comparison of the same areas in the two limbs, especially in cases of unilateral LYM, and multiplanar transverse and longitudinal scans, together with a bimodal investigation (in the standing and supine positions), are of great help for proper CDU imaging.

A few basic features and findings can be observed through careful technique and adequate ultrasound probes. A summary is proposed below:

- The presence of «lymphatic lakes,» hypoechogenic images of fluid collections, can be located mostly in the epifascial compartment and in the subcutaneous layer, but also, in more advanced cases, in subfascial tissues; these fluid extravasations can be distinguished from the collectors because of their «anarchic» disposition and their abundance and size, although some misinterpretation is always possible; the ultrasound image of the fluid collections, resembling bands of various widths, gives the tissues a stratified conformation (Fig. 23.3).
- A dilation of the lymphatic main trunks/collectors is potentially imaged through high-frequency probes (ideally 18 MHz) (Figs. 23.1, 23.4, and 23.5); usually the dilated lymphatic vessels are visible in the subcutaneous tissues, mostly along the great saphenous vein axis for the leg region (where they predominantly lie in normal subjects), or in close proximity to the major lymph nodes (pre-post-lymph node collectors). The visualization of the lymphatic trunks may be more frequent in secondary LYM, because in primary LYM, the lymphatic vessels may be atretic, hypo-functioning, or totally absent; similarly, in cases of acute

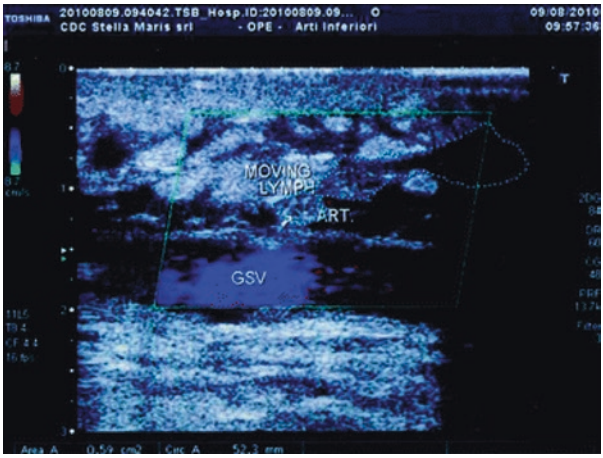

Fig. 23.3 CDU imaging in lymphedema; note the lymph movement in proximity to an arteriole, beside the great saphenous vein (*GSV*)

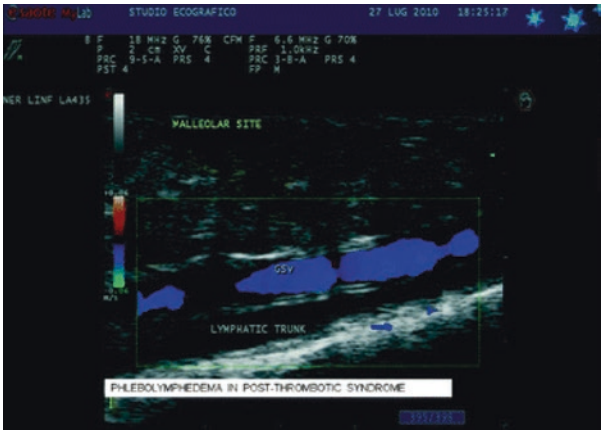

Fig. 23.4 Ectatic lymphatic vessels along the GSV at the malleolar site

dermatolymphangioadenitis or lymphocele, the lymph collectors tend to dilate functionally and are more visible on ultrasound images. The ultrasound appearance of the lymphatic channel is that of a double hyperechogenic walled tube and sometimes even valves, or thrombi [4] are highlighted inside the largest trunks. Because of the extremely small caliber of these vessels and the extremely slow lymphatic flow, CDU cannot objectively detect any «colored» fluid movement and cannot always distinguish these structures from fluid collections (the so-called lymphatic lakes) that are visible in any edematous condition [26]. Immediately before duplex ultrasound (DUS) investigation, an injection of (diluted) foamed or liquid albumin [27], a mini-trauma [4], or even a tourniquet above the edematous region [4], may enhance the ultrasound visualization of the lymphatic vessels in lymphedematous limbs or, especially, in normal limbs. Matter et al. [4] also confirmed lymph vessel ultrasound imaging through lymphatic fluid aspiration in the detected channel and through the injection of a radiopaque contrast agent within the same structure.

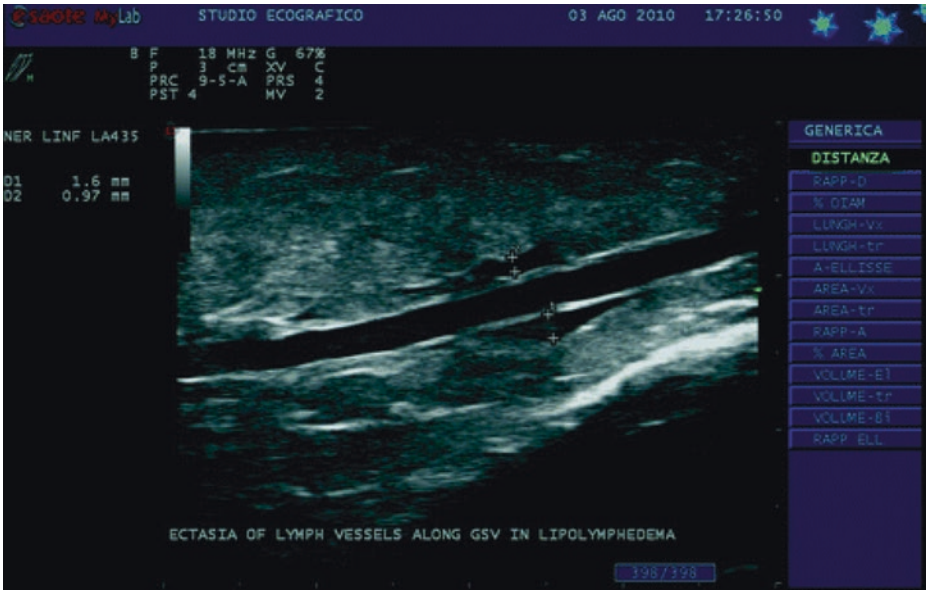

Fig. 23.5 Visible lymphatic vessels in lipolymphedema

More recently the combination of indocyanine green (ICG) lymphography with ultrasound validated the accuracy of CDU in mapping the main lymphatic trunks in the lower limb (over 90% sensitivity and specificity), which in turn may be of help when performing microsurgery in LYM patients [28].

The degree and location of echogenicity of the tissues strictly correlate with the degree of the fibrosis in the affected areas [29]; in greater detail, minimally pitting or non-pitting LYM correlates with the presence of a higher degree of fibrosis or, better, fibroadiposis, which commonly occurs in the late stages of LYM; long-lasting LYM may result in a DUS pattern that is characterized by a lack of fluid collections and by a hyperechogenicity and anarchy of the supra-subfascial tissues, with nodule-like images. However, the early stages of LYM, such as the non-swollen upper extremity after breast cancer surgery (which is clinically comparable to the contralateral limb), may also exhibit a pattern of deterioration of the architecture and an increased thickness and/or echogenicity of the epifascial layers, not necessarily showing any lymphatic lakes [5]. Suheiro and col. have recently proposed an ultrasound morphology-based scale to correlate clinical classification of LYM (as to the International Society of Lymphology) with the progressive alteration of the skin and subcutaneous tissues at the CDU imaging [30].

- Lymph node visualization, measurement, and investigation with color-Doppler flow, or power Doppler flow, should complement the ultrasound investigation in LYM cases, to differentiate abnormalities of lymph nodes related to infections, neoplasms (metastases), functional overloading, etc.

The increase in thickness of the dermis (especially in breast cancer-related LYM) [31] and/or of the subcutaneous layer and/or of the subfascial layer is a constant finding; it

involves especially the subcutaneous space until LYM frankly deteriorates, and then it involves all layers at the later stages. When acute dermatolymphangioadenitis occurs in LYM limbs, dermal structure shows relevant changes eventually elucidated by DUS [32]. The compressibility of the tissues under the ultrasound probe pressure seems to be well correlated with the degree of fibrosis/echogenicity, at least in the upper extremity [33, 34].

A few authors [3, 26, 35, 36] have described several rules to differentiate pure venous edema (phlebedema), from pure LYM and especially from lipedema (lipodystrophy of the lower limbs with fat deposition and interstitial fluid retention). In the presence of phlebedema, most hypoechogenic collections are visible in the dermal layers, while in cases of lymphostasis, the fluid collections are located in the subcutaneous region and/or in the subfascial space. More advanced LYM cases show bands of hyperechogenic reflection (which represent perilymphangiosclerosis in advanced cases). Finally, lipedema is usually characterized by diffused echoes along the whole thickness of the suprafascial tissue, with no noticeable areas of low-reflection intensity (no «lymphatic lakes» are visualized) and no increase in dermal thickness (which, on the contrary, happens in LYM). During the late stages of lipedema, lymphostasis may secondarily intervene because of the progressive deterioration of the lymphatic vessels/nodes within the fat tissues and worsening fibrosis. Thus, CDU highlights the typical low-echogenicity spaces in the areas affected by lipolymphedema (Fig. 23.6).

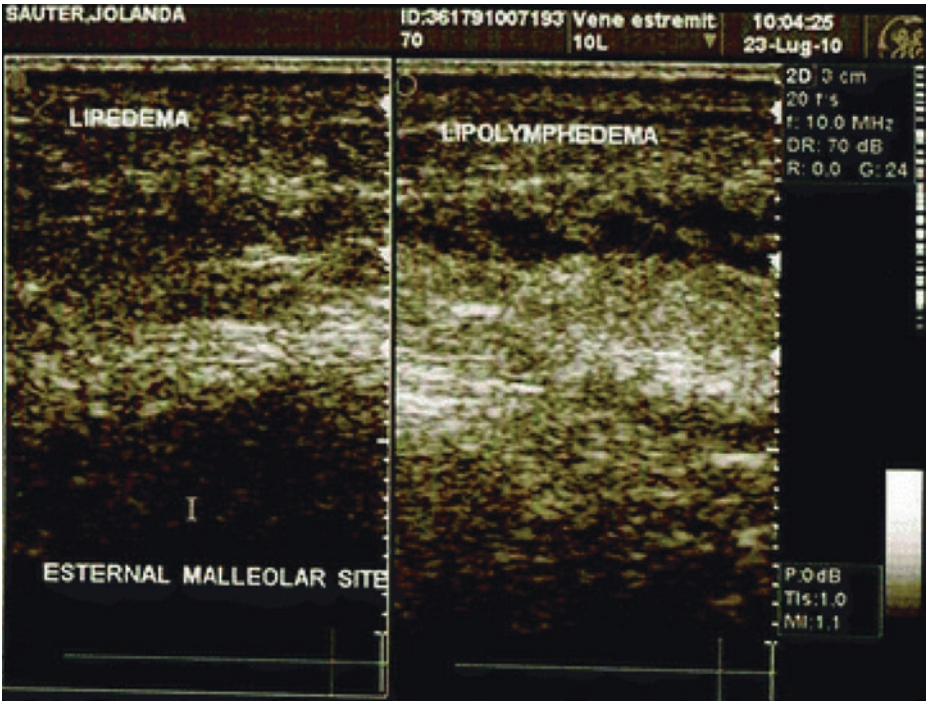

Fig. 23.6 Ultrasound images of lipedema (*left side*) and lipolymphedema (*right side*), with low-echogenicity findings in the latter condition

In case of chronic venous insufficiency, dermal edema and related lymph stasis are already visible in many patients with clinical stage 2 of CEAP classification; these ultrasound findings usually tend to progress toward cutaneous and subcutaneous layer alterations with «sclera-edematous» or «fibro-sclerotic» patterns and in C3 or higher phlebopathic limbs [37].

It should be recalled that whichever edema reflects anyway an impaired (overloaded or organically pathological) lymphatic drainage and the common CDU findings pattern of hypoechogenic areas will be seen in several of the nonvascular clinical entities, such as heart/renal/liver failure, hypo-disprotidemia, and dependent edema in general [38].

The largest lymphatic trunk, i.e., the thoracic duct, may also be the object of investigation through CDU. Franceschi [39] first published on B/W ultrasound imaging of a thrombotic obstruction of the thoracic duct and the corresponding intraoperative findings.

Ultrasound imaging during LYM treatment is of interest and of significant utility [3, 40], and it may be based on repeated measurements at fixed locations and different measures can be highlighted (Fig. 23.7):

1. The thickness of the suprafascial tissue (having the muscular fascia as the basal marker)
2. The skin-to-bone thickness, in particular at the level of the ankle, the foot, the retromalleolar regions for the lower limb, and the forearm for the upper limb

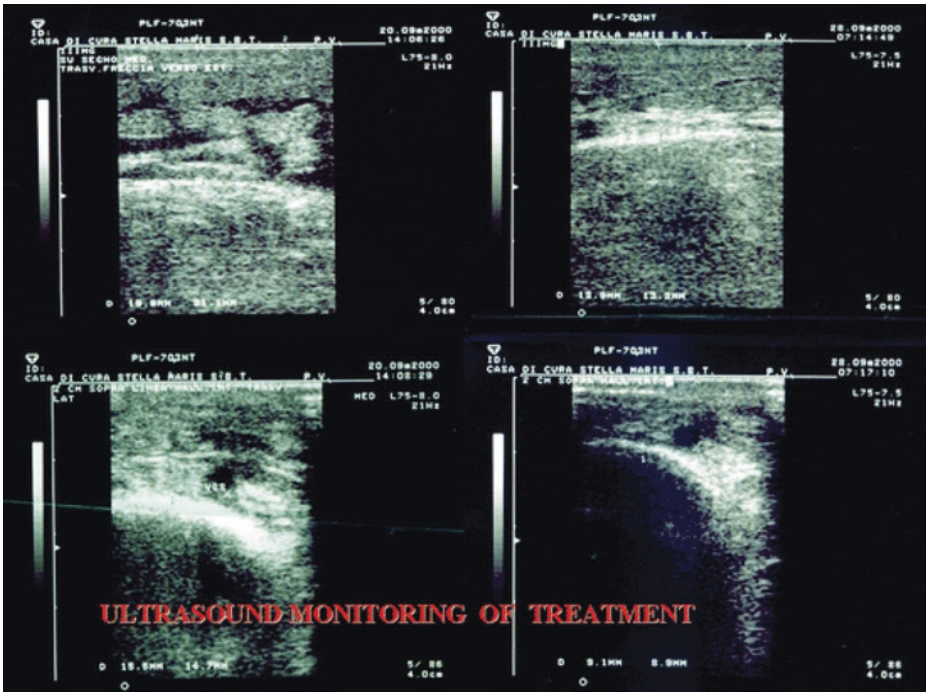

Fig. 23.7 Lymphedema treatment and CDU monitoring of the outcomes

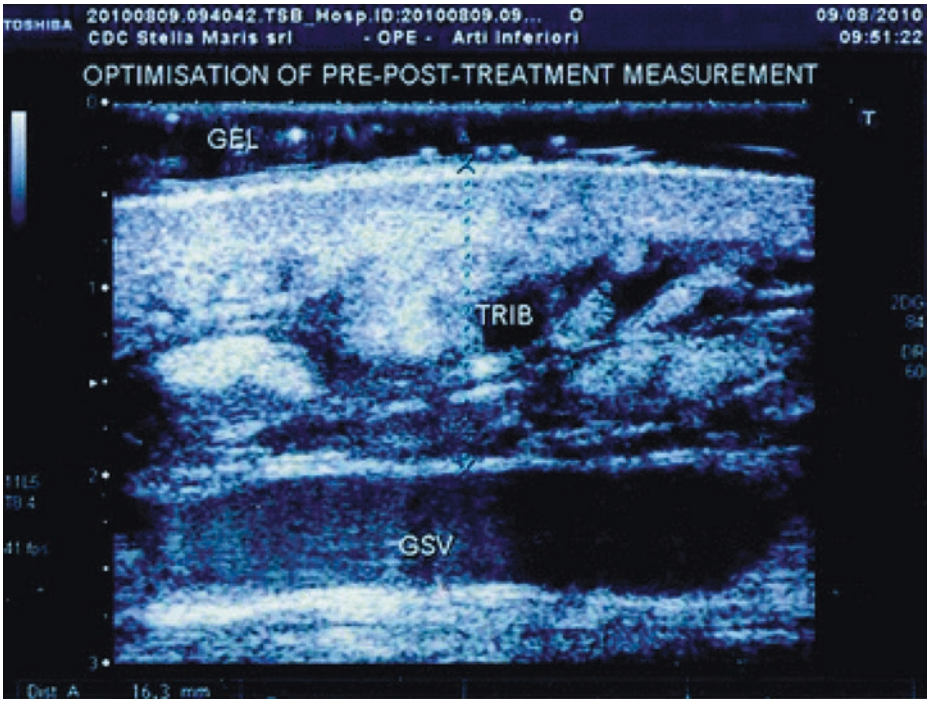

Fig. 23.8 Optimization of CDU measurement in lymphedema follow-up

If one of the main superficial veins is included in the picture/measurements, or in the case of inclusion of one or two skin markers, such as nevi or spider veins, CDU imaging reproducibility can be improved; similarly, the inclusion of abundant gel on the skin will, on the one hand, minimize the possibility of interference with the images through unwanted pressure on the skin, while, on the other hand, it will improve imaging of the most superficial layers (Fig. 23.8). A holistic, integrated therapeutic approach to LYM is often capable of producing results after a few days, and this results in a reduction (or disappearance) of extravascular layers of liquid, as well in a decrease in the echogenicity of the tissues, together with a reduction in size of the lymphatic collectors.

A further method of applying CDU investigation to LYM is by using the probe to bring out some pitting in the edematous areas [33], highlighting the nature of the edema and its fibrotic component, as well as monitoring the treatment outcomes.

With the aim to have a comprehensive diagnostic pathway, CDU has been proposed also to complement the data obtained with volumetry by means of circumference measurement and the data provided by bioimpedance analysis of tissue fluids [41].

After the introduction of ultrasound contrast agents (UCAs) for echocardiography in 1969 [42], the inclusion of albumin or other organic macromolecules in the chemical structure of these agents led us to investigate the possible usage of UCA in LYM diagnostics [27]. The possibilities and limitations of albumin-based UCA, or of foamy albumin in CDU investigation of LYM, have never been assessed in depth, and the few pertinent scientific data that were available from experiments in 2000 [27] were not, in

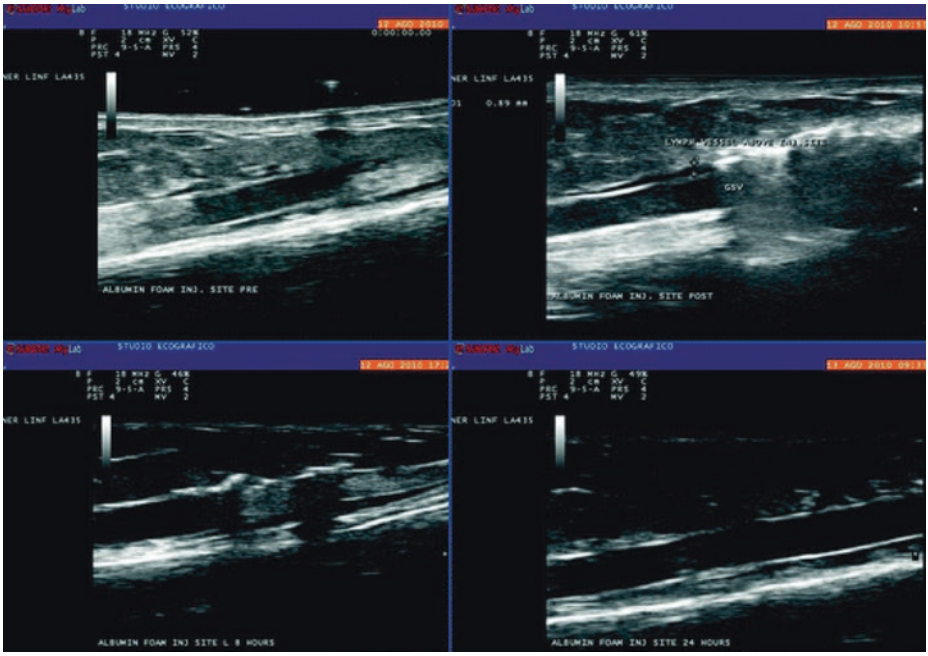

Fig. 23.9 Ultrasound imaging of injections of albumin-based ultrasound contrast agent (UCA) in a normal subject and ultrasound monitoring of UCA distribution within 24 h

fact, conclusive. Several limitations of the older, preliminary experimental studies can be possibly overcome by modern technologies and by the improved knowledge of UCA and of CDU; hence, a reappraisal of those investigations has been undertaken by our group (Fig. 23.9), and some possibly interesting data will highlight future directions for this specific diagnostic tool.

More recently elastography (ultrasound imaging with assessment of the elastic properties of the soft tissues) has been applied to LYM limbs, as an isolated tool [43] or in combination with ICG [44]; lymphedematous tissue fibrosis has been quantified, notwithstanding the objective limitations due to technical- and operator-related variables.

Overall both physicians and physiotherapists [3, 45] may complement the clinical approach to LYM patients with CDU imaging to detect the most relevant changes in the lymphedematous tissues, to improve the diagnostic pathway, and to target the relative treatment.

In conclusion, the use of CDU in the field of lymphatic diseases seems to be still in the early stages, but further technological and methodological advancements hopefully will facilitate a broader usage of ultrasound in lymphatic diagnostics and therapeutics. The technical limitations, the dependence of the accuracy on the operator, and the lack of high-level scientific evidence for CDU investigation in LYM can be counterbalanced by the noninvasive nature and low expense of this diagnostic tool, an approach that is still in its infancy.

Acknowledgments Thanks to Prof. B.B. Lee for his patience and continuous stimulus to our scientific work.

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Oil Contrast Lymphangiography

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Summary of Basic Concepts

- Contrary to what happens in the arterial and venous systems, visualization of the lymphatic system has been technically challenging and the most important obstacle for its study.
- Oil contrast lymphography using oil-soluble materials is tedious and time-consuming. However, it offers unparalleled visualization of the lymphatics and has served to identify and classify the four types of lymphatic imaging: the normal lymphatics, hypoplasia, aplasia, and hyperplasia of the trunks.
- The development of new imaging methods and new contrast agents such as dynamic contrast-enhanced MRI and color Doppler ultrasound (CDUS) provides valuable structural and functional information of the lymphatic system that was not previously available.
- Lymph flow transport as well as precise anatomy of lymphatic vessels can now be measured and defined using novel contrast materials and radiological techniques. The combination of radiological breakthroughs and contrast materials allowed us to look deeply into the elusive lymphatic system.

24.1 Introduction

Ever since the lymphatic vessels were incidentally discovered in 1622 by Gasparo, Professor of Anatomy at Pavia University in Italy [6], the anatomy and physiologic functions of these tiny structures have posed a challenge to the investigators due to their small size and the difficulties involved in its visualization. Contrary to what happens in the arterial and venous systems where their visualization is relatively easy, visualization of the lymphatic system has been technically challenging. Following Aselli's description, the lymphatics were the focus of attention of many investigators that used injections of mercury in cadavers to gain as much knowledge as possible on these intriguing little vessels. The Medical-Surgical Military Academy of Austria, founded in 1785 by Joseph II, is the oldest military school of application in Europe. It was closed in 1918, but its historical value was preserved until the present by housing the Institute of Medical History in Vienna. Among others, 1192 beautiful anatomical wax models crafted in Florence at the end of the eighteenth century are on public display. Here, one can admire unique models of whole-body dissections of the lymphatic system performed by the Italian artists.

The complex network of small lymphatic capillaries which absorb fluid from the interstitial space was described by Casley-Smith who called them «initial lymphatics» [7].

They are formed by a single layer of 10–60 μm internal diameter endothelial cells. These lymphatic capillaries drain into larger valved channels of the dermis and subcutaneous tissues that run along the veins above the muscular fascia. Visualization of the initial lymphatics was the subject of the 1984 International Symposium in Zurich,

Switzerland, and a publication edited by A. Bollinger, J. Partsch, and J.H.N. Wolfe [1] where demonstration and functional evaluation of superficial lymphatics were explored using fluorescence microlymphography [8] and Iotasul [9] (indirect lymphography). Of course all these efforts came after the pioneering work of Professor John B. Kinmonth of Saint Thomas' Hospital in London, who made the lymphatic system and its visualization by lymphography, classification, and function the focus of his life.

It is compelling to read in the introduction to the first edition of his book in 1972 the following citation: «*The chief author had the good fortune to work in the years after the war with Professor Sir James Patterson Ross at St Bartholomew's Hospital. At that time there was no satisfactory clinical method of investigating lymphatic function. Pure speculation reigned. One eminent authority on vascular diseases even stated that «he doubted if the lymphatics existed. And if they di, they were of no importance». Another said that such research was valueless «you won't find anything out and if you do, no-one will believe you». But Sir James was encouraging. When on a ward round at Bart's he saw a picture of one of the first successful deep lymphangiograms he said, «don't lose that slide, it is going to be very important». Much of our early studies were on patients with lymphedema with aplasia or hypoplasia of the lymphatics. We did not know it but we had chosen the most difficult subjects for lymphography. Often we felt like the poet W.B. Yeats «the fascination of what is difficult has dried the sap out of my veins»* [2]. After the groundbreaking investigations of Hudack and McMaster who injected Patent Blue dye intradermally and demonstrated small lymphatics in the skin [3] in 1933, Servelle in 1944 [4] and Kinmonth in 1952 [10] explored the use of Patent Blue in the experimental and clinical visualization of the lymphatic vessels. This pioneering work culminated with the description of the technique of lymphography as preliminary step to visualize the dermal and subcutaneous lymphatics, cannulate them, and inject contrast materials that produced some of the first radiologic imaging of the lymphatic vessels. Kinmonth devoted the following 25 years of his life to the study of the lymphatic system and to develop techniques of lymphatic visualization that produced the first lymphangiographic and clinical classification of lymphedemas. By the time he published his book, he had performed more than 2000 direct lymphographies. This author had the privilege to have met and worked in 1957 with Professor Kinmonth during a visit to his close friend and my mentor, Harvard Professor Richard Warren of the Peter Bent Brigham Hospital in Boston. Professor Kinmonth gave me a small bag containing several grams of Patent Blue Violet powder (also known as Patent Blue V, Alphazurine 2G) with detailed instructions on how to prepare an 11% sterile aqueous solution of the vital dye whose capacity to diffuse into the tissues and be absorbed by the lymphatics was higher than other vital dyes. Professor Kinmonth's visit sparked my lifelong interest in the lymphatic system and my efforts to study the lymphatics in different edema-producing conditions. An apparatus of my own design to measure intra-lymphatic pressure (lymphomanometer) and perform direct visual and radiological lymphography was constructed and used in different types of lymphedema (◘ Fig. 24.1). The results of my investigations on lymphatic pressure escape the scope of this chapter.

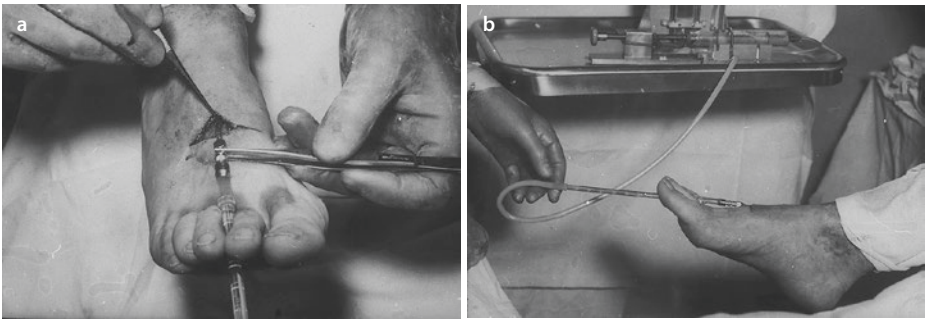

Fig. 24.1 **a** Direct lymphography after lymphomanometry. This photography shows a lymphatic vessel cannulation on the dorsum of the foot after injection of 0.2 mL of aqueous solution of Patent Blue Violet into each of three interdigital spaces of the foot. **b** A 1 mm ID diameter micropipette attached by one end to a plastic tube connected to a syringe and a U water manometer and to the other to a 30 ga needle. After the lymphatic pressure determination, a slow injection of ultrafluid Lipiodol was performed by gradual turning of the metal piston on the syringe plunger

24.2 Visual Lymphography and Radiologic Lymphography

Visual lymphography is performed by injecting 0.1–0.3 mL of Patent Blue dye through a fine needle (27 ga) into 2–3 interdigital spaces of the foot or hand. Gentle massage and active movements of the foot /hand are recommended to facilitate dye absorption and proximal progression. In patients with lymphatic truncular or nodal obstruction, a fine reticular cutaneous pattern (dermal backflow) may appear 5–15 cm proximal to the site of injection (Fig. 24.2). In addition to detection of dermal backflow, visual lymphography is widely used intraoperatively to visualize the lymphatic trunks traveling next to the greater saphenous vein or the superficial veins of the upper extremity in patients submitted to lympho-venous anastomosis or lymphatic/node reconstruction procedures. The injection of Patent Blue may be performed in other areas of the body such as the neck, testes (lymphocele, hydrocele), axilla, pelvis, etc. to visualize nodes or lymph trunks.

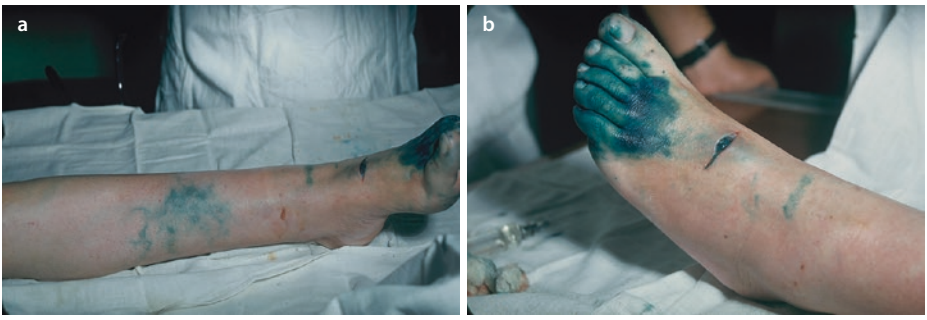

Fig. 24.2 Visual lymphograpy. Reflux of the dye to the skin is called «dermal backflow» and is strongly suggestive of lymphatic obstruction **a**. The interdigital injection of 0.2 mL of a 11% aqueous solution of Patent Blue Violet dye into 3–4 web spaces produced this image **b**

24.3 Radiologic Lymphography

After the dye has been absorbed by the lymphatics, one may often detect the blue lymph channels through the skin. A small transverse incision on the dorsum of the foot or hand is carefully performed using gentle strokes of the scalpel (Fig. 24.2b). Magnification using 4+ surgical loupes or 6+ surgical microscope is of great value to identify the lymphatic trunks and distinguish them from the neighboring veins. The lymphatic trunks appear stained in beautiful blue contrasting with the yellowish hue of the fatty tissue. Dissection of the lymphatic trunk is done carefully freeing its anterior and lateral aspects leaving the posterior segment intact to serve as support for the cannulation. We used a #30 ga hypodermic needle with four small side holes drilled by a watchmaker on its distal 5 mm. The lateral holes decrease the resistance to the injection of the contrast material.

24.4 Oil Contrast Lymphography

Oil-soluble contrast material such as ultrafluid Lipiodol was used extensively in direct lymphography. Lipiodol contains 38% of iodine and is more viscous than its aqueous counterpart «Conray» 280 or 420. The injection must be performed very slowly using automatic injectors (1 mL every 6–7 min). A total of no more than 10 mL of Lipiodol should be injected. Several radiographs are taken to monitor the progress of the dye. The calf and thigh are gently massaged to assist the oil on its centripetal flow, and further films are taken at intervals during several hours. The contrast material has the disadvantage of producing inflammation of the vessels and often lymphatic obstruction. In some cases, this complication is responsible for the lack of postoperative visualization of the lympho-venous anastomosis. This fact makes it difficult to assess patency and evaluate the benefit of the procedure. Oil lymphography may also cause allergies and on occasions, oil embolization manifested by dyspnea, pyrexia, and slight hemoptysis. In spite of its risks, the procedure was extensively used throughout the world and was instrumental in the development of an early lymphedema classification. The Kinmonth classification was based on clinical, lymphangiographic, and histopathologic studies. The lymphangiographic studies were classified as: (A) normal lymphatic system, (B) hypoplasia of the lymphatic trunks, (C) hyperplasia or varicose dilatation of the lymph trunks (megalymphatics), and (D) aplasia of the trunks and lymph nodes. Primary lymphedemas have trunk aplasia or hypoplasia with or without node aplasia. Secondary lymphedemas have abnormal patterns of lymph transport secondary to damage to the lymph trunks or to the nodes such as in lymphadenectomy for malignancy and/or radiation, trauma, infection, filariasis, etc.

Lymphangiography, as described, provided good information on the anatomy and morphology of the lymphatics. However, the procedure was tedious and time-consuming and required exquisite patience and skill. Furthermore, it did not provide dynamic information and its use has been practically abandoned. Like many findings in science, lymphangiography has been a stepping stone in the progress toward the development of better technologic procedures.

24.5 Lymphoscintigraphy

It was the next step in the effort to visualize and obtain information on lymph flow dynamics and transport of fluids [11–14]. With the introduction of technetium-99 m human serum albumin, and advances in the digital gamma camera, improved resolution of the entire body lymphatic system can be obtained [15, 16].

The lymphoscintigraphy technique as utilized in our department [16], requires the subcutaneous injection of 1 millicurie of Tc-Sb_2 S_3 mixed with 0.3–0.5 mL of normal saline subcutaneously into three interdigital web spaces of each foot. Before injecting the isotope, the patient is asked to walk for 5 min. Images are obtained in a gamma camera at 10 min intervals with a large field of view. Inguinal nodes are observed usually at or before 30 min. A normal lymphoscintigraphic pattern is when there is symmetric bilateral transit and observation of the tracer at the inguinal nodes within 1 h. Abnormal lymphoscintigraphic patterns are dermal backflow, complete obstruction, lymphoceles, reflux, and lateral channels. Because the tracer enters the lymphatics by diffusion rather than direct endolymphatic injection, lymphoscintigraphy accurately and reliably depicts the anatomy and function of the lymphatic system [17].

Magnetic resonance imaging (MRI) has shown its value in congenital vascular anomalies. It has been useful in the differential diagnosis of lipedema, venous edema, and lymphedema. Patients with lymphedema show a typical honeycomb pattern of the subcutaneous tissue. An advantage of the method is that it is possible to visualize the lymphatic trunks or nodes proximal to lymphatic obstruction, something that lymphoscintigraphy cannot do [5].

There is no doubt that the field of lymphatic imaging continues to evolve as demonstrated with the development of newer imaging methods such as positron emission tomography (PET), dynamic contrast-enhanced MRI (DCE-MRI), and color Doppler ultrasound (CDUS). These techniques provide structural and functional information using minimally invasive interstitial imaging techniques with new contrast agents. As it occurs in the field of congenital vascular malformations, multimodal techniques might be more appropriate to diagnose and study lymphatic diseases [18].

The poor resolution of the conventional diagnostic method of radionuclide-based imaging has served as incentive to investigate the potential of MRI and new contrast agents in the functional evaluation of the lymphatics and lymph nodes in the diagnosis of lymphatic circulation disorders particularly in primary lymphedema. In a recent study, contrast-enhanced lymphangiography was performed with a 3.0-T MR unit after intracutaneous injection of gadobenate dimeglumine into the interdigital webs of the foot. This study demonstrated the possibility to visualize the precise anatomy of the lymphatic vessels and the characteristics of the lymphatic nodes in patients with lymphedema. An added advantage is the potential to obtain functional data of lymph flow transport in the lymphatic vessels and nodes [19].

24.6 Summary

From the direct lymphography of Kinmonth to the current array of novel imaging techniques and newer contrast materials, many years of clinical and experimental investigations have elapsed always in search of better methods and techniques to visualize the

lymphatic vessels and find out the true significance of the elusive and challenging lymphatics in health and disease.

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Microscopic Lymphangiography

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Summary of Basic Concepts

- Venous capillary, interstitium and microlymphatic, constitutes a single functional microcirculatory unit of drainage.
- Microlymphography can be employed to study lymphatic pathophysiology in common micro- and macrocirculatory diseases.
- Microlymphography allows to investigate the number, morphology, permeability, diameter of open microlymphatics, superficial diffusion of fluorescent dye, and intralymphatic and interstitial pressures.
- In healthy individuals, few cutaneous microlymphatics are visualized since there is good drainage into the deep lymphatic circulation.
- In CVD an increased number of loops and a typical fragmentation are observed.
- In early-stage lymphedema, the number of microlymphatic loops is high, and the microlymphatic pressure is much higher than the normal range, due to initial insufficiency.
- In II–III stage lymphedema, fewer irregular, dilated, microlymphatics are depicted, and staining is much slower. At the most advanced stages, IV–V , microlymphatics cannot be seen because of fibrosis.

Like the blood capillaries, the lymphatic microvessels are formed by a thin layer of endothelial cells resting on a delicate basal membrane. This structure, particularly at the initial segment, is widely fenestrated. The cells are anchored to filaments which, as interstitial pressure increases, are believed to open the fenestrations and allow the lymph to enter the lymphatic microvessel [1, 6]. The cutaneous microlymphatic circulation is formed by two superficial networks joined by small perpendicular vessels through which the lymph drains from the superficial into the deep network. This deep network is connected by channels that run in a perpendicular direction from the skin downward to the lymphatic precollectors [1, 2, 6]. The lymphatic system is currently conceived of as an integral component of a drainage network originating from the venous end of microcirculation. Together with the venous portion of the capillary circulation and the interstitium, it constitutes a single system that may be defined as a functional microcirculatory unit [2, 6–9]. The venous and the lymphatic systems work together (Fig. 25.1); they are connected by tiny lymphovenous anastomoses that activate when the pressure in the lymphatic system rises [10–12]. Persistent venous stasis will lead to functional overload in the lymphatic system that may result in dynamic insufficiency because the fluid overload exceeds the transport capacity of the lymphatics. In these conditions, lymphangiopathy develops which, in turn, exacerbates edema, which is no longer only of venous but also of lymphatic origin [2, 13–18].

With today's technologies, the initial lymphatics in any body compartment can be visualized and investigated.

Microlymphography is performed using a moving arm with a fluorescence videomicroscope (Wild Leitz). Using magnification (*100×)* the microlymphatic network is visualized after a subepidermal injection of 0.01 mc OF FITC dextran 150,000, 5 cm above the medial malleolus. Photomicrographs are filmed using a video camera (Ikegami ITC-410)

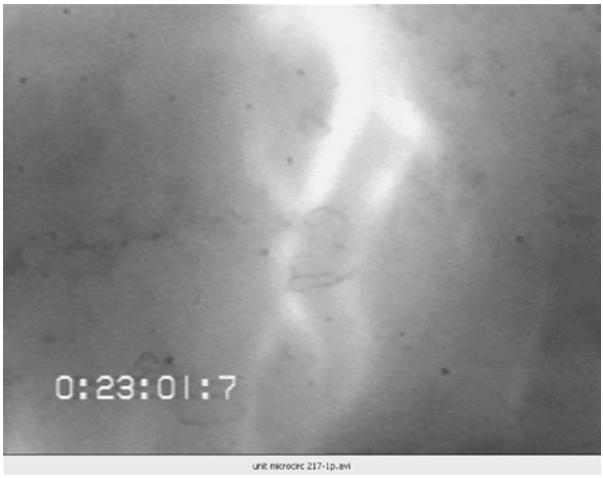

Fig. 25.1 Anastomosis between microlymphatic system fluorescent and blood capillaries

and transformed into video signals to a digital videorecorder (Sony SLV-415), simultaneously depicted on two or more monitors. Recordings last for at least 15 min.

From the collected images, the following can be studied:

1. Morphology of the lymphatic network [1, 19–21].
2. Mean diameter (in μ) of the microlymphatics using morphometric computerized elaboration applied to ten among the best stained meshes [1, 19–21].
3. Velocity of fluorescence staining or the time needed to visualize (i.e., stain) the microlymphatic network from the time of intradermal inoculation [1, 19–21].
4. «Permanency» or the amount of time that the microlymphatic remains stained.
5. «Extension» or the distance from the inoculation area to the depiction of the microlymphatic network.
6. Diffusion or the loss of fluorescent dye into perilymphatic tissues.

Parameters c–f are directly related to the opening of lymphatic collectors, degree of lymphatic hypoplasia, and the integrity of the lymphatic vessels in response to increased interstitial cutaneous pressure.

The servo-nulling system apparatus (MODEL 5A) consists of a pressure transducer (Mod 915), a video signaI control (515), and a micromanipulator. With 3.2× magnification, we can measure [5, 25]:

1. *Intramicrolymphatic pressure* by introducing a 1 μ microneedle probe on the micromanipulator into the most densely stained lymphatic, connected to the Mod 5A to yield an intraIuminal pressure for at least 1 min. Computer analysis thereafter provides the range and mean of the intraIuminal lymphatic pressure recorded.
2. *Interstitial pressure* by introducing the microneedles into the adjacent tissue. Interstitial pressure is determined and used as a reference for intralymphatic pressure readings including initial lymphatics.

Therefore, this method can be used to measure interstitial pressure, besides intramicrolymphatic pressure, in healthy individuals and in those with chronic venous disease and lymphedema.

Studies by Allegra et al. using the system have improved our knowledge of the pathophysiology of the lymphatic circulation in healthy subjects and in patients with chronic venous disease, lymphedema, and other vascular conditions [3, 22–24].

25.1 Lymphatic Vasomotion and Lymphatic Flow Motion

Several important findings were discovered by chance. After having recorded thousands of microlymphographs and fast-forwarded several images, we noticed that it was sometimes possible to recognize, even with the naked eye, flow movement inside the microlymphatics. We digitized several microlymphographs and observed and measured lymphatic flow. For the first time, the velocity of lymphatic flow was visualized and measured in vivo in a human. We noted two different types of intramicrolymphatic flow: a very slow granular flow, which we termed «lymphatic flow motion» (about 10 ± 4 m/s), and a pulsating, «stop and go» flow pattern, faster than the former (about 91 ± 58 m/s), with periodic accelerations, which we termed «lymphatic vasomotion.» The periodicity of the flow accelerations was about 1 min ± 25 s.

We were unable to visualize either type of flow pattern in healthy subjects; however, in patients with CVD (CEAP 2,3), we sometimes found a pulsating flow (lymphatic vasomotion) in the proximity of the precollectors, but never granular flow (lymphatic flow motion). In patients with soft edema, we more often found a granular flow pattern, but rarely a periodic flow pattern in the proximity of the precollectors [3, 22–24].

That granular flow pattern is visible only in a setting of soft lymphedema but not in patients with CVD or healthy subjects; it may be linked to an increase in the superficial flow that compensates for obstruction of normal deep flow.

In the setting of lymphedema, the presence of a pulsating flow (lymphatic vasomotion) is related to deep drainage because of the opening of the precollectors, probably resulting from critical pressure levels. As regards CVD, the pulsating flow pattern is related to similar dynamics, even if the underlying pathophysiological mechanism is failure of the microlymphatic system and increased interstitial pressure due to capillary stasis [3, 22–24]. In healthy subjects, neither flow pattern is detected since the lymph flows not in the superficial but, rather, in the deep network through the collectors and therefore cannot be visualized. Recent developments in monitoring and studying lymphatic flow have provided insights into the pathophysiology of lymphatic circulation [24].

25.2 Microlymphography in Healthy Individuals, in Chronic Venous Disease, and in Lymphedema

As microlymphography permits the visualization and study of microlymphatic vessels, it can be employed to study lymphatic pathophysiology in common micro- and macrocirculatory diseases [16]. In *healthy individuals*, few microlymphatics are ordinarily

Fig. 25.2 Microlymphography in healthy subject

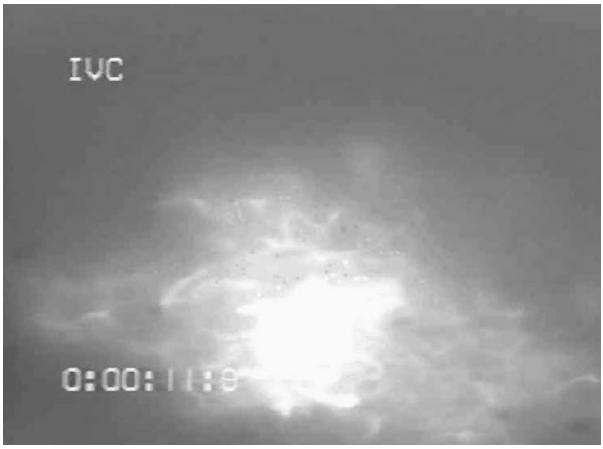

Fig. 25.3 Microlymphography in chronic venous disease. CEAP 2–3

visualized because there is good drainage of contrast material into the deep lymphatic circulation [19] (Fig. 25.2). Involvement of the microlymphatics in *chronic venous disease* (CVD) offers a characteristic microlymphatic pattern, displaying an increased number of loops and typical fragmentation [1, 3, 22] (Fig. 25.3).

25.2.1 Compressible Primary Lymphedema, I Stage

Compared with healthy subjects, in compressible primary lymphedema, a greater number of initial lymphatics, enlarged and organized into a more extensive network, are observed. Moreover, after injection of fluorescent dextran, the microlymphatic network is rapidly depicted similarly to controls, though diffusion into the surrounding tissue is slower and persistence of microlymphatic staining is prolonged [1, 2, 6–17]. Both endolymphatic and interstitial pressures increase [24] (Tables 25.1 and 25.2).

Table 25.1 Microlymphatic network changes in primary lymphedema using fluorescent microlymphography

Parameters	Compressible	Moderately compressible	Noncompressible	Control
Initial lymphatics (#)*	32 ± 5	30.6 ± 8.23	10.6 ± 7.2	7 ± 5.03
Diameter (μ)	121 ± 48	166 ± 51	142 ± 47	54 ± 1
Velocity (sec)	1.5 ± 0.6	120 ± 42	250 ± 39	1 ± 0.3
Diffusion (μ)	13.83 ± 7	21 ± 11	32 ± 16	3.07 ± 1.1
Extension (μm)	40 ± 8.7	30 ± 2.5	18 ± 1	6 ± 2
Permanence (min)	8 ± 3.5	20 ± 4.8	17 ± 5.9	0.48 ± 1.7

*x±SD

Table 25.2 Microdynamic pressures in primary lymphedema

Pressure (mmHg)	Compressible	Moderately compressible	Noncompressible	Control
EP	8.2 ± 1.7	10.03 ± 2.1	11 ± 1.5	4.19 ± 1.9
IP	4.31 ± 1.98	5.18 ± 1.48	7.2 ± 1.9	0.65 ± 1

EP endolymphatic pressure, *IP* interstitial pressure

25.2.2 Moderately Compressible Primary Lymphedema, II–III Stage

In this setting, compared with healthy subjects, the microlymphatic network is greater, with enlarged meshes, but with slower diffusion, reduced velocity of microlymphatic staining, and greater permanence of staining. The microlymphatic network is more extensive than in controls, but less extensive than in compressible primary lymphedema. Both endolymphatic and interstitial pressures are higher than in controls and higher than in compressible primary lymphedema [24] (Tables 25.1 and 25.2).

25.2.3 Noncompressible Primary Lymphedema, IV Stage

At this more advanced stage, fewer microlymphatic vessels are depicted. They appear tortuous, irregular, sometimes damaged, or obstructed albeit dilated, but still more extensive than in healthy subjects, yet less extensive than in compressible and moderate compressible lymphedema. Staining is much slower and delayed than in compressible and moderate compressible lymphedema. Diffusion is slower and permanence

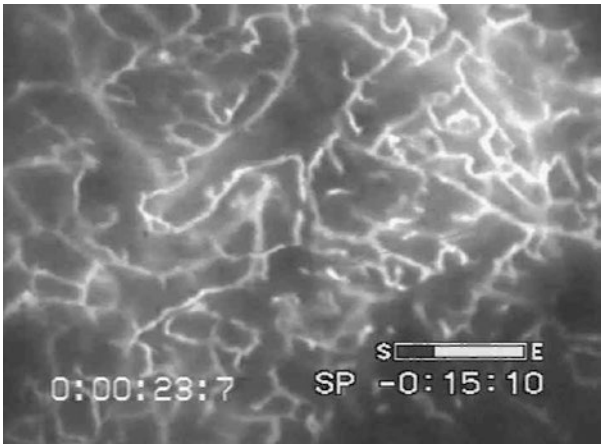

Fig. 25.4 Microlymphography in lymphedema

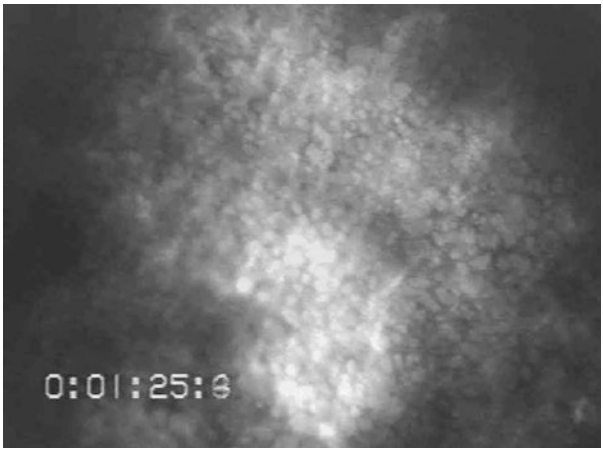

Fig. 25.5 Microlymphography in fibrosis

greater. Endolymphatic and interstitial pressures are both significantly increased [24] (Tables 25.1 and 25.2).

In early-stage lymphedema, the number of microlymphatic loops is particularly high and the microlymphatic pressure is much higher than the normal range. This finding can be interpreted as a mechanism of initial insufficiency (Fig. 25.4) [1, 4, 23].

In long-standing lymphedema, the microlymphatics are cannot be seen because of fibrosis [1, 24] (Fig. 25.5).

When the data from dynamic capillaroscopy and capillary blood velocity (CBV) are combined with microlymphography, a more complete picture can be obtained for understanding the pathophysiology of a microcirculatory unit [1, 2, 6, 8, 11, 19, 20, 26].

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Near-Infrared Fluorescent Lymphography

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Summary of Basic Concepts

Near-infrared fluorescent lymphography using indocyanine green (ICG), ICG lymphography, clearly visualizes superficial lymph flows in real time without radiation exposure. Dynamic ICG lymphography allows pathophysiological severity staging, evaluation of lymph pump function, and navigation for lymphatic surgery with only one ICG injection.

26.1 Lymphedema Evaluation Using ICG Lymphography

Although lymphoscintigraphy is considered a gold standard, its image is obscure, and it has a risk of radiation exposure [6]. Near-infrared fluorescent lymphography, or indocyanine green (ICG) lymphography, has been reported in 2007 for lymphedema evaluation. Since then, ICG lymphography is becoming popular, as it allows visualization of superficial lymph flows far more clearly than other modalities such as lymphoscintigraphy in real time without radiation exposure [1, 2, 7]. ICG lymphography has been applied in various lymphedema evaluations, including arm, leg, facial, and genital lymphedema, and used for pre−/intraoperative navigation for lymphatic surgeries such as lymphaticovenular anastomosis (LVA), vascularized lymph node transfer (LNT), and liposuction [1–3, 8–13]. Dynamic ICG lymphography, dual-phase ICG lymphography, has been developed to allow all of the above-mentioned three evaluations with only one ICG injection (Fig. 26.1) [4, 14].

26.2 Dynamic (Dual-Phase) ICG Lymphography

Dynamic ICG lymphography is performed with one ICG injection and two-phase observations: early «transient» phase for the evaluation of lymph transportation capacity and late «plateau» phase for lymph circulatory evaluation and navigation lymphatic surgery [2–4, 13, 14]. Dynamic ICG lymphography is performed as follows: An examinee is kept still for 10 min, and 0.05 –0.2 ml of ICG is subcutaneously injected at the

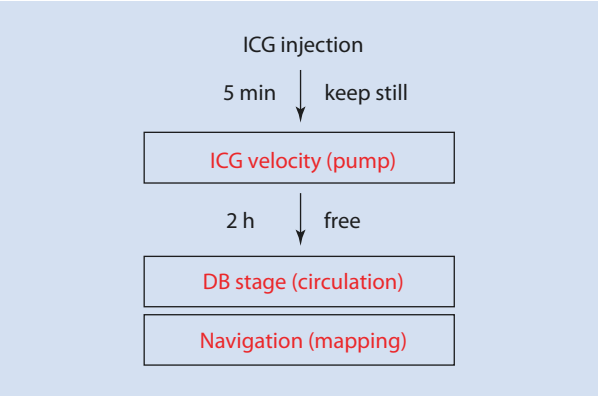

Fig. 26.1 Dynamic (dual-phase) ICG lymphography

second web space for extremity and genital lymphedema and at the glabella and the philtrum for facial lymphedema. Immediately after ICG injection (transient phase), fluorescent lymphatic images are obtained using an infrared camera system. An examinee is kept still in supine position for 5 min during lymph pump function measurement. At 5 min after ICG injection, ICG velocity is calculated as mentioned in ▶ Sect. 26.2.1 and an examinee is allowed to move freely [4, 14].

Twelve to eighteen hours after ICG injection (plateau phase), ICG movement usually reaches a plateau. In a plateau phase, lymph circulatory conditions are assessed based on ICG lymphography findings as mentioned in ▶ Sect. 26.2.2, which allows pathophysiological severity staging for secondary lymphedema and classification for primary lymphedema and pre−/intraoperative navigation for lymphatic surgeries [1–3, 8–12, 15–17]. For more rapid and convenient evaluation, an examinee can ask a patient to move their extremity rigorously; ICG can reach a plateau 2 h after ICG injection with this instruction. Plateau phase usually continues until 72 h after ICG injection. Thus, evaluation of lymph circulatory conditions is possible between 2 and 72 h after ICG injection.

26.2.1 ICG Velocity for the Assessment of Lymph Transportation Capacity

A major advantage of ICG lymphography is that it allows real-time evaluation. Lymph transportation capacity, or lymph pump function, can be easily and directly measured by observing ICG movement at a transient phase. Although several methods have been reported to evaluate lymph transportation capacity, ICG velocity is the most practical one. Unlike other methods that sometimes require 1 h or longer for lymphedema evaluation, the measurement of ICG velocity can be completed within 5 min after ICG injection [4, 14]. The distance between the ICG injection point and the farthest point where ICG fluorescence can be detected is measured 5 min after ICG injection. ICG velocity is calculated as the following simple formula:

ICG velocity = Distance / Time (cm/min).

When ICG fluorescence reaches the groin/axilla in leg/arm lymphedema cases within 5 min, ICG velocity is calculated by dividing the distance between the ICG injection point and the groin/axilla by the time required for the transition. With lymphedema progression, ICG velocity decreases, representing loss of lymph pump function. When interventions to lymphedema are successful, ICG velocity increases, representing restoration of lymph pump function. ICG velocity is a quantitative assessment and allows quite easy evaluation of changes in lymph transportation capacity before and after treatments or during follow-up.

26.2.2 Assessment of Lymph Circulatory Conditions

With progression of obstructive lymphedema, ICG lymphography pattern changes from normal linear pattern to abnormal dermal backflow (DB) patterns. DB patterns include splash (mild DB), stardust (moderate DB), and diffuse (severe DB) pattern (◘ Fig. 26.2) [1]. Lymph flow is obstructed after dissection and/or radiation of lymph

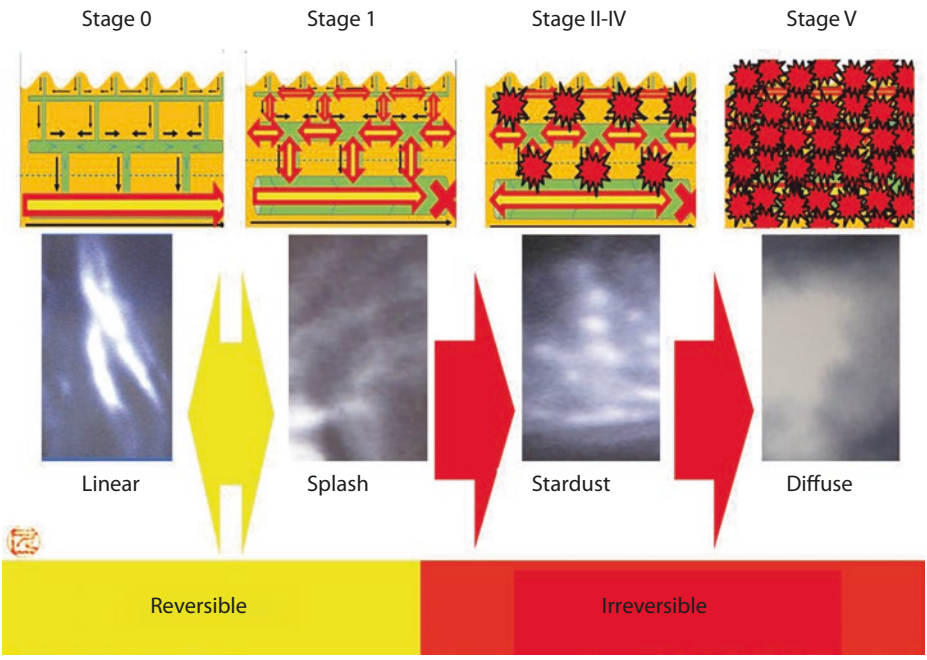

Fig. 26.2 Lymph circulatory conditions according to ICG lymphography findings

nodes, which leads to lymphatic hypertension, dilatation of lymphatic vessels, lymphatic valve insufficiency, lymphosclerosis, and lymph backflow. Lymph backflow is visualized as DB patterns on ICG lymphography [1–3, 8, 9, 13, 18]. Splash pattern represents dilated superficial lymphatic precollectors and capillaries that can work as collateral lymph pathways. Lymph extravasation takes place when the collateral fails to compensate lymph overload, which is visualized as spots on ICG lymphography: stardust pattern. With progression of lymph extravasation, the number of spots on ICG lymphography increases the point where spots cannot be distinguished from each other: diffuse pattern. In obstructive lymphedema, DB patterns usually extend from proximal to distal region. Assessment of abnormal lymph circulation using ICG lymphography allows pathophysiological severity staging and prediction of lymphatic vessels before lymphatic surgery.

DB Stages for Pathophysiological Severity Evaluation of Secondary Lymphedema

DB stages, or pathophysiological severity staging systems for secondary lymphedema, are determined based on ICG lymphography findings. Four DB stages have been reported: arm DB (ADB) stage for arm lymphedema, leg DB (LDB) stage for leg lymphedema, facial DB (FDB) stage for head and neck lymphedema, and genital DB (GDB) stage for genital and lower abdominal lymphedema [2, 3, 8, 9, 19]. Each DB stage consists of 6 stages from stage 0 through stage V.

ADB stage is a severity staging system for secondary arm lymphedema (Fig. 26.3) [3, 13, 20]. In ADB stage 0, no DB pattern is detected. In ADB stage I, splash pattern is

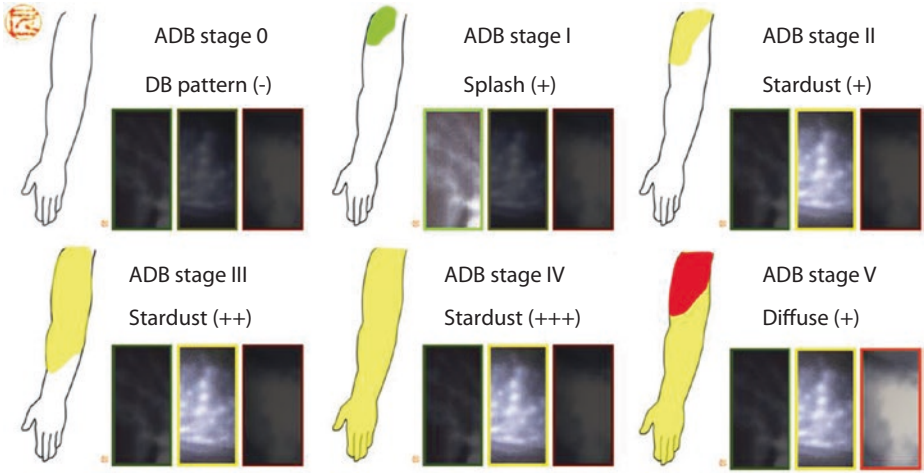

Fig. 26.3 ADB stage for pathophysiological severity staging of arm lymphedema

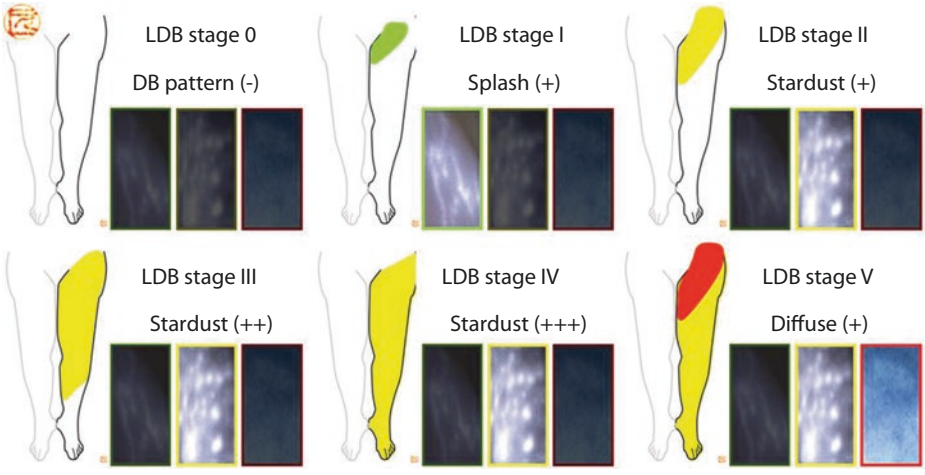

Fig. 26.4 LDB stage for pathophysiological severity staging of leg lymphedema

detected around the axilla. In ADB stages II through V, stardust pattern is detected. In ADB stage II, stardust pattern is limited in the upper arm (one region). In ADB stage III, stardust pattern is detected in the upper arm and the forearm (two regions). In ADB stage IV, stardust pattern is detected in the upper arm, the forearm, and the hand (three regions). In ADB stage V, diffuse pattern is observed with background of stardust pattern, and no linear pattern is detected.

LDB stage is a severity staging system for secondary leg lymphedema (Fig. 26.4) [1, 2, 20]. In LDB stage 0, no DB pattern is detected. In LDB stage I, splash pattern is observed around the groin. In LDB stages II through V, stardust pattern is detected. In LDB stage II, stardust pattern is limited in the thigh (one region). In LDB stage III,

stardust pattern is detected in the thigh and the lower leg (two regions). In LDB stage IV, stardust pattern is detected in the thigh, the lower leg, and the foot (three regions). In LDB stage V, diffuse pattern is observed with background of stardust pattern, and no linear pattern is detected.

FDB stage is a severity staging system for secondary head and neck lymphedema [9, 13, 20]. In FDB stage 0, no DB pattern is detected. In FDB stage I, splash pattern is observed around the neck. In FDB stages II through V, stardust pattern is observed. In FDB stage II, stardust pattern is observed in the neck (one region). In FDB stage III, stardust pattern is detected in the face and neck (two regions). In FDB stage IV, stardust pattern is detected in the neck, the face, and the head (three regions). In ADB stage V, diffuse pattern is observed with background of stardust pattern, and no linear pattern is detected.

GDB stage is a severity staging system for secondary lower abdominal and genital lymphedema [8, 13, 20, 21]. In GDB stage 0, no DB pattern is detected. In GDB stage I, splash pattern is observed around the groin. In GDB stages II through V, stardust pattern is detected. In GDB stage II, stardust pattern is observed in the lower abdomen (one region). In GDB stage III, stardust pattern is detected in the lower abdomen and the labia majora (two regions). In GDB stage IV, stardust pattern is detected in the lower abdomen, the labia majora, and the labia minora (three regions). In GDB stage V, diffuse pattern is observed with background of stardust pattern, and no linear pattern is detected.

Pathophysiological Classification for Primary Lymphedema

Primary lymphedema consists of a wide variety of etiologies. Evaluation of lymph structures and flows is important for the management of primary lymphedema. ICG lymphography may not be an optimal modality for primary lymphedema evaluation, because of the inability to visualize deep lymph flows directly. However, superficial ICG lymphography findings represent deep lymphatic's conditions and have been reported to be useful to evaluate and classify primary lymphedema [5]. The ICG lymphography-based primary lymphedema classification includes four patterns: proximal DB (PDB), distal DB (DDB), less enhancement (LE), and no enhancement (NE) patterns (Fig. 26.5).

In PDB pattern, DB patterns extend distally from the proximal lymph flow obstruction site as in DB stages for secondary lymphedema. Patients with PDB pattern should be evaluated regarding pelvic malignancy, because the lymphography findings are the same as seen in cancer-related lymphedema. As an etiology, lymphatic malformation in the trunk is suspected. Therapeutic strategy is also the same as for secondary lymphedema. Earlier interventions work better for the improvement of lymph circulation [22]. Since lymph flow obstruction is considered as a cause, LVA is recommended for compression-refractory cases.

In DDB pattern, DB patterns are detected only in the distal part but not in the proximal part. Localized distal malformation or lymphatic valve malformation is suspected as cause. Patients with DDB pattern are usually affected by inflammation caused by cellulitis. As for patients with PDB pattern, patients with DDB pattern are also recommended to undergo LVA surgery when compression therapy is not enough.

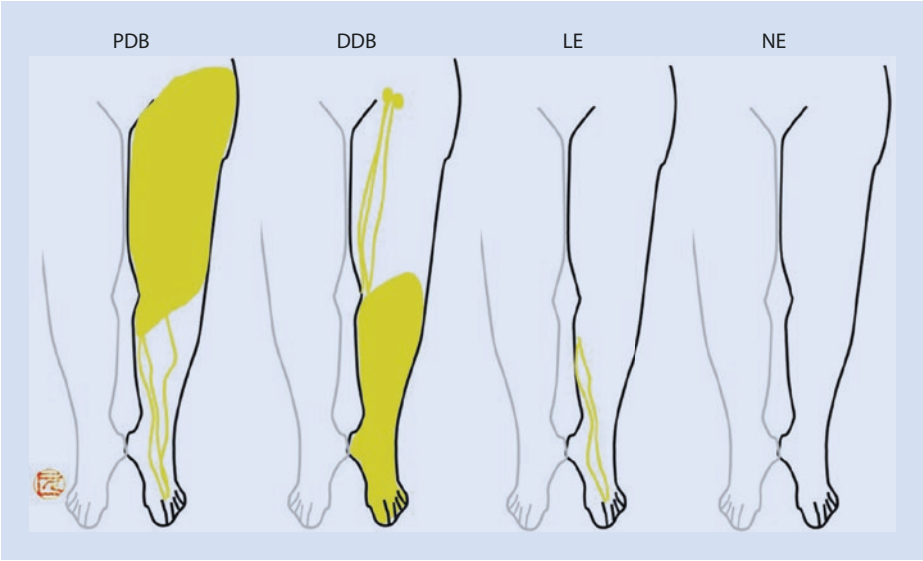

Fig. 26.5 ICG lymphography classification for primary lymphedema

In LE pattern, linear pattern is detected only in the distal part, and no DB pattern is detected. Hypoplastic superficial lymphatic system and aging-related pump dysfunction are considered as causes. Patients with LE pattern usually find themselves prone to physiologic temporary leg swelling before clinical manifestation of pathological leg edema. Since lymph flow obstruction is not suspected, strong compression therapy is recommended rather surgical treatment.

In NE pattern, no fluorescent image is obtained other than in the injected sites; there is neither linear pattern nor DB pattern. Segmental lymphatic aplasia and severe lymph malabsorption are suspected as causes of the disease. Most patients with NE pattern are congenital and suffer from more severe lymphedema compared with those with PDB, DDB, and LE patterns. Lymphovenous shunt operations rarely work to improve the disease, and LNT is better indicated.

26.2.3 Navigation for Lymphatic Surgeries

As ICG lymphography allows real-time lymph flow visualization, it is very useful for pre−/intraoperative guidance/navigation of lymphatic surgeries [10, 11, 15, 16, 23–27]. As mentioned above, different ICG lymphography patterns represent different lymph circulatory conditions. With progression of ICG lymphography pattern (linear to splash, stardust, and finally to diffuse pattern), lymphatic vessel becomes more sclerotic with less lymph flow [1, 13, 18, 28]. External diameter of lymphatic vessel is approximately 0.5 mm in linear/splash/stardust regions, whereas 0.3 mm in diffuse region. As detection rate of lymphatic vessel and efficacy of LVA is expected to be low, diffuse region should

be avoided for LVA [13, 19, 29, 30]. For a less-experienced surgeon, it is quite difficult to find a small and translucent lymphatic vessel. Intraoperative ICG lymphography significantly reduces time for dissection of lymphatic vessel and skin incision length and allows precise evaluation of LVA patency intraoperatively [10, 11, 17]. When anastomosis patency is not good, a surgeon can immediately decide to revise the anastomosis.

In LNT surgery, ICG lymphography can be used to guide the procedures: mapping for lymph node flap harvest and reverse mapping for the prevention of donor site lymphedema [31]. A surgeon can intraoperatively confirm that a lymph node flap is raised in an appropriate region without sacrificing major lymph flows in a donor site. ICG lymphography navigation is essential when the efferent lymphatic vessel of lymph node flap is anastomosed for better lymph flow restoration; efferent lymphatic vessel is difficult to find without ICG lymphography.

ICG lymphography can be helpful for liposuction. To prevent damage to lymphatic structures, liposuction should be avoided where ICG lymphography shows linear pattern. ICG lymphography navigation can prevent lymphedema deterioration, lymphorrhea, seroma formation, and cellulitis after liposuction [32, 33].

26.3 Lymphedema Management Using ICG Lymphography

A prospective observational cohort study revealed that splash pattern is a reversible lymph flow change, whereas stardust pattern is an irreversible change [34]. Thirty-one percent of patients showed splash pattern (LDB stage I) after cancer treatments, of which 16% improved to linear pattern (LDB stage 0), 55% stayed in splash pattern (LDB stage I), and 29% progressed to stardust pattern (LDB stage II). Once stardust pattern is detected, it never improves to splash or linear pattern even with compression therapy. Patients in DB stage I should be carefully followed as «subclinical» lymphedema to prevent lymphedema development and overtreatment [2, 30]. On the other hand, patients in DB stage II should undergo LVA or other reconstructive lymphedema surgeries, because conservative treatments cannot improve lymph circulation [13, 18, 34].

Conservative therapies should be applied first when lymphedema treatments are indicated; conservative treatments are also important for preoperative conditioning of lymphedema surgery [13, 15, 22]. For progressive cases refractory to conservative treatments, lymphatic surgeries are indicated. For DB stage I (subclinical lymphedema) or DB stage II (early-stage lymphedema) patients, LVA would be the choice of treatment, because LVA is effective to compression-refractory cases and less invasive compared with other lymphatic surgeries. LVA can be performed via a small skin incision under local infiltration anesthesia [13, 17, 30]. Especially for DB stage I, minimally invasive methods such as minimally invasive lymphatic supermicrosurgery (MILS, millimeter incision LVA under ICG lymphography navigation) or efferent lymphatic vessel-to-venous anastomosis (ELVA) is recommended. LVA is also recommended for DB stage III (progressed lymphedema) cases, but treatment efficacy is sometimes not enough to improve lymph circulation and especially difficult to reduce lymphedematous volume in DB stage V patients [2, 15, 22, 35–38]. When lymphedema is refractory to LVA, LNT with or without debulking procedure such as liposuction is indicated [13, 30]. For decision-making of lymphedema management, ICG lymphography is useful to maximize treatment efficacy and to minimize a risk of overtreatment (Table 26.1).

Table 26.1 Lymphedema management according to ICG lymphography-based DB stage

DB stage	ICG pattern	Clinical condition	Management
Stage I	Splash (+)	Subclinical	Follow or CTs ± LVA
Stage II	Stardust (+)	Early	LVA
Stage III	Stardust (++)	Progressed	LVA ± LNT ± liposuction
Stage IV	Stardust (+++)		
Stage V	Diffuse (+)		

ICG indocyanine green, *DB* dermal backflow, *CTs* conservative treatments, *LVA* lymphaticovenular anastomosis, *LNT* lymph node transfer

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MR Lymphangiography

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Summary of Basic Concepts

MRL is distinctly superior in providing high-resolution imaging of lymphatic system and real-time observation of lymph flow in lymphatic and lymph node.

The imaging of lymphatic system is much difficult than that of blood circulation due to several reasons. Firstly, lymphatic vessels are slender, fragile, and transparent. Thus, to approach lymphatic vessel and deliver contrast directly is not easy. Secondly, the diameters of lymphatic are small, and the wall has less smooth muscle cell that leads to a weak contraction at a low rhythm. Lymph flows at a lower speed is a nonconstant stream under normal condition. Therefore, lymphatic pathway may not always be visualized during imaging. Thirdly, the composition of lymphatic system network is more complex than the blood system. There are around 600 lymph nodes in the human body, which distribute between every two or more efferent and afferent lymph vessels [6]. The commonly used lymphoscintigraphy with isotopic contrast agent has insufficient resolution to accurately outline the internal anatomy of lymph node and lymphatic vessels. Lymphangiography using iodine oil agent, which is capable of visualizing the lymphatics, is no longer routinely performed because it is highly invasive and difficult to perform and also can lead to life-threatening complications. As a new diagnostic test, 3D high-resolution MR lymphangiography (MRL) has been proven to be useful in the diagnosis of peripheral lymphatic system disorders in recent years [1–4]. Around 2000 patients have been examined in the author's clinic since 2007. MR lymphangiography with gadobenate dimeglumine quickly and sufficiently visualized the lymphatic pathway and lymph nodes draining from the intracutaneous injection sites in lymphedematous limbs and gives both morphological and functional assessment of tested lymphatic system.

27.1 Contrast Agent and Material Administration

The specificity of absorption and transportation of the contrast agent by lymphatic system made it possible to visualize the finely detailed morphological changes of the lymphatic as well as regional lymph node under high-resolution MR imaging. Paramagnetic contrast agent gadobenate dimeglumine (Gd-BOPTA) (MultiHance, Bracco, Milano, Italy) is an extracellular, water-soluble, small molecular (molecular weight 1 kDa) paramagnetic contrast agent with a gadolinium (Gd) concentration of 0.5 mol/L. This contrast agent is not subject to metabolization and is excreted unchanged by passive glomerular filtration. Experimental animal models have demonstrated merely minor tissue damage after non-intravenous injection or extravasation [5]. Therefore, the agent offers an acceptable safety profile for intracutaneous administration. For injection of Gd-BOPTA, a thin needle (24 gauge) is used. A total amount of 8 mL contrast material and 1 mL mepivacainhydrochloride 1% are subdivided into eight portions and injected intradermally into the dorsal aspect of each foot or hand in the region of the four interdigital webs. Mepivacainhydrochloride1% is administered with the contrast material to alleviate the pain for the patients at the time of injection.

27.2 MRL Examination

Patient is in the prone position for lower limb and pelvic cavity inspection and in the supine position for the examination of arm lymphedema. MR examinations are performed with a clinical 3.0 T MR unit (Achiva, software release 2.1; Philips Medical Systems, Best, the Netherlands) with a maximum gradient strength of 80mT/m and a slew rate of 200 mT/(m ms). Patient is placed in the supine position with feet first. Four stations are examined: the lower leg inferior segment and foot region, the lower leg superior segment and upper leg inferior segment including the knee region, middle upper leg, and the inguinal region and the proximal upper leg. In these stations, a dedicated six-element phased-array sensitivity encoding (SENSE) cardiac reception coil is used (Philips Medical Systems, Best, the Netherlands). Before interstitial MRL, a 3D heavily T2-weighted MRI with an optimized protocol is performed for imaging stationary fluid to obtain high signal intensity. The serial turbo sequences included fat saturation and half-scan acquisition single-shot fast spin-echo sequence (SSFSE). The fast spin-echo is a strong T2-weighted multiecho sequence with a repetition time (TR) of 2820 ms and an echo time (TE) of 740 ms. The scan field of view (FOV) is 360 × 285. Fifty five to 85 slices with 2-mm thickness and a 240 × 190 matrix are selected in SSFSE. Maximum-intensity projection (MIP) and source images are used to reconstruct images of the lymphatic system.

For MRL, 3D fast spoiled gradient-recalled echo T1-weighted images with a fat saturation technique (T1 high-resolution isotropic volume excitation, THRIVE) are initially acquired prior to the administration of gadopentetate dimeglumine. The MR imaging parameters are as follows: TR/TE, 3.5/1.7; flip angle, 25; FOV, 360 cm × 320 cm; matrix, 300 × 256; slices, 55–95; voxel size, 1.5 mm × 1.2 mm × 1.2 mm; the number of signal average, 2; and acquisition time, 0 min 40 s. The first station is repeated at 5, 10, 15, 20, 25, and 30 min after intracutaneous application of the contrast material. The remained three stations are subsequently examined once after first station completion. To outline lymphatic vessels, MIP reconstruction images are calculated as well.

27.3 Image Interpretation

After data acquisition, image post-processing and subsequent analysis are performed. The MR images are evaluated on a workstation connected to the MR unit (ViewForum, Version 2.5, Philips, the Netherlands). Each data set is given a unique code, and all annotations are removed from each original image before image analysis. For the 3D data sets, both source and MIP images are reviewed. Lymphatic vessels are evaluated regarding their visibility with a beaded appearance, size, and collaterals. According to these features, the visualized dilated lymphatic vessels are counted and compared in MIP. The contrast enhancement of the lymph vessels and lymph nodes of lower extremity and inguinal region can be qualitatively and quantitatively evaluated. The appearance and distribution pattern of lymphatic pathway in the diseased extremities and the morphological characteristics of inguinal nodes on pre- and post-contrast MR images are analyzed. In the meantime, the existence and location of edema in the affected limbs are also evaluated.

Quantitative analysis, including:

1. The rapid transportation of contrast agent by draining the lymphatic and regional lymph node ensures a consecutive and real-time inspection of transporting function of lymphatic and lymph node within a reasonable length of time. Tracing the movement of enhanced flow within lymphatic vessel allowed quantitative assessment of abnormal lymph flow kinetics by assessing the time course of enhancement of lymph flow in the vessels directly draining from the injection sites. After contrast injection, the measurement of contrast movement in a contrast-enhanced lymphatic is started from the ankle region along its course toward proximal part in a series of 5–6 successive images along the enhanced lymph vessel with clear outline. The length of the enhanced vessel on the final image is recorded, and the speed of contrast movement is calculated with formula as speed (cm) = total length of visualized lymph vessel (cm)/inspection time (minute).

The measurements of contrast enhanced speed of lymph flow are made in a group of 25 cases. Among them 23 limbs in 20 cases are available for dynamic observation of the contrast-enhanced flow at a series time points. The speed of enhanced lymph flow in this study ranged from 0.301 to 1.48 cm/min (Fig. 27.1). It is notable that the speed of lymph transport might be largely individual dependent. For example, for a patient with primary lymphedema on the left lower extremity over 20 years, the tested speed of flow is 1.25 cm/min, which is among the highest scores of those patients, while the diameter of the tested vessel is 6.1 mm, also in the highest range. The appearance of enhanced lymphatic channel in post-contrast MR image reflected that the lymphatics remained spontaneous contraction and transportation capability in the examined primary and secondary lymphedema limbs.

2. The assessment of enhancement of inguinal lymph node directly draining from the injection sites. For evaluating the results of enhancement of these lymph nodes, the ratio of signal intensity (SI) of lymph node against signal intensity of adjacent muscle is estimated. The operator-defined regions of interest (ROIs) are drawn on the coronal post-contrast images. At least one pair of inguinal nodes is measured. The ROI on

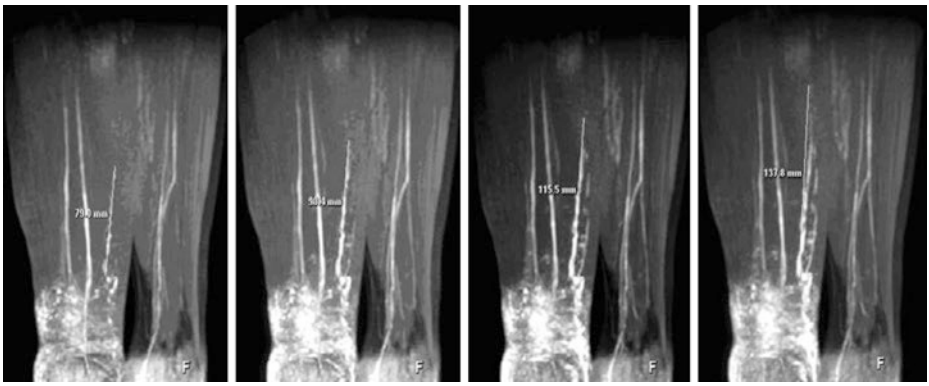

Fig. 27.1 Real-time observation of the velocity of lymph flow by measuring the enhanced lymphatic vessel after intradermal injection of contrast

the muscles is selected in the upper portion of the thigh near inguinal region with approximately equal size of the lymph node. The ratio of node/muscle SI is compared between lymphedema and contralateral limbs on post-contrast MR images. In patients the dynamic enhancement of contrast in bilateral nodes are estimated, the wash-in and wash-out curves are derived from designated ROI, and the peak enhancement time and lymph node/muscle SI ratio at peak time are directly compared.

The inspection of the enhancement of contrast in inguinal nodes started 30–40 min after intracutaneously contrast agent injection. At this time, the inguinal nodes of the healthy volunteers and the clinical non-edema limbs are markedly enhanced. The comparison of lymph node versus muscle signal intensity ratio between nodes of edema limbs and contralateral nodes showed remarkable asymmetrical accumulation of contrast between the nodes of edematous limbs and contralateral limbs of patients with unilateral lymphedema (Fig. 27.2) as well as in patients with bilateral lymphedema in whom edema is

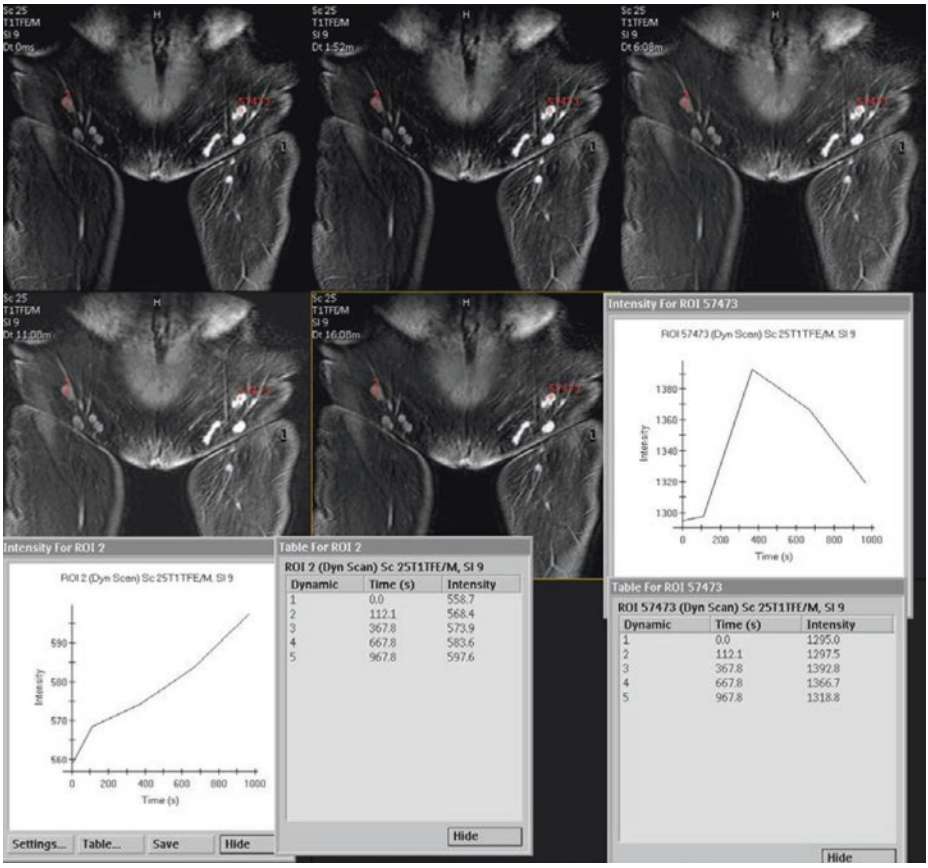

Fig. 27.2 Real-time observation of contrast flow in and flow out through the inguinal lymph nodes of lymphedema patient. The filling of contrast in the lymph nodes which was slower in the right side (lymphedema limb) was significantly delayed than that in lymph nodes of left (no lymphedema limb)

serious in one limb and mild in the other. Therefore, comparison of dynamic nodal enhancement between edema and contralateral limbs and analysis of the time–signal intensity curves could clarify the delayed or declined transport of lymph in individual node and allow quantitative assessment of abnormal nodal lymph flow kinetics.

Qualitatively and morphological observation:

1. Lymphatic Drainage Patterns

The enhancement of these lymphatic pathways persisted throughout the examination time around 40 min. On the initial images, the enhancement of lymphatic channels may be light and discontinued. But the signal intensity increased, and the channels gradually become totally opacified with time. The lymphatic vessels in the edematous limbs are irregular in shape or uneven diameter and twisted, and the characters made it easily being distinguished from venous. The number of contrast-enhanced lymphatics in lymphedematous limbs varied from single to numerous. The diameters of visualized lymphatics ranged from 1.2 to 8 mm. The identical patterns of lymphatic pathway in the primary lymphedema limb are diverse [7]: radiating arranged-enhanced vessels in the lower leg assemble to medial portion of the knee and went up to the thigh, discontinued, and lightly enhanced but dilated vessels in the medial portion of lower limb; bunches of extremely dilated and significantly highlighted lymphatic located mainly in the media and less in the lateral portion of the thigh; remarkably dilated and opacified lymphatic went from the lower leg directly to inguinal node with few branches (Fig. 27.3a, b, c).

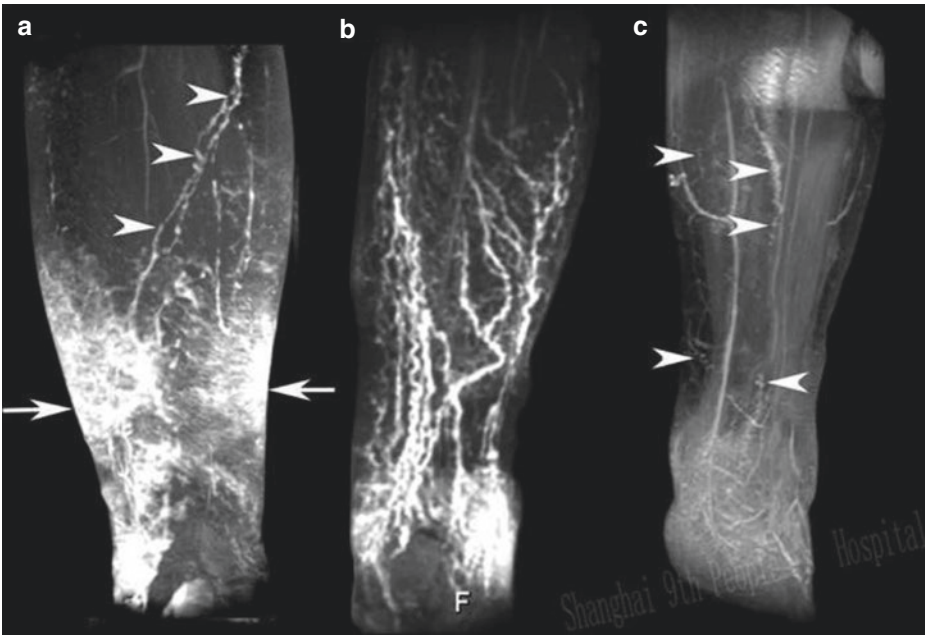

Fig. 27.3 Dynamic three-dimensional MR angiography showed varied malformations of the lymphatic in the lower extremities of primary lymphedema. **a** A fewer dilated lymphatic vessels (*arrowheads*) and dermal backflow (*arrows*); **b** radiating arranged dilated vessels in the lower leg of primary lymphedema; **c** enhanced lymphatic vessels (*arrowheads*) distributed as slender network over the lower extremity

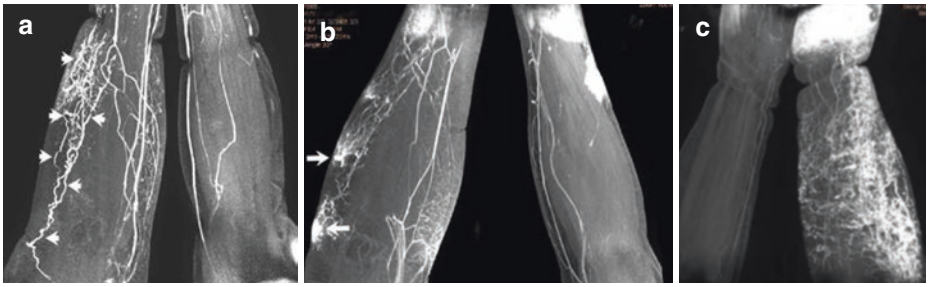

Fig. 27.4 MR lymphangiography of secondary arm lymphedema. **a** Tortuous and significantly dilated collecting lymphatics (*arrows*). **b** Lymph collector disruption and lymphorrhea (*arrows*) in the forearm. **c** Significantly dilated lymphatic collectors with extensive opening of numerous communication branches

In secondary lymphedema limb after tumor surgery, there are numerous opacified collateral lymphatic vessels with relatively even diameter indicative of lymphatic neovascularization [8] (Fig. 27.4). Leakage of contrast from the lymphatic vessels may be seen in lymphedematous limbs of secondary etiology at a relatively early stage [9].

The visualization of contrast-enhanced lymphatic channel in the affected limb is coexistence with accumulation of edema fluid in the tissue in almost all tested cases. Therefore, lymph circulation disorder should highly be suspected when contrast-enhanced lymphatics are visualized with this test. Generally no or single contrast-enhanced lymphatic vessel is visualized in the limbs of healthy individuals, neither in limbs with lipedema [1].

2. Morphological Characteristics of Inguinal Lymph Nodes

Lymphatic circulation disorders may be caused solely by lymph node abnormal or a lymphatic vessel problem, or a combination of lymphatic and lymph node abnormalities [7]. The morphological changes including nodal size, internal lymph node architecture, and lymph node borders are evaluated. The shape of inguinal lymph node in contralateral side and healthy volunteers is spherical or oval, numbered from 2–3 to 7–8 with a diameter around 1.0 cm. Compared with contralateral limbs, the morphological abnormalities of inguinal nodes in edema limbs observed in present study are absence of node, single large or multi small fibrotic nodes, small nodules, node with irregular border and hemogeneous structure, irregular nodal outline with homogeneous architecture, and markedly enlarged nodes with increased number. Dynamic MR demonstrated abnormal patterns of contrast filling in the draining inguinal nodes. Post-contrast MR lymphangiographic images however displayed more structural abnormalities as no contrast enhancement in the nodes which may indicate a total fibrosis of the nodes, uneven nodal enhancement which indicates structural anomalies, and partial enhancement within the nodes which may be a congenital pathology of the nodes. Moreover, enhanced MR lymphangiography has been proven to be a promising imaging modality in diagnosing and staging of malignant lymph nodes [10]. (Fig. 27.5).

The combination of the lymphatic and lymph node images may then outline the integral picture of the affected lymphatic system.

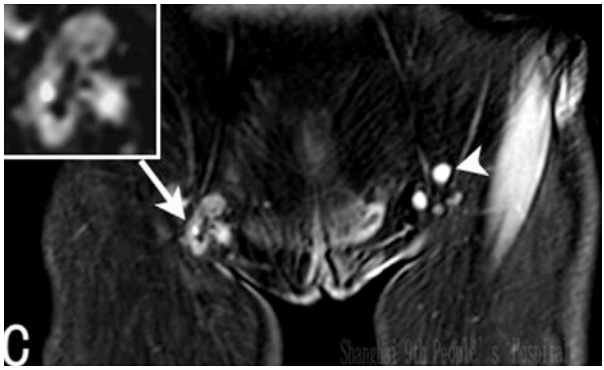

Fig. 27.5 MR lymphangiography shows inguinal lymph nodes (*arrow*) with irregular shape and partial contrast filling on the right limb of primary lymphedema and homogeneous filling of contrast in the lymph nodes (*arrowhead*) of no edema limb post-contrast injection

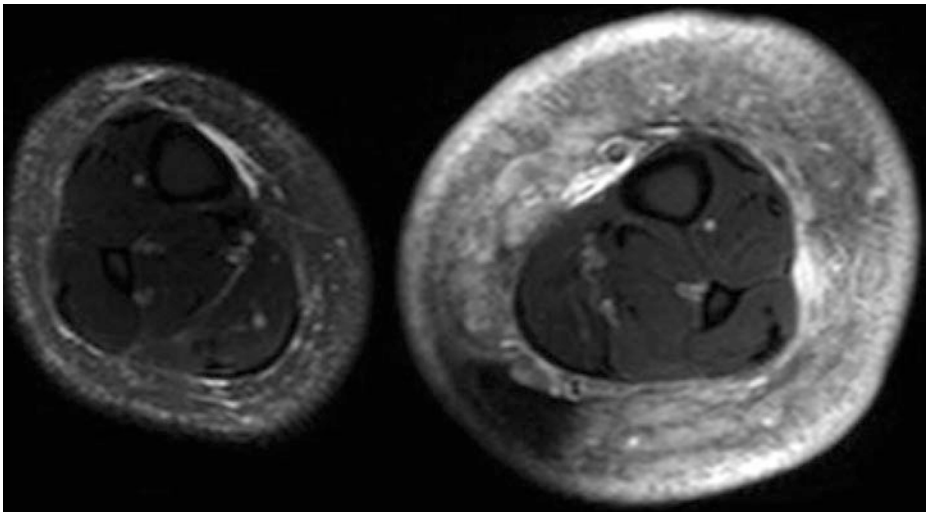

Fig. 27.6 MRI shows lymphedema at early stage with small amount of water in the subcutaneous layer of the limb (*left*) and a significant thickening and fat tissue deposition in the subcutaneous (*right*)

3. Lymphedema Confirmation

The morphological and structural characteristics of lymphedematous limbs are evaluated for confirmation of clinic diagnosis during MR inspection [1]. The pre- and post-contrast MR image provided not only detailed information of the lymphatic system but also extralymphatic involvement such as (1) the location and extent of edema fluid (in general the fluid is accumulated above deep facial membrane or diffused in subcutaneous in late stage of the disease; edema within muscles and intramuscular space resulting from venous backflow disorder (Fig. 27.6)); (2) fat tissue deposition, which is prominent in very thickened subcutaneous tissue (Fig. 27.6); and (3) blood vascular abnormalities as hemangioma and varicose vein. Based on the information by MR imaging, it is easy to stage a lymphedematous limb and differentiate lymphedema from venous

edema or lipedema. In the meantime, «dermal backflow», that is, the contrast-enhanced stagnant lymph fluid flow back into the dermal tissue, is a common phenomenon in chronic lymphedematous tissue.

Contrast MR lymphangiography with gadobenate dimeglumine is capable to visualize the precise morphological status of lymphatic vessels and lymph nodes in lymphedematous limb. In the meantime, it provided comprehensive information concerning the function status of lymph flow transportation in the lymphatic and the nodes. This method is minimally invasive, easy, and safe and combines morphological and functional examination in a single acquisition, and the enriched data suffice to characterize lymphatic and lymph nodes in the limb with lymph circulation disorders. The comprehensive information provided by contrast MR lymphangiography may also be useful in staging and classifying the primary and secondary lymphostatic diseases and assessment of the response of treatment. It is also helpful in seeking more direct and effective treatment, avoiding damage of lymphatic and lymph nodes that are still working during surgical procedure.

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Combined Role of Lymphoscintigraphy, X-ray Computed Tomography, Magnetic Resonance Imaging, and Positron Emission Tomography in the Management of Lymphedematous Disease

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Summary of Basic Concepts

Various imaging options exist for the evaluation of lymphedematous diseases. Although each imaging technique can be considered separately, according to its principles and technical methodologies, the interface among these techniques has become indistinct in practice. Indeed, most of the apparatuses used today for lymphoscintigraphic (LySc) investigations utilize a combination of single photon emission computed tomography dual-headed devices (SPECT) with an X-ray computed tomography machine (CT or SPECT-CT). When positron emission tomography (PET) systems are considered, these are nearly always combined with CT devices. Although these CT scans may not conform to high radiological diagnostic standards, they allow easy fusion of the SPECT or PET images with other high-quality and high-resolution X-ray CT or magnetic resonance images, thus providing additional diagnostic data. The techniques can then be used in an orderly fashion:

- The interface among imaging techniques of lymphedema has become indistinct in clinical practice.
- Lymphoscintigraphy and/or SPECT-CT lymphoscintigraphy can be used and interpreted by taking into account the origin of the lymphedema and the clinical stage of the disease.
- SPECT-CT lymphoscintigraphy (after conventional three-phase planar acquisition) is particularly useful in patients with chylous reflux or/and leakage.
- For the evaluation of lymphangiomas, lymphoscintigraphy is clinically useful in order to demonstrate the exact anatomical connections and the relationships among the lymphatic structures.
- In the management of secondary upper and/or lower lymphedemas, PET-CT can be useful when serum tumor markers are increasing or when the lymphedema becomes treatment-resistant.
- Heavily T2-weighted magnetic resonance imaging may have greater sensitivity, and the MRL image may have enhanced legibility for the detection of pathologically modified lymphatic vessels and accompanying complications. Magnetic resonance imaging also permits visualization of deep-lying, ordinarily inaccessible lymphatic vessels, such as those of the retroperitoneum in chylous reflux syndromes.
- MRI techniques offer good anatomical resolution, but are more expensive and have been used in only relatively small series of patients. The potential renal toxicity of the imaging contrast agent must be considered. On the other hand, lymphoscintigraphic techniques have been evaluated in very large series of patients and are relatively less expensive, but require radiation exposure and offer reduced anatomical resolution. Because MRI lymphangiography requires intradermal injections, its functional contributions may be considered to be lower than those of the lymphoscintigraphic techniques where the tracer is injected subcutaneously.

28.1 Introduction

Various imaging options exist for the evaluation of lymphedematous diseases. Although each imaging technique can be considered separately, according to its principles and technical methodologies, the interface among these techniques has become indistinct in practice. Indeed, most of the apparatuses used today for lymphoscintigraphic (LySc) investigations utilize a combination of single photon emission computed tomography dual-headed devices (SPECT) with an X-ray computed tomography machine (CT or SPECT-CT). When positron emission tomography (PET) systems are considered, these are nearly always combined with CT devices. Although these CT scans may not conform to high radiological diagnostic standards, they allow easy fusion of the SPECT or PET images with other high-quality and high-resolution X-ray CT or magnetic resonance images, thus providing additional diagnostic data. The techniques can then be used in an orderly fashion.

The choice of technique, either alone or in combination, must be made by taking into account the clinical presentation and the diagnostic and/or therapeutic questions being addressed (◘ Table 28.1). In the present chapter, we will review the use and contributions of these techniques in the management (i.e., diagnosis and treatment) of the following lymphedematous disorders: primary lymphedemas, secondary lymphedemas, genital lymphedemas, lymphedemas with chylous reflux, phlebo- and lipo-lymphedemas, and the lymphangiomatous diseases.

28.2 Lymphoscintigraphy and/or SPECT-CT Lymphoscintigraphy

Lymphoscintigraphic investigations are of proven value in the diagnosis and management of diseases of the lymphatic system [1, 6–8].

28.2.1 Lymphoscintigraphy or SPECT-CT Lymphoscintigraphy in Relation to the Clinical Presentation of the «Simple» Lymphedematous Situations

Lymphoscintigraphy and/or SPECT-CT lymphoscintigraphy can be used and interpreted by taking into account the origin of the lymphedema and the clinical stage of the disease.

In Primary Lower Limb Lymphedemas

In primary lower limb lymphedemas (praecox and, especially, tarda) in the early clinical stage (latent, intermittent, and/or spontaneously reversible, orthostatic, etc.), the classical planar lymphoscintigraphic acquisitions (instead of SPECT-CT) are adequate to assess lymphatic functional insufficiency. In such situations, the investigational protocol will evaluate the function of the lymphatic system of the limbs in standardized conditions, i.e., resting, during exercise, and after 1 h of normal activity [9]. In patients with lymphatic dysfunction, conservative management, such as massage therapy, use of compression garments, and limb elevation should be recommended initially.

Table 28.1 Respective contributions of the various imaging techniques in the management of lymphedematous diseases

		Lymphoscintigraphy		Lympho-SPECT-CT		CT		PET-CT		MRI	
		Diagnosis	Treatments	Diagnosis	Treatments	Diagnosis	Treatments	Diagnosis	Treatments	Diagnosis	Treatments
Upper limb edema(s) (ULE)											
Primary		++++	++++[a]	++++	++++[a]					++[b]	<
Secondary	«Oncological»	++	++++[a]	+++	++++[a]	+/++	+	++	<	++[b]	++++[b]
	Others	++++	++	++++	<	+++	<	?			
Lower limb edema(s) (LLE)											
Primary	«Congenital»	++	++++[a]	+	++++[a]	+				+[b]	++++[b]
	«Praecox»	+++	++++[a]	++	++++[a]	++	+	?		++[b]	++++[b]
	«Tarda»	++++	++++[a]	+++	++++[a]	+++	++	+		+++[b]	++++[b]
Secondary	«Oncological»	++	++++[a]	++	++++[a]	+/++	+	++	<	?	++++[b]
	Others	+++	++	++++	<	+++	<	++	<		
Lipo(lymph) edema		++	+/++	+++	+	++				?	?

(continued)

Table 28.1 (continued)

		Lymphoscintigraphy		Lympho-SPECT-CT		CT		PET-CT		MRI	
		Diagnosis	Treatments	Diagnosis	Treatments	Diagnosis	Treatments	Diagnosis	Treatments	Diagnosis	Treatments
«Phlebo-lymphede-mas»		+++	+/++	++	+?	++		+		?	?
Lymphan-gioma		+		++		++++	<			++++[b]	+++[b]
Lymphangi-omatosis		+		+		++++	<			++++[b]	+++[b]
Chylous Reflux disorders		++	+/++	′++++	+++	++				++++[b]	++++[b]
Genital Lymphedema	Males	++	+/++	′++++	′++	+		?		++[b]	++++[b]
	Females	++	+/++	′++++	′++	+		?		++[b]	++++

[a]With additional injections at the root of the limbs
[b]With injection of contrast medium

In other kinds of primary lower limb lymphedemas, such as congenital disorders, clinically more severe disease and, in particular, the descending forms (extending from the root of the limb toward the foot and suggesting lymph nodal obstructions or lymph-adenodysplasias), SPECT-CT may be useful in addition to the planar investigations to precisely evaluate the intra-abdominal lymph node status, especially among obese patients.

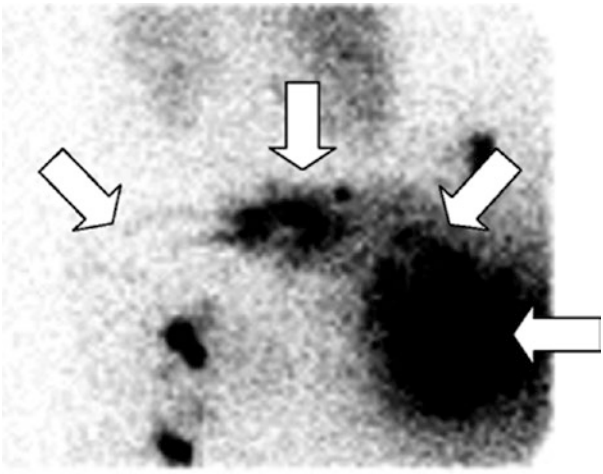
In Secondary Lymphedemas

In secondary lymphedemas, SPECT-CT, in addition to planar investigation, is beneficial for the following applications:

- In lower limb edema, for evaluation of intra-abdominal lymph node status, particularly among obese patients.
- In upper limb edema, for localization of various lymph nodes of potential importance (humeral, axillary, apical, retro, or supraclavicular).

Lymphoscintigraphy to Demonstrate the Collateralization Path ways

When no lymph nodes are visualized in the inguinal and/or iliac regions after peripheral subcutaneous injections of the radiolabeled colloid in the feet, and when no lymph nodes are visualized in the axillary and/or clavicular areas after peripheral subcutaneous injections of the radiolabeled colloid in the hands, it may be necessary to perform intradermal injections of the same tracer in the external part of the root of the edematous limb(s) to demonstrate lymphatic collateralization pathways [10] (◘ Figs. 28.1 and 28.2).



◘ **Fig. 28.1** Posterior view centered on the pelvis obtained in a woman with congenital right lower limb primary lymphedema. Peripheral injection showed no lymph nodes on the right side and only inguinal nodes on the left side. Intradermal injection of the 99mTc-HAS-nanocolloid was then performed in the external and lateral part of the right buttock (*horizontal arrow*). With manual lymphatic drainage, the tracer was shown to flow posteriorly through superficial dermal collateralization toward the right costo-lumbar area (*right to left oblique arrow*), to reach and cross the midline (*vertical arrow*), and from there to reach the left inguinal nodes through normal right-sided lymphatic vessels (*left to right oblique arrow*)

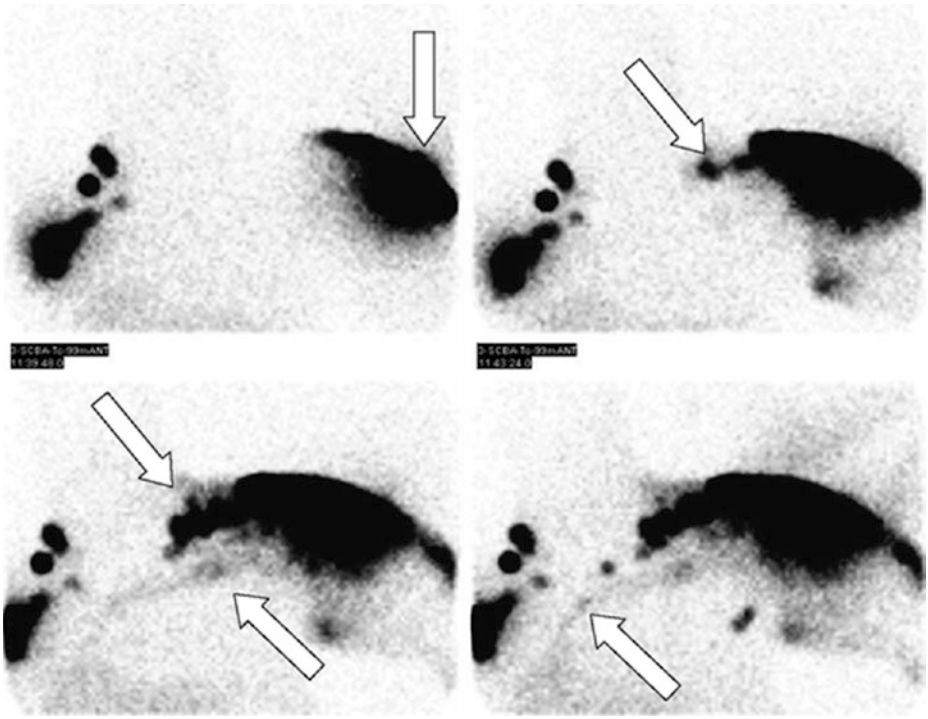


Fig. 28.2 From left to right and from top to bottom, anterior views centered on the axilla in a woman with post-therapeutic left upper limb lymphedema where the subcutaneous injection of 99mTc-HAS-nanocolloid in the first interdigital space of the hands showed normal right axillary nodes, but no node in the left axilla. Intradermal injection was then performed at the level of the upper and external part of the left arm (*vertical arrow*), and the tracer was shown to spontaneously flow toward the retro-clavicular lymph nodes (*left to right oblique arrows*) and also toward the left anterior chest wall, to cross the midline to reach the opposite axillary lymph nodes (*right to left oblique arrows*)

The results of such injections will be of the utmost importance for physical therapists, so that they can be informed of the possible collaterals requiring stimulation.

28.2.2 SPECT-CT Lymphoscintigraphy for the Lymphedematous Disorders Complicated by Chylous Reflux and/or Leakage

SPECT-CT lymphoscintigraphy (after conventional three-phase planar acquisitions) is particularly useful in patients with chylous reflux and/or leakage, either clinically obvious [11–14] or suspected. According to our experience, abdominal SPECT-CT should be performed in the following situations:

- In any patient in whom activity is observed in the abdomen that does not correspond with classical anatomical localization of infra-diaphragmatic lymph nodes (Figs. 28.3 and 28.4).
- When lymphatic reflux and dermal backflow are observed in the genital organs and/or at the level of the abdominal wall (Figs. 28.5 and 28.6).

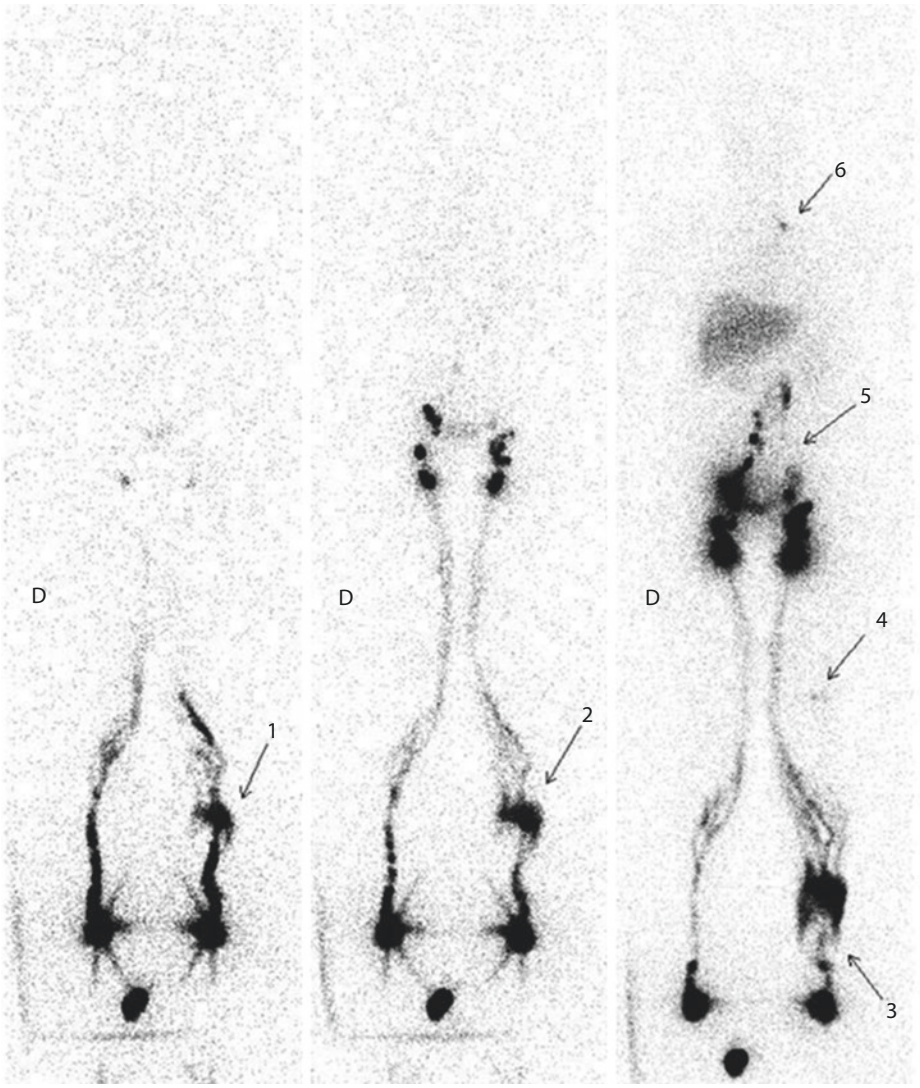


Fig. 28.3 Anterior whole-body scanning (WBS) obtained (after one subcutaneous injection of 99mTc-labeled HAS nanosized colloid in the first interdigital space of each foot, the patient lying on the examination table), from right to left, after 30 min without movement, after 5 min of tiptoeing, and after 1 h of walking. This man was sent for evaluation of right lower limb lymphedema (he also had prepubic edema on clinical examination) secondary to surgery and radiotherapy for prostatic carcinoma. After 30 min without movement, the tracer has reached the first inferior inguinal node on the right side (*arrow 1*), but has progressed only to the level of the knee on the left side. After 5 min of tiptoeing, lymphatic reflux is seen in collaterals toward the external part of the right buttock (*arrow 2*), up to and in the mid internal part of the thigh (*arrow 3*), and in the right prepubic area (*arrow 4*). One right common iliac lymph node is observed (*arrow 5*) as well as – faintly – two left retro-clavicular lymph nodes (*arrow 6*), proving that the thoracic duct is patent. After 1 h of walking, the reflux of lymph in the superficial collateralization lymphatics extends to the upper and inner half of the right thigh (*arrow 7*), but one abnormal zone of activity is also demonstrated in the mid suprapubic part of the abdomen (*arrow 8*)

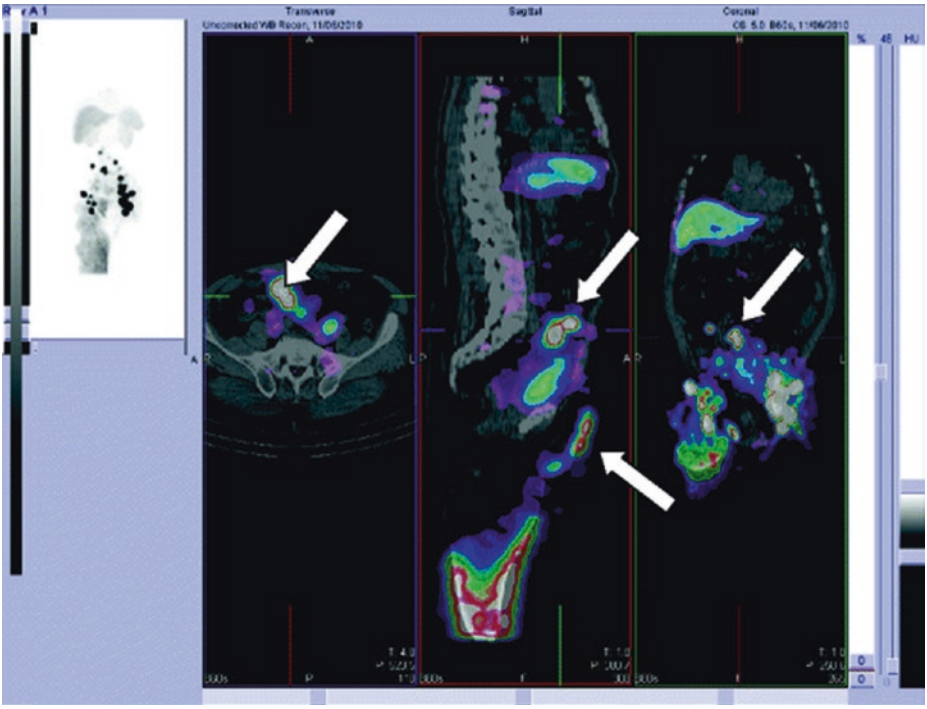
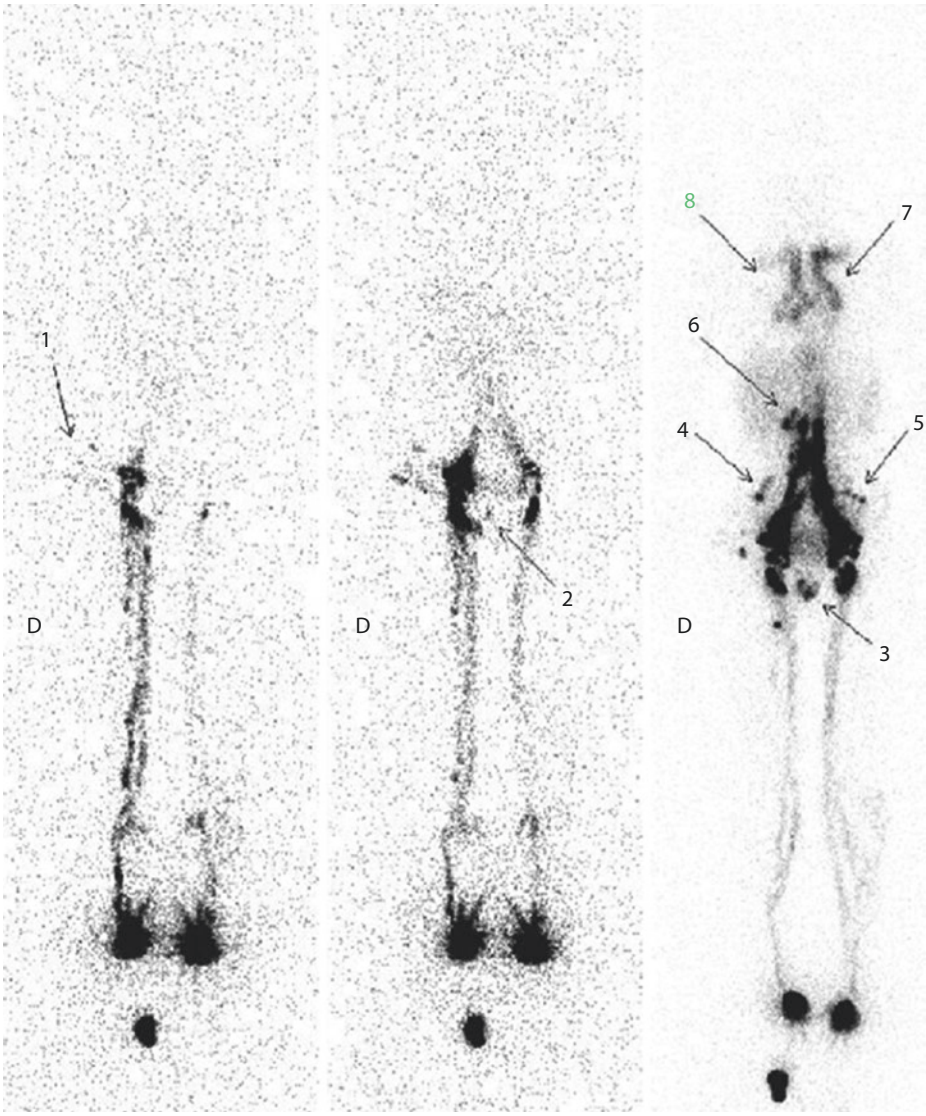


Fig. 28.4 From left to right, selected transverse, sagittal, and coronal/frontal fused slides from the SPECT-CT across the abdomen and pelvis showing nicely [6] (*top to bottom oblique arrows*) that the abnormal zone of activity seen on the planar WBS image in the mid suprapubic part of the abdomen corresponds, in fact, to lymph flowing back from lumbar aortic nodes in the digestive tract and [7] (*bottom to top oblique arrow*) dermal back flow in the right prepubic area

Fig. 28.5 Anterior WBS obtained (after one subcutaneous injection of 99mTc-labeled HAS nanosized colloid in the first interdigital space of each foot, the patient lying on the examination table), from right to left, after 30 min without movement, after 5 min of tiptoeing, and after 1 h of walking. This young woman did not complain of lower limb edema, but was referred for evaluation of intermittent lymph leakage at the level of her right labium majorum. After 30 min without movement, the tracer reached the first inferior inguinal node on the left side and all the inguinal nodes on the right side, but with lymphatic collaterals appearing from the inguinal nodes toward the external part of the buttock (*arrow 1*). After 5 min of tiptoeing, infra-diaphragmatic lymph nodes are now seen on both sides (and right collaterals are confirmed); the beginning of lymphatic reflux in the right labium majorum can also be observed (*arrow 2*). After 1 h of walking, the reflux of lymph in the right magna labia is now obvious (see *arrow 3*), but abnormal zones of activity are also demonstrated in the right and left lateral part of the abdomen (*arrows 4* and *5*) as well as at least two right para-renal lymph nodes (*arrow 6*), and, at the supradiaphragmatic level, there is a completely abnormal presentation of the great lymphatic thoracic duct with right and left components persisting (*arrows 7* and *8*) (For more information on these anomalies, see Bourgeois et al. [33])

28.2.3 Lymphoscintigraphy, Lymphoceles, and Lymphangiomas?

Identification of lymphangioma by lymphoscintigraphy is rarely reported [15–18]. In these patients, as in some patients with lymphoceles, SPECT-CT lymphoscintigraphy will be of clinical utility in order to demonstrate the exact anatomical connections and relationships between the lymphatic collectors and the lymphatic vessels or nodes.



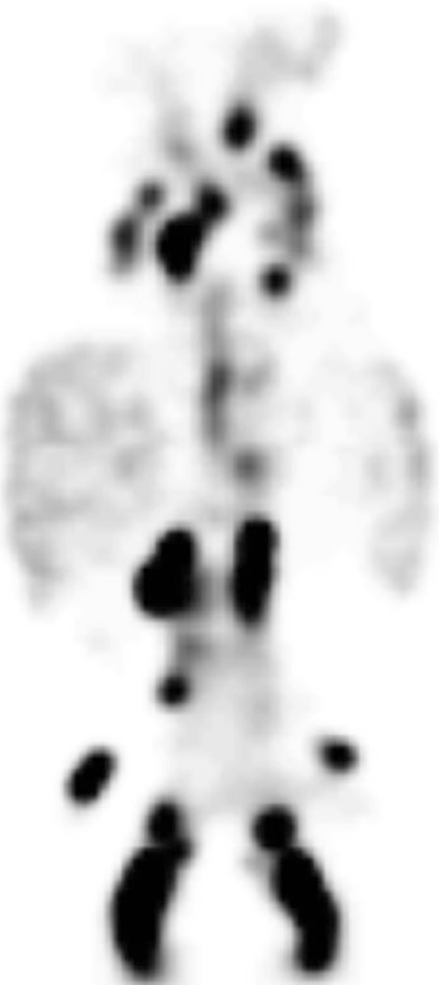


Fig. 28.6 Coronal/frontal image from the SPECT across the chest, the lumbar aortic nodes, and the ilioinguinal nodes showing nicely, in the mediastinum, serpentine channels forming the thoracic duct and, in the abdomen, the lake of lymphatic activity in the right and left digestive tract

28.3 X-ray Computed Tomography?

Computed tomography is rarely necessary for the diagnosis of simple lymphedematous disorders, but may be useful for the pretreatment evaluation and initial work-up, because it provides an objective depiction of anatomical abnormalities [19].

Computed tomography will be of greater clinical utility and is particularly useful, in patients with lymphangiectasia, lymphangioma, or lymphangiomatosis. In these patients, CT can be used to assess both the nature and distribution of lesions [2] or to facilitate their catheter-guided percutaneous sclerosis or obliteration [20].

28.4 Positron Emission Tomography or Positron Emission Tomography Combined with X-ray Computed Tomography?

As mentioned in the Introduction, the use of PET alone is becoming progressively less prevalent in the nuclear medicine department, being replaced by hybrid devices combining PET and CT.

In the management of secondary upper and/or lower lymphedemas, PET-CT imaging using an appropriate tracer (18F–DG, 11C–Choline, etc.) is useful, for instance, when serum tumor markers are increasing or when lymphedemas become treatment-resistant. Focusing on the use of CA 15–3 in breast carcinoma and CA 125 in ovarian carcinoma, Pecking et al. [21] found the sensitivity and predictive value of PET-CT with 18F–FG to be nearly 100%. An additional application of PET-CT in such patients is to exclude and/or demonstrate distant (non-nodal) metastases.

As shown in ◘ Figs. 28.7 and 28.8, this can also be useful in some patients who receiving an initial diagnosis, as with primary lymphedemas.

28.5 Magnetic Resonance Imaging and/or Lymphangio-MRI with Injection of Contrast Enhancement?

28.5.1 Magnetic Resonance Imaging in the Diagnosis of Pathologically Positive Lymph Nodes?

With regard to the possible use of MRI to evaluate malignant involvement of lymph nodes (sometimes responsible for the development, aggravation, and/or treatment resistance of lymphedema), Klerckx et al. performed a systematic review and meta-analysis of existing data on the accuracy of gadolinium-enhanced MRI for staging lymph node metastases [22]. The weighted estimates of sensitivity and specificity for all studies combined were 0.72 (95% confidence interval [CI] = 0.66–0.79) and 0.87 (95% CI = 0.82–0.91) respectively. Estimates of sensitivity and specificity were essentially unchanged for studies that used a single malignancy criterion (n = 11 studies) or multiple malignancy criteria without contrast enhancement (n = 6 studies). The sensitivity increased to 0.84 (95% CI = 0.70–0.92), with a specificity of 0.82 (95% CI = 0.72–0.89), for the nine studies that incorporated contrast enhancement in their multiple malignancy criteria.

Heavily T2-Weighted Imaging or Magnetic Resonance Lymphangiography for Lymphedemas?

According to Lu et al. [23], heavily T2-weighted imaging has greater sensitivity, and the MRL image has higher legibility for the detection of the pathologically modified lymphatic vessels and accompanying complications.

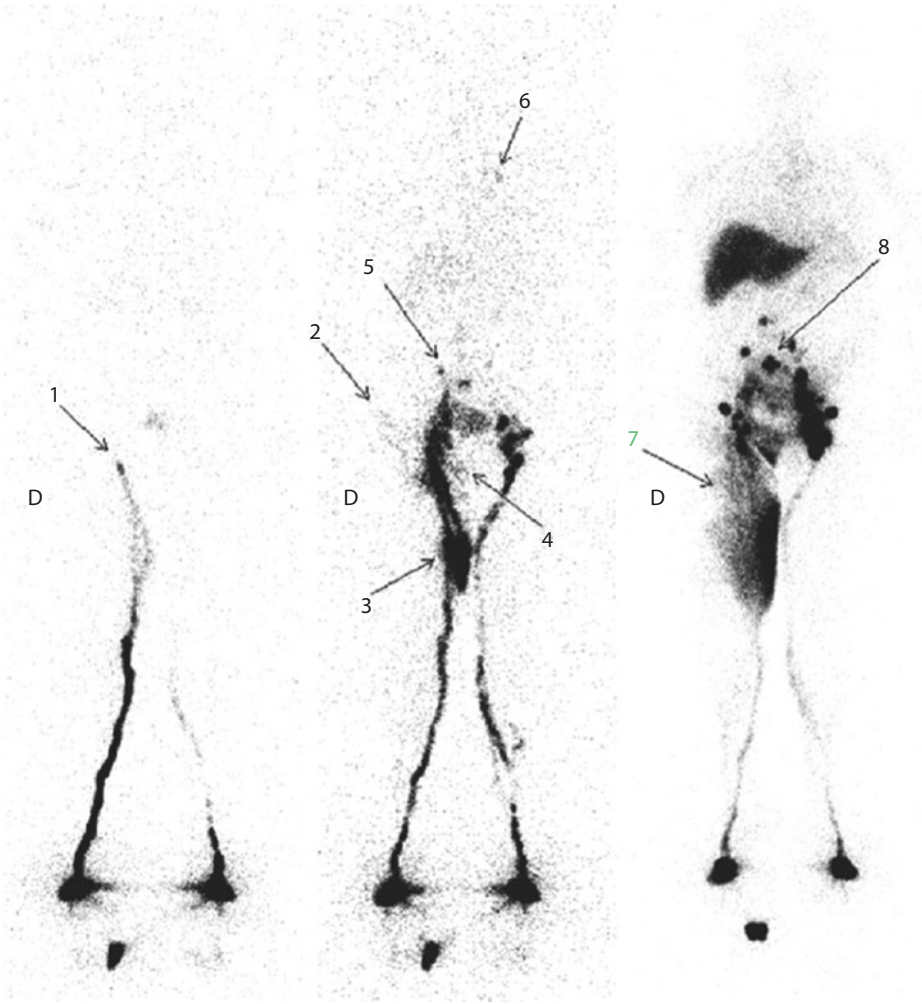


Fig. 28.7 Anterior whole-body scanning (WBS) obtained (after one subcutaneous injection of 99mTc-labeled HAS nanosized colloid in the first interdigital space of each foot, the patient lying on the examination table), from right to left, after 30 min without movement, after 5 min of tiptoeing, and after 1 h of walking. This woman was sent for evaluation of left lower limb lymphedema. After 30 min without movement, the tracer has reached the first inferior inguinal node on both sides, but the beginning of lymphatic reflux is seen at the level of the distal part of the left calf (*arrow 1*). After 5 min of tiptoeing, lymphatic reflux in the left calf is more obvious (*arrow 2*). After 1 h of walking, the reflux of lymph in the superficial collateralization lymphatics is obviously extended to the left ankle (*arrow 3*), one left popliteal lymph node (*arrow 4*), and one left retro-clavicular lymph node (*arrow 6*), but not the left common iliac nodes (*arrow 5*). On the basis of this lymphoscintigraphic examination, the diagnosis of primary lymphedema tarda was proposed

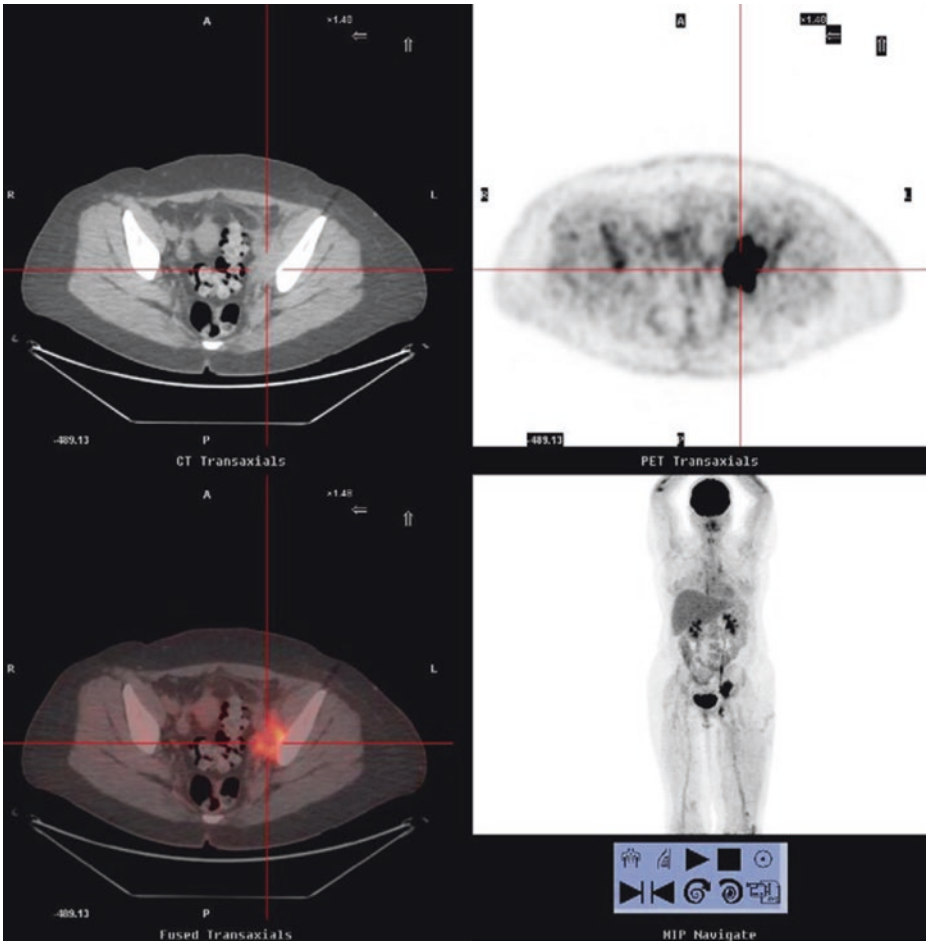


Fig. 28.8 The patient later developed left sciatica, and blockage of the common iliac vein was suspected. PET-CT after IV injection of 18F–DG was performed and demonstrated (on the selected transverse PET-CT slides) a hypermetabolic process later histologically proven to represent metastatic tumor of uterine cervix origin

MRI or MRL in Lymphedemas?

In a series of 39 patients (27 male and 12 female) with lower extremity lymphedema and/or skin lymphorrhea of the abdominal wall or external genitalia with peripheral and central lymphatic malformations, Liu et al. [3] reported that non-contrast 3D MRI provided extensive information on the anatomy of the dysfunctional vasculature as well as on the effects of lymphatic dysfunction on local structures and tissue composition.

With the intracutaneous injection of gadobenate dimeglumine into the interdigital webs of the dorsal foot of 27 patients with primary lymphedema, the same authors [24] reported, more recently, that contrast MR lymphangiography was capable of visualizing the precise anatomy of lymphatic vessels and lymph nodes in lymphedematous limbs

and also provided information concerning the functional status of lymph flow in the lymphatic vessels and lymph nodes.

Notohamiprodjo et al. reported on the use of intracutaneous injection of gadolinium-diethylene-triamine-pentaacetic acid in 16 patients, [25] concluding that MRL at 3.0 T provides very high spatial resolution and anatomical detail of normal and abnormal peripheral lymph vessels. However, they also stated that the examination was non-diagnostic in one case where contrast medium was injected subcutaneously instead of intracutaneously and that venous contamination (always present) was diagnostically problematic in another patient.

In a small series of patients, Lohrmann et al. [26, 27] also demonstrated the efficacy of MRI in lipo-lymphedemas and in post-traumatic edemas of the lower extremities.

MRI in Chylous Reflux?

Magnetic resonance imaging permits visualization of deep-lying, ordinarily inaccessible lymphatic vessels, such as those of the retroperitoneum in chylous reflux syndromes [28]. Combined transaxial and coronal imaging allows visualization of these lymphatic vessels and provides visual guidance for the injection of sclerosing agents for the obliteration of external lymph leakage (e.g., skin, vagina) or bulky lymphangiomas [28]. Non-enhanced MRI is also a feasible option for locating and depicting the morphological features of the thoracic duct [4] and, thus, might be of interest in chylothorax situations.

MRI and Lymphangiomatosis?

Lohrmann et al. [29] confirmed the utility of MRI in 15 patients with diffuse lymphangiomatosis, using magnetic resonance lymphangiography with T1-weighted 3D spoiled gradient-echo and a T2-weighted 3D–TSE sequence.

MRI and Lymphangiomas?

Because MRI accurately predicts subsequent intraoperative findings and accurately demonstrates lymphatic architecture at different tissue levels, Liu et al. [3] consider MRI the diagnostic modality of choice in lymphangioma. In contrast, Dubois et al. [30] suggest that Doppler ultrasound should be the initial imaging technique and that MRI can be used to evaluate the extent of the lesion(s) prior to treatment. Kuhlmann et al. [31] preferred MR imaging when intravenous contrast material cannot be given for CT.

28.6 Lymphoscintigraphy and/or MRI?

Our estimation of the relative advantages and drawbacks of lymphoscintigraphic and MRI imaging techniques is presented in ◘ Table 28.2. To summarize, MRI techniques offer good anatomical resolution, but are more expensive and, up until now, have been used in only relatively small series of patients. Additionally, the potential renal toxicity of the imaging contrast agent must be considered. On the other hand, lymphoscintigraphic techniques have been evaluated on very large series of patients and are (relatively) less expensive, but require radiation exposure and offer reduced anatomical resolution. Because MRI lymphangiography requires intradermal injections, we considered its functional contributions lower than those of the lymphoscintigraphic techniques where the tracer is injected subcutaneously, [6, 32] which may be more useful in stage 0–2 lymphedema.

Table 28.2 Lymphoscintigraphic and MRI techniques: the pros and cons

	LySc	SPECT-CT LySc	MRI	Lymphangio-MRI
Overall anatomical contribution	+	++	+++	++++
Functional imaging of the lymphatic system	+++	+++	+?	++?
Value established in large series?	++++	+	++	+?
Potential limitations	Pregnant?		Obese, claustrophobia, pacemaker, metallic prosthesis: availability of the imaging agent?	
Irradiation	+	++	/–/	/–/
Potential toxicity of the imaging agent	/–/	/–/	/–/	+? (kidneys?)
Cost	+	++	+++	++++

Conclusions

Conventional oil-contrast lymphography has, in the past, been the mainstay for lymphatic imaging. Lymphoscintigraphy now more easily permits imaging of peripheral lymphatic vessels and provides insight into lymph flow dynamics. It is indispensable for patients with known or suspected lymphatic circulatory disorders to confirm the diagnosis and to delineate the pathogenesis and evolution of lymphedema. In several cases, the injection of radiolabeled colloid at the root of the edematous limbs will demonstrate lymphatic collateralization pathways and provide useful information for the physical therapists. In patients with lymphadenodysplasia, with reflux and/or leakage of lymph and/or chyle, and with suspected abnormalities at the level of the thoracic duct, SPECT-CT lymphoscintigraphy is useful in providing detailed anatomy of the abnormalities. PET-CT after injection of 18F–DG is efficacious in patients with secondary lymphedema and/or increased serum tumor markers. Patients with a provisional diagnosis of peripheral lymphatic dysfunction or idiopathic edema after lymphoscintigraphy should, in select cases, undergo MR imaging to verify diagnostic accuracy, pinpoint the specific abnormality, and help guide subsequent therapy, especially surgery [5]. MR imaging will also complement lymphoscintigraphy in the monitoring and treatment of more complex lymphatic circulatory disorders, whereas CT will facilitate catheter-guided percutaneous sclerosis or obliteration of specific lymphangiectasia or lymphangioma syndromes. The choice of technique, either alone or in combination, must be made by taking into account the clinical presentation and the diagnostic and/or therapeutic questions being addressed (Table 28.1).

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Alternative Assessment and Measurement Tools

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Summary of Basic Concepts

- Many of the «alternate» assessment and measurement tools have a firmly cemented history and have reasonable levels of validation and support for them. However, with the advent of technology modernization, many basic ones are no longer used, and newer portable ones based around indurometry, bio-impedance spectroscopy, and tissue dielectric constants to measure fiber and fluids and their location are not thought about.
- All of these tools have a very important role in improving our and the patients' understanding of lymphedema, ranging from early detection through to its staging and to determining the impact of treatment strategies upon it.
- A very important advantage is that most of these «alternate» tools are portable (in some cases, they are the hands of the health professional) and can be taken to wherever their patient is, be that in a rural or remote outpost or into the patient's own home. Further, with basic instruction, patients can often use these tools to assess the status of their lymphedema often relieving some of the burden of travel and time of employment.

29.1 The Context of Our Measurements

29.1.1 Impact of Limb Dominance

In the latent and early phases of lymphedema, the changes in the limb composition, limb size, and volume can be quite small, with the latter being in the range of 1–2 cm difference or less than 100 ml in volume. But we know that a limb which is a «dominant» can be more than 2 cm difference at times and at places where there is enhanced musculature and more than 100 ml difference in fluids (noting about 70% of muscle is fluid). So how can we say anything about these subtle early changes and how can we respond to them appropriately if we don't know or don't consider arm dominance? It seems of late also that the limb (arm) one describes as the dominant one may not be the one you write with! So we may be perpetuating an inaccurate or inappropriate diagnosis (or we miss one) if we don't seek information about the true dominant limb [1].

29.1.2 Measurement of Limb Volume and Circumference

While limb volume and circumference are often seen as traditional measures of limb change, often their full value is not exploited, nor their accuracy utilized.

There are a number of ways to measure these variables. Perometry [6] is suited to larger clinics, while water displacement and/or determination of segmental or whole limb volume by calculation following the use of a tape measure [7] is often easier for smaller ones. All can be equally accurate and reliable, but accuracy is dependent on their correct use.

Perometry, for instance, can discriminate at 1 mm for circumferences and to the nearest 10 ml for volume. Similar accuracy is possible with water displacement. Both can be used to assess segmental changes in limb volumes, but water displacement needs additional circumference measurements to be made, which facilitate cross-checking [2].

When tape measurement at specified positions is used, care must be taken to minimize errors in the tension on the tape, the placement of the tape, the distance between measurement sites, and the side of measurement. Excel or other statistical programs can be used to calculate volume. Tape measurement is able to discriminate to 1 mm, but due to the variables identified, 5 mm is more realistic. The Australasian Lymphology Association has defined a program to ensure accuracy and repeatability in measurement (► www.lymphology.asn.au). Such strategies can be used to add accuracy to the measurement for garment selection (in addition to manufacturers' recommendations regarding intervals and limb position for measurement) and can reduce the rate of patient rejection of garments, reduce the potential for a tourniquet effect of garments, and improve patient compliance.

A number of studies comparing traditional volume estimations and circumference measurements have occurred with the newer strategies such as perometry showing good concordance 4, and as mentioned above, other studies have shown concordance between US, BIS, and circumferences – but the fits and associations are not always perfect – so be careful.

29.1.3 Measurement of Fluid Content

One of the early signs of a failure of the lymphatic system is the accumulation of small amounts of extracellular fluids in the affected lymphatic territory or the whole limb. Fluid accumulation is a sign that, regionally, the lymphatic system is failing or a sign that the lymphatic system is overloaded and hence at risk of failure (chronic edema). The patient or clinician may not be able to detect or measure this subtle indication of lymphatic system failure. As there is no detectable increase in limb volume or circumference when measured by the more traditional techniques of tape measurement, the early detection of fluids is possible using multifrequency bio-impedance [8]. Current equipment is claimed to detect differences and changes in limb extracellular fluids as small as 5 ml. There is a large range of bio-impedance devices available at the moment, but not all have been clinically tested. At this time, the SFB7 is best suited for sole practitioner or small clinic use (ImpediMed Queensland); for larger, more complex clinical care settings, multifrequency (which measures the whole body composition) (ImpediMed), InBody Biospace (South Korea), BodyStat (United Kingdom), or the SOZO (ImpediMed) as examples are useful for multipurpose applications.

There is also a radiofrequency-based unit that can detect local area fluids, based on tissue dielectric constants (Delfin, Finland) [9]. Alone or in combination with devices or strategies to detect fibrotic tissues (described below), these devices can provide valuable information about subtle changes in the latent phase (non-clinically manifest) of lymphedema and of the impact of treatment on the lymphedema once it becomes clinically apparent.

Importantly, early use of these devices or techniques may detect the subtle changes of early lymphatic failure and enable early treatment, reducing the risk and severity of clinically manifest stage 1 (ISL classification) lymphedema. As with many of the other strategies used to assess all aspects of lymphedema, there have been comparisons; for instance, the correlation between bio-impedance and US and circumferential measures [3] shows reasonable concordance but not for every position or site of measurement. So as with any measure, the message is to choose a technique you have access to and stick with it from go to whoa for any given patient. And if you are comparing results from different techniques purported to measure similar parameters, be careful to check if a comparison is valid.

29.1.4 Measurement of Fibrotic Induration

Perhaps one of the first noticeable sequelae of surgery and radiotherapy is the formation of local or diffuse fibrous tissue. This is part of the tissue repair process, but also can be associated with a wound infection. Scarring associated with the surgical or radiotherapeutical sites at the root of the extremity may significantly reduce the ability of new lymph capillaries and collectors to grow or existing ones to regenerate.

In addition, as lymphedema progresses, so too does the extent and distribution of fibrotic tissue, with fluids being replaced by fatty and then fibrous tissues. The rate of this progression varies greatly.

At a very basic level, we should recall the Stemmer sign whose details were first published by Robert Stemmer in 1979. It estimates the thickness of the tissues in the skin fold above the first joint of the toe and fingers. The Stemmer sign is positive if a skin fold can't be picked up and it's a characteristic of lymphedemas (generally more so in the middle/later stages of it) [10]. It is potentially a quick and easy test to help a clinician determine if, for example, there is a CVI, edema, or a lymphedema. Knowing this may lead to a different more effective targeted treatment program which is the ultimate aim of all diagnostic testing [11].

Next in line of ease and simplicity is tonometry, which measures the resistance of the tissues to compression and is an indicator of the extent of underlying fibrosis [12]. It has been used since 1976 and, when used over the major lymphatic territories or at the watersheds, can indicate the extent of induration and of the impact of treatment. Tonometry is quickly and easily performed and can be used by individuals with minimal training. It does not measure the actual amount of fibrous tissues but, rather, the tissue resistance to compression by measuring the depth of compression of the tissues when a standard weight is placed on them. With current tonometers (made by BME at Flinders Medical Centre), accuracy to 1 mm is possible. Recently there have been an increasing range of portable instruments which do the same as this progenitor instrument. These are the indurometers (BME, Flinders Medical Centre) and a FibroMeters (Delfin). There have been a number of cross-validation studies undertaken to confirm their similarity in measurement outcomes and of their benefit in detecting fibrotic induration or changes in it (Vanderstelt et al. [13]).

Variations in fibrotic tissue can also be cross-confirmed with ultrasound (or CT if necessary initially) when this is performed at the same site as tonometry. When fibrotic induration is detected, treatment strategies such as low-level laser or frictional massage or

special MLD can be used to target it. Of course the other very useful aspect of the diagnosis of the presence of tissue fibrosis is that we can be more certain that it's a lymphatic system issue (lymphatic failure-lymphedema) rather than just a vascular/venous issue.

29.1.5 Measurement of Functional Status of the Lymphatic System

While lymphoscintigraphy might also be regarded as a traditional technique, it is often used inappropriately or inaccurately (Cross ref. chapter on LS).

While initially expensive, in reality it can be a cost-effective technique for determining lymphatic system status. It is best used in patients in whom the treatment outcome has been poor because of case complexity. The initial cost can be worthwhile in terms of the range of information it can provide, including the functional status of the lymphatic system, the location of functional (and dysfunctional) collectors, relationships between the deep and superficial lymphatics, and areas of dermal backflow. Importantly, the information can be used to help the health professional direct flow to functional pathways [14, 15]. There are quantitative aspects to lymphoscintigraphy, in the interpretation of the location of the radiotracer and its density and distribution, but also quantitative aspects in terms of the rate and time of arrival at specified regions of interest, such as the groin or axilla. Graphs of these events can help determine functional status, and repeat measures can show the effect of any intervention. Accuracy is possible at the level of millimeters per minute of travel of the tracer, although most often graphs are compared for slope and tracer counts at specific times within a region of interest. There are situations where the lymphoscintigraphy might be combined with other tools such as SPECT/CT imaging to provide better details of issues of dermal collaterals, backflow, and the soft tissues generally [16].

While the technique of indocyanine green for superficial lymphatic visualization has been around for many years, it is only recently that it is becoming more frequently used to assess superficial lymphatic function and in this respect it's proving quite effective and useful [17, 18] (Cross reference to ▶ Chaps. 24 and 25).

29.1.6 Measurement of the Structural Status of the Lymphatic System and Limb

If the basic «gold standard» of structural information is sought, the most effective method would seem to be ultrasound and, perhaps, its fractal analysis. Ultrasound is useful for informing us about changes in the thickness of the deep and superficial fascias and of the thickness of fibrotic or other changes in the epifascial compartment. Again there are qualitative and quantitative aspects to these analyses, with the measurement of thicknesses and depths able to be undertaken to an accuracy of 1 mm. Even if this is only done once (at tonometry points described above), for reassessments, only tonometry will need to be undertaken. Of course SPECT, MRI, and other, similar techniques offer greater accuracy and discrimination, but cost and easy availability often preclude their use.

29.1.7 Measurement of the Status of the Vascular System

It is clear that there are often significant changes to the vascular inflow and outflow patterns. Laser Doppler and other strategies such as fractal ultrasound allow these changes to be determined and interventions to be undertaken. Recent studies indicate that we should be paying more attention to changes in the vascular system inflow and outflow loads [19] and patterns, as well as to the lymphatic pumping mechanisms, [20] not only in a limb with lymphedema but also limbs at risk. As mentioned earlier, a simple test like the Stemmer sign may enable us to differentiate between a vascular and lymphatic basis for a limb swelling as a minimum.

29.1.8 Measurement of the Subjective Parameters

Lymphedema is more than just a swelling of the tissues [4, 21]. Its symptoms, even in the early stages, including heaviness, tension, aches, and pains, have significant impacts on the quality of life and on the ability to undertake the activities of daily living. For some patients, it is these that are important, even more so than the size of the limb or its range of movement.

If we are going to help a patient deal with his problem from a holistic perspective, then we must also undertake measurement of these variables and other subjective parameters, using visual analog and other scales. There is a range of simple and validated test instruments, some specific, such as the LYMQOL [5] (LBCQ, [22]) and the recently developed International Classification of functioning, disability, and Health Core Sets [23] and of course others more general, such as the SF −12 or −36.

29.2 Treatment Outcomes

Often, in lymphedema, treatment impacts how the limb feels, followed by softening and then, perhaps, by subtle changes in the volume of extracellular fluids, and, finally, by a change in volume or circumference. Detection and response to these changes can not only help the health professional to determine the impact of treatment but can also be used to indicate to the patient that change is occurring and that the treatment from the professional is working or that the patient's self-management strategies are effective. Patients often suffer treatment fatigue, and so it is important to give them continuing feedback or to encourage them if able to evaluate the treatment impact themselves. Some or all of the described alternate assessment and measurement methods would seem to provide effective opportunities to accomplish this goal. What is important is to use the assessment and/or measurement method as early as possible in the interaction with your patient (if not ideally prior to any intervention and for high-risk patients), to be clear on what each test is able to measure and what its limitations are, and to be consistent in its use, and importantly to recognize and allow for limb dominance. That way no matter how basic or fancy your assessment equipment is, you and the patient will have a reasonable idea of the problem and of how any treatment program is working.

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Physical and Medical Management

Contents

General Overview

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Summary of Basic Concepts

The status of lymphedema patients can clearly be improved and stabilized with the prompt and judicious application of effective treatment strategies.

- The nonsurgical treatment of lymphedema relies upon decongestive physiotherapy.
- In the acute treatment phase, multilayer bandaging augments lymphatic contractility and flow and decreases tissue lymph production.
- When edema volume has decreased to its minimum, the patient will be fitted with compression garments to maintain the therapeutic gains.
- Regular exercise has an ameliorating effect in lymphedema, provided that external compression is maintained. Self-care strategies should be emphasized.
- Intermittent pneumatic biocompression has been shown to improve edema during the initial and maintenance phase of decongestive physiotherapy.
- Low-level laser therapy has been reported to produce subjective and objective improvement in lymphedema. Application of vibration, heat, and external magnetic fields have all had proponents, but few data exist to support efficacy.
- Pharmacology has, until now, enjoyed very little application in the therapeutic approach to lymphedema. Standard broad-spectrum antibiotics are typically employed to treat and prevent soft-tissue infection in lymphedema. Diuretics have little therapeutic benefit in pure lymphatic vascular insufficiency.
- There is mounting evidence for the role of inflammation in the pathogenesis and maintenance of the tissue pathology in lymphedema, suggesting that anti-inflammatory strategies may hold promise.

Therapeutics for lymphedema and other lymphatic disorders have, generally, lagged behind the treatment advances for their twenty-first-century counterparts in the compendium of human disease. This fact notwithstanding, the status of lymphedema patients can clearly be improved and stabilized with the prompt and judicious application of effective treatment strategies.

The nonsurgical treatment of lymphedema is centered upon the techniques of decongestive physiotherapy [7]. This aggregate of physical maneuvers is, to date, the approach with the best documented efficacy in lymphedema, given the capacity to achieve and maintain limb volume reduction and to preserve the integrity of the cutaneous and subcutaneous structures [8].

During the acute phases of treatment intervention, the optimal reduction in limb volume reduction is achieved through a stepwise approach. At the conclusion of each physiotherapeutic encounter, sustained augmentation of lymphatic function is assured by the application of short stretch bandaging materials. During physical activity, this multilayer bandage serves to augment the stimuli that improve lymphatic contractility and flow [9]. In addition, the formation of the lymph is reduced through the external tissue compression, with its effect of increasing interstitial hydrostatic pressure.

When edema volume has decreased to its minimum, the patient is fitted with compression garments to maintain the therapeutic gains achieved by multiple cycles of compression and manual lymphatic drainage. Critical to the success of this intensive

physiotherapy is compliance with the use of compressive garments. Regular exercise has an ameliorating effect in lymphedema, provided that external compression is maintained with garments or by hydrostatic force (as in swimming). Of note, resistance training appears to have benefit, both in the treatment and the prevention of breast cancer-related lymphedema [10].

Efficacy of decongestive physiotherapy has been demonstrated in numerous prospective trials [11–13]. Self-care strategies are paramount in the efficacy of the physical therapies for lymphedema [12].

Additional modalities have been advocated to provide adjunctive benefit to the core elements of decongestive physiotherapy. Intermittent pneumatic biocompression is the most widely used of these adjunctively employed treatment strategies. The more advanced forms of intermittent pneumatic compression attempt to replicate the low pressure, rhythmic effects of manual lymphatic drainage. Lymph clearance is augmented through the distal-to-proximal sequential graduated compression. IPC has been advocated by some physiotherapeutic schools of thought [14, 15]. It has been shown to improve edema during the initial and maintenance phase of decongestive physiotherapy without significant adverse reactions [16].

Beyond pneumatic biocompression, other devices have enjoyed some application in the treatment of lymphedema. The use of low-level laser therapy has been reported to produce subjective and objective improvement in lymphedema [17–20]; purportedly, low-level laser therapy has both anti-inflammatory and lymphangiogenic effects in lymphedema [21]. Application of vibration, heat, and external magnetic fields have all had proponents, but few data exist to support efficacy [22].

Pharmacology has, until now, enjoyed very little application in the therapeutic approach to lymphedema.

The most straightforward applicability of drug therapy has been in the use of antibiotics to treat and prevent recurrent episodes of soft-tissue infection in lymphedema. Standard broad-spectrum antibiotics are typically employed in either oral or parenteral forms of administration. The course of treatment must often be protracted. The abnormal biology of the lymphedematous tissues [1] dictates a longer duration of treatment to allow for complete pathogen eradication in a state of poor pathogen clearance and impaired immune traffic.

The use of diuretics in lymphedema can be controversial. They have little beneficial effect in patients with isolated lymphatic vascular insufficiency. However, in states of combined lymphatic and venous vascular impairment, when venous hypertension accompanies or perpetuates the biology of lymphedema, low dose diuretic therapy, to reduce the afterload on the capillary bed, may be useful as a complement to standard decongestive lymphatic therapies [2].

Beyond these two categories, current pharmacology has been shown to have little, if any, benefit. Large-scale, blinded, randomized control trials are generally lacking. One category that has received prior emphasis is that of the benzopyrones (coumarin, hydroxyethylrutin). A combination drug composed of coumarin and troxerutin, an antioxidant, is marketed in Europe as a venous and lymphatic health herbal medicine. The benzopyrones are thought to reduce fibrosis in proteinaceous states through activation of the mononuclear phagocytic system. However, meta-analysis of the small trials of benzopyrones in lymphedema was not supportive of a treatment benefit [3]. Future drug targets may be aimed at the fibrosis that occurs in lymphedema [23–25].

Of late, there is mounting evidence for the role of inflammation in the pathogenesis and maintenance of the tissue pathology in lymphedema [26], creating the hope that suppression of inflammation can bring resolution of disease [4–7, 27]. Another emerging focus in medical therapy is the use of immunomodulation to mitigate the effects of inflammation in lymphedema. Intralesional corticosteroids have been used to decrease the fibrosis associated with lymphedema [28]. More recently, intra-arterial injection of autologous lymphocytes has produced improvement in lymphedema swelling [29]. It is postulated that injection of L-selectin-expressing lymphocytes may abate the inflammatory feedback that occurs in the affected limb. These and other lines of investigation hold great promise for the evolving medical therapeutics of lymphedema. The promise of molecular therapies is discussed in ▶ Chap. 36.

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Complete Decongestive Physiotherapy

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Summary of Basic Concepts

Lymphedema is a chronic condition; therefore, in clinical practice, therapy is intended to return the disease to its latent phase (a condition relatively free from edema, despite the limited function of the lymphatic drainage system) and thereby to attain prolonged control of signs and symptoms of lymphedema.

- The objectives of physiotherapy include improvement of lymphatic vascular function, to soften fibrosclerotic irregularities, to reduce collagen deposition, and to reduce cutaneous microbial growth.
- The components of CDP are manual lymph drainage and compression therapy.
- The physiological effects of compression include displacement of fluid from the interstitium and reduction of venous pressure, reduction of lymphatic preload, increase in lymph formation, and increase in lymph flow through existing conduits, particularly during exercise.
- Complete decongestive therapy is a two-phase therapy.
- Contraindications to CDP include acute erysipelas, acute thrombophlebitis, phlebothrombosis, decompensated heart failure, and Stage IV peripheral artery occlusive disease.
- Patients with chronic lymphedema must be prepared for lifelong medical compression.
- Long-term results of conservative treatment of lymphedema with complete decongestive physiotherapy depend not only on the stage of lymphedema, during which treatment has begun, but also on the compliance of the patient, as well as the presence of comorbidities that aggravate edema as well on the skill of the therapist.

31

31.1 Introduction

Lymphedema is a chronic condition; therefore, in clinical practice, therapy is intended to return the disease to its latent phase (a condition relatively free from edema, despite the limited function of the lymphatic drainage system) and thereby to attain prolonged control of signs and symptoms of lymphedema.

As early as 1892, Winiwarter recognized physiotherapy as the most effective form of therapy. In his book *Krankheiten der Haut und des Zellgewebes* (Skin and Cellular-Tissue Disorders [6]), he describes a «new» therapeutic concept that was intended to coordinate various physical measures, like massage, methodical compression, exercise, and skin care. He was already emphasizing the need for comprehensive medical care.

In recent decades, physiotherapy for lymphedema has experienced a revival and has developed into «complete decongestive physiotherapy» (CDP). Its objectives are:

- To improve the lymphatic vascular function
- To soften fibrosclerotic irregularities
- To reduce collagen deposition
- To reduce microbial growth on the skin to prevent opportunistic infections

In addition, the attainment of an individuated, active, and age-appropriate quality of life is essential.

The adequate administration of CDP enables patients to integrate into their social surroundings and to secure their schooling and professional education. Among geriatric patients, the imminent need for high-maintenance care can be forestalled for many years. The quality of life of patients of all ages can be improved. The goals of therapy should be set by both the doctor and patient, in a shared decision-making process.

CDP is the basic therapy for limb lymphedema, even if the possibility of surgical intervention is entertained. The components of CDP are:

- Manual lymph drainage [7, 8]: a massage technique that is described extensively in ▶ Chap. 30.
- Compression therapy [1]: this form of therapy generally is carried out with medical compression bandages in Phase I of CDP (see below) and with made-to-measure compression garments in Phase II. Short-stretch bandages of various widths are used, with appropriate padding.

The effects of compression therapy are [9–11]:

- Displacement of fluid from the interstitium and reduction in venous pressure; these, in turn, have an anti-edematous effect.
- Normalization of a pathologically raised ultrafiltration, i.e., a reduction of the lymphatic preload.
- Accelerated inflow of tissue fluid into the lymph capillaries, i.e., an increase in lymph formation.
- Increase in lymph flow in the extant, functioning lymph vessels, particularly when combined with exercise.

Medical compression bandages are required:

- To give an optimal, even distribution of pressure while taking into consideration the condition of the skin
- To leave movement unrestricted
- To be applied firmly without slipping or induction of pain

Composition of medical compression bandages [2, 12]:

For the desired therapeutic and protective skin-care indications, a cotton wool tubular dressing is wrapped around the skin to protect it. Padding materials made of synthetic fibers or thin layers of foam are applied over this cylindrical bandage, for an even distribution of pressure. Uneven foam padding materials can be used, too, in order to achieve a micro-massage effect during movement. Compression pressure is finally secured with short-stretch elastic bandages. It should be taken into account that, in addition to the layer of protective padding material, skin wrinkles and indentations must be filled with made-to-measure pieces of foam. Fingers and toes are wrapped with double layers of elastic bandages. ◘ Table 31.1 shows the desired compression, the type of protective padding material, and the wearing time of the medical compression bandage, according to the patient age.

Table 31.1 Compression bandaging depends on the age of the patient and the stage of the lymphedema

		Pressure	Padding		Maximum application time
Children	6 months–2 years	10–20 mmHg	Smooth (padding bandages/foam)		12–16 h
	2–6 years	20–30 mmHg	Smooth	Padding bandage	16–20
			Uneven	Foam	
	6–12 years	20–30 mmHg	Smooth	Padding bandage	16–20 h
			Uneven	Foam	
Adults	Stage I	20–30 mmHg	Smooth	Padding bandage	12–16 h
			Smooth	Foam	
	Stage II	30–46 mmHg	Smooth	Padding bandage	18–22 h
			Uneven	Foam	
	Stage III	46 mmHg and stronger	Smooth	Padding bandage	18–22 h
			Uneven	Foam	
	Lymphedema combination forms	Individual	Individual		Individual
Geriatric	60–70 years	30–46 mmHg	Smooth	Padding bandage	18–22 h
			Uneven	Foam	
	Over 70 years	20–30 mmHg	Smooth	Padding bandage	12–16 h

Medical compression stockings, optimally, are custom-made [13], flat-knitted garments, intended to prevent re-accumulation of edema fluid. Their stretchability should match that of the short-stretch bandages. Patients with chronic lymphedema must be prepared for lifelong medical compression, even if the lymphedema can be successfully reduced to its latent state with therapy. The type of compression stockings a patient requires (Table 31.2) can change over the course of his life, relative to the receding of the lymphedema or the occurrence of new illnesses (orthopedic, neurological, etc.).

The positive effects of decongestive kinesiotherapy on venous hemodynamics and lymph flow have been experimentally and clinically substantiated [14, 15]. The contraction and relaxation of the skeletal muscles lead to an increase of pressure in the interstitium,

Table 31.2 Compression stockings depend on the stage and localization of the lymphedema

Location	Stage I	Stage II	Stage III
Toes/foot	Toe caps CCl. I	Toe caps CCl. I	Toe caps CCl. I
	Socks CCl. I	Socks CCl. II	Socks CCl. III
Lower leg + toes/foot	Toe caps CCl. I	Toe caps CCl. I	Toe caps CCl. I
	Knee stockings CCl. II	Knee stockings CCl. II	Knee stockings CCl. IV
Whole leg + toes/foot	Toe caps CCl. I	Toe caps CCl. I	Toe caps CCl. I
	Groinal stocking CCl. II	Groinal stocking CCl. III	Groinal stocking CCl. IV
Truncal quadrant + whole leg + toes/foot	Toe caps CCl. I	Toe caps CCl. I	Toe caps CCl. I
	Tights with one leg CCl. II	Tights with one leg CCl. III	Tights with one leg of CCl. IV
		Truncal garment CCl. II	Truncal garment CCl. II
Truncal quadrant + both legs + toes/foot	Toe caps CCl. I	Toe caps CCl.	Toe caps CCl. I
	Tights CCl. II	(a) Knee stockings CCl. III	(a) Knee stockings CCl. IV
		(b) Half hose CCl. II	(b) Half hose CCl. II/ III
Lower arm + hand	Long glove CCl. I	Long glove CCl. II	Long glove CCl. II or III
Whole arm + hand	Sleeve CCl. I	Sleeve CCl. II	Sleeve CCl. II or III
	Glove CCl. I	Glove CCl. II	Glove CCl. II

which transfers to the lymphatic wall, resulting in an increase in the pulsation of the lymphangions. Depending on the position of the body, intensive abdominal breathing can have a similar effect on the central part of the veins and lymphatic trunks. Decongestive kinesiotherapy and respiratory therapy can be performed as a single treatment or as group therapy. In addition, the patient should learn an individual training program, devised according to his age and profession, which would then be continued as long-term therapy. Walking, Nordic walking, cycling, treadmill exercise, stationary cycling, swimming, and endurance sports are all specifically suitable.

Dry, itchy skin is often a part of chronic lymphedema. Due to the disturbance in the physiological balance between the moisture and lipid content of the skin, bacterial and mycotic infections, including congestive dermatitis, frequently occur [3, 16]. The application of disinfectant and antimycotic agents is indicated as the therapy for infections. Antihistamine agents are shown to be effective against congestive dermatitis. Topical corticosteroids can also be temporarily indicated. Urea, ceramides, and choles-

terol-containing moisturizers have proven themselves capable of restoring the physiological balance between moisture and lipid content. Since skin maceration and intertrigo can occur in deep wrinkles, powder and, if necessary, padding are indicated to dry the skin after disinfection.

31.2 The Use of CDP

Complete decongestive therapy is a two-phase therapy [4, 17–19]. Phase I is aimed at mobilizing the congested, protein-enriched fluid and is intended to initiate reduction of any increased connective tissue present. Instruction and information regarding self-treatment procedures and a suitable lifestyle are given during this phase. Phase II involves optimizing and preserving the successes achieved by the therapy in Phase I. The procedures to be undertaken (Table 31.3) depend on the stage of lymphedema in which therapy is commenced.

Table 31.3 Prevention and two-phase treatment of lymphedema with CDT

Stage	Symptoms	Phase I decongestion	Phase II optimization	Phase III preservation
Stage 0	No swelling, pathological lymphoscintigram	Prevention when lymphedema risk factors present		
Stage I	Edema of soft consistency, raising of the limb reduces swelling	MLD: 1 × per day, compression bandaging, exercise, duration 14–21 days		MLD: in series compression garments as required or consistent in the long term
Stage II	Edema with secondary tissue alterations, raising of the limb without effect	MLD: 2 × per day, compression bandaging, exercise, duration 24–28 days	MLD: 1–2 × per week for the duration of 2–5 years, compression garments and bandaging, exercise, repetition of Phase I	MLD: in series or 1 × per week, compression garments worn consistently in the long term, exercise
Stage III	Elephantiasic hard swelling, often of lobular form with typical skin alterations	MLD: 2–3 × per day, compression bandaging, exercise, duration 28–35 days	MLD: 2–3 × per week for the duration of 5–10 years, compression garments and bandaging, exercise, repetition of Phase I	MLD: in series or 1–2 × per week, compression stockings worn consistently in the long term, exercise

The long-term success of complete decongestive physiotherapy depends on the comprehensive medical care of the patient. Notoriously, the extent of the restriction in function of the lymphovascular system is only a part of the pathophysiology of lymphedema. The clinical picture and also the therapy requirements are influenced by several comorbidities that lead to an increase in the amount of fluid to be transported. Diseases that influence the function of the arteries, blood capillaries, veins, and ground substance impede lymph formation or increase lymphatic loads. Such pathophysiological processes can aggravate both primary and secondary lymphedema. Patients who suffer from chronic limb lymphedema require a complete medical assessment before complete decongestive physiotherapy has begun and later, as is often the case with chronic illnesses, a regular medical checkup. Adequate treatment of diseases that aggravate lymphedema is essential if complete decongestive physiotherapy is to succeed.

31.3 Indications, Contraindications, and Modification of CDP

In order to prevent any side effects of CDP, awareness of the indications, contraindications, and forms of its modification is mandatory [20]. There are many diseases that require an individual adaptation of the application of complex decongestive physiotherapy to the condition of the patient. The most commons include:

- Hypertension
- Coronary heart disease
- Heart failure
- Diabetes mellitus
- Chronic venous insufficiency
- Malignancies
- Rheumatic disorders
- Peripheral artery occlusive disease
- Peripheral polyneuropathy

Contraindications to CDP include:

- Acute erysipelas
- Acute thrombophlebitis
- Phlebothrombosis
- Decompensated heart failure
- Stage IV peripheral artery occlusive disease

Treatment of genital and head and neck lymphedema with complete decongestive physiotherapy demands a substantial experience and should only be carried out under specialized clinical conditions.

Quality of life and patient satisfaction during treatment with complete decongestive physiotherapy depend to a large extent on realistic therapy goals and their attainment. Many patients can only achieve their therapy goals through adequate psychosocial support. Professional therapy and assistance are essential. The diagnosis of lymphedema alone and the implementation of the necessary self-treatment procedures call for a great psychosocial effort on the part of the patient and his family to adjust to the diagnosis and its implications. Psychotherapy is usually required to help with this [5, 21, 22].

31.4 Long-Term Therapy Results

Long-term results of conservative treatment of lymphedema with complete decongestive physiotherapy depend not only on the stage of lymphedema, during which treatment has begun, but also on the compliance of the patient, as well as the presence of comorbidities that aggravate edema as well on the skill of the therapist.

As a rule, primary lymphedema in infancy presents without concomitant diseases. A clinical trial including 452 children over 12 years showed that in 85% of cases, the success of therapy after Phase I of CDP could not only be preserved but could be further improved. Treated individuals had unimpaired educational and professional life attainment when compared with unaffected children [22, 23].

A second clinical trial to assess the long-term success of treatment was carried out with 512 adult patients. It showed that there was a strong correlation between the prevalence of comorbidities and edema relapses: in patients with lymphedema of the lower limb without concomitant diseases, therapy success after Phase I of CDP can be maintained for 15 years. In patients with combined forms of lymphedema, 91% of cases repeated Phase I of CDP due to edema relapses over the same length of time [24].

In geriatric patients, long-term success and goals of therapy not only depend on comorbidities but also on the mental state of the patient.

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Decongestive Lymphatic Therapy

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Summary of Basic Concepts

- DLT encompasses non-surgical treatment options of compression, massage and exercise to stimulate lymphatic drainage in order to reduce swelling and achieve long-term maintenance of results. DLT comprises an 'intensive therapy' phase and a longer-term 'maintenance' phase.
- DLT is often termed 'conservative therapy', but this is misleading as curative surgical treatments are not suitable for the majority of patients.
- Management should focus on the needs of the individual patient, but aims of treatment are to improve lymph drainage and reduce their swelling, soften fibrotic tissues and improve the skin's function as a barrier to infection, reduce the rate and severity of cellulitis, reduce associated discomfort from the oedema and improve limb function/mobility.
- Successful DLT requires a motivated and compliant patient and one that understands that daily use of compression is necessary to maintain the long-term benefits of treatment.

32.1 Introduction and Definition

Lymphoedema is a chronic condition comprising swelling of one or more body sites. It occurs as a result of lymphatic failure (either intrinsic or extrinsic) causing accumulation of protein as well as water within the swollen tissues. Unfortunately there is no definitive curative treatment for lymphoedema. Management is aimed at improving swelling through physical treatments designed to stimulate flow through existing or collateral lymphatic drainage routes.

The management of lymphoedema varies greatly around the world. In developed countries, the emphasis is more on physical forms of therapy such as decongestive lymphatic therapy (DLT) with adjuvant surgery for select cases [6, 7]. In poorer, hotter countries where hosiery and appropriate bandages are too costly, debulking surgery may be the mainstay of treatment.

DLT encompasses non-surgical treatment options of compression, massage and exercise to stimulate lymphatic drainage in order to reduce swelling and achieve long-term maintenance of results. The literature is awash with synonymous terms for DLT including 'complete decongestive therapy' or 'complex decongestive physical therapy'. The term DLT was proposed during the 1998 Cancer Workshop meeting by leading specialists in the field and has remained the term of choice amongst many physicians [8]. Regardless of the term used to describe non-surgical lymphoedema management, the cornerstones of treatment are identical, with an emphasis on compression therapy. Lymphoedema treatment should be holistic, because of the significant impact of disease on both the physical and psychological well-being of the patient.

DLT is often termed 'conservative therapy', but this is misleading for patients as curative surgical treatments are not suitable for the majority. A patient should not be under the false impression of their healthcare provider failing to aggressively treat their lymphoedema by recommending DLT rather than surgery. Even patients undergoing surgical treatment will need some form of DLT/compression in the post-operative

period. It is vital that all patients are able to access non-surgical treatments to ensure their lymphoedema does not deteriorate and complications do not arise.

Decongestive lymphatic therapy is employed to improve a patient's lymphoedema, but the results will be short-lived unless measures are taken to maintain treatment outcomes. Therefore, DLT comprises two different phases: an initial 'intensive therapy' treatment programme (utilising inelastic compression bandages or Velcro strapping systems), followed by the longer 'maintenance' phase (daily use of compression hosiery).

Unfortunately, there is limited research to inform evidence-based guidelines on the treatment of lymphoedema. Nevertheless, robust guidelines on the implementation and benefits of decongestive lymphatic therapy have been developed through consensus by experts in the field [1].

32.2 Assessment Prior to Undertaking DLT

A patient with lymphoedema should undergo assessment prior to receiving DLT. Medical assessment aims to identify and exclude other causes of peripheral oedema that require additional management. This can be undertaken by an experienced lymphoedema therapist, but a junior therapist may require the assistance of a physician in order to determine a patient's suitability for DLT. In circumstances where systemic causes for peripheral oedema, for example, congestive cardiac failure, have led to or coexist with the lymphoedema, then treatment of the medical condition must be undertaken before embarking on specific lymphoedema therapy. Otherwise, the patient may suffer complications, e.g. exacerbation of cardiac failure, as a result of significant fluid shifts during DLT. Where necessary, appropriate investigations should be performed to confirm lymphoedema and to identify treatable underlying causes (e.g. active cancer) or comorbidities (e.g. superficial venous incompetence).

A full assessment of the patient will determine the presence of contraindications to undertaking DLT. It may be possible to optimise the patient's health prior to undergoing lymphoedema treatment, i.e. associated health problems should not prevent DLT, but only delay it until the acute medical issue has been appropriately managed to reduce the risk of complications.

A number of conditions are absolute contraindications to undertaking DLT on a patient, but they are few in number. Several medical conditions are deemed relative contraindications to undertaking DLT. In these situations, it is advisable to undertake treatment with caution and to closely monitor the patient for signs of deteriorating health.

Concomitant medical conditions requiring further treatment or careful monitoring during DLT include [1]:

- *Peripheral neuropathy* can result in reduced/impaired sensation of the region requiring compression therapy. The clinician should screen for this disorder in patients at risk, e.g. those with diabetes mellitus. The patient and therapist must be vigilant, by means of visual inspection, in monitoring for signs of trauma or excessive compression to the skin.
- *Impaired arterial circulation* of the limb that requires compression. The ankle-brachial pressure index (ABPI) is a Doppler assessment that provides an objective measure of the patency of the large arteries supplying blood to the foot. It is

calculated from the ratio of the highest ankle systolic blood pressure for each limb to the highest systolic pressure in the arm. Normal values range from 1.0 to 1.3, and levels less than 0.8 may indicate a degree of lower limb arterial occlusive disease that can preclude the use of high-compression therapy. Patients with an ABPI of less than 0.5 may suffer ischaemic complications from compression therapy (from intensive bandaging or maintenance hosiery) and should therefore be referred to a vascular surgeon for further assessment and treatment. These patients may receive compression once they have received successful revascularisation treatment. Patients with ABPI of 0.5–0.8 can receive compression therapy but must be carefully monitored.

- Poorly controlled *congestive cardiac failure* and/or *ischaemic heart disease*. A sudden fluid shift from a lymphoedematous limb into the blood vascular circulation may overwhelm the patient's cardiac capacity and cause respiratory or cardiac distress.
- Recent *deep vein thrombosis* (DVT) of the limb that requires compression. However, compression therapy may be introduced once the patient is fully anticoagulated with a therapeutic INR.
- Acute *cellulitis* (erysipelas) should be treated with appropriate antibiotics before commencing DLT. Failure to do so could result in an exacerbation of the infection by manipulation of bacteria into the bloodstream, potentially resulting in full-blown sepsis. DLT may be commenced as soon as the acute infection has been treated, but the lymphoedema therapist should closely monitor the patient for signs of recurrent infection.
- *Active malignancy* is considered a relative contraindication to undertaking DLT. Historically, there has been concern amongst therapists that MLD massage can encourage the distant metastatic spread of cancerous cells within the lymphatic system. Many lymphoedema therapists choose to avoid intensive lymphoedema treatment until a patient has completed their cancer treatment. However, if a patient with active malignancy (e.g. breast cancer) has reached the stages of palliative care and there are no additional options to cure their cancer, then common sense would prevail and permit these patients to receive decongestive lymphoedema treatment in order to ease their discomfort. Oncologists have demonstrated that patients with cancer-related lymphoedema obtain relief with DLT, regardless of whether they had locoregional disease contributing to their symptoms. They believed that DLT should not be withheld because of persistent or recurrent disease in the draining anatomical bed of the malignancy [9].

32.3 Indications of DLT and Treatment Goals

Decongestive lymphatic therapy should be considered for all patients with lymphoedema. Management will focus on the needs of the individual patient, but the aims of treatment, for both 'therapy' and 'maintenance' phases, are to [6] improve lymph drainage and reduce their swelling, [7] soften fibrotic tissues, [8] improve the skin's function as a barrier to infection (e.g. treating skin problems such as elephantiasis, lymphorrhoea and wounds), [1] improve limb function/mobility and [9] reduce any associated pain/discomfort from the oedema. Additional treatment benefits include a reduction in the frequency and severity of cellulitis of the affected site [10].

Therapy assessment will include setting the benchmarks against which improvement can be judged, for example, limb volume measurement, mobility and functional assessments. A treatment plan should be tailored to the individual and will depend on the site and severity of the lymphoedema and the need to engage other services, for example, leg ulcer, tissue viability or wound care, as well as oncologists or vascular surgeons.

Central to a successful management plan is enabling patients to understand their condition and know what they can do for themselves. Only then can a high level of motivation and treatment compliance be generated [11]. It is important to explain to patients that their lymphatic drainage relies on local changes in tissue pressures generated by exercise and movement, unlike that of blood which is propelled by the heart. Decongestive lymphatic treatment exploits these principles, enhancing lymph flow as much as possible within the limits of the patient's compromised drainage system. It should be appreciated that lymph flow still exists in lymphoedema, albeit sluggishly; otherwise swelling would be a relentlessly progressive process.

DLT comprises an 'intensive therapy' phase and a 'maintenance' phase. Not all patients will require intensive treatment, but all patients should receive maintenance treatment. Intensive treatment typically comprises the use of several (but not necessarily all) modalities including skin care, manual lymphatic drainage massage, compression bandaging and exercise. The primary goals are to achieve significant limb volume reduction and tissue changes prior to fitting the patient with compression hosiery that will maintain treatment results. Delivery and frequency of intensive treatment varies significantly and will depend on local facilities and funding. For example, it is not uncommon for patients in some countries to receive twice daily MLD and compression bandaging whilst residing in bespoke inpatient treatment centres. Other centres will offer outpatient treatment at a frequency between 2 and 5 times per week, depending on resources. Treatment outcomes depend on the frequency of bandaging, but a balance between available resources and optimal treatment has to be reached.

Intensive therapy, comprising a 2–4-week course of daily skin care, MLD, multilayer bandaging and exercises, is indicated for patients with moderate to severe limb swelling, poor limb shape or tissue changes such as fibrosis, elephantiasis or lymphorrhoea. Once intensive treatment is complete, maintenance treatment with hosiery is commenced immediately. Whilst decongestive lymphatic therapy has become accepted first-line therapy, evidence for best treatment is weak [8]. Patients with mild limb lymphoedema, no discernible tissue fibrosis and no shape distortion can be started immediately on maintenance treatment with compression hosiery and exercise.

32.4 'Therapy' and 'Maintenance' Phases of DLT

The 'intensive therapy' and 'maintenance' phases of DLT incorporate the cornerstones of lymphoedema treatment. These include compression therapy, manual lymphatic drainage, exercise and skincare. Compression is the most important component of DLT and cannot be replaced by any other modality [2]. Manual lymphatic drainage (MLD) may be offered more readily in some treatment centres, depending on local resources. A perceived lack of evidence demonstrating long-term benefits of MLD has led to the reduction of financial support in some countries, resulting in reduced availability of this treatment modality.

The 'intensive therapy' phase of DLT is usually offered to patients with significant swelling (of any body site) in order to achieve significant volume reduction (with inelastic bandages or Velcro strapping systems) before fitting them with compression hosiery with a view to maintaining the smaller (limb) volumes. The majority of patients with mild lymphoedema, typically of a limb, do not require intensive bandaging therapy and can be directly measured for appropriate compression hosiery. Intensive therapy is typically offered in the outpatient setting, but a few centres across the world may offer inpatient treatment, depending on local reimbursement pathways. The duration of intensive therapy varies across the globe but typically involves daily MLD, bandaging and exercises once daily (including weekends at inpatient facilities) for an approximate duration of 2–4 weeks. Treatment duration will be determined by the assessing physician or lymphoedema therapist but should be continued until pitting oedema has resolved and long-term compression hosiery commenced [1]. A small number of patients require a prolonged course of treatment if they have significant limb distortion or severe, neglected chronic lymphoedema.

32.5 Cornerstones of Treatment

32.5.1 External Compression

Compression is the most important component of DLT and cannot be replaced by any other modality [2, 12]. Compression garments and bandaging have been discussed in detail in the subsequent chapter. This section will not focus on the science behind compression therapy, rather the practicalities of undertaking treatment.

External compression (hosiery, bandages or pneumatic compression) complements any exercise programme that is designed for each patient. Compression is not intended to 'squeeze' the fluid out of a limb but rather to act as a counterforce to muscle activity, thereby generating higher tissue pressures during contractions. This provides the most powerful stimulus to lymph drainage. Compression also limits capillary filtration by opposing capillary pressure, thereby reducing swelling from excessive fluid overload. Compression is not truly effective without exercise. Patients should be fully informed that DLT is not a passive form of treatment, rather an active one that relies on the cooperation of the patient in order to achieve success.

Inelastic Bandaging

Multilayer bandaging can be used for limb volume reduction but has the added benefit of restoring limb shape so that subsequent use of compression garments (hosiery) is more effective at controlling swelling.

Bandaging may be the only method suitable for huge misshapen limbs and for controlling lymphorrhoea (leakage of lymphatic fluid through the skin). Layers of strong, non-elastic (short-stretch) bandages are applied to generate a high pressure during muscular contractions but low pressure at rest (see ▶ Chap. 31 for more detail on compression bandaging). The digits should be bandaged in order to control swelling of the fingers or toes (◘ Fig. 32.1). The use of foam or soft padding helps to distribute pressure more evenly and to protect the skin (◘ Fig. 32.2). The strategic positioning of padding 'evens out' pockets of swelling and deep skin crevices. Multilayer bandaging is a skill

Fig. 32.1 Careful bandaging of individual digits ensures they will reduce in volume. Failure to do so will result in increased swelling of the fingers/toes as a result of a distal fluid shift during DLT

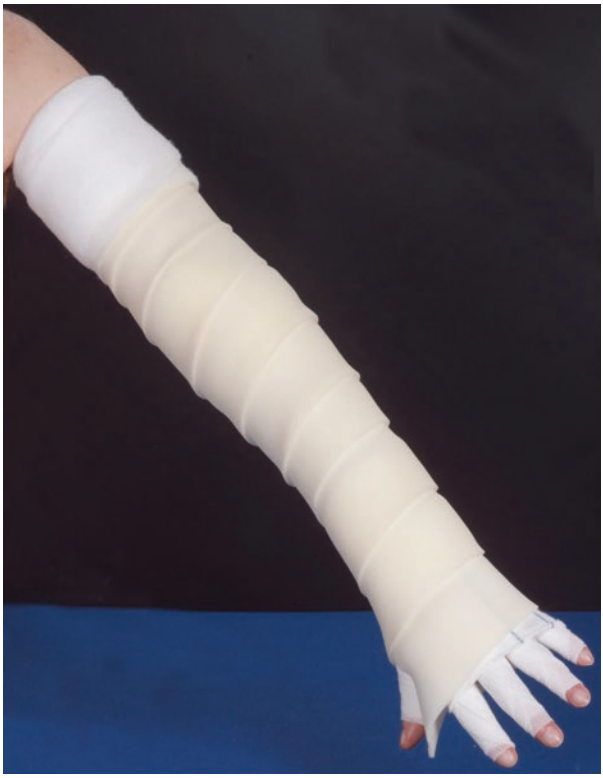

Fig. 32.2 The use of foam or soft padding helps to distribute pressure more evenly and to protect the skin. This is especially important when managing a severely distorted limb shape, resulting from chronic, neglected lymphoedema

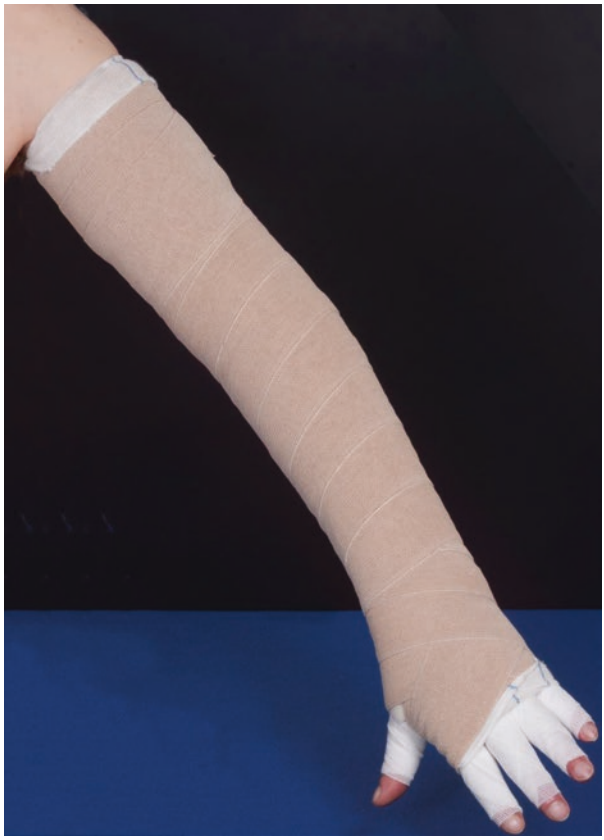

Fig. 32.3 Intensive therapy comprising the application of multilayer inelastic bandaging

that takes time to learn and should not be undertaken by any professional without appropriate training (Fig. 32.3). The degree of compression administered may have to be modified in certain situations, e.g. cancer-related lymphoedema requiring palliative treatment, moderate limb ischaemia or in the presence of neurological deficits.

Randomised controlled trials confirm that treatment regimens incorporating the use of compression bandaging treatments achieve greater results when compared to compression hosiery alone. For example, Badger et al. reported that a 24-week regimen incorporating daily lymphoedema bandaging for 18 days followed by the daily use of compression hosiery achieved a 31% volume reduction. In contrast, the daily use of compression hosiery alone only achieved a 15.8% volume reduction after 24 weeks [3].

Compression Hosiery

Compression hosiery limits the amount of fluid building up in the limb. It acts as a counterforce to muscle contractions to improve lymphatic drainage. Compression garments have a graduated compression (more strength at the foot/hand than at the top of the garment), ensuring lymphatic fluid is directed towards the root of the limb (groin/axilla). Effects are enhanced when a patient wears their compression hosiery during exercise. Compression hosiery is available in many different styles (below-knee or full-length stockings, half or full tights and sleeves) and degrees of asserted pressure (Fig. 32.4). Complex limb lymphoedema may require the use of high compression

Fig. 32.4 Bilateral below-knee open-toe compression hosiery. The patient has also been fitted with toecaps in order to apply increased pressure to individual digits

and/or double layers of garments. Most garments last no more than 6 months. A minimum of two sets of garments should be provided (one to wear whilst the other is washed). Washing of garments is necessary in order to maintain the compression properties of the garment. The patient's technique for the application, removal and care of garments is crucial for a successful outcome. Several studies confirmed that compression garments are useful in the management of lymphoedema and that it is possible to achieve volume reduction with compression hosiery and exercise alone [13, 14].

Velcro Compression Systems

Compression can be achieved with the use of Velcro strapping systems applied to swollen limbs (Fig. 32.5). These adjustable garments have been available for several years and were utilised in the 'maintenance' phase of DLT treatment, often for patients with significant comorbidities that were unable to comply with standard compression hosiery. These Velcro garments can be applied by the patient and/or carers after minimal training. One advantage over bandaging is the option to adjust them (i.e. apply more pressure to the limb) during the day to overcome issues with 'slippage' during periods of limb

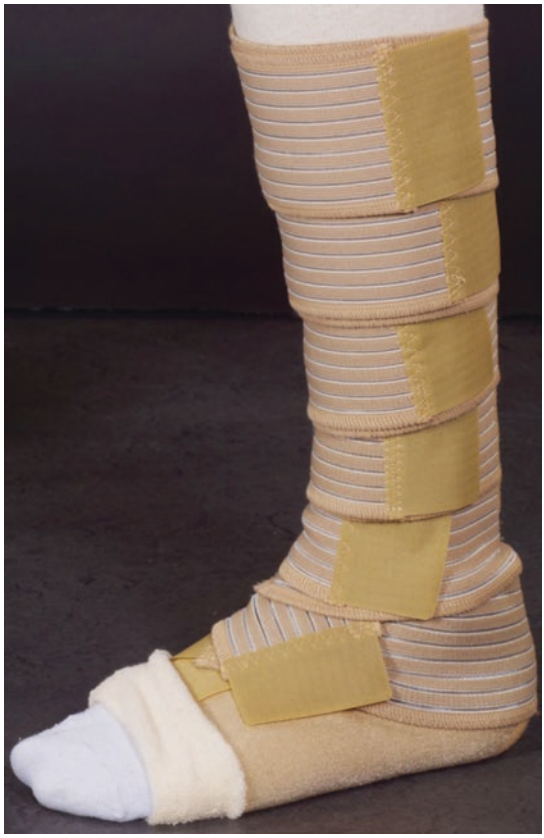

Fig. 32.5 Velcro strapping system applying compression to the foot and below-knee region. The Velcro the patient to adjust and improve upon the amount of compression delivered to the limb

volume reduction. In recent years, we have come to realise that these Velcro strapping systems can also be utilised in the 'intensive therapy' phase. A recent randomised controlled trial demonstrated significantly more leg volume reduction from the use of the Velcro system when compared to conventional inelastic bandages [4].

Intermittent Pneumatic Compression

Pneumatic compression therapy (intermittent/sequential pneumatic compression) should not be used in preference to exercise and compression garments but can be a useful adjunct in the treatment of mixed lymphovenous oedema or for infirm patients [15]. An inflatable boot or sleeve is connected to a motor-driven pump, and lymph is displaced proximally towards the root of the limb. If hosiery is not fitted immediately following pneumatic compression therapy, the swelling will rapidly recur. Pneumatic compression may soften the tissues and reduce limb volume during treatment, but it is doubtful that any long-term benefit is gained over hosiery and exercise alone.

32.5.2 Exercise

Exercise has been reported to improve psychological function, aerobic fitness and vitality scores in patients with lymphoedema [16, 17]. Unfortunately, there is a lack of

evidence supporting the benefit of exercise upon lymphoedema volumes. However, exercise and movement are known to be crucial to lymphatic drainage [18]. Dynamic muscle contractions (isotonic exercises) encourage both passive (movement of lymph along tissue planes or through non-contractile lymphatics) and active (increased contractility and therefore propulsion of lymph within contractile lymphatics) phases of lymph drainage. It is acknowledged that overexertion and excessive static (isometric, e.g. gripping) exercise increases blood flow, which may increase lymphoedema.

32.5.3 Skin Care

Elephantiasis skin changes, occurring as a result of poorly managed chronic oedema, are not only unsightly but lead to malodour, lymphorrhoea, restricted movement from fibrosis (pseudoscleroderma), poor wound healing and increased risk of infections. Regular application of an emollient will hydrate the hardened skin, rendering it more supple and discouraging hyperkeratosis. Tinea pedis is a frequent consequence of lower limb lymphoedema because of the closely opposed swollen toes – circumstances not improved by use of compression hosiery. Modern antifungal creams unfortunately macerate skin further, and therefore it is suggested that terbinafine cream is applied for 2 weeks followed by an alcohol wipe (assuming the skin is not broken). For deep cracks and crevices that bacteria may readily colonise, regular cleansing is necessary followed by an antiseptic soak, for example, potassium permanganate. Hyperkeratosis may be improved through the regular application of 5% salicylic acid ointment. However, the best treatment to reverse elephantiasis skin changes is long-term compression treatment. Areas that constantly leak lymph will also respond to sustained compression.

Prevention of infection, particularly cellulitis/erysipelas, is vital to maintain control of a patient's lymphoedema. Each episode of infection causes further lymphatic damage, causing increased lymphoedema and subsequent increased risk of further infection (due to impaired immune surveillance in the areas of impaired lymphatic drainage). Care of the skin, good hygiene, control of tinea pedis and good antisepsis following abrasions and minor wounds are important in reducing the risk of cellulitis, as maintenance of skin integrity and an effective barrier will reduce the entry of microorganisms.

32.5.4 Manual Lymphatic Drainage (MLD) Massage

Manual lymphatic drainage (MLD) massage is an important component of treatment, particularly for midline lymphoedema where there are few alternatives [7]. MLD should not be used in isolation in the management of lymphoedema, but as part of a bespoke treatment programme. Treatment sessions of MLD will vary in duration, depending on the area being treated and the severity of the lymphoedema. MLD typically takes 30–60 minutes per treatment session when utilised prior to 'intensive therapy' treatment with inelastic bandaging or Velcro system wrapping. Patients receiving regular MLD massage (e.g. weekly or monthly, usually in the private sector due to funding issues) may choose to receive longer sessions.

MLD is a massage technique performed by lymphoedema therapists with the aim of re-routing the accumulation of lymph away from the swollen region via collateral lymphatic pathways towards lymphatic basins that are able to drain normally. The initial

step in MLD is to decongest central/proximal areas before massaging the oedematous regions. This facilitates the drainage of lymph via lymphatic vessels/pathways that have been stimulated by the massage technique. MLD consists of light, rhythmical and pumping hand movements to stretch the skin and stimulate the lymphatic system to drain more efficiently. Tissue movement must be gentle if it is to stimulate lymph flow without increasing blood flow [19]. A number of MLD techniques are available (e.g. Vodder, Leduc, Foldi, Casley-Smith), but no single method appears to be superior. MLD is widely practised and many patients, therapists and physicians advocate the benefits. Continuous MLD delivered by a therapist is expensive, and few healthcare providers will fund this long term. There is a lack of consistent evidence to support its effect. Simple lymphatic drainage (SLD) is a simplified form of MLD that may help to maintain the results of MLD. SLD can be delivered by a partner or carer trained in the technique.

The recent development of lymphofluoroscopy (indocyanine green lymphography) as a tool to map patient's superficial lymphatic drainage pathways is proving of interest to patients and lymphoedema therapists alike. Lymphatic drainage pathways differ between patients as a result of differences in normal anatomy and damage from external factors (e.g. cancer treatment or infection). Lymphofluoroscopy mapping involves the intradermal injection of indocyanine green (ICG) tracer that is taken up by the initial lymphatic vessels. The tracer is detected by an external camera, and the superficial lymphatic pathways can be mapped out on the skin and documented for future MLD treatments. For enhanced drainage, individual pathways can be marked and recorded following lymphofluoroscopy, allowing for the therapist to drain to these routes. This imaging technique should facilitate the development of a bespoke treatment protocol, maximising the benefits of MLD, for each patient.

32.5.5 Additional Treatments

Weight Management

The body mass index (BMI) of a patient strongly correlates with the incidence and severity of lymphoedema [20]. An elevated BMI also correlates with a reduction in patients' quality of life (QoL) score [21]. Excessive weight gain is likely to impair lymph drainage in the same way as it impairs venous drainage, and obesity reduces mobility (and therefore exercise). Weight management in combination with lymphoedema treatment may be sufficient to induce complete resolution of lymphoedema in some patients. Weight loss irrespective of type of diet has been shown to reduce arm volume over and above what would be expected from fat loss alone in BCRL [22, 23]. Patients must be encouraged to adopt a healthy eating plan in combination with regular exercise.

Breathing, Postural Exercise, Elevation and Rest

Patients may be instructed on breathing and postural exercises as adjunctive lymphoedema treatments. These exercises are important for clearance of lymph from the thorax and abdomen. Without the dispersal of truncal lymphatic fluid, the peripheral limb oedema cannot not drain proximally. Elevation of a limb will not improve lymphatic drainage per se, but lowering of the venous pressure with leg elevation (and therefore lowering capillary filtration) can help to reduce swelling. However, rest and elevation alone are not the correct treatment for lymphoedema!

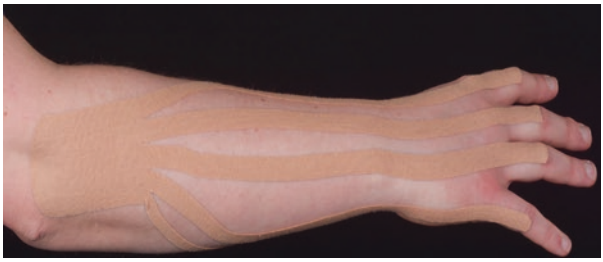

Fig. 32.6 Kinesio Tape has been applied to the skin to lift it, thereby increasing lymph flow and encouraging lymphatic fluid drainage

Hyperbaric Oxygen (HBO), Low-Level Laser Therapy (LLLT) and Kinesio Taping

Hyperbaric oxygen (HBO) and low-level laser therapy (LLLT) have been recommended in the management of breast cancer-related lymphoedema [24–26] although a recent randomised controlled trial failed to demonstrate significant benefits from HBO treatment [27]. However, LLLT may be a useful adjunct in reducing limb volumes and pain in patients with BCRL [29].

Kinesio Taping involves the use of an adhesive tape applied to the skin of lymphoedematous (and surrounding unaffected) skin (Fig. 32.6). The tape lifts the skin during physical activity and movement, thereby increasing lymph flow and encouraging lymphatic fluid to migrate towards decongested regions and draining lymph nodes (29). Kinesio Taping may be used in isolation when treating lymphoedema or tissue fibrosis of the breast or head and neck regions.

32.6 Adapting Compression Bandaging for Different Areas

Lymphoedema of the trunk, breast and genitals can prove a therapeutic challenge to the inexperienced lymphoedema therapist. However, DLT can be adapted in order to achieve significant volume reduction and improvements in local tissue changes within these regions. A combination of the four treatment cornerstones can be used to manage these areas, but therapists may need to be creative when it comes to applying compression bandaging and accept that a degree of bandage slippage is inevitable. Bespoke and 'off-the-shelf' compression garments are available to compress the trunk (e.g. compression vests), breast (compression bras) and genitals (compression shorts).

32.7 Additional Support for the Patient

Lymphoedema is a chronic disorder and will have a significant impact upon the physical and mental health of a patient, and these issues should be addressed as part of the patient's treatment plan in order to increase the chances of long-term success.

Psychological support of patients with lymphoedema is often lacking. Patients with breast cancer-related lymphoedema experience functional impairment, psychosocial maladjustment and increased psychological morbidity [19].

Employment is also affected by lymphoedema. In one study over 80% of patients had taken time off work due to their lymphoedema, with an estimated mean time off work of 10.5 days per year for medical appointments. Overall, 9% stated that the lymphoedema affected their employment status, with 2% of respondents having to change jobs as a result of the lymphoedema and 8% having to give up work because of it [15].

Patients will often talk about the difficulty in finding clothes or shoes to fit and how this creates social problems. Poor footwear will further compound the swelling by discouraging a normal gait or enough exercise.

The ideal lymphoedema treatment programme would offer direct access to specialist services (e.g. psychologists, dietitians), employment support and advice and guidance on where to obtain suitable footwear and clothing.

32.8 Complications of DLT

Complications resulting from DLT are rare and can usually be prevented by a thorough assessment prior to commencing treatment. They include exacerbation of congestive cardiac failure, ischaemic damage to a limb or digit, traumatic ulceration secondary to neuropathic damage and falls secondary to cumbersome bandages and/or inappropriate footwear.

Cellulitis can complicate DLT, especially during the 'intensive therapy' phase. This is more likely to occur in patients with a past history of cellulitis, possibly as a result of bacteria lying dormant in the tissues and being 'awoken' by manipulation of affected tissues. Intensive bandaging or use of Velcro strapping systems should be temporarily suspended until the cellulitis has been treated with appropriate antibiotics, i.e. the erythema has subsided and the patient feels systemically well. However, the patient should be monitored closely for recurrent or 'grumbling' cellulitis when DLT is reintroduced. The use of prophylactic antibiotics may be necessary for some patients: (1) patients with two or more episodes of cellulitis per year should benefit from low-dose daily penicillin V (e.g. 250 mg twice daily for a year) in order to reduce the risk of recurrent infection and further lymphatic vessel damage [5]; (2) patients developing an acute cellulitis each time they receive intensive bandaging treatment will benefit from a 2-week therapeutic course of antibiotics commenced a few days before the DLT (personal experience of the authors).

32.9 Long-Term Management

The key to achieving successful long-term results from DLT is to promote self-management and empower the patient to comply with the cornerstones of treatment. The lymphoedema physician/therapist should encourage patients to take control of their condition and learn when to ask for increase support/adjust their management regimen when necessary. For example, a patient suffering an increase in limb volume following an episode of cellulitis may require another course of intensive therapy treatment with bandages prior to get their lymphoedema under control once more. Failure to do so may lead to a disheartened, frustrated patient that may enter a slow, steady path of deterioration. However, an empowered patient is more likely to deal with small setbacks and be confident in managing their chronic condition. Regular (e.g. six monthly) consultations with a lymphoedema therapist permit the regular provision of compression hosiery and allow early identification of disease complications.

Conclusion

Decongestive lymphatic therapy can achieve significant volume reduction in lymphoedematous limbs (or other body sites) utilising a combination of compression therapy, exercise, skin care and manual lymphatic drainage (Fig. 32.7a–c). Early intervention yields better results, as chronic lymphoedema skin changes and fibrosis are rarely completely reversible. Severe lymphoedema should be managed with intensive therapy utilising compression bandaging or Velcro strapping systems, before introducing compression hosiery to maintain the results of treatment. Patients with mild lymphoedema can forgo intensive therapy as they can be managed with hosiery from the beginning of their DLT. Successful DLT requires a motivated and compliant patient and one that understands that the daily use of compression is necessary to maintain the long-term benefits of treatment.

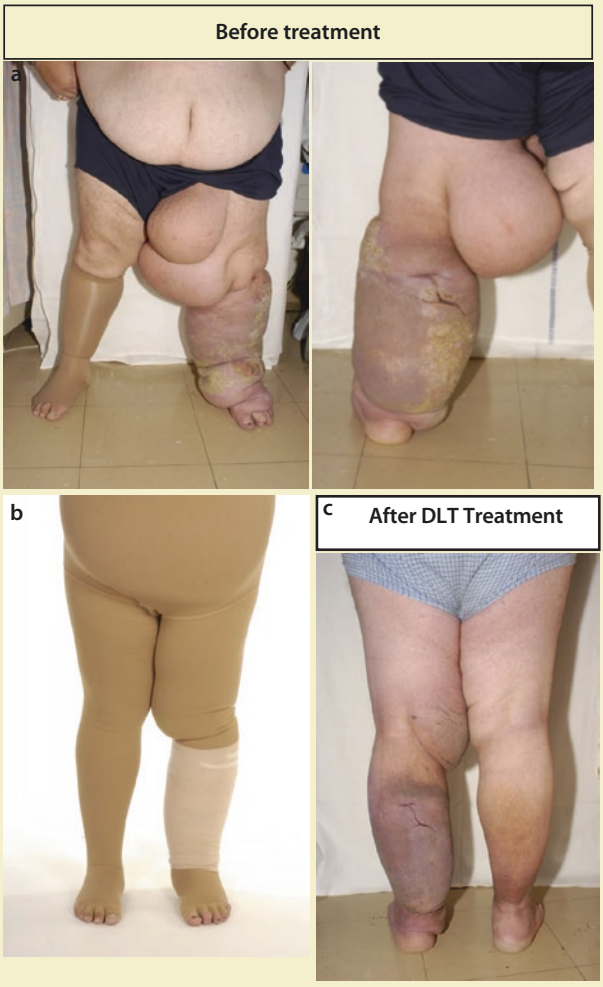

Fig. 32.7 **a** A patient with severe bilateral lower limb lymphoedema secondary to obesity and deep venous thrombosis. **b** Four weeks of intensive DLT therapy have achieved a significant reduction in limb volumes, improved limb shape and improved skin changes. **c** The results of intensive DLT can be maintained with the daily use of compression hosiery

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Compression Therapy

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Summary of Basic Concepts

- Compression therapy is the cornerstone of conservative therapy in lymphedema patients.
- Decongestive therapy is initiated with the use of multicomponent bandage materials with high stiffness; these should be applied only by trained healthcare professionals.
- Thereafter, lifelong sustained compression is essential in order to maintain the edema reduction. Usually, compression hosiery is prescribed, which facilitates self-management.
- Adjustable Velcro devices are often easier to handle and can be a good alternative, even for the initial therapy phase.
- Intermittent pneumatic compression has been employed in the medical approach to vascular diseases for more than 80 years and may be used as a supporting regime, both in the initial treatment phase and in the maintenance phase in addition to an established management with sustained compression.
- Self-care is limited by patients' compliance, which will improve by counseling the patient and, especially, through positive experiences related to the beneficial impact of proper compression treatment.

Decongestive lymphatic therapy (DLT), which consists of compression, exercise, manual lymphatic therapy, and skin care, is the universally accepted basis of conservative treatment of lymphedema. Among its components, compression is the most important single measure which cannot be replaced by any other modality [6].

33.1 Rationale and Mechanisms of Action

Compression therapy aims to alleviate symptoms, prevent progression, and reduce the risk of skin infection.

The most impressive effect of compression therapy is the reduction of edema, which is achieved through four main mechanisms [7]:

1. Compression reduces microcirculatory filtration, due to a shift in Starling's equilibrium. Increasing the tissue pressure will reduce the transmural pressure gradient, resulting in a reduction of the lymphatic load.
2. Compression promotes lymphatic drainage, both in the initial lymphatics and in the lymph collectors, resulting in an augmentation of the lymphatic pump.
3. Compression shifts tissue fluid toward the non-compressed parts of the limb.
4. Compression softens fibrotic tissue changes.

Experimental data demonstrate that these effects are modulated by the underlying pathological conditions: the relevant variables include the identity and severity of the lymphatic pathology, the consistency of the tissue, and the pressure exerted by the external compression during rest and movement [6, 7].

33.2 Compression Modalities

Historically, wraps with leather and different textiles were already used centuries ago. After the discovery of rubber, elastic stockings were introduced. Different kinds of mechanical pumps were developed in the last century, and recently «hybrid systems» reflecting a combination of sustained and intermittent pressure pumps have been commercialized [8].

Compression in lymphedema starts with a *therapy phase*, in which edema will be removed and an attempt is made to reshape, as much as is feasible, the swollen extremity toward a normal appearance. The preferred materials to achieve this goal are inelastic bandages or Velcro devices [6].

During this treatment phase, proper sustained compression should be applied continuously, both day and night [9].

In order to keep the tissue decongested, the *maintenance phase* will follow. This phase is intended to keep the tissue soft and free from edema. This can be achieved by lifelong daily use of compression stockings or of adjustable Velcro devices in most instances.

Intermittent pumps are helpful in both treatment phases but should not replace sustained compression [10].

33.3 Compression Bandages

33.3.1 Materials

Modern compression bandages typically are composed of a mixture of different materials [11]. The pressure of a bandage during rest depends on the force exerted during application, the number of layers, and the elastic properties of the textiles in relation to the curvature and consistency of the individual body region. In a consensus document which has been generated for the classification of compression bandages, the PLACE acronym was introduced to commemorate these elements essential to the performance of a bandage: *P* for pressure, *LA* for layers, *C* for components of the bandage, and *E* for the elastic property [12].

The thickness and number of layers and the surface properties («nonadhesive, adhesive, or cohesive») should be considered. In addition, the structure of different bandage components (e.g., padding layers) will influence the elastic property of the final bandage.

With these concepts in mind, the terminology of «elastic» (maximal extension more than 100%) and «inelastic» (maximal extension less than 100%) is logically applied to single textiles, but not for composite bandages. A four-layer bandage consisting mainly of elastic individual components will acquire inelastic properties, especially covered by a cohesive layer. In vivo measurement of sub-bandage pressure at rest, with standing, and during exercise is the only way to assess the elastic properties of such composite bandages applied to the extremity. Stiffness of a compression device is defined by the

pressure increase under the device elicited by an increase of the leg circumference with standing up from the lying position («static stiffness index» [SSI]) or by walking («dynamic stiffness index» [DSI]). An increase in pressure of more than 10 mm Hg, measured at approximately 12 cm above the medial malleolus, characterizes a stiff product [12, 13].

As an example of a completely inelastic fabric, a zinc paste bandage applied with an initial pressure of 60 mm Hg produces high-pressure peaks during dorsiflexion («massage effect») and a pressure increase on standing of more than 120 mm Hg. In contrast, an elastic stocking applied with the same initial resting pressure shows much lower-pressure changes during ankle movement and with standing (Fig. 33.1).

Inelastic materials represent the preferred choice as a compression medium, especially in lymphedema patients, precisely because of the high-pressure amplitudes produced during movement. The intermittent pressure peaks exert a massaging effect on the edematous tissue and facilitate softening of fibro-sclerotic skin areas.

Specially formed padding materials, like chip bags composed of shredded foam chips layered between two pieces of fabric, have been recommended to promote local massaging of indurated areas. However, too much padding material may restrict movement and should be avoided. Modern two-component systems may replace the classical multilayered multicomponent lymph bandage.

These bandages behave as a nonelastic envelope. As muscle contraction evokes pressure in the limb, there is a variable response of the pressure within the bandaged part in relation to the contraction intensity [1]. The bandaging materials affect the quality of the treatment response: the use of nonelastic, low-stretch bandaging materials will result in a resistance to stretching that will maximize the pressure generated during muscle contraction. Daily sequential treatment in this manner results in a progressive decline in limb volume (Fig. 33.2). The most significant reduction in volume typically occurs during the first week of treatment.

Figure 33.3 shows a clinical example of a patient treated with compression bandages and walking exercises alone.

The handling of stiff materials, particularly in relationship to severely distorted lymphedema limbs, is not easy and requires training. The use of these materials resembles the work of a sculptor, adjusting the exerted pressure to the individual configuration of the limb, exerting higher pressures over bulging areas, and avoiding folds and dips, which can be filled with soft padding material. Local pressure may be reinforced by using tapes.

The law of Laplace should be kept in mind, avoiding heavy stretch over sharply curved areas (low local radius) and using strong compression over areas with rather flat curvatures [7]. In order to avoid edema distal to the bandage, the digits should additionally be wrapped, at least in the first phase of treatment.

Patients must be able to wear comfortable footwear with their compression bandages to facilitate mobility, and they should walk immediately after the bandage application.

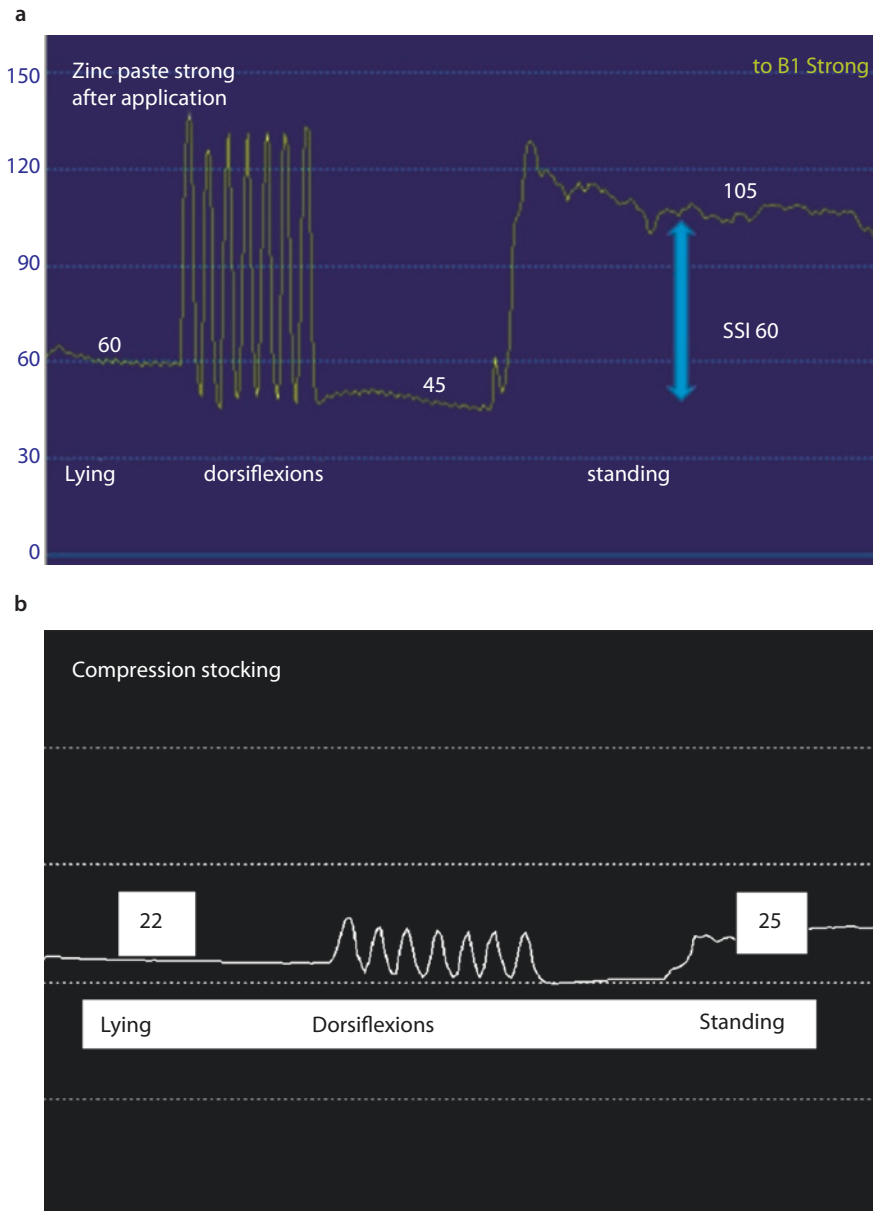

Fig. 33.1 Sub-bandage pressure at the distal lower leg. **a** Under a tightly applied zinc paste bandage, the resting pressure is 60 mm Hg. The pressure rises to more than 120 mm Hg during dorsiflexions. There is an immediate pressure drop to 45 mm Hg and an increase to 105 mm Hg with standing. The difference between standing and supine pressure, the static stiffness index (SSI), is 60 mm Hg. **b** Under a compression stocking, the resting pressure is 22 mm Hg and rises to peak pressures of 26 mm Hg by dorsiflexions and of 25 mm Hg during standing. The SSI is 3 mm Hg

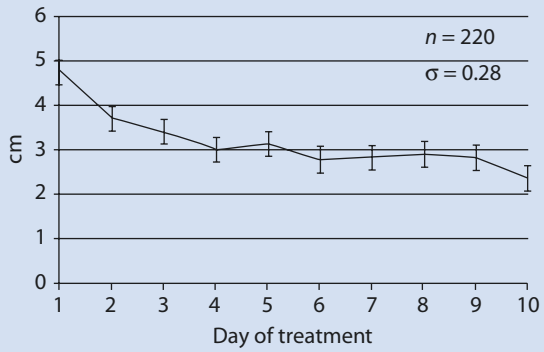

Fig. 33.2 The impact of daily multilayered bandaging upon edema volume in lymphedema (Reproduced with permission from Leduc et al. [1])

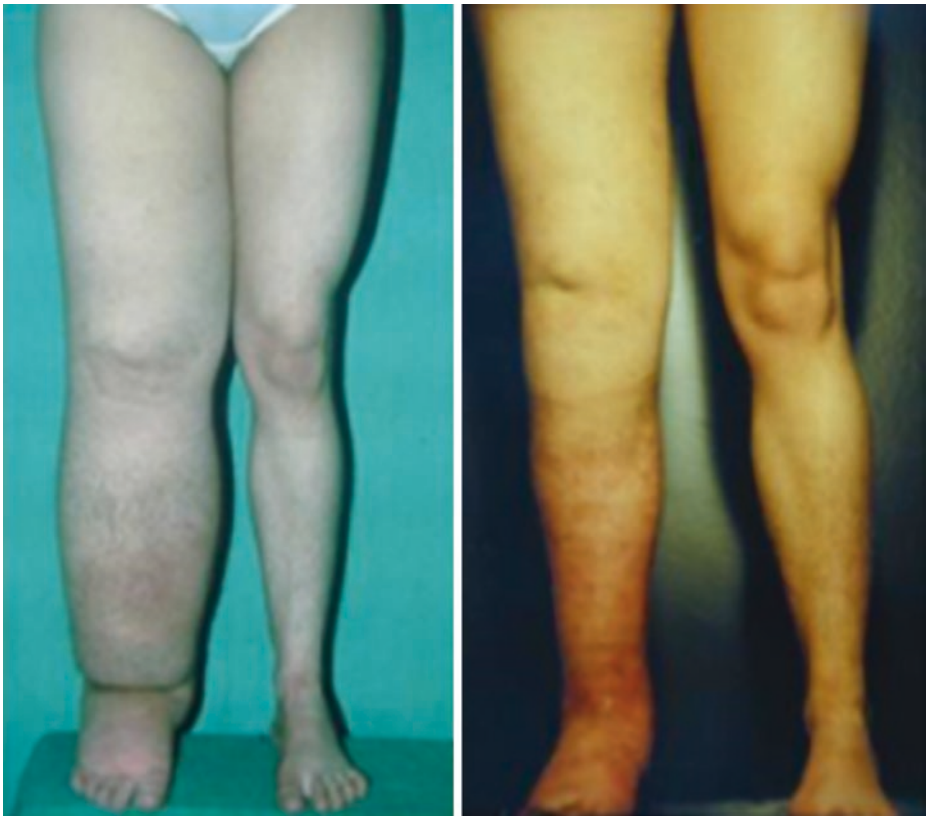

Fig. 33.3 A 17-year-old girl with congenital lymphedema of the right leg before and after 6 weeks of compression therapy, consisting of zinc paste bandages covered by a short stretch textile bandage, which was renewed twice weekly

33.3.2 Pressure

The optimal pressure to achieve maximal edema reduction is still under debate. A comparison of the effect of low (<30 mm Hg) versus higher pressures in patients with breast cancer-related arm edema suggests that lower pressure achieved more volume reduction after 2 h than what could be accomplished at higher pressures [2]. Analogous results were demonstrated in patients with chronic leg edema, where pressures exceeding 70 mm Hg were counterproductive [14]. The pressure of a bandage depends primarily upon the tension during wrapping and therefore on the skill and the experience of the therapist, who will require special training. Measurement devices, such as the Kikuhime™ or the PicoPress™, which permit continuous pressure recordings, can be used for training purposes.

The initial bandage pressure (30 mm Hg for upper and 60–70 mm Hg for the lower extremities) will drop immediately after bandage application, primarily due to instantaneous edema reduction [14]. This pressure drop determines the time at which the bandage should be reapplied. For modern two-component bandages, an optimal frequency for sequential bandage changes of twice weekly was recommended in one study [15]. If bandages are renewed every day, it is desirable to avoid very high pressures (exceeding 70 mm Hg) on the lower extremities.

Self-management can be performed by Velcro systems, with compression hosiery, and by pumps.

33.4 Adjustable Velcro Compression Devices

The main advantages of these devices are:

1. Velcro straps are the only inelastic material which can be handled by the patients or by untrained personnel.
2. The pressure loss can be readjusted by the patients according to subjective sensations.
3. For individual brands a measuring card is able to provide information on the local pressure on the extremity.

Based on these advantages such systems may be used not only for the maintenance phase but also for the initial phase of treatment. This was demonstrated in a randomized controlled trial, in which volume reduction of lymphedema legs by conventional lymph bandages and by a Velcro device was compared [3]. As shown in Fig. 33.4, the Velcro system achieved a significantly more pronounced leg volume reduction when compared to the conventional bandage, despite the fact that the initial mean subbandage pressures were in the same range for the two systems. The superiority of the Velcro device can mainly be explained by the absence of pressure loss of the compression device which was avoided in the Velcro group through readjustment by the patient.

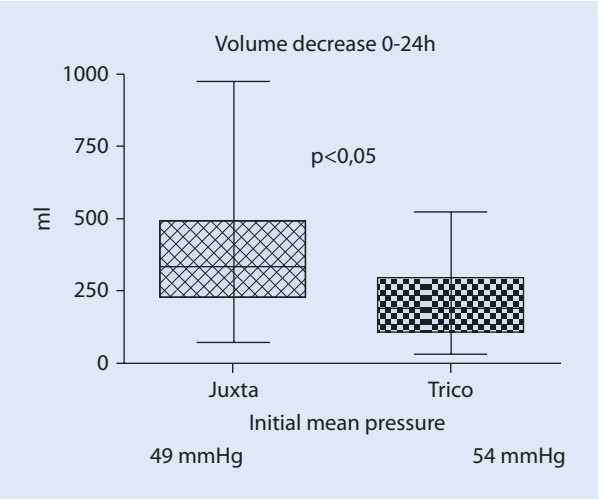

Fig. 33.4 Decrease of volume in 30 patients with stage II lymphedema of the legs after 24 h use of a Velcro device (Juxta-Fit) ($n = 15$) or a conventional lymph bandage ($n = 15$). Despite comparable starting pressures (49 vs 54 mm Hg), there was a greater volume reduction in the Velcro group ($p < 0.05$) (Data from [3])

33.5 Compression Hosiery

Compression stockings are mainly used in the maintenance phase to sustain the effect achieved during the treatment phase. Usually fitted garments of higher-compression classes (30–40 mm Hg) are used. Donning two or more compression stockings in an overlapping fashion can serve as an alternative. Custom-fitted garments should be prescribed, particularly for deformed lymphedema extremities. Flat knitted material, which exerts a stronger massaging effect due to its higher stiffness, is recommended.

Sleeves generally extend to the upper reaches of the arm and end below the axilla, although shoulder attachments and anchoring devices are also available. For the legs, although knee-length stockings can be purchased, either thigh-length garments or a panty hose-style garment is frequently recommended for use by patients with lymphedema.

Once a level of compression is selected, the garment is carefully fitted on the basis of meticulous limb measurements. Such garments lose their compressive capabilities after 3–6 months and must be replaced.

Perhaps the greatest impediment to the chronic utilization of maintenance compression is the difficulty that patients encounter when donning the garments. Higher degrees of compression become limiting especially in the settings of advanced age, obesity, or arthritis. Donning several stockings over each other may offer an alternative. Fortunately, many manufacturers provide assistive devices that partially combat this problem [16].

Having completed an active treatment phase with properly applied inelastic bandages, patients are often disappointed when it comes to self-management with compression stockings, mainly because of the difficulty with donning and doffing. Velcro devices are a good alternative in this situation.

Patient compliance is essential in this phase of self-management, which can be improved by education, proper fit of the garment, and subjective comfort. The style of the compression stocking, which may be available in a variety of colors, may have positive psychological implications.

Usually compression hosiery is worn during daytime and removed during bed rest at night.

33.6 Intermittent Pneumatic Compression

Intermittent pneumatic compression (IPC) devices are pneumatic cuffs connected to pumps that mimic the naturally occurring pump effect of muscle contractions.

Such pumps are useful adjuncts to conventional compression therapy but should not be used as stand-alone treatment. Particularly in the active treatment phase, patients need sustained day and night compression. IPC devices can be used in addition. They can be indicated especially in patients with restricted mobility [10].

A variety of pumps are available. Nonsegmental and segmental home models have distinguishing attributes. Sequential compression devices (SCD) utilize sleeves with separated inflation chambers, squeezing the limb in a «milking action.» The most distal areas will initially inflate, and the more proximal chambers will follow in an analogous manner.

Models for half or full extremity, with or without calibrated gradient pressure, must be distinguished. They are provided with varying numbers of chambers, garment shapes, times of inflation and deflation, regulation of inflation pressure, and calibrated gradient pressure.

Recently devices for intermittent compression of the trunk and of the head-neck region have been introduced, and devices have been developed that provide treatment to the trunk and chest concurrently to the affected limb(s) [17], thereby mimicking the principles of MLD.

Such advanced segmental devices, with calibrated gradient pressure, provide modulation of individually determined pressures to each chamber. These can be adjusted by pressure, duration, and frequency of the inflation cycles.

Based on experiments measuring compression pressure on the skin and subcutaneous tissue, in addition to fluid shifts assessed by plethysmography, Zaleska et al. recommend pressures between 60 and 120 mm Hg and long inflation periods of 1 min. To prevent fluid backflow and accumulation of venous blood, the distal chamber should not be deflated during the cycle [18]. The data suggest that the pressure within the tissue under intermittent compression was lower than that in the chambers.

Comparative studies concerning the efficacy of several devices are few: sequential high-pressure intermittent pneumatic compression (SIPC) is superior to single cell low-pressure external pneumatic compression in the acute reduction of lymphedema [19], and advanced systems seem to be superior to conventional devices [20].

Near-infrared fluorescence lymphatic imaging (NIRFLI) is a promising new technique with its ability to demonstrate lymph flow in vivo. In a study performed in patients with venous leg ulcers, it was demonstrated that sequential pneumatic compression caused proximal displacement of the indocyanine green contrast material, away from the active wound, by newly recruited, functional lymphatic vessels, emptying of distal lymphatics, or proximal movement of extravascular fluid [21].

After each IPC session, sustained compression, using bandages or stockings, should be continued. Without this step, edema will return immediately, because with IPC, more water than protein will have been removed from the tissue and the oncotic tissue pressure will therefore increase. Long-term maintenance of reduced limb girth has been demonstrated in 90% of lymphedema patients treated with sequential IPC and compression stockings [22].

In a recently published retrospective analysis of a large group of patients with both cancer-related and non-cancer-related lymphedema, significant reductions in episodes of cellulitis and outpatient care and costs within a 1-year time frame were associated with the use of advanced segmental IPC [4].

33.7 Scientific Evidence and Future Research

One major flaw in assessing the efficacy of compression therapy in lymphedema is the fact that, in nearly all randomized controlled trials, this treatment modality is never considered as an isolated variable but, rather, always considered in aggregate with the other components of DLT. This fact provides a potential explanation for the poor level of evidence for any conservative treatment modality, either for treating lymphedema [23, 24] or for preventing secondary lymphedema after surgery [25].

Present reviews and meta-analyses suggest that adequately powered randomized controlled trials of the various interventions are recommended. Efforts should be undertaken to compare different compression strategies without additional treatment modalities and to establish standardized outcomes, not only emphasizing edema reduction, but also the comfort and compliance attributes of the compression product utilized, and on quality of life [5, 26].

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Intermittent Pneumatic Compression Therapy

Stanley G. Rockson

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Summary of Basic Concepts

The use of intermittent pneumatic compression (IPC) devices in the therapeutic approach to lymphedema is perhaps the most controversial element of what is traditionally termed complex decongestive physiotherapy. In the United States, historically, pneumatic compression has been the mainstay of lymphatic therapy for decades.

- IPC, preferably accomplished with multi-chamber pumps, effectively removes excess fluid from the extremity.
- IPC can be incorporated into a multidisciplinary, therapeutic program; the guidelines for patient and device selection continue to evolve.
- Adjunctive IPC provides symptom relief and reduces episodes of cellulitis and ulceration in lower extremity lymphedema.
- Use of certain IPCs may be associated with significant reductions in cellulitis events, use of medical resources, and cost of care in lymphedema.
- The observed benefits of IPC correlate well with experimental physiological observations, in which the promotion of lymph formation by tissue compression is related to the number of compressions applied and the time interval between each compression.
- Compression of limb lymphedema tissues by IPC may lead to the formation of tissue channels that provide functional pathways for the clearance of edema fluid.

The use of intermittent pneumatic compression (IPC) devices in the therapeutic approach to lymphedema is perhaps the most controversial element of what is traditionally termed complex decongestive physiotherapy. In the United States, historically, pneumatic compression has been the mainstay of lymphatic therapy for decades [6]. IPC, preferably achieved with multi-chamber devices, is able to effectively remove excess fluid from the extremity [6–14].

The earliest enthusiasm for the benefits of IPC was tempered by a theoretical concern that the elevated pressures generated by these devices might damage skin lymphatics [15, 16]. The generation of genital edema can be a theoretical concern for the use of IPC in patient with lower extremity edema [17]. Concern for the development of a ring of fibrous tissue above the proximal margin of the IPC garment has also been raised [18].

Although the use of IPC has been historically controversial, with an alleged threat of complications to be incurred, the American Cancer Society Working Group on the Diagnosis and Management of Lymphedema has nevertheless designated the use of intermittent compression pumps as a possible component of decongestive lymphatic physiotherapy when used as an adjunct to the other elements of decongestive therapy [19]. In this regard, prospective, randomized investigation of the safety and relative efficacy of intermittent pneumatic compression therapy for the treatment of patients with breast carcinoma-associated upper extremity lymphedema has been undertaken, in concert with multilayer bandaging and manual lymphatic massage [1]. Twenty-three previously untreated patients were randomized to receive either decongestive lymphatic therapy (DLT) alone or decongestive therapy with daily adjunctive IPC. The addition of IPC to standard DLT yielded additional mean volume reduction (Fig. 34.1). In 27

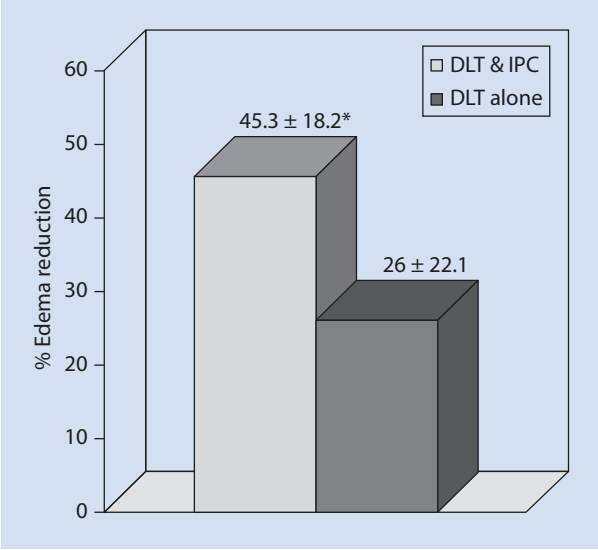

Fig. 34.1 The effect of adjunctive, intermittent pneumatic compression (IPC) on initial decongestive lymphatic therapy (DLT) in patients with breast carcinoma-associated lymphedema. The data depict the percentage reduction in volume of the limb attained after 10 days of daily therapy with either [6] DLT plus IPC or [7] DLT alone. The data are provided as the mean ± standard deviation for each group. The *asterisk* denotes a statistically significant difference ($p < 0.05$) (Reprinted with permission from Szuba et al. [1])

additional patients assessed during the maintenance phase of therapy, the addition of IPC to DLT enhanced the therapeutic response. In both the acute and maintenance phases of the study, IPC was well-tolerated, without detectable adverse effects on skin elasticity or joint range of motion.

The use of IPC in lymphedema has been hampered by individual reports of complications and lack of efficacy [2], yet focused attempts to document the adverse effects, such as the study cited above, fail to support the adverse outcomes from IPC, particularly when the treatment modality is utilized in an *adjunctive* manner. The observed benefits of IPC correlate well with experimental physiological observations, in which the promotion of lymph formation by tissue compression is related to the number of compressions applied and the time interval between each compression. Thus, it would seem that the benefit accrues through centripetal emptying of the terminal lymphatics, such that the vessels refill after each compression is released [20]. A recent study of 100 patients, treated with IPC for a minimum of 3 months, confirms that the adjunctive treatment provides symptom relief and reduces episodes of cellulitis and ulceration in lower extremity lymphedema. The therapy was well-tolerated by these study patients; the study authors thus recommend IPC as an adjunct to standard lymphedema therapy [21]. Limb circumference is decreased (or does not increase further), and the elasticity of the tissues is increased and maintained [22]. Furthermore, there is some early clinical evidence that compression of limb lymphedema tissues by IPC leads to the formation of tissue channels that provide functional pathways for the clearance of edema fluid [23].

Recent published evidence also suggests that IPC has a beneficial impact on both the cost of care and the utilization of health-care resources by lymphedema patients. Retrospective analysis of de-identified health claims over a representative 6-year period disclosed that, while lymphedema is associated with high health-care costs, the use of IPC resulted in significant decreases in both adverse clinical outcomes and costs [3].

It is likely that continued refinement in the bioengineering and programmability of the pneumatic compression devices will enhance their efficacy in translating the physiological effects of intermittent compression to the therapeutics of lymphedema. As an example, in recent years, an adaptation of IPC has been introduced that purports to mechanically simulate the effects of manual lymphatic drainage. This device, the Flexitouch® System, delivers minimal, phasic external compression to both the affected limb(s) and the trunk in a programmable fashion. When prospectively examined for its role in patient self-management, the device has demonstrated objectively demonstrable outcome benefits (Fig. 34.2) [4]. Furthermore, 155 lymphedema patients (93 with cancer-related lymphedema), before and after treatment assessment with the 12-Item Short-Form Health Survey, demonstrated significant improvement in all areas of perceived physical and emotional health [24].

It has been suggested that IPC can be incorporated into a multidisciplinary, therapeutic program [1, 2, 6, 24]; the guidelines for patient and device selection continue to evolve. Several factors are involved in these therapeutic decisions, including the choice of a simple versus an advanced device (the latter offering the option, in various combinations, of multi-chamber design, programmability, and advanced technologies to permit individual, lymphedema-specific therapeutics) [2]. In addition,

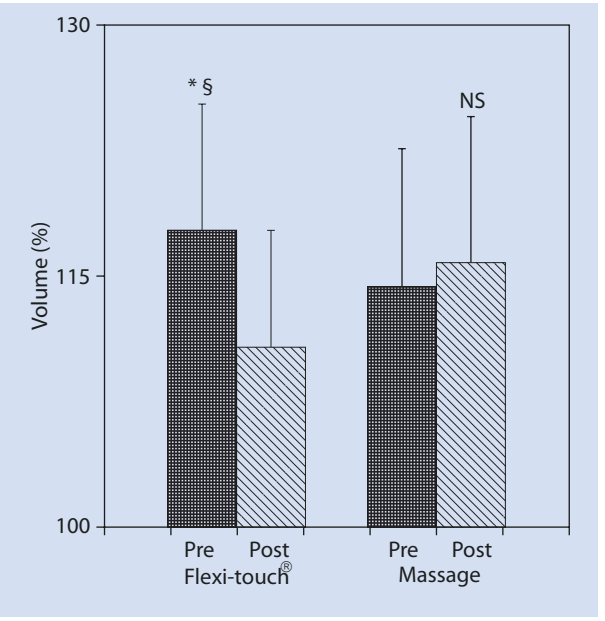

Fig. 34.2 A prospective, randomized, crossover study of maintenance therapy (Flexitouch® versus manual lymphatic drainage [MLD]) was performed in ten patients with unilateral breast cancer-associated lymphedema of the arm. Excess volume of the affected arm is expressed as a percentage of the volume of the contralateral, normal arm. The effect of treatment on the percentage excess volume compared with the contralateral arm was significant for Flexitouch™, but not for MLD (mean ± SD; *$p = 0.0005$ compared with the pretreatment value; §$p = 0.003$ compared with response to MLD) (Reprinted with permission (▶ https://creativecommons.org/licenses/by/4.0/legalcode) from Wilburn et al. [4])

Table 34.1 Intermittent pneumatic compression device selection

Patient considerations
Severity of lymphedema
Responsiveness to conservative therapies
Lymphedematous involvement of the trunk, breast, or genitalia
Pain
Open wounds
Complications that contraindicate the use of simple, non-programmable devices
Simple versus advanced design
Multi-chamber design
Programmability
Advanced technologies to permit individuated, lymphedema-specific therapeutics

patient selection factors must determine not only the desirability of adding IPC to the treatment regimen but also the choice of the specific device. These patient factors include the severity of lymphedema; response to conservative therapies; lymphedematous involvement of the trunk, breast, or genitalia; presence of pain or open wounds; heterogeneous, regional variability in the severity of the edema; and/or presence of complications that contraindicate the use of simple, non-programmable devices (Table 34.1). The use of these advanced devices may imply benefits for a broader component of the lymphedema population: in a recent study, use of an advanced, programmable IPC device was associated with reductions in adjusted rates of cellulitis episodes (from 21.1% to 4.5% in a cancer cohort and 28.8–7.3% in a non-cancer cohort; $P < .001$ for both), along with similar reductions in use of lymphedema-related manual therapy and in outpatient visits. Among the cancer cohort, total lymphedema-related costs per patient, excluding medical equipment costs, were reduced by 37%; the corresponding decline in costs for the non-cancer cohort was 36% [5].

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Other Contemporary Treatment Modalities

Neil Piller

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Summary of Basic Concepts

The individuality of a person's lymphatic system is being recognized through improved structural/functional imaging and acknowledged as important in the targeting of treatment.

Differential diagnosis is critical since there are many other conditions which appear to be like lymphedema and which are not. Detecting and dealing with these prior to dealing with the lymphedema can lead to improved outcomes.

Based on objective findings, the planned targeting and sequencing of treatment is essential to gain the best outcomes.

There are many treatments available which are achieving purportedly good results, but larger-scale well-controlled trials are needed.

Treating and managing the person at risk of or with lymphedema holistically is important; only some traditional and contemporary treatments consider this need.

With increasing obesity and the chronic edema it brings, an already overloaded lymphatic system is just that much closer already to failure; we will see situations in the future where even apparently minor interventions involving the lymph nodes or vessels may lead to lymphedema; this means any conservative treatment be it traditional or contemporary must be rapidly introduced, but we need to ensure they are appropriately sequenced and targeted.

35.1 Conservative Therapies for Secondary Lymph Edema

We have a plethora of treatments and strategies for dealing with lymphedema. Even for our traditional ones, there are strong differences of opinion regarding the benefit of treatment forms such as manual lymphatic drainage and compression [44]. So it is no great wonder patients and practitioners shift toward alternate treatment modalities when they are searching the net or talking to friends or others with issues similar to theirs [4]. We must advance our knowledge in the breadth of treatments with an open mind, but must provide evidence for their efficacy so that patients and practitioners know what to expect. For many new treatments, the trials are often small with design flaws, but some are well designed and are objective with rigorous evaluation, so we can have confidence in at least some of the outcomes.

35.2 Contemporary Treatments

Patients may seek contemporary treatments from others or the Internet. It is important for therapists to be aware of these contemporary options, just as it is important to be aware of any comparative benefits of this range of therapies.

35.3 The Groupings of Contemporary Treatments

Some are patient-based with no therapist input and some are administered by a therapist or clinician.

They can be broadly categorized into those that vibrate the tissues (encompassing a range of frequencies and amplitudes), those involving a pharmacological agent that induces or promotes a biological event, those that electrically stimulate the lymphatics, those that vary tissue pressures including exercise and activity, those that encourage diet change, and those that are a result of the placebo effect.

35.4 Methods

This overview is limited to patient populations with clinically diagnosed limb lymphedema secondary to cancer treatment and to articles written in English. Online health databases, lymphatic societies, and lymphology journals were searched, with the primary study outcomes to include: a change in limb volume (generally measured by perometry and water displacement or calculated via circumference measurement), subjective symptoms, and/or quality of life/activities of daily living (cross ref. with my other chapter). The quality of each article was assessed according to Mulrow and Oxman [6] Reviews that match the above criteria are also included.

35.5 Pharmacogenomics and Medications Targeting the Lymphatic System

There have been a range of treatments that have targeted the lymphatic system or its components pharmacologically, the best known of which are the flavonoid/benzopyrone groups. Studies included those of Pecking et al. [7, 8] who first investigated Daflon, and Cluzan et al., who studied Cyclo Fort [9], both of whom had significant objective improvements for the patient group tested. Lodema provided good outcomes for patients in terms of reducing their lymphedema according to one report, [10] but another showed it to have little objective effect [11]. Anecdotal information suggested excellent outcomes. The use of coumarin (5-6-benzo-α-pyrone) for the treatment of lymphedema had hepatotoxic effects for some, but we now know that this was a consequence of a genetic metabolic problem relating to the breakdown of coumarin [1]. Developing genetic and genomic knowledge will mean that in the future we will be able to determine who will respond well (and who may not) and overcome the above adverse outcomes. It may be that this group of medications may be able to return as an option for lymphedema treatment again.

35.6 Low-Level Scanning and Handheld Laser

The first trials of the low-level laser in lymphedema were reported in 1995 [12], although the general benefits were first reported in the late 1960s [13]. Of key importance is the dose and delivery. Double-blinded, crossover placebo-controlled trials have been conducted using laser with good subjective and objective outcomes [14]. One of the issues of general lymphedema treatment and perhaps an explanation for less than expected outcomes at times may have been the faulty decision-making process used for its sequencing. Trials [12, 14] of scanning and the handheld laser have

shown that its application is particularly beneficial when there is fibrotic induration of the tissues (associated with surgical or radiation-induced scarring), in reducing swelling, softening of the tissues, improving scars, and improving how the limb feels [2, 15]. The low-level laser has a role to play in the early phases of treatment of lymphedema as well as in its later management (when fibrotic induration has spread through the lymphatic territories), both from the perspectives of the health professional and the patient. Optimal treatment time is generally short with gaps between treatments [16].

35.7 Lymphatic Drainage Massage Delivered by Partners/Carers and Mechanically

Massage aimed at improving lymphatic drainage administered by trained lymph therapists possesses a body of evidence supporting its effectiveness [17], but it is far from complete. However, it is very important that therapists, clinicians, and patients are aware of what can be expected when using tools that also can improve lymphatic drainage by mimicking therapist massage and from partner/caregiver massage.

Massage, in general terms, is known to encourage the entry of fluids into the initial lymphatics, to facilitate transport along lymph collectors and to open anastomoses between adjacent collectors or lymph territories. It does this by means of changes in tissue pressures, and perhaps we need to start to give more thought to pressures and their importance. We tend to always think of pressure as necessarily positive and with a gradient, but what we ignore is negative pressure! We have negative pressures when we breathe, the *endermologie* treatment described below creates a negative pressure, a newly promoted PhysioTouch device relies on negative pressure, and we all know of the importance of negative pressure in wound healing – so maybe we need to pay more attention to it [40]! However, now back to the positive pressure of massage, Piller et al. [18] showed that when partners/caregivers were trained by lymphedema therapists, the objective and subjective results were similar to those of professional treatment programs. Perhaps the partner/caregiver knows the patient's body better and when the limb is responding and when it is not. Such programs need further research because they can empower the patient, reduce costs and travel time, and reestablish a touching relationship.

While there is a plethora of massage pads/units, only a few have been subjected to a formal trial in lymphedemas, and trial sizes are often small. A trial [43] of a massage pad on leg lymphedema showed that, in order to gain a good outcome, the pad had to be used so that it facilitated clearance of the lymph territories, just as in professional lymphatic drainage massage programs. Patients gained and maintained good reductions in their limb volume, with 1 h of pad use per day. Improvement also occurred in tissue softness and how the limb felt. Patients felt more in control of the medical condition and felt better able to undertake activities of daily living. In a trial of a handheld massage unit [19] in a moderate secondary arm lymphedema used for 25 min each evening for 1 month, there were significant volume reductions and improvements in the perception of limb size and range of movement. Again, patient control and use in their own time and at their own pace were important.

Another strategy that varies tissue pressures by tissue movement revolves around «wobbling» the limbs from side to side. It is, in fact, a form of vibration, albeit slow. In this trial patients used the equipment while supine with the legs elevated on the unit, for periods of from 3 to 12 min twice per day for 3 weeks. The results [20] were similar to the massage pad trial in that the limbs reduced in size and volume, they softened, and the limbs felt better.

Patients felt more in control and were better able to undertake their activities of daily living, a common theme with home-based management.

35.8 Mild Exercise (Tai Chi)

Tai Chi and Qi Gong can easily be performed by the patient. These actions vary tissue pressures more effectively and, when combined with variations in intrathoracic and intra-abdominal pressures, help lymphatic system loading and flow. Patients with arm lymphedema who used Tai Chi 10 min daily achieved reductions within the same range as more demanding treatments and were able to maintain them [21]. A water-based version of this type is used in the Encore program operated in Australia and around the world, but the outcomes are yet to be published.

35.9 Moderate Exercise (in and Out of Water)

A common question is: How much exercise can I do? Most studies [3, 22] indicate that mild exercise is good for the lymphatic loading and transport because of variation in tissue pressures. However, as we go up the scale of exercise intensity, we must know the capacity of the damaged lymphatic system to handle an augmented lymph load. Getting the balance right is very important. It is also becoming clear that some comorbidities of lymphedema such as the swelling may be better undertaken in water, while others such as shoulder function may benefit from land-based programs [5].

One good way to undertake exercise, but at the same time to have tissue support through external pressure, is through the range of water-based programs. Some studies provide good evidence for this [23–25]. The temperature of the water is important, but it is physiologically sensible to have temperatures within the range of normal skin temperature: 28 °C has been suggested [23].

There are specific exercise classes available to patients with arm and leg lymphedemas. Casley-Smith [26] suggested gentle movement, deep breathing, and slow rhythmic exercise of the proximal and distal muscles melded with self-massage routines. Bracha and Jacob [27] showed this program to reduce limb volume and improve quality of life in some participants.

More strenuous exercise programs using weights have also been reported [28, 29]. In one trial, patients with arm lymphedema were asked to undertake increasing levels of weight lifting while performing a series of predetermined exercises to evaluate the maximal exercise points without worsening the lymphedema. In most cases, while there was a slight increase in limb volume immediately after the exercise, the effect was short-lived as long as patients resumed their activities of normal daily living [30]. This study indi-

cated that patients can undertake significant and even strenuous amounts of exercise/activity without worsening their lymphedema, but obviously, it is crucial that the patient know the limit of exercise and stay below it. The impact of exercise and significant activity has been reviewed and shows an overall positive impact (varying in magnitude among studies) on limb size, range of movement, muscle strength, subjective limb symptoms, and quality of life [22]. In all studies, a cooling-down period is essential. The question of when to begin an exercise program after surgery seems to have been answered by Todd et al. [30] who indicated that a delay of 1 week for any full shoulder mobilization reduced lymphedema incidence.

35.10 Electrostimulation

Lymphatics pulsate between six and ten times per minute and are myogenically and neurogenically regulated. Anecdotal evidence indicates that mild electrostimulation has an effect on lymphedema and can reduce size and volume. A study of secondary leg lymphedema [31] indicated that electrical stimulation has such benefits over current best practice self-management. Pain, heaviness, tightness, and perceived leg size also improved. Truncal fluid was also reduced, indicating a possible additional clearance of major lymphatic trunks. Other units (such as the *circulation booster*) which are similar in function and principle to a TENS unit have also been shown anecdotally to reduce lymphedemas, but quality trials are needed to support these claims.

35.11 Tissue Manipulation

A technique originating in France, called *endermologie*, has generated evidence for the treatment of cellulite and obesity. Given the similarities among mid-stage lymphedema, cellulite, lipedema, and obesity (the adipose connection), it is likely to be beneficial in the treatment of lymphedema. A single, blinded, randomized study of arm lymphedema comparing *endermologie* with traditional manual lymphatic drainage (MLD) over a 4-week period demonstrated the greatest reduction in limb volume and circumference in the first week, but showed benefit to continue over the 4 weeks of the trial [32]. Results were similar to MLD, although achieved in a shorter time. There were improvements in tissue hardness and subjective indicators. Better outcomes were achieved when combined with bandaging and with more time spent on clearance of the trunk and axillary area, [32] as is well known in CPT programs. As indicated above this unit works by creating a negative pressure within the tissues. There are currently other units (PhysioTouch) in the use and in the process of clinical testing which also work by the creation of negative pressure and gradients, so fluids move from higher-pressure regions to the lower-pressure ones.

35.12 Kinesio Taping

Kinesio Taping is believed to improve lymph drainage by lifting the skin away from the underlying fascial planes of the musculature, perhaps reducing interstitial pressures there, and facilitating blood and, particularly, lymph flow along these lower-pressure

areas. It can do this because of the puckering effect of the tape. It is widely used in sports injuries, but has recently been applied in treating lymphedemas [33, 34] and seems likely to be useful in hot and/or humid climates. In an audit of the use of Kinesio Tape for breast and other edemas, Finnerty et al. [35] showed that Kinesio Tape was being used in lymphedema management, particularly in the more challenging areas (breast, chest) where traditional bandaging and garments are difficult to use. Good-quality trials are lacking. One trial of seroma following axillary clearance for breast cancer treatment showed significant benefits of Kinesio Taping in reducing the severity and duration of the seroma, as well as subjective indicators [36].

35.13 Diet and Abdominal Issues

Long-chain triglycerides are absorbed (as chylomicrons) via the mesenteric lymphatics, adding to the lymphatic load. If their structure or function is compromised, this absorbed load of fats may find its way into other organs/structures by retrograde flow [37]. Replacing long-chain triglycerides with mid- and short-chain ones is believed to reduce the incidence of this retrograde flow (chylous reflux). There are a number of suggested diets revolving around medium-chain triglycerides (MCT). The evidence is poor in the scientific literature, but is strongly represented in the «gray» literature. Other issues of diet [4], gastrointestinal bloating, and constipation also appear in the «gray» literature and make sense empirically if the potential exists to create significant external pressure on the abdominal lymphatic collectors.

Evidence in the scientific literature is poor but strong in the gray and anecdotal literature (71).

There is an increasing shift toward other aspects of diet, namely, a consideration of the basics of diet, with ones rich in omega-3 being considered as anti-inflammatory while those rich in omega-6 considered as pro-inflammatory. A shift to a less «inflammatory» diet could have benefits, especially when we know that when lymph flow is compromised that the concentration of inflammatory mediators (cytokines and lymphokines) increase in the affected area with the outcome an exacerbation of the inflammatory process, for the cells in the affected areas. Further research in this area is underway led by Dr. Karen Herbst of the University of Arizona.

35.14 Placebo

The placebo effect is linked with the release of brain endorphins [38] associated with the anticipation of receiving active treatment. Placebos have a benefit in studies with continuous subjective outcomes measurement [39], a phenomenon that is relevant to studies on lymphedema therapeutics.

Some of the studies cited in this chapter have used placebo groups in which patients have responded to placebo treatment, generally reporting symptomatic improvement (not usually accompanied by significant changes in limb volume). The trial investigating the effects of 5–6-benzo-α-pyrone by Loprinzi et al. [11]. showed that, despite an arm volume increase in both groups, there were similar positive responses to perceived arm swelling, tightness, heaviness, and arm mobility in the active treatment and the placebo

groups and, even after 12 months, there was a slight preference for the placebo over the active intervention! Similar results arose in a study by Pecking et al. [7, 8] who investigated Daflon. Both the placebo and the active group reported statistically significant reductions in arm discomfort and an improvement in the perception of constant heaviness. There were no objective changes in the placebo group. Cluzan et al. [9] investigated Cyclo Fort versus placebo and found that while quantifiable edema volume increased in the placebo group patients, they nevertheless reported improvements in both arm heaviness and mobility. Casley-Smith et al. [10] investigated the effect of coumarin and found a similar improvement in patient perceptions.

Box et al. [24] studied the effects of hydrotherapy compared with a control group who did not receive any active treatment. Although the control group demonstrated an increased arm volume after 7 weeks, they reported improvements in aching, limb appearance, heaviness, tightness, and work/leisure activities. A handheld laser study by Carati et al. [14] involved a placebo group receiving sham laser with 1 and 3 months' follow-up. At 3 months, the placebo group experienced an increase in arm volume, but reported significant improvements in the overall mean perceptual score and activities of daily living.

The placebo effect may be used to the advantage of both the therapist and the patient. The patient's expectations, the therapist's belief in the treatment being offered, and the patient–therapist relationship [39, 41, 42] can accentuate the placebo effect. Being aware of these influences may help the therapist to initiate improvements in subjective symptoms, even if this is not necessarily followed by changes in more objective parameters.

Every treatment and management program needs to be balanced in terms of cost and benefit and linked to any contraindications. Treatment complacency must be avoided and perhaps changing therapy is one way around this. The overarching effect of even placebo on the patient's quality of life and frame of mind may encourage them to undertake other treatments that will have an impact on limb size, composition, and volume.

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Medical Treatment Options

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Summary of Basic Concepts

Despite advances in the diagnosis and management of lymphedema, a paucity of pharmacological approaches exists for the treatment of lymphedema patients.

- Diuretics play little, if any, role in the management of isolated lymphatic vascular insufficiency because the pathogenesis of the fluid accumulation in lymphedema relies upon the elevated interstitial oncotic pressures conferred by macromolecules, rather than upon inappropriate retention of water and electrolytes.
- It is impossible to judge the effectiveness of benzopyrones on the basis of available published clinical trials. Benzopyrones are not available in all parts of the world, and caution is warranted in the use of systemic coumarin in the face of the reported risk of hepatotoxicity.
- One common context for medical therapy in lymphedema is the recognized frequent occurrence of soft tissue infection in these patients.
- In recent years, mechanistic investigation has underscored the role of abnormal lymphatic function in obesity, salt-sensitive hypertension, and altered cholesterol metabolism. With great promise, there has been recent focused and growing interest in the role of inflammation in the pathogenesis and maintenance of lymphedema.

In strictest terms, medical treatment implies that the treating physician will venture beyond available physiotherapeutic and surgical options to address lymphedema with pharmacotherapy. However, despite advances in the diagnosis and management of lymphedema, a paucity of pharmacological approaches exists for the treatment of lymphedema patients.

In 1998, the American Cancer Society convened a working group to consider the problem of lymphedema and breast cancer. When delivering its recommendations for the diagnosis and management of lymphedema [1], the working group touched upon three categories of pharmacotherapy: *benzopyrones*, such as coumarin [7], are not available for use in all parts of the world (coumarin has not been approved by the Food and Drug Administration for use in the United States); *bioflavonoids* [8], for which efficacy outcome data are still largely lacking; and systemic *antibiotic* prophylaxis. *Diuretics* play little, if any, role in the management of isolated lymphatic vascular insufficiency [2] because the pathogenesis of the fluid accumulation in lymphedema relies upon the elevated interstitial oncotic pressures conferred by macromolecules, rather than upon inappropriate retention of water and electrolytes. However, in cases in which hydrostatic pressure is also elevated, such as, for example, in the post-phlebitic syndrome with secondary lymphatic hypertension, low-dose, thiazide-induced diuresis may play a beneficial complementary role to the primary indicated intervention, which is compression.

36.1 Benzopyrones and Bioflavonoids

Benzopyrones are derived from naturally occurring substances. Preparations of benzopyrones can, however, be either wholly or partially synthetic [9]. The α-benzopyrones include coumarin derivatives, and the γ-benzopyrones are flavonoids, including flavones and flavonols, such as diosmin, and flavanes, such as hesperidin.

The proposed mechanism of action of this drug class is the reduction of vascular permeability [9] with the capacity to thereby reduce the lymphatic load. It has also been suggested that benzopyrones might increase tissue macrophage activity [10], thereby encouraging proteolysis and degradation of interstitial proteins, with an implied favorable effect on fluid clearance and tissue composition [11].

In 2004, Badger et al. [11] undertook a focused review of the available prospective studies of benzopyrone efficacy in lymphedema. Of the 63 available publications, 47 were considered to be ineligible for further analysis. The authors concluded that it is impossible to judge the effectiveness of benzopyrones on the basis of these trials. On an individual basis, patients may report an improvement in symptoms such as heaviness, tightness, or aching when taking these preparations, but any improvement should be weighed against the lack of objective validation. Furthermore, caution is warranted in the use of systemic coumarin, in the face of the reported risk of hepatotoxicity.

36.2 Antibiotics

One common context for medical therapy in lymphedema is the recognized frequent occurrence of soft tissue infection in these patients [2]. Four published randomized controlled trials, reflecting the outcomes in 364 randomized patients, are available for analysis of the pre-emptive use of antibiotics in lymphedema. Two of the trials investigated the use of intensive physical therapy with randomization to the addition of selenium (as an anti-inflammatory agent) versus placebo. These trials were not considered to be properly conducted randomized controlled trials [3], and, therefore, the results are inconclusive. More recently, however, it has been emphasized that sodium selenite may show promise as a cost-effective, nontoxic anti-inflammatory agent. Treatment with sodium selenite lowers reactive oxygen species (ROS) production, causes a spontaneous reduction in lymphedema volume, increases the efficacy of physical therapy for lymphedema, and reduces the incidence of soft tissue infections in patients with chronic lymphedema [12].

Two additional studies have examined the effects of antifilarials combined with penicillin as prophylaxis. In these two studies, penicillin reduced the mean number of inflammatory episodes, when combined with suitable foot care. While this is an encouraging result, it is clear that the paucity of properly conducted trials significantly hampers the ability to draw any conclusions [3].

36.3 Prospects for Emerging Therapies

In recent years, mechanistic investigation has underscored the role of abnormal lymphatic function, among others, in obesity [13], salt-sensitive hypertension [14, 15], and altered cholesterol metabolism [16, 17]. Further exploration of the interplay between lymphatic function and altered physiology may provide future avenues for pharmacotherapeutic applications.

Of late, there has been focused and growing interest in the role of inflammation in the pathogenesis and maintenance of lymphedema [4]. In lymphedema, there is significant upregulation of genes related to acute inflammation, immune response, complement

activation, wound healing, fibrosis, and oxidative stress response [4]. Targeted inhibition of these inflammatory pathways can result in significant structural and functional amelioration of experimental, acquired lymphedema (Fig. 36.1) [5, 6].

Inflammation is, of course, a complex pathological response, and it is unquestionable that the pharmacological mechanism of the chosen anti-inflammatory agent(s) will be critical to the lymphedema treatment response. In experimental models of acquired lymphedema, inhibition of transforming growth factor-beta (TGFβ) expression diminishes inflammation, migration of T-helper type 2 (Th2) cells, and expres-

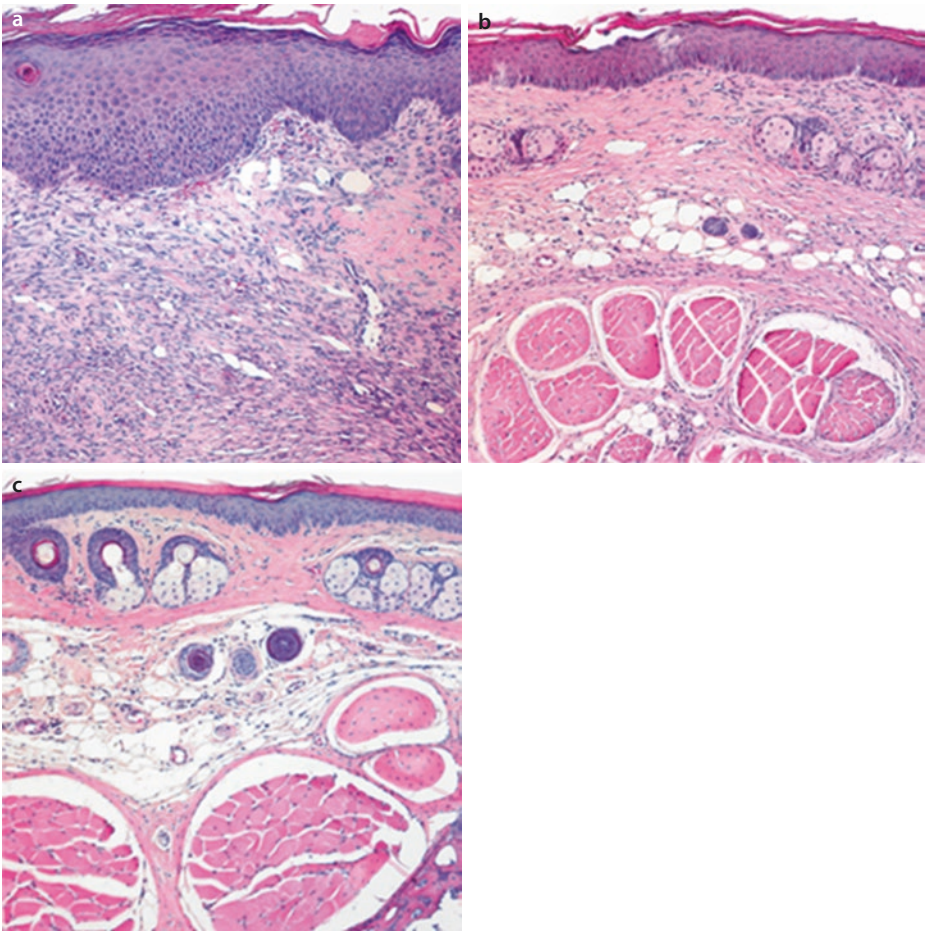

Fig. 36.1 Representative cutaneous histology in an experimental, murine model of acquired lymphedema. The specimens represent **a** untreated lymphedema; **b** lymphedema following systemic, targeted anti-inflammatory therapy; and **c** normal skin for comparison. Untreated lymphedema skin is characterized by hyperkeratosis, epidermal spongiosis and edema, irregularity of the epidermal/dermal junction, elongation of the dermal papillae, and a substantial expansion of tissue between the bone and the epidermis. There are numerous dilated microlymphatics and increased cellularity, including a large infiltration of neutrophils. Anti-inflammatory treatment normalizes these pathological findings (Adapted from Nakamura et al. [5])

sion of profibrotic Th2 cytokines, accompanied by an increase in lymphangiogenesis and an improvement in lymphatic function [18]. Th2 cytokines inhibit lymphangiogenesis, suggesting that manipulation of anti-lymphangiogenic pathways may represent a novel and potent means of improving lymphangiogenesis [19]. Finally, it appears that excessive generation of immature lymphatic vessels is essential for edema pathogenesis and maintenance in lymphedema and that this mechanism is dependent upon a CD4-macrophage interaction; in this context, the experimental lymphedema can be ameliorated through atorvastatin-mediated inhibition of T-helper type 1 and T-helper type 17 cell activation [20]. These and other lines of investigation suggest a promising future for pharmacological approaches to the treatment and prevention of lymphedema.

Conclusion

In summary, based upon the extant medical literature, there is little, if any, support for the role of pharmacology in the current approach to lymphedema patients. Investigative advances in mechanistic insights, coupled with the design and execution of suitable, well-designed, multi-center, randomized clinical trials, show great promise in their ability to provide evidence-based, efficacious options for lymphedema in the near future.

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Diagnosis and Management of Infection in Lymphedema

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Summary of Basic Concepts

The lymphatic system in limbs and organs detects, transports away, and neutralizes microorganisms penetrating integuments.

Obstruction of lymphatic pathways brings about tissue fluid/lymph stasis and subsequently retention of microorganisms continuously penetrating sole and hand skin. These microbes proliferate in the lymphedematous tissues and evoke immune reaction of the host. The inflammatory condition is called dermato-lymphangio-adenitis (DLA).

Acute episodes respond to 3–7 days of wide-spectrum antibiotic therapy. However, the microbes are not eradicated and according to the present state of knowledge change into the persister form with decreased metabolism and no responsiveness to antibiotics. To prevent revival of dormant microbes, low-dose long-term (benzathine) penicillin should be administered for years to patients with lymphedema decreasing the incidence rate of recurrent DLA.

37.1 General Overview

Infections and inflammation of lower and upper limb skin and soft tissues are more common than those of other skin regions, because of exposure to the environment. Hands and feet have a direct contact with surrounding matter covered by microorganisms and chemical substances. Easy damage to the epidermis as abrasions, cuts, pricks, and closed injuries create ports of entry of environmental bacteria [6, 7]. Skin surface and appendices as sweat and sebaceous glands and hair follicles are inhabited by commensal bacteria, mostly *S. epidermidis* and coagulase-negative strains. There are also *S. aureus* and corynebacteria. Additionally, the feet and calf may be colonized by pathogenic microbes originating from the perineal region as *Enterococcus*, *Enterobacter*, *Acinetobacter*, *Proteus*, *E. coli*, and *Pseudomonas*. These microbes float down from perineum on desquamated epidermal scales.

The commensal microbes are not pathogenic as long as they remain in their physiological niche. Once they have penetrated the epidermis, the local host defense response is initiated. This response depends on the mass of penetrating microbes. The 10^5 mass of bacteria per gram of tissue is the threshold value. Interestingly, the skin colonizing bacterial strains are sensitive to most antibiotics.

37.2 The Primary and Secondary Infections

37.2.1 The Primary Infections

They include (a) lymphangitis, (b) erysipelas, (c) necrotizing fascitis, and (d) other rare conditions. The predisposing conditions are (a) lymph stasis in a form of latent or overt lymphedema and (b) chronic venous insufficiency.

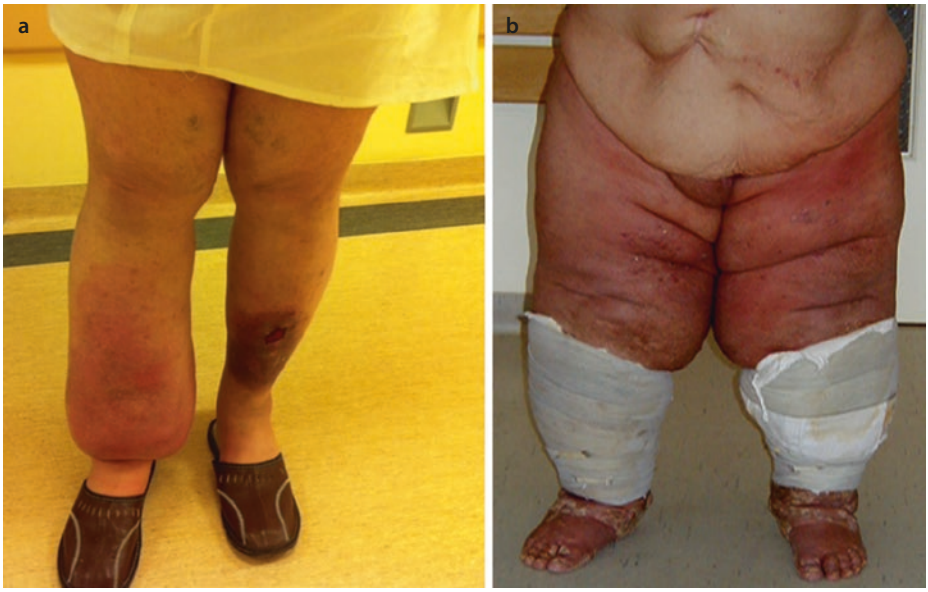

Fig. 37.1 **a** Patient with acute dermato-lymphangio-adenitis (DLA) of right lower limb stage IV. Edema and erythema. Left leg with skin changes after DLA 2 years ago in lymphedema stage I. Discoloration and hardening of skin and subcutis. **b** Patient with lymphedema of both lower limbs stage IV after inguinal lymphadenectomy because of seminoma. Erythema reaching the inguinal level and edema fluid leakage from calf surfaces soaking dressings. Systemic symptoms of sepsis

Lymphangitis

Lymphangitis is characterized by the occurrence of an inflammatory streak (red, warm, and painful) whose topography is that of the superficial lymphatic vessels. It is accompanied by fever. There is no inflammatory spreading lesion [8] (Fig. 37.1a, b).

Erysipelas

Erysipelas is a non-necrotizing bacterial hypodermal inflammation usually associated with streptococcal infection [1, 9–13]. Group A beta-hemolytic *Streptococcus* (GABHS, *Streptococcus pyogenes*) is the usual etiologic agent. It may sometimes be a complication of chronic lymphedema [2]. Erysipelas is often of a sudden onset, marked by frank systemic signs—fever >38°5, chills—and general malaise. Local signs develop within a few hours: a red, warm, painful, inflammatory spreading lesion, with centrifugal extension within a few days. Inflammatory, satellite adenopathy and lymphangitis are associated with erysipelas.

Necrotizing Fascitis

Necrotizing dermo-hypodermal bacterial infection or necrotizing fasciitis is characterized by necrosis of the fascia and myositis, resulting in a presentation of infectious gangrene. Diffuse, indurated edema extends beyond the margins of the erythematous

and sometimes slightly inflammatory spreading lesion. Deep necrosis may be manifested in the initial stage solely as a cyanotic, grayish-blue, poorly demarcated swelling, with a geographical maplike presentation. Fever is a usual finding but can be mild or absent. A septic syndrome (with hemodynamic signs, hypoxia, and thrombocytopenia) develops subsequently. This should prompt emergency hospitalization of the patient.

Other Rare Conditions

Other acute forms of dermo-hypodermal bacterial infection are caused by *Erysipelothrix rhusiopathiae* (Rouget's swine erysipelas), *Haemophilus influenzae*, *Pasteurella multocida*, and *Borrelia burgdorferi*.

37.2.2 Secondary Infections Dermato-lymphangio-adenitis (DLA)

Chronic DLA

Each case of lymphedema is predisposed to infections and chronic DLA [14]. This is due to impairment of bacterial elimination via lymphatics. Lymphedema is complicated by infection of skin and deep tissues in around 40% of cases, irrespective of what is the primary etiological factor for development of this condition. In the upper extremities after mastectomy and local irradiation, infection of the swollen limb, expressed as acute and later as chronic inflammation, ranges between 20 and 40% [15]. The recurrency rate of acute attacks of the dermato-lymphangio-adenitis (DLA) is higher in cases with long duration of edema. It is followed by fast increase in limb volume. In lower extremities, infection with inflammation affects around 50% of patients. It is most common in the postinflammatory type of lymphedema, followed by the posttraumatic and postsurgical types. Lower limbs are particularly exposed to the environmental microbial flora. The bacterial, fungal, and viral infections are more common there than in other skin regions. In advanced stages of lower limb lymphedema, systemic septic accidents requiring hospitalization and intensive antibiotic therapy are common, especially in tropical countries.

Acute DLA

Severe systemic symptoms during attacks of DLA resemble those of septicemia. The clinical characteristics are local tenderness and erythema of the skin, sometimes red streaks along the distribution of the superficial lymphatics, and enlarged inguinal lymph nodes. Systemic symptoms include malaise, fever, and chills. In its subacute or latent form, only skin involvement is observed. Each episode of DLA is commonly followed by worsening of leg swelling. Patients with acute episodes of DLA reveal bacteriemia in a

high percentage of cases [16]. Blood bacterial isolates were found in 21% acute and 26% subacute cases. Diversity of blood and tissue bacterial isolates in these patients points to a breakdown of the skin immune barrier in lymphedema and subsequently indiscriminate bacterial colonization of deep tissues and spread to blood circulation. Fatal cases were observed.

37.3 Differential Diagnosis of Lymphangitis, Erysipelas, and Dermato-lymphangio-adenitis

There is a lot of misunderstanding on the differences between these three conditions, which is pondering upon the type of therapy. (a) Lymphangitis is a primary local non-systemic non-spreading change in the skin and subcutaneous tissue caused by own skin flora, with a mild clinical course. It may lead to the development of lymphedema. (b) Erysipelas is a primary acute local spreading condition in the skin with systemic reaction. It is caused by streptococci. It may be contagious. It either develops in lymphedematous tissues or is the primary factor for its development. (c) Dermato-lymphangio-adenitis is a secondary condition complicating limb soft tissues lymphedema caused by colonizing staphylococci but not streptococci which cause erysipelas [3]. It is noncontagious and has a tendency for recurrency. DLA is sometimes called cellulitis. This is a misnomer as cellulitis is a cosmetic term describing accumulation of painful adipose tissue in the thigh and calf.

37.4 Pathomechanism of Tissue Infection and Inflammation in Lymphedema

Under normal conditions, microbes which penetrate the sole or palm skin are transported away from tissue via lymphatics and eliminated in the regional lymph nodes (Fig. 37.2). These are the strains permanently residing on the skin and acquired from the environment. The bacterial load is low and there is no clinically detectable reaction. In lymphedema, the lymphatic transport is restricted or totally halted. The penetrating microbes colonize tissues, proliferate, and evoke local inflammatory reaction with recruitment of host immune cells. Frequently, bacteria begin to proliferate rapidly, and inflammation of all limb soft tissues and systemic septic symptoms with bacteriemia develop. On histology, infiltration of dermis and epidermis by mononuclear cells and granulocytes, macrophages, and Langerhans' cell is seen (Fig. 37.3). The response to infection is clearly seen on lymphoscintigrams (Fig. 37.4).

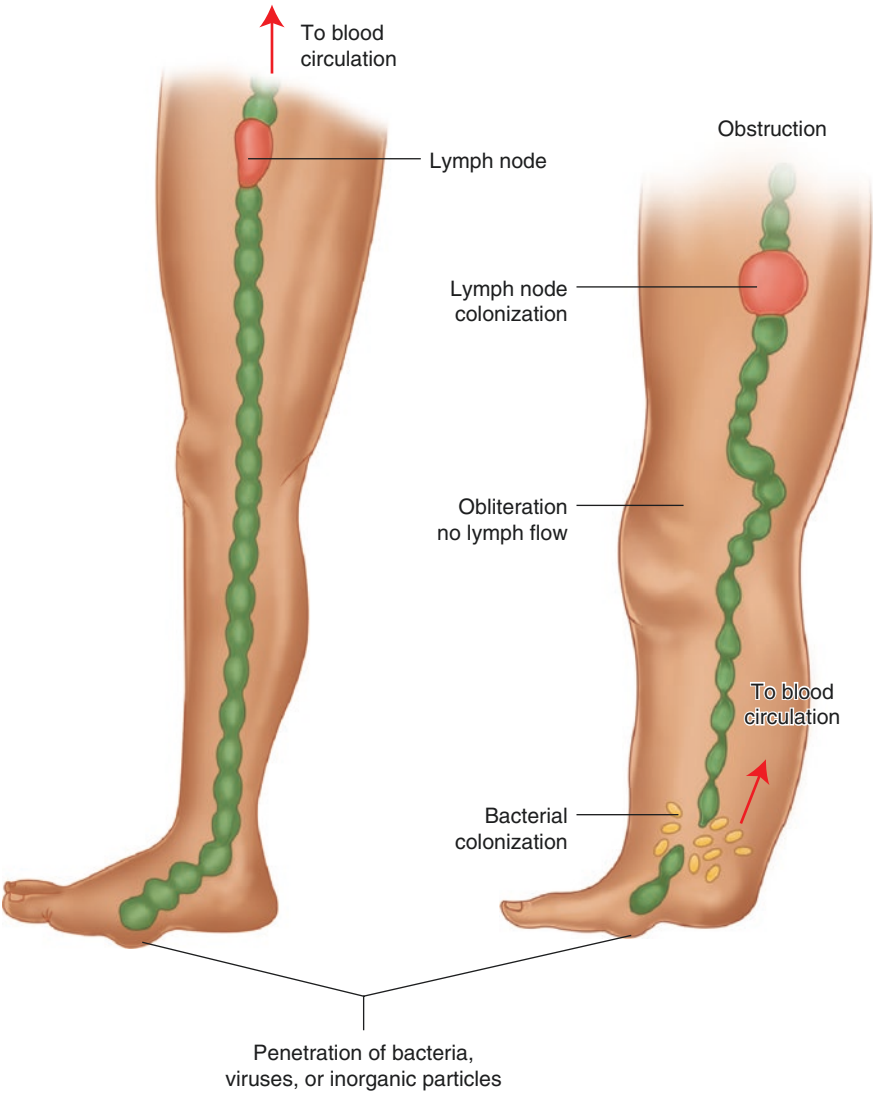

Fig. 37.2 Schematic presentation of the pathways of spread of skin bacteria in deep tissues and penetration to blood circulation in lower limb lymphedema

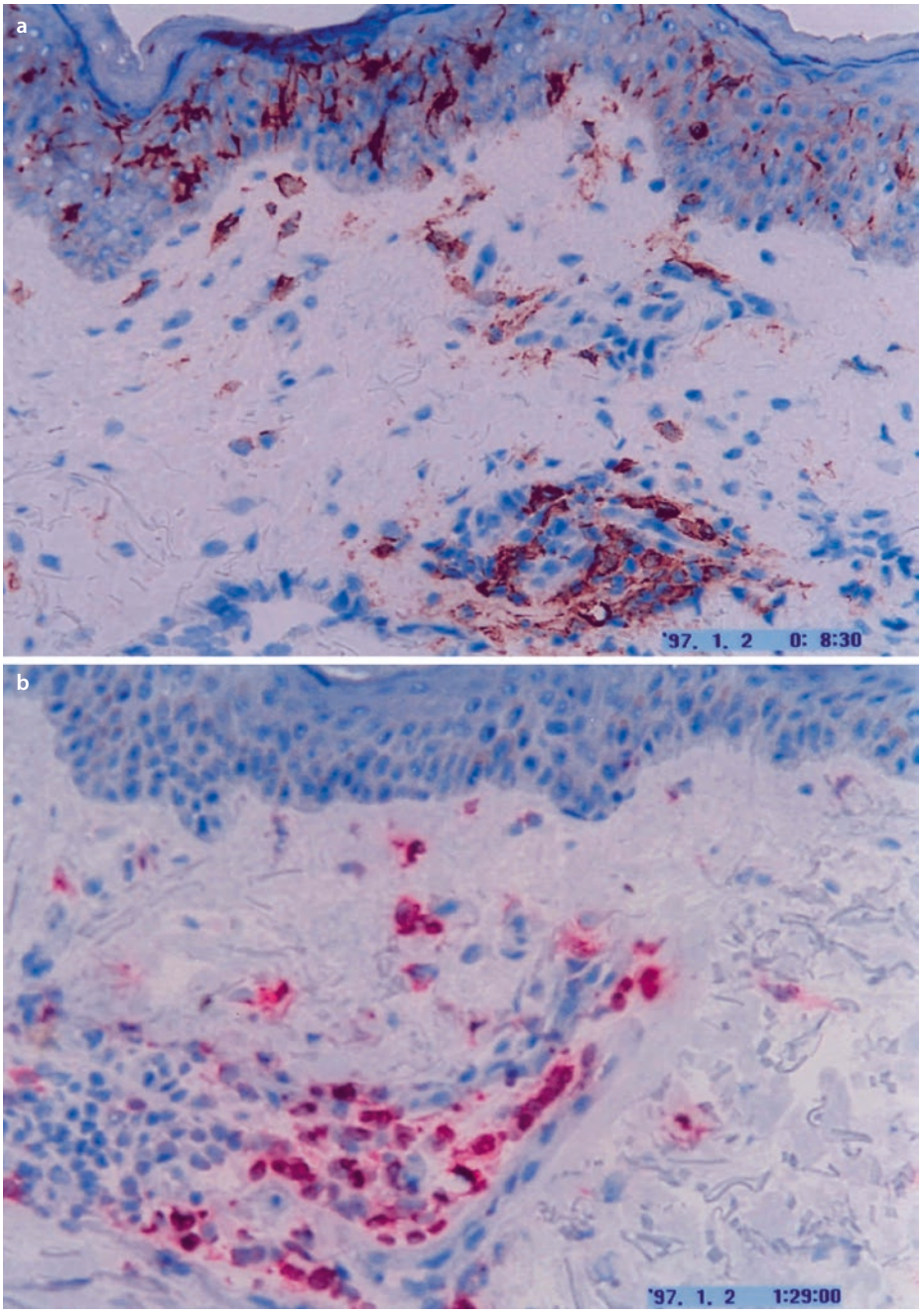

Fig. 37.3 Inflammatory cell infiltration of skin in lymphedematous skin in chronic dermato-lymphangio-adenitis (DLA). **a** Langerhans cells (*brown*) migrating from blood vessel to the epidermis and accumulation between the keratinocytes. **b** Granulocytes (*red*) extravasate mostly around the dermal blood vessels. The topography of infiltrates' and granulocytes' reaction point to the presence of chemotactic factors in skin, most likely secreted by bacteria. Dense Langerhans' cells' infiltrate takes place in chronic inflammation

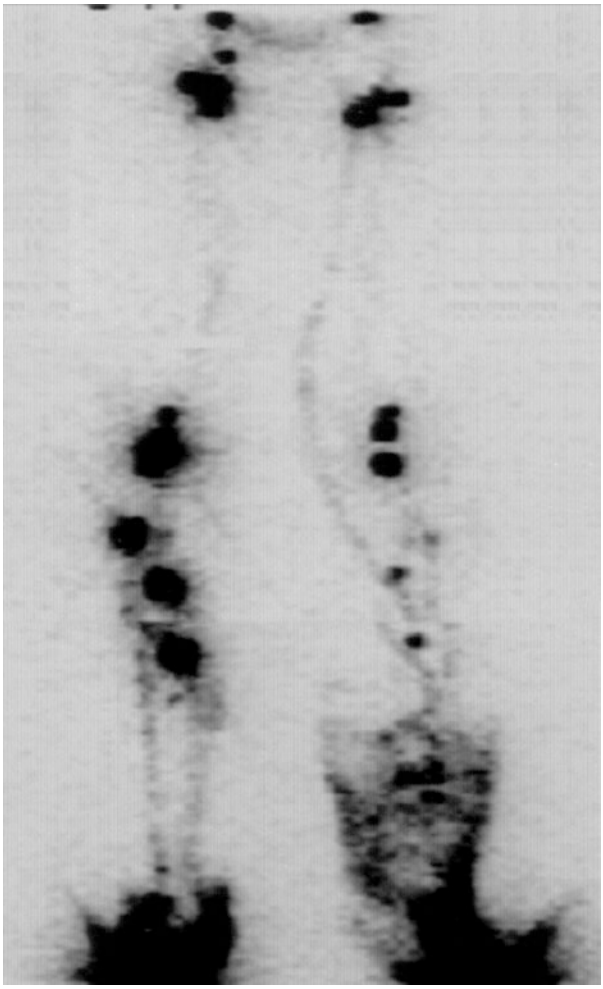

Fig. 37.4 Lymphoscintigram of lower limbs in a patient 5 years after dermatitis in both feet and calves. Left limb lymphedema stage IV and right stage II. Right limb: enlarged popliteal lymph nodes and collateral edema fluid flow through skin lymphatics (previously called dermal backflow). Left limb: enlarged popliteal lymph nodes seen only in cases with limb soft tissue infection. Picture proves involvement of the lymphatic system into inflammatory processes in lower limbs

37.5 Bacteriology of Lower Limb Skin

37.5.1 Bacterial Flora of Normal Foot and Calf Skin

Swabs taken from foot and calf skin surface reveal the presence of microbes in 100% (Table 37.1) [3]. The dominant species are cocci (60%). Among them, *S. epidermidis* and other coagulase-negative strains amount to 90% of all isolates. The other less frequent strains are *E. coli*, *Citrobacter*, *Corynebacterium*, *Acinetobacter*, *Proteus*, and *Bacillus cereus*. These strains originate from patient's perineum and anal skin.

Table 37.1 Prevalence of bacterial isolates from specimens obtained from lower limb tissues, lymph, and lymph nodes of 54 European patients with secondary lymphedema. In parentheses are values from 30 healthy volunteers

Specimen	Number of specimens		% of positive cultured
	Total	Positive	
Toe-web swab	52	52	100 (100)
Calf skin swab	52	52	100 (100)
Calf surgical incision swab	41	4	10 (7)
Leg lymph	20	12	60* (7)
Inguinal lymph node	20	6	33* (0)

*$p < 0.05$

37.5.2 Bacterial Flora of Normal Leg Lymph

S. epidermidis was detected in 12% of samples collected in volunteers in the studies of lymphatic lipid transport (Table 37.1).

37.5.3 Bacterial Flora of Lymphedematous Leg Lymph

Cocci were isolated in 60% of samples from the European population with dominating *S. epidermidis* and occasionally *S. aureus* (Tables 37.2 and 37.3). In the Indian population with high risk exposure to environmental infections, the values were higher and reached 70% of isolates, mostly cocci, in lymph and lymph nodes [3] (Fig. 37.5a, b).

37.5.4 Bacteria Persisters

Treatment of bacteria with antibiotics brings about death of most cells. However, some of them undergo transformation into a persister form or small colony variants (SCV) with minimum metabolism. They do not incorporate antibiotics and do not dissolve antibiotics. They live in our tissues and resume normal function upon signals from the host and proliferate [4, 5, 17] (Fig. 37.5c). Single widely dispersed cocci may be seen in tissues on electron microscopy (Fig. 37.6).

Table 37.2 Numerical prevalence of bacterial strains in tissues and fluid specimens from lymphedematous leg of 54 European patients

	Toe-web swab	Calf skin swab	Surgical wound swab	Lymph	Lymph node
Number of specimens	52	52	41	20	20
Enterococcus					
durans		2			
faecium	2	2			
Citrobacter	3	2			
Coryneforms					
group 2	2				
ANF	3	11			
pseudo	1				
minutissimum	1				
group F	1				
xerosis	3				
Klebsiella					
oxytoca	1				
pneumoniae	1	1	1		
Acinetobacter	5	6			
Escherichia coli	2				
Priopionibacterium	1				
Neisseria flava	1	1			
Bacillus subtilis	2	4			

Table 37.3 Numerical prevalence of microorganisms isolated from specimens obtained from lymphedematous legs of 54 European patients

	Toe-web swab	Calf skin swab	Surgical wound swab	Lymph	Lymph node
Number of specimens	52	52	41	20	20
Micrococcus					
species	31	28			
luteus	6	11		2	2
Staphylococcus					
aureus	4	9			
capitis	2	4		2	
cohnii	11	7			
epidermidis	24	15			
haemolyticus	4	6	2		4
hominis	20	18		6	
lentus	2	1			
simulans	1		1		
sciuri	3			2	
saprophyticus	6	4			
warneri	6	2			
xylosus	6	3			
Streptococcus					
milleri		2			
mitis		1			
faecium	3	2			

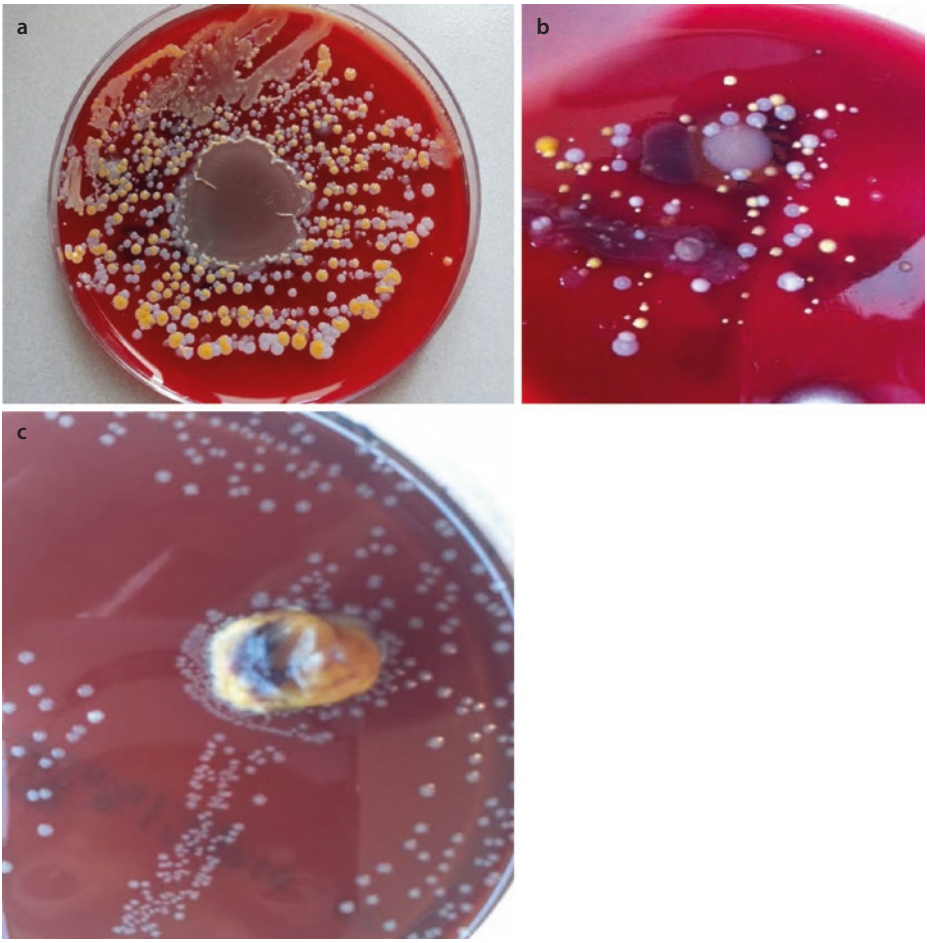

Fig. 37.5 Bacterial colonies on Hemoline plates from a drop of lymph harvested from the lymphedematous limb with chronic DLA. **a** Single and confluent colonies of *Staphylococcus epidermidis*, *S. albus*, and *S. aureus*. In the center of plate necrosis of crowded confluent bacterial colonies. **b** Diversity of bacterial strains in a drop of lymph, staphylococci, micrococci, enterococci, and *Candida* colonies. **c** Bacterial persisters. A fragment of inguinal lymph node surrounded by colonies of small colonies variant (SCV) *S. epidermidis*. After adding of liquid medium, small colonies spread around. These small colonies are of persisters (dormants, cryptics)

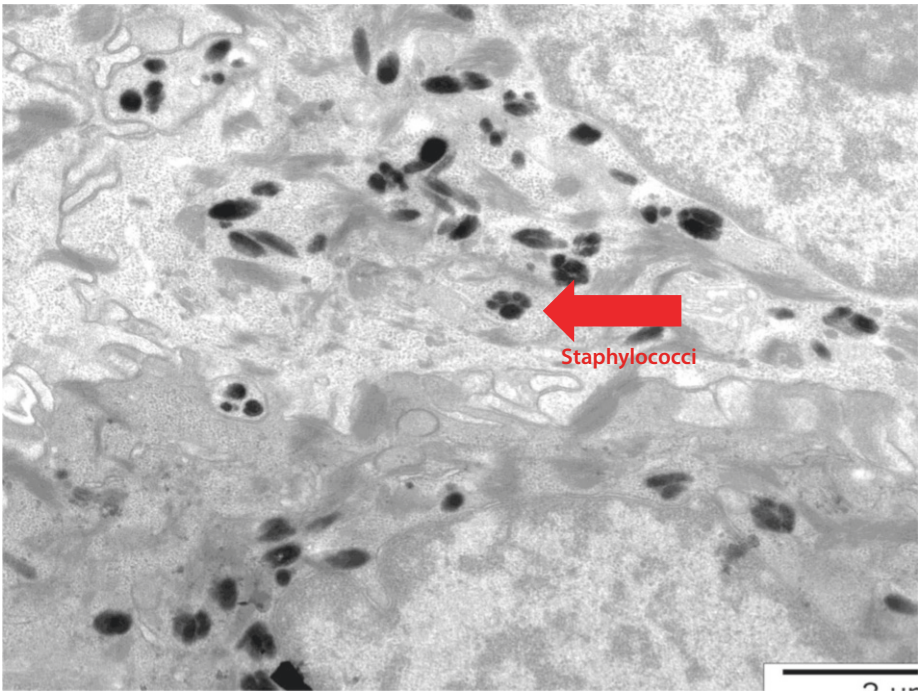

Fig. 37.6 Electron microgram of subcutaneous tissue from a lymphedema patient with single and dividing staphylococci spread between cells and collagen bundles

37.5.5 Sensitivity of Isolates to Antibiotics

The skin, subcutaneous tissue, lymph, and lymph node isolates, both from lymphedema and normal subjects, were sensitive to most antibiotics (Tables 37.4 and 37.5). Surprisingly, the least sensitivity showed microbes to penicillin, although this antibiotic turned to be very effective in prevention of DLA attacks in a long-term administration protocol. The high-level sensitivity of most strains suggests their environmental but not hospital origin.

Table 37.4 Sensitivity to antibiotics of bacterial isolates from skin surface, surgical skin incision, lymph, and lymph nodes in 54 European patients with lymphedema of lower limbs and 30 normal controls (in %)

	Gram-neg cocci, bacilli, coryneforms			
	Lymphedema		Normals	
	+++	+	+++	+
Penicillin	67[a]	0	27	5
Cefotaxime	100	0	80	25
Kanamycin	67	0	100	0
Tobramycin	83	0	100	0
Amikacin	67	0	100	0
Gentamicin	86	14	100	0
Tetracycline	71	0	80	0
Quinolones	83	17	100	0
Cotrimoxazole	67	0	80	0

[a]Percent of isolates

Table 37.5 Sensitivity to antibiotics of bacterial isolates from skin surface, surgical skin incisions, lymph, and lymph nodes of 54 European patients with secondary lymphedema of lower limbs and 30 normal controls

	Cocci			
	Lymphedema		Normals	
	+++	+	+++	+
Penicillin	24[a]	0	28	2
Oxacillin	72	0	73	0
Meticillin	80	0	80	0
Kanamycin	68	6	44	8
Tobramycin	74	5	75	15
Gentamycin	79	3	85	4
Tetracycline	49	0	61	2
Minocycline	96	4	100	0
Erythromycin	49	4	59	8
Lincomycin	60	14	69	6
Pristinamycin	92	1	100	0
Fosfomycin	57	6	45	8
Nitrofurantoin	85	6	54	25
Quinolones	72	18	62	12
Rifampicin	91	6	91	9
Fusidic acid	81	11	77	18
Vancomycin	92	0	88	2
Teicomycin	92	0	79	0
Clotrimoxazole	78	4	80	0

[a]Percent of isolates

37.6 Prophylaxis of Recurrent DLA

37.6.1 Chronic DLA

The DLA is of bacterial etiology and has a tendency for recurrency. The chronic bacterial prophylaxis is then necessary. It should be of long duration or even permanent since the effect of acute treatment is only temporary. It requires the use of penicillin: (a) intramuscular benzathine penicillin 1.2–2.4 million units every 2–3 weeks or (b) oral penicillin V 2–4 million units in 2–3 doses a day [18–20]. The intramuscular route with local anesthetic ensures better compliance and has proven effective. (c) The alternative, although less effective, is oral 2 g amoxicillin with clavulanic acid for 3 days every 2–3 weeks. Longer breaks between antibiotic administration turned to increase the DLA recurrency rate. (d) In the case of ß-lactam allergy, it is advisable to prescribe a macrolide as, e.g., roxithromycin. New antibiotics have recently been introduced as dalbavancin, oritavancin, and tedizolid with high therapeutic efficiency [21, 22].

We investigated the clinical course of lymphedema with respect to the prevalence of DLA in patients receiving injections of long-acting penicillin (benzathine penicillin). (a) Recurrent episodes of DLA that occurred in the PCN-treated group during 1 year decreased from 100% to 9% ($p < 0.002$) [18]. (b) There was increased prevalence of cocci and gram-positive bacilli with a concomitant decrease of gram-negative bacilli on the foot and calf skin surface. Simultaneously, decreased prevalence of gram-positive cocci and gram-negative bacilli isolates in limb deep tissues and lymph was seen. (c) No resistance to penicillin and other tested antibiotics developed in isolates from the skin surface, deep tissues, and lymph.

37.6.2 Treatment of Acute DLA Attacks

All wide-spectrum antibiotics are effective in controlling acute DLA. We recommend oral 2 g amoxicillin with clavulanic acid for 3–5 days. It should be followed by administration of benzathine penicillin in a scheme as for chronic DLA.

37.7 Results

Recurrency rate of DLA has been decreased in patients with both lower limb lymphedema and upper limb lymphedema (Tables 37.6 and 37.7).

Table 37.6 Recurrency rate of DLA attacks in patients with lymphedema of lower limbs treated for 12 m with long-term penicillin ($n = 74$)

	No of patients	% of patients with DLA attacks	
		Before	After treatment
I. Penidur treated	40	100	15.6
II. Non-treated	34	100	76.4

Table 37.7 The effect of long-lasting penicillin on recurrency of DLA attacks after mastectomy in a 5-year follow-up ($n = 162$)

Frequency rate of DLA	76% (3–12 attacks/year)
Long-term penicillin prophylaxis	
No recurrency	64%
Recurrency (one sporadic attack)	36%

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The Prospect for Genetic and Growth Factor Therapy

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Summary of Basic Concepts

Revascularization of the pathologically altered lymphatic circulation is an application of vascular biology that continues to be a focus in the development of therapeutics for lymphedema and other disorders of the lymphatic vasculature [6, 7]. The potential to alter the growth of lymphatic vessels also presents an opportunity to modulate the biology of tumor metastasis. Promising approaches to pro- and anti-lymphangiogenic gene therapies and to exogenous molecular treatment methods are under current, active investigation.

- Current treatment strategies for lymphedema do not address the underlying molecular pathogenesis and, therefore, only moderately delay the onset of the end-stage sequelae of the disease, including the architectural remodeling of tissues, the physical disfigurement, and the loss of function.
- VEGF-C is the chief lymphangiogenic factor, with a less well-defined role for the other VEGFR-3 ligand, VEGF-D; VEGF-A stimulates lymphangiogenesis in a less direct manner.
- Postnatal lymphangiogenesis plays a role in the setting of wound healing and of inflammation.
- Perhaps the most promising scenario for gene therapy is to be found in the context of autosomal dominant congenital lymphedema, commonly referred to as Milroy's disease.
- A variety of causal mutations for additional primary lymphedema syndromes have more recently been identified, posing additional theoretical opportunities for future molecular intervention.

Revascularization of the pathologically altered lymphatic circulation is an application of vascular biology that continues to be a focus in the development of therapeutics for lymphedema and other disorders of the lymphatic vasculature [6, 7]. The potential to alter the growth of lymphatic vessels also presents an opportunity to modulate the biology of tumor metastasis. Promising approaches to both pro- and anti-lymphangiogenic gene therapies and to exogenous molecular treatment methods are under current, active investigation.

The growth of lymphatic vessels is regulated by a large number of growth factors (Fig. 38.1) [8]; in aggregate, this developmental process is called *lymphangiogenesis*. This topic is discussed in greater detail in ▶ Chap. 2.

The vascular endothelial growth factor (VEGF) family occupies a central position among the known lymphangiogenic factors [9, 10].

Of these, VEGF-C is the chief lymphangiogenic factor, with a less well-defined role for the other VEGFR-3 ligand, VEGF-D [11, 12]; VEGF-A stimulates lymphangiogenesis in an indirect manner [13].

In addition to the VEGFs, several additional growth factors have a potential role in the process of lymphangiogenic processes. Fibroblast growth factor-2, hepatocyte growth factor, platelet-derived growth factor-B, and insulin-like growth factor-1 (IGF-1) and insulin-like growth factor-2 (IGF-2) can induce experimental lymphangiogenesis [14]. The angiopoietins also play a potential role as growth regulators of

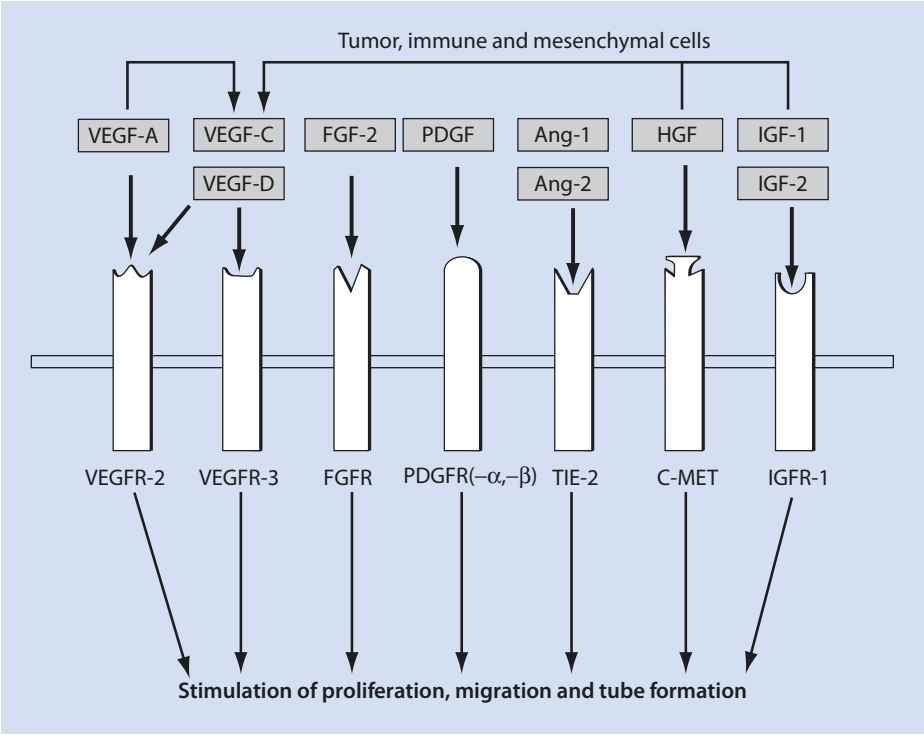

Fig. 38.1 Lymphangiogenic growth factors and their cognate receptors (Adapted from Van der Auwera et al. [8])

lymphatic vessels. The Ang1 receptor, Tie2, is expressed both in lymphatic endothelial cells and in intact lymphatic vessels [15, 16]. Ang1, Ang2, and Ang3/Ang4 have all been shown to stimulate lymphangiogenic sprouting, with Ang1 having the highest activity [17].

38.1 Postnatal Lymphangiogenesis

Lymphangiogenesis has been most actively investigated within the context of either normal development or the implications for tumor biology, where there is accruing evidence that active upregulation of VEGF-C and VEGFR3 expression and signaling promotes the process of metastatic transformation [18–21]. However, in addition, secondary (i.e., postnatal) lymphangiogenesis plays a role in the setting of wound healing and of inflammation [22]. Human diseases that entail chronic inflammation are associated with profound stimulation of new lymphatic vascular development [23–25].

Angiogenic revascularization of the lymphatics *via* therapeutic angiogenesis is an area of research that is believed to be applicable to edematous disorders of lymphatic development or acquired dysfunction [6]. In various animal models of lymphedema, both administration of recombinant VEGF-C [26] and gene therapy, using either naked

plasmid or virus-associated gene transfer, can produce the desired lymphangiogenic response, accompanied by a diminution in edema [27–29].

38.2 Molecular Therapy for Primary Lymphedema

The primary lymphedemas are those in which developmental disorders of the lymphatic vasculature produce a failure of the lymphatic contribution to regional or systemic fluid homeostasis. Most commonly, these disorders present clinically at or after the onset of puberty, a syndrome that has been historically labeled hereditary lymphedema praecox or Meige's syndrome [30]. At present, the genetic substrate of lymphedema praecox has still not been identified [31], but, in some aspects of its clinical presentation, it resembles lymphedema–distichiasis (LD), another pubertal-onset syndrome in which the genetic etiology has been characterized.

The attributes of LD include the presence of distichiasis at birth and the onset of bilateral lower limb lymphedema at or following puberty [32]. LD has an autosomal dominant mode of inheritance, the consequence of mutations in the FOXC2 gene [32, 33]. A murine FOXC2 knockout model reproduces the phenotypic and functional alterations observed in the human disease [34]. In LD, the lymphatic vessels are normal or hyperplastic, suggesting that FOXC2 might participate in the functional integrity of lymphatic vessels rather than in their primary development. In fact, FOXC2 is a critical transcription factor in pathways of metabolism, perhaps linking lymphatic dysfunction to insulin resistance [7]. A gene-based therapy for this syndrome has not yet been proposed, but it is notable that, in the mutant mice, there is abnormal pericyte recruitment to the lymphatic capillary vasculature and both lymphatics and veins demonstrate defective valve development and maintenance [35, 36]. These observations suggest an avenue for potential future molecular intervention.

The role of a SOX18 mutation in recessive and dominant forms of hypotrichosis–lymphedema–telangiectasia syndrome has been similarly been identified [37]. This rare inherited disease is characterized by a constellation of congenital hypotrichosis, lymphedema, and telangiectasia or vascular nevi on the palmar surfaces. Here again, a molecular intervention has not been proposed, but of central importance is the fact that SOX18 is responsible for signaling in lymphatic vascular development (► Chap. 4) [38].

Podoplanin/T1a knockout mice also display profound congenital lymphedema [39]. In these animals, while the lymphatic vessels are hyperplastic, there is near absence of lymphatic capillary and plexus formation. The analogous human clinical presentation of this gene knockout has not yet been identified.

Perhaps the most promising scenario for gene therapy is to be found in the context of autosomal dominant congenital lymphedema, commonly referred to as Milroy's disease. In many affected family cohorts, congenital hereditary lymphedema has now been associated with mutations in *flt4,* the gene encoding the VEGFR-3 gene [40–42]. In a murine model of Milroy's disease, characterized by a heterozygous inactivating mutation of the tyrosine kinase domain in VEGFR-3, the affected animal subjects exhibit poorly functional lymphatics [43]. These *Chy* mice develop chylous ascites soon after birth, accompanied by a hypoplastic lymphatic vasculature that mimics the human disease and the

analogous missense mutation to that identified in the human analog. Here, then, there is clear potential for ameliorative gene therapy [1, 44]: therapeutic augmentation of functional lymphatic vessel development has been demonstrated in the *Chy* mouse when adenoviral delivery of recombinant human VEGF-C results in the overexpression of VEGFR-3 ligands in these mice.

A variety of causal mutations for additional primary lymphedema syndromes have more recently been identified [45–52], posing additional theoretical opportunities for future molecular intervention. An algorithm for the approach to the primary lymphedema patient, with emphasis upon screening for the defined genetic substrates, has recently been advanced [2]; such an approach will have potential utility in the future application of molecular therapies.

38.3 Molecular Therapy for Acquired Lymphedema

Current treatment strategies for lymphedema do not address the underlying molecular pathogenesis and, therefore, only moderately delay the onset of the end-stage sequelae of the disease, including the architectural remodeling of tissues, the physical disfigurement, and the loss of function [7].

Just as growth factor therapy has demonstrated potential applicability for the reversal of lymphedema in the *Chy* mouse model of Milroy's disease, an experimentally supported role for therapeutic lymphangiogenesis has been variously described for acquired lymphedema [26, 27, 29, 53, 54].

In the initial descriptions of therapeutic lymphangiogenesis, investigated in an experimental, rabbit ear model of acquired lymphedema, either direct administration of recombinant VEGF-C [26] or plasmid-mediated gene therapy of VEGF-C [27] reverses the stable, persistent dysfunction of acquired lymphedema. Subsequently, investigation of growth factor therapy in a model of surgical lymphatic disruption in the murine tail has been similarly effective [53, 55]. More recently, in an acquired lymphedema model that incorporates surgical extirpation of lymph nodes and lymphatic collecting vessels, the administration of AdVEGF-C or AdVEGF-D reduced edema, with histological documentation of the remodeling of the vasculature, with evidence of formation of newly formed collecting vessels [29].

In aggregate, many factors have been reported to stimulate lymphangiogenesis both of cultured LECs and in vivo, including VEGF-A, VEGF-C, VEGF-D, FGF-2, PDGF, IGF-1, IGF-2, Angiopoietin-1, and HGF [3, 56–60].

38.4 Cell-Based Therapy for Therapeutic Lymphangiogenesis

Despite the potential promise of VEGF-C gene and growth factor therapy, various concerns remain, including the temporal limitations in the treatment effect, the potential for blood vascular adverse effects, and the limited functionality of the resulting lymphatic hyperplasia [4, 28, 61]. As an alternative approach, there has been growing interest in cell-based therapies using lymphatic endothelial progenitor cells. In addition, there is evidence that embryonic stem cells, induced pluripotent stem cells, and

mesenchymal stem cells have the ability to differentiate to a lymphatic endothelial phenotype [4]. There is particular interest in the mesenchymal cell approach because of the possibility of autologous cell donation. These non-hematopoietic adult postnatal stem cells are found in various tissues, including adipose [62]. When exposed to VEGF-C, adipose-derived stem cells express Prox-1, VEGF-C, and VEGF-A [63]. In experimental lymphedema, administration of adipose-derived stem cells resulted in a lymphangiogenic response to the stem cell-derived paracrine effects of secreted VEGF-C [64]. An analogous approach was successful at stimulating lymphangiogenesis in a wound-healing model [65].

While the source of adipose-derived stems cells is plentiful and harvesting of these cells engenders little donor site morbidity [4], translation of this approach to the problem of human lymphedema will require additional work. Of particular concern is the theoretical potential of transplanted mesenchymal stem cells to undergo malignant transformation [66], even though, to date, there has been no report of this phenomenon in clinical applications [67].

38.5 Augmentation of Lymphatic Growth Responses for Surgical Lymphedema Therapies

Over the last decade, there has been growing interest in surgical therapies for lymphedema, including autologous vascularized lymph node transfer (see ▶ Chap. 50). While these approaches show great potential promise, autologously transplanted lymph nodes incorporate into existing lymphatic vasculature at a low frequency [29, 68]; failure of lymphatic anastomosis to the transplant compromises the outcome, because this lymphatic engraftment is required for maintenance and function of the lymph node [69].

In order to circumvent this potential barrier to successful autologous lymph node transfer, with potentiation of endogenous lymphatic repair processes, investigators have elaborated a biological scaffold composed of nanofibrous, aligned collagen that guides cellular migration and growth [70] between the existing lymphatics and the transplanted lymph node. This biological scaffold, commercialized as the BioBridge™, has been successfully employed to promote regeneration of lymphatic collectors and resolution of hind limb edema in a porcine model of postsurgical lymphedema [5]. Clinical studies of this device as augmentation of standard vascularized lymph node transfer are underway in human lymphedema. Furthermore, it is envisioned that the use of this biological scaffold might pre-emptively promote lymphatic healing after surgical or radiotherapeutic interventions for cancer and, thereby, serve as a minimally invasive preventive strategy for acquired lymphedema. Finally, preclinical studies in a hind limb ischemia model suggest that these scaffolds can be utilized to sustain and deliver induced pluripotent stem cells [70]; therefore, in future applications, the use of cellular delivery by the scaffold to facilitate the either direct growth factor delivery or the paracrine growth factor effects of adipose-derived or other stem cells can also be envisioned. The properties of the scaffold can theoretically provide the precise three-dimensional structure required to induce interstitial flow and thereby direct reparative lymphangiogenesis.

Conclusion

Fundamental discoveries in lymphatic development have permitted the design of relevant animal models to simulate the vexing problem of human lymphedema. Application of genetic and molecular advances to the therapy of both the primary and secondary forms of lymphedema appears to be well underway. Future refinements in both scientific comprehension and biomedical technology will hopefully translate these initial experimental observations into a distinct clinical reality, which may, 1 day, incorporate both cellular- and device-based therapies.

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Adherence and Quality of Life

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39

Summary of Basic Concepts

The reader will be able to:

- Identify situational, physiological, and psychological factors that may impact lymphedema management behaviors.
- Identify gaps in our current understanding of the interaction between adherence and quality of life for patients with lymphedema.
- Identify the types of healthcare professionals needed to maximize the care of patient with lymphedema.

39.1 Introduction

Chronic health conditions affect more than 10% of the world's population, with many individuals having multiple conditions [51]. Management of a chronic health condition requires ongoing attention and commitment by patients. These pervasive, long-term conditions can significantly impair quality of life due to the potential for a high physical, emotional, and/or economic burden [25]. A self-care regimen is of particular importance for patients with chronic health conditions in order to maximize an individual's overall quality of life [2]. Although lymphedema does not receive the level of attention given to other chronic health conditions like diabetes and hypertension, it is a chronic health condition that significantly impacts a patient's quality of life [4, 5].

Individuals with lymphedema navigate a particularly complex treatment and self-management regimen, making adherence difficult [34]. Adherence can be thought of as the extent to which a patient's behavior matches the mutually agreed upon recommendations from his or her healthcare provider [6]. The term adherence is different from compliance in that it indicates a collaborative relationship between the patient and healthcare provider [6]. While compliance refers to the extent to which the patient's behavior matches the healthcare provider's recommendations, indicating a one-way line of communication, adherence is the result of bi-directional communication between the patient and healthcare provider [6]. Healthcare professionals can best support patient involvement in treatment and self-care when engaged in a collaborative relationship with the patient and relevant caregivers; thus, adherence is an important psychological construct for healthcare providers to consider if the goal is to maximize patient outcomes and quality of life. When a patient is adherent to a self-care particular regimen, his or her preferences along with unique additional factors are taken into account in planning stabilization and/or reduction of swelling, reduced symptom burden, and enhanced quality of life. Adherence to a self-care regiment is critical for optimizing these outcomes.

Our model of adherence to lymphedema therapy is adapted from Choi's [1] framework of diabetes self-management adherence and Lenz's [3] Theory of Unpleasant Symptoms. This model (Fig. 39.1) demonstrates that physiologic, situational, and psychologic factors influence an individual's adherence to lymphedema self-management behaviors which decreases symptom burden and ultimately influences health-related quality of life.

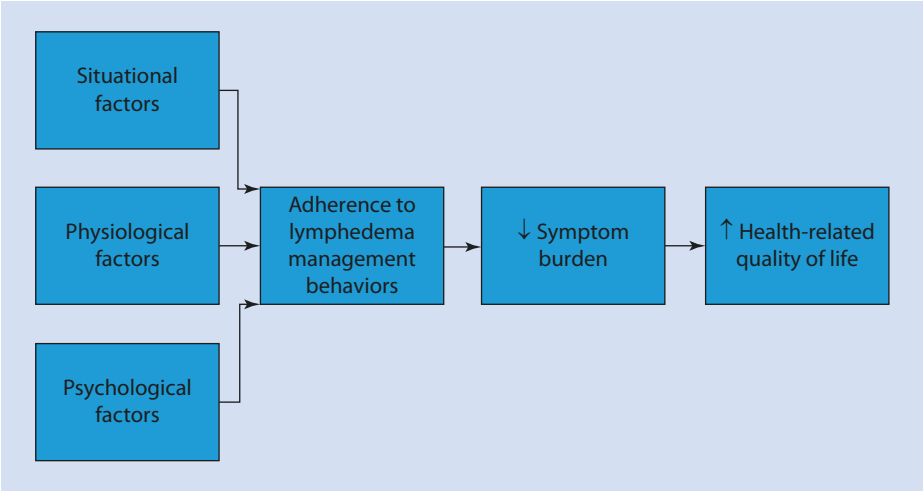

Fig. 39.1 Conceptual Framework for Adherence and Quality of Life

Situational factors can include demographic characteristics, barriers to adherence, and available support. Physiologic factors center around an individual's characteristics such as sex or the type or location of lymphedema. Psychologic factors incorporate coping response and other emotional attributes.

39.2 Adherence

Lymphedema is a chronic, progressive condition. Once lymphedema occurs, it is frequently life altering and disfiguring [19, 26, 38, 49]. Proactive, lifelong self-care is required to slow the progression of the condition and to reduce the risk of negative health outcomes, such as infection. It is important to note that swelling, which is traditionally the primary focus of lymphedema therapy, is not the only troubling symptom associated with lymphedema. Multiple studies support that altered sensations and function, fatigue, psychological distress, loss of confidence in body image, and reduction of activity occur in addition to swelling [28, 29, 35, 36, 43]. Lack of adherence to self-care could profoundly affect far more than volume, also influencing function, psychological well-being, confidence in body image, and activity levels. Given this, the benefits of adherence to lymphedema self-care can reasonably be expected to extend beyond volume maintenance/reduction and include the management of associated symptoms.

Rates of self-care adherence tend to be higher in patients with acute conditions than those with chronic conditions such as lymphedema [12], with adherence dropping most dramatically after 6 months of self-care [33]. There is a scarcity of published studies addressing lymphedema self-care practices or adherence. The studies that are available suggest that levels of adherence to lymphedema self-care are reportedly low [21, 40, 42]. Studies show that less than one-half of breast cancer survivors with lymphedema, the most highly studied population, complete prescribed self-care [24, 43] and that, strikingly, the most common lymphedema symptom self-management approach for them is

"not to treat the symptom at all" ([40], p. 17). The use of compression garments alone is probably the most frequently used type of self-care [24, 43], with bandaging, exercise, and skin care reported less often [35, 41, 42]. These findings are of great concern.

It is important for healthcare providers to understand the factors might influence self-care adherence, as many studies show direct benefits to adherent patients [30]. For example, one small study ($N = 11$) found that patients who adhered to self-care protocols following acute lymphedema treatment had significantly better outcomes than those who did not adhere to the protocol (rank sum $p = .042$) [21]. A larger study of 733 patients with head and neck cancer and with lymphedema determined that the only predictor of response to lymphedema treatment was adherence to self-care [47]. Yet another study found that non-compliance to compression techniques was also associated with increased lymphedema [50].

Situational factors that influence lymphedema self-care adherence include the considerable amount of time (treatment burden), lack of support, lack of resources, effort such care takes, and inadequate financial support for supplies [32, 45]. Medical factors such as hormone replacement and time since lymphedema diagnosis have been associated with lower levels of adherence, as has higher income [9]. Cultural influences are also important consideration when evaluating factors related to adherence. For example, in rural Nigerian communities where lymphatic filariasis is common, community-based approaches to lymphedema management have been found to be more acceptable and effective than healthcare facility-based settings [8]. Creating a situational experience in which individuals with lymphedema become better educated about the condition is ideal, as multiple studies show that knowledge and education positively influence adherence [9, 20, 32]. Findings from a large German study ($N = 742$) revealed the only significant predictive factor for use of lymphedema massage services was lymphedema education [10].

Physiological factors have been found to influence adherence. For example, in patients with melanoma and lymphedema, males had poorer coping scores than females [14]. Those with lower extremity lymphedema coped less effectively than those with upper extremity lymphedema, though this could improve overtime [14]. Heaviness of the extremity is also an identified barrier to adherence [32].

Psychologically, the results of tedious self-care may not meet expectations, discouraging continued self-care effort [42], and issues related to adherence in this patient population reflect an array of demoralizing losses reported in qualitative studies ([48], Ridner et al. 2011 EPub Ahead of Print). Specifically, psychological distress, depression, and lack of perceived control are associated with both nonadherence to self-care and reduction in utilization of available lymphedema services [7, 16, 22, 23]. On the other hand, perceived self-efficacy and perceived controllability of lymphedema positively influence adherence [46]. Thus, frustration with the unrelenting demands of self-care and recurrent grief reactions over loss of control of valued aspects of their lives may contribute to a sense of helplessness and depression, as does perceived marginalization by the healthcare community. Alternatively, empowering patients to be able to confidently manage their lymphedema will enhance patient well-being.

39.3 Quality of Life

Quality of life (QOL) is a broad and complex evaluation of an individual's current life circumstances in the context of the culture in which they live and the values they hold [17]. In recent years, the term QOL has been criticized as too general to be of use in healthcare. Thus, literature has suggested that global QOL be differentiated from health-related QOL (HRQOL). HRQOL is a multi-dimensional concept that includes domains related to physical, mental, emotional, and social functioning and focuses on the impact of health status on QOL and is the most applicable construct to consider in the context of chronic lymphedema [18].

Measurement of HRQOL in individuals with lymphedema has been challenging due to a limited number of lymphedema-specific QOL scales available in the literature. A systematic review [39] found that among 17 HRQOL instruments that were used in breast cancer-related lymphedema patients, two specifically are related to lymphedema patients. At the time of the review, of the lymphedema-specific HRQOL instruments, only one (the upper limb lymphedema 27, ULL-27) had sound psychometric properties. More recently, the valid and reliable Lymphedema Symptom Intensity and Distress Survey – Arm has been published [44]. Despite the complexity and challenges in assessment of HRQOL, QOL has been frequently reported in the literature as one of the primary treatment outcomes in individuals with lymphedema. Regardless of etiologies and anatomical sites of lymphedema, data have shown that individuals with lymphedema tend to have poorer quality of life compared to their counterparts without lymphedema.

Potential factors contributing to HRQOL in individuals with lymphedema have been reported in the literature. A cross-sectional study reported that individuals with primary lymphedema had lower quality of life score assessed using the Medical Outcomes Study 36-Item Short Form Survey (SF-36) than the age- and sex-stratified national norms [31]. The study described that higher lymphedema stage, cellulitis, less exercise, and more substance use were associated with a lower physical component summary score in the SF-36; and skin lesions over edematous limbs, less humor coping, and self-blame coping associated with a lower mental component summary score in the SF-36. This study indicates that cellulitis, skin lesion, and coping strategies are possible factors influencing HRQOL in individuals with primary lymphedema.

Despite clinical improvement in cancer therapy, secondary lymphedema remains a frequent, significant health issue that considerably impacts HRQOL for many cancer survivors, including individuals with breast cancer, gynecologic cancer, genitourinary cancer, melanoma, head and neck cancer, and sarcoma [13, 15, 37]. Studies have shown that cancer survivors with lymphedema have a significantly lower HRQOL score than their counterparts without lymphedema. Beaulac et al. [11] conducted a retrospective study in early-stage (stages 0–II) breast cancer survivors and found that the survivors with breast cancer-related lymphedema reported a measureable reduction in QOL compared with survivors without lymphedema, even after adjusting for other factors influencing QOL.

39.4 Interaction of Adherence and Quality of Life

Research supports that adherence to lymphedema management behaviors positively impacts HRQOL in individuals with filarial lymphedema [27]. Empirical evidence for specific behaviors improving HRQOL for other populations of individuals with lymphedema, however, is lacking. We postulate that adherence to lymphedema management behaviors decreases symptom burden (i.e., progressive increases in swelling, infection, etc.) and thus facilitates an increase in HRQOL in individuals with lymphedema of diverse etiologies. Although adherence to lymphedema management behaviors may not eliminate or decrease lymphedema, an individual's HRQOL is enhanced by preventing the progression of lymphedema and associated sequelae.

39.5 Summary of Basic Concept

Healthcare professionals are in the first line to encounter and care for individuals with lymphedema. It is important to note that swelling is not the only symptom associated with lymphedema. Data have revealed that lymphedema results in a myriad of physical, psychological, and social issues for individuals suffering from this debilitating condition. Currently, lymphedema is an incurable and chronic condition. Individuals with lymphedema need to conduct lifelong self-care activities to control the progression of swelling, manage lymphedema-associated symptom burden, and minimize long-term negative outcomes (e.g., elephantiasis).

Given the importance of lymphedema self-care, healthcare professionals need to assess and address factors that influence adherence. Situational factors should be assessed and assistance provided to patients in overcoming any barriers to adherence such as access to care, supplies, and supportive others. Engagement of social work assistance may be needed in some cases. Likewise, situational factors that promote adherence should be supported in order to insure that they remain in place over the many years of adherence to self-care activities that are required.

Physiologic factors impacting adherence should not be overlooked. Patients with lower extremity lymphedema may require more instrumental support to conduct self-care activities. Comorbidities such as arthritis and visual impairment may also contribute to poor adherence, and collaboration with other healthcare providers to facilitate optimal management of such comorbidities may at times be warranted.

Psychosocial factors such as lack of perceived self-efficacy or controllability regarding management of lymphedema may require the development of new skill sets. For many patients and their supportive others, education regarding the necessary skillsets is needed. Additionally, continual assessment of adherence at each point of contact is paramount. In patients who are psychologically distressed or depressed, referrals for treatment of these underlying conditions may be needed in conjunction with the education if adherence is to be maximized. Clearly, a multidisciplinary approach is needed to help promote adherence and maximize the patients' HRQOL.

Patients play a central role in initiating self-care and monitoring for lymphedema. Well-informed patients are more likely to understand the disease progression and have

more confidence for actively engaging in long-term self-care of lymphedema. Assistance and support from family members is critical for patients who have difficulty in performing routine self-care activities due to physical or psychological limitations. Thus, healthcare professionals need to consider educating family members (or caregivers) and empowering them to be a part of the integrative team advocating and supporting the patients' self-care.

Despite the increased attention about the importance of adherence to self-care in decreasing lymphedema-associated symptom burden, limited literature has been available to examine how adherence to lymphedema self-care impacts the patients' HRQOL. More research is needed in this area. Furthermore, given individual differences, research efforts are warranted to identify strategies and solutions to offer the patient a personalized self-care regimen, which would facilitate better adherence and outcomes.

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Lymphedema Within the Healthcare System

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Summary of Basic Concepts

Lymphedema Incidence and Prevalence

- There are no universally applied measures and follow-up protocols used for lymphedema; however, depending on methods of assessment and criteria for diagnosis, 41–94% of breast cancer survivors may develop lymphedema within 60 months of definitive breast cancer surgery.
- Surgical advances, such as sentinel lymph node biopsy, have been helpful in reducing the incidence of breast cancer-related lymphedema.
- Lymphedema can occur months to years after cancer treatment, making it difficult to document incidence.

Impact of Lymphedema

- Lymphedema, classified as primary or secondary, can present suddenly or with gradual onset affecting various parts of the body.
- There is no cure for lymphedema and it requires lifelong management to deter progression and help prevent complications, such as infection.
- Lymphedema, and the burden of lymphedema self-management which often requires several care modalities, is reported to result in psychological, psychosocial, and physiological symptoms.
- Physiological symptoms associated with primary and secondary lymphedema are often interrelated with psychological symptoms and are reported as having a negative impact on the quality of life.
- In addition to symptoms associated with lymphedema and treatment burden, it is reported that co-morbidities are more prevalent in individuals with breast cancer-related lymphedema, compared to breast cancer survivors without lymphedema.
- Employment status and quality of work are often impacted due to symptoms and lymphedema severity.
- Marginalization, public insensitivity, nonsupportive work environments, and resource factors are major influences on negative work status.

Education and Support

- Healthcare providers' knowledge of lymphedema-associated symptoms is necessary to facilitate appropriate, timely diagnosis, referral for treatment, and follow-up care.
- Voiced concerns from patients have identified the need for healthcare providers to become more knowledgeable about lymphedema, become more involved as patient advocates, and demonstrate proactive lymphedema management.
- Healthcare providers' knowledge of lymphedema and an understanding of barriers to successful management of lymphedema significantly influence patient outcomes on psychological, psychosocial, and physiological levels.

Economic Impact on Patients, Payers, and Healthcare Systems

- Consumption of healthcare resources to treat or manage breast cancer-related lymphedema results in a substantial economic burden for patients, payers, and healthcare systems.
- An increased number of patients diagnosed with long-term cancer-related sequelae, such as lymphedema, impact costs associated with training of healthcare personnel, such as physical therapy programs that specialize in treating lymphedema.
- In a study of 228 patients affected with lymphedema, 29% of interviewed patients reported at least one infection and 15% reported one or more hospitalizations with 12 days reported as an average length of stay.
- Over a two-year period, management of lymphedema and costs associated with complications, such as infections, were reported to account for a difference of $20,000–$31,000 (2015 USD), compared to breast cancer patients without lymphedema.
- Higher outpatient costs in patients diagnosed with lymphedema are associated with increased number of office visits, diagnostic imaging, prescription costs, and mental health services.
- Patients and their families may be burdened with out-of-pocket expenses for uninsured treatment and supplies, co-pays for increased number of office visits, transportation, domestic services, and family and other caregiving support.
- Indirect costs associated with loss of work productivity or employment interruption due to the inability to perform job functions, loss of work due to medical appointments, and absenteeism due to lymphedema-related symptoms create a significant burden on patients and families.

Economic Comparisons of Clinical Management

- Two models of care currently exist for the treatment of lymphedema: a traditional medical model used to prescribe treatment at the time lymphedema is reported to the healthcare provider and the prospective surveillance model, which monitors patients to identify and treat lymphedema at the earliest stage.
- Significant cost savings have been reported with the prospective surveillance model using preventive compression ($86–$350) compared to intensive complete decongestive therapy (CDT) with later progression ($1400).
- A systematic review comparing early-onset lymphedema treatment with traditional CDT reported an annual savings greater than $2400 per patient with the prospective surveillance model.
- A retrospective analysis of patients with both cancer-related and non-cancer-related lymphedema reported reduction in outpatient treatment costs in both groups using the prospective surveillance model.
- Consistent with current literature, there are significant reported differences between the total costs (direct and indirect) of the prospective surveillance model and the traditional model with reported cost savings of 37%–54%, which support prospective surveillance implementation as a viable course of treatment for patients with breast cancer-related lymphedema.
- There is no uniform insurance coverage for lymphedema treatment and current coverage is inadequate.

40

Prospective Surveillance

- A prospective surveillance program takes a holistic approach to patient care, meeting patient needs for education, treatment, and psychological support, including perceptions of self-efficacy.
- Most programs have been implemented with patients at risk for cancer treatment-related lymphedema; however, rigorous study with patients diagnosed with non-malignancy-related lymphedema may benefit, as well.
- Early detection of lymphedema offers the best opportunity for more efficacious treatment and subsequent preservation of quality of life.
- A prospective surveillance program for patients at risk for breast cancer-related lymphedema begins preoperatively and continues throughout survivorship.
- Components of a prospective surveillance program should include assessment of preoperative bilateral baseline arm volume, medical and social history, education, symptoms and symptom management strategies, quality of life, and self-efficacy/self-regulation.
- Prospective surveillance is a logical shift in care that alleviates economic burden and, most importantly, improves the overall well-being of patients with lymphedema and those at risk.

40.1 Introduction

The incidence and prevalence of lymphedema are elusive because there is no single standardized measure or universally accepted criteria used to diagnose lymphedema [6, 7]. There is also no universally applied protocol for follow-up for the person at risk of developing lymphedema. For example, lymphedema can occur within months to decades after breast cancer treatment, making follow-up difficult [8]. Incidence of breast cancer-related lymphedema has been reported as low as 3% following breast conservation and sentinel node biopsy; [9] however, depending on the methods of assessment and criteria for diagnosis, 41–94% of survivors may develop lymphedema within 60 months of surgery [10]. In one cohort of 923 survivors followed over a 20-year period, 80% of those studied who developed lymphedema did so within 3 years after surgery [11]. The average time to development is consistently reported as a median of 18 months post-breast cancer treatment [8]. Documenting lymphedema incidence is difficult, due in part to lack of standardization of measures and modalities; lack of professional knowledge regarding assessment, diagnosis, and treatment; and the lack of rigorous research that operationalizes the definition of lymphedema. This results in an underestimation of persons with lymphedema, many of whom have not been diagnosed [6, 12]. Because of the preponderance of numbers in both survivorship and incidence, much of the research in secondary lymphedema has been done in the area of breast cancer survivorship. The impact of lymphedema on the consumer and economic and healthcare systems can be extrapolated to other secondary lymphedema and to primary lymphedema.

40.2 Consumer-Level View of Lymphedema and Its Impact

40.2.1 Impact of Lymphedema

Lymphedema can present in the extremities, trunk, abdomen, head and neck, external genitalia, and internal organs, with an onset that can be gradual or sudden. In the Western Hemisphere, patients most often develop secondary lymphedema related to treatment for various cancers (breast, uterine, prostate, bladder, lymphoma, and melanoma). Primary lymphedema, with no known extrinsic cause but sometimes attributable to a genetic predisposition, develops at different stages of life. Lymphedema may be triggered by events such as trauma and deep vein thrombosis. In developing countries, parasites associated with filariasis account for millions of cases [13]. If left untreated, lymphedema is likely to progress. While we currently do not have a cure for lymphedema, evidence-based management has been shown to be effective in stabilizing lymphedema and deterring progression. However, the burden of daily management often exacts psychological, psychosocial, and physiological tolls.

40.2.2 Psychological and Psychosocial Symptoms and Impact

Psychological and psychosocial symptoms such as anxiety, depression, emotional distress, and sexuality issues potentially impact adherence to self-management, thereby increasing the risk of lymphedema progression and infection [14–16]. Cancer survivors are potentially affected with multiple stressors that place them at higher risk for psychological and psychosocial distress, such as changes in self-image, cognitive impairment, and co-morbidities. In addition, they may experience stressors of living along, being of younger age and female, having young children, and having a prior history of physical or sexual abuse [17]. A systematic review was conducted by Fu et al. [18] examining the psychosocial impact on women with breast cancer-related lymphedema, finding statistically significant poorer social well-being in persons with lymphedema. Of 23 studies reviewed, negative psychological impact (negative self-identity and emotional and psychological distress) and negative social impact (marginalization, financial burden, perceived diminished sexuality, social isolation and abandonment, public insensitivity, and nonsupportive work environment) were identified [18].

Over the past decade, there has been an increase in patient-oriented research using qualitative frameworks to identify patient perceptions of lymphedema and barriers to self-management. Although most research has focused on secondary lymphedema, barriers to self-management for both primary and secondary lymphedema are similar, given that most treatment modalities are the same. Table 40.1 illustrates themes most commonly reported by patients with lymphedema. Qualitative studies have enabled patients' voices to be heard and have played a large role in helping healthcare providers understand the importance of patient perceptions in developing individualized plans of care and support. In addition, increased longevity has placed a responsibility on healthcare providers to be more cognizant of long-term survivorship, treatment outcomes, and lymphedema-related sequelae.

Table 40.1 Patient-reported themes regarding lymphedema self-management

Psychological distress	Psychosocial factors	Physio-logical factors	Treatment burden	Education	Co-morbidities
Symptom distress	Social isolation	Heaviness of extremity	Imbalance between patient burden of treatment and their capacity to cope	Education about BCRL and self-management is not always provided	Loss of function/ ROM (i.e., arthritis)
Anxiety	Lack of support	Numbness	Reduced QOL	Need exists for expanding the variety of formats for BCRL education	Age
Depression	Spiritual crisis	Swelling	Decreased time for family, leisure activities due to time spent for BCRL treatment	Patient-centered strategies are needed to address both cognitive and affective levels	Cognitive changes (i.e., stroke, dementia)
Emotional disturbance (i.e., sadness)	Perceived diminished sexuality	Skin changes			Co-association of medications
Fear	Marginalization by healthcare providers	Stiffness			Sedentary lifestyle (cardiovascular implications)
Decreased perceptions of self-efficacy	Financial burden	Pain			
Stress					

QOL quality of life, *BCRL* breast cancer-related lymphedema, *ROM* range of motion
Used with permission [21]

Psychological and psychosocial impact of lymphedema was explored with a mixed-methods qualitative study ($N = 379$) using repeated administration of the Lymphedema Breast Cancer Questionnaire (LBCQ) up to 2.5 years post-breast cancer diagnosis and treatment. Participants reported altered body image, imposed lifestyle and occupational changes, and negative impact on family and interpersonal relationships as contributors to psychological distress [19]. In another study, patients with both primary and secondary lymphedema reported a lack of psychosocial well-being and resources, treatment challenges, and difficulties accessing quality care [20].

40.2.3 Physiological Symptom Impact

Lymphedema is measured by severity using a grading system established by the International Society of Lymphology. The grading system classifies lymphedema into four stages: 0–III, with no swelling represented by Stage 0, and lymphedema with the most severe signs and symptoms represented by Stage III [22]. Symptoms of breast cancer-related lymphedema mainly affect the arm, hand, breast, and trunk; however, it has been reported that even minimal limb volume changes (5.0–9.9%) impact quality of life (QOL) [23].

A self-report survey sponsored by the National Lymphedema Network (NLN) was conducted between March 2006 and January 2010. Questions regarding subjective symptoms in patients with upper and lower extremity lymphedema ($N = 1837$) were answered online. Symptoms reported by patients diagnosed with lower extremity lymphedema ($n = 1114$) were compared to symptoms experienced by patients with upper extremity lymphedema ($n = 723$), with significant differences found ($p < 0.0001$). The most frequently reported lower extremity symptoms included swelling (98.7%), heaviness (87.1%), stiffness (76.3%), current pain (69.8%), reduced range of motion (65.8%), and numbness (59.2%). The most commonly reported upper extremity symptoms were swelling (96.8%), a feeling of extremity heaviness (76.2%), current pain (67.3%), stiffness (65.8%), numbness (63.9%), and decreased range of motion (48%) [24]. In addition, symptoms were more frequently reported by patients with lower extremity lymphedema [24].

Physiological symptoms are often interrelated with psychological symptoms and have a negative impact on quality of life [1] and the ability to adhere to self-management regimens [21]. Depending on the severity, the treatment for lymphedema involves self-care modalities that can be few and simple to numerous and complex. Treatment for both primary and secondary lymphedema may consist of several self-care modalities including manual lymphatic drainage, using a combination of specialized massage techniques, compression bandaging of the extremity, exercises, compression garments, and meticulous skin care [25–27]. Together these are considered complete decongestive therapy (CDT). These modalities have been reported as burdensome, time-consuming, and potentially impacting quality of life [28–33].

In addition to treatment burden, lymphedema-related symptoms also represent a burden to self-management, especially in individuals over the age of 65 who may have

co-morbidities associated with other illnesses. In a study comparing women with breast cancer survivors with lymphedema ($n = 74$) to breast cancer survivors without lymphedema ($n = 75$), findings identified obesity (BMI >30), orthopedic problems, hypertension, and arthritis as more prevalent in the lymphedema group [34]. It is important for healthcare providers to encourage self-report of symptoms, as it may help discriminate between at-risk survivors and survivors with lymphedema based on the number of symptoms [35]. In a study conducted by Fu et al. [35], a diagnostic cutoff of three symptoms was used to discriminate breast cancer survivors with lymphedema ($n = 42$) from healthy women ($n = 60$) with a sensitivity of 94% and a specificity of 96% (area under the curve = 0.96). A diagnostic cutoff of nine symptoms discriminated between at-risk survivors and survivors with lymphedema with a sensitivity of 64% and a specificity of 80% (area under the curve = 0.72). In the event that lymphedema assessment yields no objective measurements, a symptom count may be useful for detecting lymphedema. Symptom burden and a higher incidence of infection is experienced with both primary and secondary lymphedema; therefore, it is critical that healthcare providers evaluate each patient for symptom burden, as well as provide education on signs and symptoms of infection [24, 36] and appropriate reporting to healthcare providers.

40.2.4 Work-Related Impact of Lymphedema

Besides psychological, psychosocial, and physical problems, persons with lymphedema may also face employment concerns [78]. Employment status and work quality depend on the combination and interaction of individual factors, work environment, social policy, and resources [37–39]. Based on a 2003 UK study, more than 80% of patients with lymphedema reported absenteeism from work, with 9% of them experiencing a negative effect on work status [40]. Lymphedema is one of the factors associated with a longer delay in return-to-work after breast cancer treatment [41]. An Indian study assessed impact on weavers with filariasis-related lymphedema and hydrocele on their work quality and quantity [42]. Many patients could no longer weave due to the physical demands on the weaver, leading to reduced earnings and lost work time equivalent to almost 1 month a year. Quinlan et al. [39] limited the reduced work capacity variable to reflect breast cancer-related arm problems, changes, and work limitations due to arm morbidity. Lymphedema was the major factor causing long-term arm pain and range-of-motion limitations, including an inability to perform typing or lifting [39]. A recent quantitative study surveyed online 361 women who either had breast cancer without lymphedema ($n = 209$) or breast cancer with lymphedema ($n = 152$). Results found the lymphedema group had more work time off due to medical reasons [43]. Bifulco et al. found employment experience (employment status and working time) was affected by lymphedema in persons with gynecologic cancers (including endometrial, cervical, and ovarian), as well as breast cancer, especially for younger patients [44]. Lymphedema severity, individual willingness to continue working, work schedule flexibility, workplace medical confidentiality, relationship with colleagues, and resources to assist with work re-entry and social stigma management are identified as individual, work environment, social policy, and resource factors combining and interacting as influences on employment status and work quality [37–39].

40.2.5 Healthcare Provider Education and Support

Increasing healthcare providers' knowledge of lymphedema-associated symptoms and barriers to self-management is necessary to facilitate the use of screening tools for appropriate evaluation, treatment, and referral for follow-up care [17, 45]. Tam et al. [45] invited 2469 clinicians, including primary care physicians, surgeons, oncologists, and nurse practitioners, to participate in a 10-min Web survey about lymphedema. With 887 participants, findings revealed that clinicians with a higher lymphedema knowledge score about breast cancer-related lymphedema were more likely to make referrals. With increasing numbers of breast cancer survivors, lymphedema education for clinicians is warranted [45]. Patient dissatisfaction with care has been reported due to the lack of education and information about lymphedema, inadequate information, and conflicting information [46, 47].

One of the three major themes resulting from a qualitative analysis of responses from three focus groups of breast cancer survivors with lymphedema ($N = 21$) was reported as "self-advocacy by default," with associated subthemes including the need to proactively manage lymphedema complications, the need to educate healthcare providers, and feelings of marginalization by the healthcare system [48]. Another study of perceptions of patients with both primary and secondary lymphedema reported a feeling of marginalization by healthcare providers who were uninformed about lymphedema and its treatment [49]. In addition, a meta-synthesis of qualitative research identified the importance of healthcare provider awareness of lymphedema in developing plans of care that offer strategies for positive coping, education, and support [50]. It appears clear that healthcare providers' knowledge of lymphedema and the issues faced by patients significantly influences patient outcomes on psychological, psychosocial, and physiological levels.

40.3 System-Level Economic and Health Service View of Lymphedema

40.3.1 Economic Burden of Lymphedema

As a sequelae of breast cancer treatment that remains incurable in the current state of medical approaches and technologies, breast cancer-related lymphedema exerts substantial economic burden for patients, payers, and the healthcare system as a whole. A comprehensive assessment of costs associated with a specific disease will include four categories of costs: health sectors, other sectors, patient/family, and productivity losses (also known as indirect costs) [51]. In the context of breast cancer-related lymphedema, for example, where most of the economic research has been conducted, costs in the health sectors category will include costs of managing lymphedema (e.g., diagnosis, physical therapy, medical supplies for bandaging, or compression pumps) or complications of lymphedema, such as infections. Costs in the other sectors will capture resources consumed from other non-health sectors to care for lymphedema patients. For example, investing in physical therapy training programs specialized in lymphedema therapy to ensure that there is sufficient supply of qualified therapists for the projected number of lymphedema patients utilizes

resources from the non-healthcare sector to provide services for patients inside the healthcare system. Patient/family costs will include out-of-pocket expenses for lymphedema-related healthcare services, transportation between home and the treatment facility, parking at the treatment facility, and other expenses incurred, such as childcare, due to lymphedema treatment. Lastly, productivity losses will quantify reduced productivity, both in the form of absenteeism and presenteesim [52], from patients as a result of morbidity or even mortality associated with lymphedema or from patients and family members when patients are undergoing treatment. Similar to most cost studies of other diseases in the economic evaluation literature, the vast majority of economic studies of lymphedema focused primarily on the first cost category, namely, healthcare resources consumed to treat or manage the disease, as well as its downstream events.

The first study that documented the economic impact of lymphedema was from a survey of 228 patients with chronic edema in London, United Kingdom [40]. While the study did not formally provide cost estimates, it offered important insights on the possibility of more intensive use of healthcare resources, as well as productivity loss among patients affected by lymphedema. Over a 12-month duration, 29% of patients interviewed had at least one acute infection and 15% reported experiencing one or more hospital admissions for their edema; the average length-of-stays of these hospitalizations was 12 days. In addition, over 80% of patients took time off from work due to their condition. The average time absent from work for medical appointments was 10.5 days. Employment interruption was documented, with 2% of the survey respondents reporting job change because of edema and 8% reporting having to give up work. Patients interviewed in this study were not limited to those with lymphedema related to cancer treatments and the authors did not differentiate between primary and secondary lymphedema in their analysis.

Shih et al. published the first cost estimate of breast cancer-related lymphedema in 2009 [2]. Using 1997–2003 commercial data from the MarketScan Health and Productivity Management (HPM) database, Shih and colleagues identified an incident cohort of female breast cancer patients and defined the breast cancer-related lymphedema cohort as those who were diagnosed with lymphedema within 2 years of initiating breast cancer treatment. Lymphedema was determined via ICD-9 codes 457.0 and 457.1 from medical claims data in the HPM. To understand whether breast cancer-related lymphedema was associated with higher medical costs, the authors constructed a one-to-three matched control cohort of breast cancer patients with similar treatment profile as the breast cancer-related lymphedema group but without ICD-9 codes indicative of lymphedema within 2 years of treatment initiation. Costs of breast cancer-related lymphedema were estimated as the difference in total medical costs between the lymphedema and non-lymphedema groups in the 2-year duration. In addition, the study also kept track of complications and classified them as those that were most likely associated with lymphedema, such as lymphangitis and cellulitis, and those that may be lymphedema-related, such as septicemia, bacteremia, phlebitis, and thrombophlebitis, among others [2].

Of the 1877 incident cases of breast cancer identified in this study, approximately 10% (180 of 1877) were patients who had claims indicating breast cancer-related lymphedema. Predictors of breast-cancer-related lymphedema included treatment with full axillary node dissection and chemotherapy. On average, total medical costs for the 2-year study duration were $15,000 to $23,000 (in 2006 US dollars) higher for the lymphedema group. When enumerated in 2015 US dollars, the above difference amounts

Table 40.2 Comparison of 2-year healthcare resource utilization for non-cancer-related outpatient care for women with and without DX_BCRL

Cost category	DX_BCRL	Non-DX_BCRL	Difference	p value
Total # of office visits	73.1	56.1	12.0	<0.001
Total # of prescriptions	48.7	36.0	12.7	<0.001
Proportion of patients with utilization				
% hospitalization	27.3%	27.1%	0.2%	0.997
% level IV and V visits[a]	97.1%	95.5%	1.6%	0.370
% MH-related services[+]	74.1%	65.9%	8.2%	0.05
% diagnostic imaging[#]	98.8%	94.1%	4.7%	0.012
% upper arms	20.6%	13.2%	7.4%	0.019
% chest	84.7%	76.4%	8.3%	0.023
% abdomen	49.4%	32.4%	17.0%	<0.001
Average counts per patient				
Level IV and V visits	8.7	7.2	1.4	0.014
Diagnostic imaging	6.1	4.7	1.4	<0.001
Average number of days patients' usual activities were interrupted due to hospitalizations or physician office visits				
Total # of days	58.7	46.5	12.2	<0.001
Days in hospitals	2.6	2.4	0.2	0.793
Days in office visits	56.1	44.1	12.0	<0.001

Note: *DX_BCRL* diagnosed breast-cancer-related lymphedema, *MH* mental healthE
[a]Level IV and V visits are outpatient visits that involve medical decision-making for patients with moderate or high complexity; diagnostic imaging included radiologic examinations, computed tomography, and magnetic resonance imaging
Used with permission [2]

to $20,000 to $31,000. Compared to the matched cohort of non-lymphedema patients, those in the lymphedema group were twice as likely to report infectious complications; the higher complication rates then contributed to higher medical costs observed in the lymphedema group. Although the lymphedema group also incurred higher costs from the use of physical therapies and medical supplies, these two items only accounted for a small percentage of cost difference between the lymphedema and non-lymphedema groups. Other cost drivers included office visits for reasons unrelated to cancer treatments and utilization of outpatient prescription drugs [2].

The authors further explored reasons that could contribute to higher outpatient costs observed in the breast cancer-related lymphedema group. As shown in Table 40.2,

in the 2-year study period, patients in the lymphedema group on average had 12 more office visits than those in the non-lymphedema group. The higher outpatient costs were driven by a larger proportion of lymphedema patients utilizing mental health services (74.1% vs. 65.9%) and diagnostic imaging (98.8% vs. 94.1%), as well as higher frequencies of level IV and V office visits involving patients with moderate or high complexity (8.7 vs. 7.2 visits) or imaging tests (6.1 vs. 4.7 tests). This study also provided an indirect estimate of productivity loss, noting that the number of days in hospitals or having an office visit were significantly higher for patients in the lymphedema group (58.7 vs. 46.5 days, $p < 0.001$). This finding suggested that lymphedema patients could lose 12 more days from work (in a 2-year duration) than those in the non-lymphedema group.

Basta et al. [3] estimated inpatient costs associated with lymphedema [3]. Using 2006–2012 state inpatient databases from five states (Arkansas, California, Florida, Nebraska, and New York), they identified adult women with a diagnosis of breast cancer who underwent lumpectomy or mastectomy with a concurrent axillary lymph node procedure. The findings revealed a 20% incidence of lymphedema after axillary dissection and no difference with or without reconstruction. The authors defined breast cancer patients with "complicated lymphedema" as those who had any hospital admission for a diagnosis of lymphedema or related complications within 2 years of breast surgery and compared cumulative hospital charges in the 2-year duration between patients with and without complicated lymphedema. Of the 56,075 surgically treated breast cancer patients included in this study, 1279 (2.3%) were classified as having complicated lymphedema. Women with complicated lymphedema experienced five-fold more all-cause admissions compared with women without lymphedema. Multivariable analyses that adjusted for potential confounders such as age and co-morbidities showed that hospital charges were significantly higher for breast cancer patients with complicated lymphedema than those without ($58,088 vs. $31,819 per patient in 2014 US dollars). These substantially higher charges were attributed to increased office visits and therapy, diagnostic imaging, treatment for infections, and mental health services. Shih and Xu [53] cautioned that the $26,000 difference in inpatient costs reported in the above study was likely overestimated, as the estimate was based on hospital charges, which tended to be substantially higher than costs [53]. The difference in inpatient costs would likely be reduced to less than $13,000 after applying the cost-to-charge ratio.

Patient/family costs associated with breast cancer-related lymphedema was explored in a prospective study conducted in Australia [4]. Schmitz et al. [4] followed 287 Australian women with early-stage breast cancer for up to 18 months, starting from 6 months after breast surgery, to estimate patient-borne financial burden associated with adverse events related to breast cancer treatments. Breast cancer-related lymphedema was one of the complications explored in this study, and the authors used two criteria to assess lymphedema clinically: bioimpedance spectroscopy (BIS) [54] and sum of arm circumferences (SOAC) [55]. A patient was considered to have breast cancer-related lymphedema if her lymphedema index (L-DEX) score was greater than 10 BIS or if the difference in their SOAC between the affected and unaffected arm was greater than 5 cm. Questionnaires administered in this study covered a fairly comprehensive list of economic questions, including medical expenditure specifically attributable to breast cancer, use of physical and social support programs as well as domestic services, family

and other caregiving support, out-of-pocket expenses, and lost income associated with paid and unpaid work reductions. While this study reported higher direct, indirect, and total costs among patients who reported fatigue, reduced upper-body function, or upper-body symptoms or those who had four or more persistent treatment-related effects, self-reported patient-borne financial burden was not significantly different between breast cancer patients with and without lymphedema. However, it is not clear whether the null difference observed in this study can be explained by insurance coverage unique to the healthcare system in Australia.

40.3.2 Economic Evaluation of Clinical Management of Lymphedema

Lymphedema takes an emotional and economic toll on patients and their families. As noted, aside from the direct lymphedema treatment costs, there are associated potential complications that increase the economic burden. These include functional impairments, discomfort, and infection. Cellulitis can result in sepsis and hospitalization for intravenous antibiotic therapy. As such, effective treatment or symptom management strategies can potentially reduce the economic burden of illnesses. In the case of lymphedema, interventions that alleviate symptoms or reduce complications associated with lymphedema can potentially reduce the healthcare cost of lymphedema. Several studies have assessed the economic impact of interventions or management strategies related to lymphedema.

Prospective surveillance for the early identification and early treatment of lymphedema has potential to serve as a cost saving measure. Stout et al. [5] compared two surveillance strategies of breast cancer-related lymphedema: prospective surveillance model vs. traditional care model [5]. This study demonstrated significant cost savings of the prospective surveillance model, reporting costs of $693 per patient for those in the prospective surveillance model vs. $3212 per patient for those in the traditional care model. This study also provided cost information on physical therapies related to breast cancer-related lymphedema. For example, the authors showed that a full course of complete decongestive therapy including 13 visits in a 3-week duration would cost $1400; the cost of one pair of a custom-made arm sleeve with gauntlet was around $350, whereas that of a ready-made pair would be $86.

A systematic review by Stout et al. compared direct costs of treating early-onset lymphedema with the costs of traditional complete decongestive therapy and found a potential savings greater than $2400 per patient per year using the prospective surveillance model [56]. Karaca-Mandic et al. did a retrospective analysis of cancer-related and non-cancer-related lymphedema patients treated with an advanced pneumatic compression device [57]. Patients were followed for 1 year post-treatment with the advanced pneumatic compression device. Among the cancer lymphedema cohort, total costs per patient were reduced by 37% from $2597 to $1642. There was 54% reduction in outpatient costs. Cost reductions were similar in magnitude for the non-cancer lymphedema cohort.

Larouche and Witty [58] demonstrated the potential cost savings of a prospective surveillance model over the traditional impairment-based treatment/management

model in an exploratory study evaluating the costs of clinical management using a budget impact model for cancer-related lymphedema in Quebec. The study estimated the costs and resources utilized for treatment through the 5-year period after lymphedema diagnosis. The authors defined two distinct phases of treatment for the management of lymphedema: an intensive phase, ranging from 2 to 4 weeks and directed toward reducing the limb volume, and a maintenance phase aimed at maintaining the reduction in volume. This study reported breast cancer-related lymphedema treatment costs averaging $422 per patient during the intensive phase. This cost included the average prices of compression bandages, physiotherapy assessment, and bandage application. These authors estimate the annual average cost of an intensive-phase lymphedema management program for the first 5 years to be around $219,700 or $329,500, depending upon the proportion of patients treated (10% or 15%, respectively). The annual average cost of maintenance-phase treatment was reported to be $1217 per patient. This results in an estimated annual average cost of between $6 million and $9 million for a maintenance-phase management program for the first 5 years, increasing to between $8 million and $12 million annually by the fifth year of the program, using the premise of a 10–15% incidence of secondary lymphedema. Results of this study were supported by a later study demonstrating that breast cancer survivors who had experienced mild lymphedema faced a three-fold increase in their risk of developing moderate to severe lymphedema.

A recent study conducted by Mahoney [59] sought to determine the impact of the direct and indirect costs of a prospective surveillance model for breast cancer-related lymphedema, as compared to the costs of a traditional impairment model. Direct costs in this study included physical therapy visits and durable medical equipment, whereas the indirect costs comprised days lost from work and hospitalizations secondary to infections. In the traditional impairment-based model, only hospital charges were found to have a positive relationship to total costs of the model ($p < 0.001$). There was a significant reported difference between the total costs of the prospective surveillance model and the traditional impairment-based treatment model in regard to direct and indirect costs. These study results support prospective surveillance implementation as a viable course of treatment for patients with breast cancer-related lymphedema, as compared to the traditional impairment-based model.

Another recent study, by Chance-Hetzler et al., examined the effectiveness of prospective surveillance in postsurgical breast cancer patients ($n = 49$) [60]. The retrospective analysis evaluated the time required for completion of bilateral limb measurements and the Lymphedema Breast Cancer Questionnaire (LBCQ), referral to lymphedema management with limb volume increase (LVI) and/or LBCQ symptoms, and the cost of lymphedema management at lower LVI (>5%–<10%) versus the traditional threshold for referral (>10%). The time required for circumferential measurements in minutes by frequency revealed the majority of measurements were completed in 20 min or less by an experienced staff member. Referral to rehabilitative services for further evaluation was significantly correlated ($p < 0.001$) with the presence of both LBCQ symptoms and LVI. Patients presenting with LBCQ symptoms only or LVI only were much less likely to be referred for lymphedema treatment. The cost analysis comparing referral for two treatment-matched patients developing lymphedema at the reduced threshold versus the traditional threshold provided evidence of cost savings (49%). The results of this

study are also congruent with a study conducted by Hayes et al. [55], which demonstrated that integration of a prospective surveillance model was beneficial and translated to earlier diagnosis and treatment, resulting in more manageable lymphedema, with 80% of those diagnosed with breast cancer-related lymphedema not exceeding a 20% limb volume ratio.

Arsenault et al. [61] evaluated the impact of a complete decongestive therapy program on the cumulative incidence of hospitalizations for patients with recurrent lymphedema-related cellulitis [61]. While no cost estimate was provided in this study, the authors conjectured that reduced hospitalizations would lead to cost savings. They found that the complete decongestive therapy program implemented in their study was associated with a sharp drop in the number of hospitalizations, with the average number of hospitalizations reduced from 8.5 admissions per year to less than one.

A study by Brayton et al. demonstrated that cancer-related lymphedema affects a significant and increasing population (0.95% in 2007 to 1.24% in 2013) of cancer survivors [62]. Prior studies have indicated that lymphedema adds significantly to the cost of disease management. Brayton et al.'s study evaluated the overall healthcare cost of lymphedema management. The authors conducted a retrospective analysis of a de- identified Normative Health Information (dNHI) claims database for calendar years 2007 through 2013 to identify the population trends in lymphedema prevalence and healthcare costs of lymphedema using a pre-/post-design to evaluate the 12-month before and after pneumatic compression device therapy. The dNHI database includes the enrollment from both commercially insured and Medicare Managed Care of a US national managed care healthcare insurer. The dNHI database population was geographically diverse (16% west, 20% midwest, 36% south, and 27% northwest) and was inclusive of both medical (facility and professional) and pharmaceutical claims data. Pneumatic compression device use was significantly associated with decreased rates of hospitalization (45% vs. 32%, $p < 0.0001$), outpatient visits (95% vs. 90%, $p < 0.0001$), and use of physical therapies (50% vs. 41%, $p < 0.0001$). The average baseline healthcare cost was $53,422 but decreased to $41,589 ($p < 0.0001$) post-pneumatic compression device purchase.

40.3.3 Insurance Coverage of Lymphedema Treatment

In the United States, there is no uniform insurance coverage for lymphedema treatment. Medicare will not pay for compression garments unless there is coincident wound care. Medicare will cover medically necessary therapy, but there are annual therapy financial limits or "caps" and there are regulations governing payment for intermittent compression pumps. Payers other than Medicare vary widely in coverage for lymphedema therapy, garments, and intermittent compression pumps. The 1998 Women's Health and Cancer Rights Act (WHCRA) [63] mandates commercial insurance coverage for any external breast prostheses that are needed before or during reconstruction. WHCRA also mandates coverage for any physical complications at all stages of mastectomy, including lymphedema. Lack of medical insurance or restrictive coverage is a barrier to adequate lymphedema treatment and increases the risk of complications and care costs. Coverage for breast cancer survivors with lymphedema is perhaps the broadest coverage for lymphedema in the United States, but it is still inadequate to fully meet the needs of

survivors with breast cancer-related lymphedema. Coverage for non-breast cancer-related lymphedema is more limited and disparate.

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40.3.4 The Promise of Prospective Surveillance

There are an estimated 246,660 new breast cancer cases that will be diagnosed in women during 2016 [64], and according to the Surveillance, Epidemiology, and End Results Program (SEER) data, there are currently 3.1 million breast cancer survivors in the United States [65]. The emergence of breast cancer-related lymphedema within months to decades post-breast cancer treatment and the lack of a standardized measure or universal criteria for diagnosis is problematic in determining incidence and in diagnosing patients at the earliest stage due to lack of follow-up [6, 7, 66, 67]. A 2-year cumulative rate of breast cancer-related lymphedema incidence was reported as 10% for sentinel lymph node biopsy plus radiotherapy, 19% for axillary lymph node dissection without radiation therapy, and 30% for axillary lymph node dissection plus radiation therapy in a study of 627 patients diagnosed with breast cancer who underwent 664 mastectomies between 2005 and 2013 [68]. Although surgical advances have improved, lymphedema resulting from treatment for malignancy has been reported to occur in up to 49% of breast cancer, 20% of gynecologic cancer, 16% of melanoma, 10% of genitourinary cancer, and 6% of head and neck cancer survivors after lymph node dissection and/or radiotherapy [69].

There is significance in understanding the magnitude of the problem of delayed diagnosis of lymphedema, given the large numbers of patients that are affected. With high healthcare costs as a main focus, the importance of earlier lymphedema diagnosis has been reported as a cost savings to healthcare facilities [3, 5, 60]. From a surgical standpoint, earlier-stage lymphedema has been shown to retain intrinsic contractility of the lymphatics and lack the typical chronic inflammatory change seen in later stages [70, 71]. Another prospective surgical study was conducted to determine pre- and post-surgical upper limb constitutive differences in pump pressure and lymphatic transport rate measures with female breast cancer patients ($N = 26$) [72]. Findings demonstrated higher pump and transfer measures preoperatively in women who later developed breast cancer-related lymphedema than in those who did not, suggesting that preoperative screening for predisposition to lymphedema could be beneficial in a prospective surveillance program [72, 73].

Patients voice unmet needs for education, treatment, and psychological support in managing lymphedema throughout survivorship [1, 21]. Early detection of lymphedema through prospective surveillance and early treatment gives the best opportunity for more efficacious treatment and subsequent preservation of quality of life. Stout et al. [67] conducted a breast cancer morbidity trial using the Clinical Pathway for the Prospective Physical Therapy Model of Care, in which 196 women breast cancer survivors participated in visits to monitor arm measures at 3-month intervals up to 18 months [67]. Using criteria of an upper limb increase of ≥3% compared to the preoperative measurement of the affected extremity to diagnose subclinical lymphedema, it was hypothesized that a light compression garment for a short time would alleviate the subclinical lymphedema and could then be discontinued. An age-matched group was used for comparison. Of 43 women who developed subclinical lymphedema, a statistically

significant mean volume decrease (48 mL) was reported after the intervention ($p < 0.0001$). Successful treatment of subclinical lymphedema (up to 150 mL interstitial congestion) with prospective surveillance at 3-month interval visits may reduce progression to a later stage requiring costly aggressive treatment [67].

A multidisciplinary approach to prospective surveillance programs for both primary and secondary lymphedema management makes logical sense as a shift from the current problem-oriented traditional approach. The majority of prospective surveillance programs have been focused on malignancy-related lymphedema; however, programs for both malignancy- and non-malignancy-related lymphedema require more rigorous study in order to create evidence-based standards of care. A preoperative history and physical, including bilateral arm volume measurements, allows for baseline information that is reliable as a prognostic indicator with postoperative and future interval measurements. A baseline preoperative measurement is more reliable than a single post-op measure because there is no surgical swelling to inhibit accuracy [67, 74]. In addition to physical measures, quality of life measures; education; symptom management questionnaires, specifically the Lymphedema Breast Cancer Questionnaire (LBCQ); and ongoing psychosocial support should be added [75]. A holistic view of persons with lymphedema should include assessment of self-efficacy and self-regulation, as well as evaluation of how confident patients are with their ability to manage their lymphedema and apply effective coping mechanisms [33, 76, 77]. Cost savings are significant with prospectively managing patients at risk for lymphedema and for ongoing care for those that have developed lymphedema. Most importantly, interventions to enhance patient outcomes with improved adherence to risk-reduction behaviors and lymphedema management, decrease progression to chronic and debilitating stages, and subsequently improve patients' quality of life should be implemented sooner, rather than later.

Concluding Remarks

Additional research is needed on the economic burden of lymphedema and the cost-effectiveness of lymphedema-related interventions. The limited information from current literature suggests that patients with breast cancer-related lymphedema incur higher medical costs, accrue more days off work, and some even report job loss or a change of job function [38, 39, 78]. Studies taking the perspective of payers or healthcare system have shown higher costs of breast cancer-related lymphedema [2, 3, 53]. Interestingly, one international study taking the patient's perspective found that self-reported patient-borne financial burden was not higher for patients with breast cancer-related lymphedema in a country with national health insurance [4]. Given the variations in insurance coverage policies and treatment patterns across countries, it is important to interpret findings of economic studies in the context of the healthcare system and reimbursement environment in which the study was conducted. In addition, studies have shown that interventions leading to early detection or reducing symptom burden of lymphedema have the potential to improve health outcomes and reduce healthcare costs. Developing strategies and innovative technologies that facilitate early detection and timely symptom management hold great promise in improving the overall welfare of lymphedema patients and those at risk.

Take-Away Points

1. There is high-level consensus on the need for more studies on lymphedema outcomes within the context of both the healthcare system and on the personal, family, and community levels.
2. There is a need for goal-setting within the international professional communities to accomplish universal standardization and benchmarks in assessment, diagnosis, and management of lymphedema.
3. We cannot truly make a difference in morbidity outcomes without standardization in metrics for diagnosis and implementation of adequate and uniform treatment coverage for lymphedema.
4. Implementation of prospective surveillance is key in providing appropriate follow-up care and support for persons at risk of developing lymphedema and in recognizing lymphedema complications for those living with lymphedema of all causes.

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Practical Issues in the Physiotherapeutic Approach to Lymphedema

Contents

Lower Limb Lymphedema

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Summary of Basic Concepts

Lower limb lymphedema accounts for the majority of all lymphedema case; therefore its decongestion represents an important field of lymphedema care. The various components of physiotherapy (manual lymph drainage, pneumatic compression, exercise, kinesiotaping, Linforoll treatment) and compression (bandaging, classical and new forms of stockings) are explicated in an actualized way.

41

41.1 Introduction

Lower extremity lymphedema accounts for the majority of all lymphedema cases. Therefore its treatment deserves particular attention.

It is hardly found in its pure form, because underlying pathophysiology (e.g., ischemic heart disease, diabetes, chronic venous insufficiency, etc.) and accompanying factors (e.g., administration of medications causing peripheral edema) may further affect Starling equation. Chronicity is reached when the lymphatic drainage trying to overcome the increased load of extravasated fluid decompensates. The associated circulatory, lymphatic, and soft tissue changes therefore require a comprehensive management including the treatment of comorbidities [6].

Basically, both primary and secondary lymphatic insufficiencies are incurable conditions that have been historically defied by predominantly compression/physiotherapy-based therapeutical interventions against its progressive nature. Hence, the difference in their characteristics and behavior often influences the elements of treatment approaches [1, 2, 7, 8].

41.2 General Consideration

Manual lymph drainage (*MLD*)*-based complex decongestive physiotherapy* (*CDP*) is now the mainstay of lower limb lymphedema treatment regimen; it consisted of three different phases: intensive, transition, and maintenance phases. Each phase has unique role with distinctively different aims to improve the condition, and they were thoroughly reviewed through previous ▶ Chap. 9.

However, MLD as the first component of the CDP still fails to clear lingering doubt on its real value despite strong empirical body advocating its benefits. Numerous clinical studies argue its effect in decongestion [10, 11]; however recent research data were able to demonstrate its potential on volume reduction [12] and on the amelioration of lymph vessel contractility [13].

Nevertheless, MLD has been known to soften and relax skin [14] and increase arterioral, capillary [15], and venous flow [16]; has peripheral analgesic, central sedative, antiserotonin, and antihistamine effect [15]; evokes vagotonic reaction [15]; and improves muscular recovery after physical exercise [17]. A recent report, similar to the traditional daily practice, strongly encourages its use as a component of other decongestion maneuvers [12]. Of particular interest, MLD appeared to be efficient in breast cancer treatment-related secondary lymphedema prevention; however the same investigation has never been conducted regarding leg lymphedema prevention [18].

Hence, proper application of MLD in various forms of leg lymphedema is worthy for a revisit to emphasize its unique efficacy. Indeed, different condition of uni- or bilateral and primary or secondary lymphedema influences proper application of MLD to lower limb lymphedema significantly.

The treatment of «*unilateral*» *primary leg lymphedema* [9] should follow appropriate steps of *central treatment*, either in supine position or prone position, followed by *leg treatment* also in supine position or prone position with correct regimen, which were also thoroughly reviewed in ▶ Chap. 9.

However, precise application of every step of each treatment in right sequence either in supine or prone position cannot be overemphasized. Leg treatment steps should be repeated so as to treat all regions several times.

Treatment of «*bilateral*» *primary leg lymphedema* [9] is consistent with unilateral primary leg lymphedema treatment, but there is an exception on the following steps: central treatment in supine position should include axillar lymph nodes of both sides, and both lower edematous body quadrants should be decongested to the direction of axillary lymph nodes of identical sides.

In prone position, the treatment of inguino-axillar anastomoses on both sides should be incorporated, and gluteal region should be decongested to the direction of axillar lymph nodes of identical sides.

Treatment of «unilateral» secondary leg lymphedema [9] would follow the same rule for the central treatment, either in supine position or prone position, as well as the leg treatment, which are consistent with primary lymphedema care.

However, the *treatment of «bilateral» secondary leg lymphedema* [9], which is generally consistent with unilateral secondary leg lymphedema treatment, has some exception as follows: central treatment in supine position axillary lymph nodes of both sides should be treated together, in addition to the decongestion of both lower edematous body quadrants to the direction of axillary lymph nodes of identical sides. In prone position, the treatment should include inguino-axillar anastomoses on both sides and also the decongestion of gluteal region to the direction of axillary lymph nodes of identical sides.

41.2.1 Intermittent Pneumatic Compression (IPC)

In accordance with the International Compression Club (ICC) Consensus, high level of evidence supports the use of IPC in lymphedema (Grade 1B) [19].

IPC has been assumed to reduce edema by decreasing capillary filtration, rather than by accelerating lymph return; however a recent finding was able to show the formation of tissue channels providing the conduction for excess interstitial fluid [20]. IPC alone is particularly effective in nonobstructive edemas, while MLD is strongly recommended before IPC to stimulate lymphatic flow in obstructive ones. Clinical trials prefer the utilization of multichambered pumps to single-chambered ones [2, 21], but the pressures should be adjusted according to individual response. In general, pressures of 30–60 mmHg are mostly applied. According to the latest results, higher pressures and long inflation time are advocated for efficient decongestion in lymphedema [22, 23]. Nonetheless, venous insufficiency requires high pressure with rapid inflation [24].

Lower pressures (20–30 Hgmm) might be advised in palliative care. IPC is very efficacious in the edema treatment of immobile patient [25]. IPC reduces the amount of interstitial fluid to an adequate amount leading to an increase of the oncotic tissue pressure necessitating a continuation of compression therapy [26]. IPC may exacerbate or cause congestion at the noncompressed root of a treated limb and also in the adjacent genital region [27]. IPC seems to be an ideal device for edema control in a home-based setting. It is also able to diminish the frequency of bacterial infection attacks (e.g., cellulitis, erysipelas) and improve patient's own lymphedema-related perceptions [28, 29]. In conclusion, the quality of available clinical data does not reach the adequate scientific merit; thus further randomized controlled studies are needed for the accurate assessment of IPC efficacy [30]. Furthermore, IPC has a multimodal activity in the improvement of arterial and capillary hemodynamics and a positive impact on hemostasis [31].

Treatment with Stendo suits represents an alternative of IPC therapy [32].

41.2.2 Compression

Compression therapy has been thoroughly reviewed through ▶ Chap. 9.

Nevertheless, the fact that the compression therapy is the most effective treatment modality among the CDP components cannot be overemphasized. However, until recently, evidence of its efficacy was based mostly on empirical studies and experimental data concerning the effect of conventional compression therapy on lymphedema are sparse. But lately IUP guideline as well as AVF guideline for the lymphedema management endorses this mode of the therapy with strong recommendation fitting to Evidence 1A. [3]. A meta-analysis of the ICC found that strong level of evidence could be attributed to the application of bandages in lymphedema (Grade 1B) [19].

Patients with lower limb lymphedema with reduced ankle-brachial pressure index (ABPI) of 0.5–0.8 should not receive sustained compression exceeding 25 mmHg. Patients with ABPI <0.5 can receive only intermittent compression. [33].

The most common tools of compression are bandages, stockings, and Velcro bandages. Typical lymphedema compression with bandages is performed in a multilayer fashion [7]. To achieve optimal volume reduction, high initial interface pressures are necessary to compensate pressure decrease. The pressure drop of inelastic material is already significant after 2 h and mainly caused by volume reduction explaining the need for a more frequent bandage change in the beginning of lymphedema therapy compared to the current practice where change of bandage system is recommended once a day in the initial phase [34].

In general, inelastic compression can be worn overnight without major influence on microcirculation; hence sub-bandage pressure does not significantly interfere with capillary function in supine position.

Unlike inelastic compression, elastic bandages are normally not prescribed in overnight situation due to the fact that in a supine position interface pressure remains high, the influence of gravity is excluded, and in case of diminished arterial influx serious side effects can occur. According to experimental data, upper limb decongestion requires relatively light, while lower limb lymphedema relatively strong pressures [4].

Multilayer bandage systems may behave as inelastic systems even though the individual layers act as elastic materials due to the friction generated between bandage layers.

Therefore, it is proposed that in the case of multilayer bandage systems and kits, the terms «high or low stiffness» should be used to characterize the behavior of the final bandage. Stiffness may be characterized by the increase of interface pressure measured in the gaiter area after postural change from supine to standing position. A pressure increase of more than 10 mmHg measured in the gaiter area is characteristic of a stiff bandage system [3].

A relatively new two-component system is an easy-to-use kit adhering high patient compliance with notable efficacy [35, 36].

41.2.3 Use of Elastic Bandages

In some situations (ineffective calf muscle pump, phlebolymphedema, large volume loss is predicted), the inelastic bandages may be replaced with elastic ones. The stiffness produced by multiple layers produces high working pressure. However, the resting pressure is higher than with inelastic systems [3].

41.2.4 Special Compression Material

Inelastic adjustable compression with velcros enhancing comfort and patient compliance is an effective alternative to compression garments [5] and produces more significant volume decrease than inelastic multicomponent compression system in the initial therapeutical phase.

41.2.5 Medical Compression Stockings

The main areas of compression garment utilization comprise the long-term management of lymphedema in maintenance phase, prophylaxis, and initial treatment or may serve the only form of compression used in time-consuming controlled compression therapy, where interstitial fluid is gradually squeezed out from affected limb by garment size reduction using sewing machine or in steady-state condition by ordering new stockings in decreasing sizes [37]. In general, most patients wear garments during waking hours including exercises.

Prophylactic use of medical compression stockings in breast cancer-related lymphedema prevention seems to be of invaluable practical importance [38], and this conception has been partially extrapolated to legs as vulval cancer treatment-related lymphatic impairment was successfully prevented with the use of graduated compression stockings [39]; however a latter clinical trial discouraged the application of class II compression hosieries in the prevention of lower limb secondary lymphedema manifestation [40].

Limbs with relatively normal shape require round-knitted stockings, while flat-knitted stockings better fit to limbs with unusual shape or remarkable distorsion than round-knitted ones.

In general, compression stockings have a lower stiffness index than inelastic bandages, especially when these bandages are worn in a multilayered fashion. Superimposement of

medical compression stockings has an increasing impact on practical lymphology. While upper limb lymphedema often requires interface pressure no more than 40 mmHg, in case of leg lymphedema, particularly in primary lymphatic insufficiency, «subgarment» pressure measured at medial gaiter area may even exceed 60–80 mmHg corresponding to the superposition of two to even four medical compression stockings with various compression classes properly retaining edema and maintaining reduced volume. MCSs drop their pressure to a much less degree compared to compression bandages [41, 42].

Double-layered ulcer stockings appeared to assist not only venous leg ulcer healing but efficient volume reduction of lymph- and venous edema [43].

Even sports socks are able to exert decongestive effect to a significant degree [44].

41.2.6 Exercise

Exercise/movement should be tailored to the patient's needs, ability, and disease status. Compression should be worn during exercise whenever it is possible. Walking, swimming, cycling, and low-impact aerobics are recommended. Exercise varies interstitial tissue pressure and influences both lymph propulsion and clearance, helping to transport fluid and inflammatory-causing proteins from the site of formation and from the swollen limb or affected area [45]. Studies demonstrated that both mechanical limb elevation and passive exercise [46] or 5 min of instructed deep breathing plus self-massage followed by 30 min of isotonic and isometric limb exercises [47] can produce a reduction in limb volume and subjective improvements in symptoms. In aqua lymphatic therapy, the selection of optimal water temperature is mandatory; hence exercises at 28 °C produce volume reduction, but a temperature of 34 °C results in a slight increase in volume [48]. Underwater leg exercises proved to significantly enhance the efficacy of decongestive physiotherapy especially from the perspective of patient own perception [49, 50].

41.2.7 Lymphedema Severity-Adopted Forms of CDP

Initial management of leg lymphedema implements psychosocial support; education; skin care; exercise/movement; elevation and management of any concomitant medical conditions, pain, or discomfort; and the utilization of various forms of compression.

Stage I lymphedema The pressure used should be guided by the patient's vascular status and their ability to tolerate compression and manage the garment. Skin care, exercise/movement, elevation, and self-drainage should be taught alongside self-monitoring and proper application, removal, and care of hosiery. Patients should be examined 4–6 weeks after initial fitting and then after 3–6 months if response is satisfactory. The patient should be examined at each stocking order (every 3–6 months).

Stage II and III lymphedema Intensive treatment comprises the standard elements of CDP and can be tailored to patient ability and comorbidity status.

Standard intensive therapy (*>45 mmHg*) is undertaken daily with a sub-bandage pressure >45 mmHg.

Intensive therapy with reduced pressure (*15–25 mmHg*) corresponds with the previous therapeutical regimen. Patients are selected for this treatment when high levels of compression are either unsafe or difficult to tolerate (moderate peripheral arterial occlusive disease (ABPI 0.5–0.8), mild neuropathy, lipedema, cancer under palliative treatment, comorbidities requiring less aggressive reduction in swelling).

41.2.8 Miscellaneous

There is an emerging number of trials where *kinesiotaping* (KT) was implemented for lymphedema treatment in a comparative fashion with compression bandaging. Where lymphedema-related symptoms were reported, KT was found to be superior to compression. Paradoxically, patients receiving bandaging reported a higher QoL. KT was not found to be more comfortable than bandaging. KT should only be used with great caution where bandaging cannot be used [51].

It has been recently reported that *Linforoll device* is capable of efficient skin softening and volume reduction as an integral part of conservative or surgical lymphedema therapy of lower limbs [52].

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Upper Limb Lymphedema

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Summary of Basic Concepts

- From a pathophysiological point of view, breast cancer-related lymphedema is caused by a lymphatic pump failure instead of a blockage principle.
- The scope about BCRL is changing toward prevention, risk stratification, and early diagnosis. Therefore these items should be an integrated part in the treatment of breast cancer.
- Risk factors can be divided in changeable or not such as previous oncological treatment. The main influenceable risk factors for the development of or worsening of lymphedema are (gain of) weight and lack of mobility.
- An integrated program for prevention or treatment of lymphedema should include active intervention for overweight reduction with dietary advices, calculating the caloric intake and burn in combination with an active caloric burn program.
- Early diagnosis of lymphedema and risk stratification should be performed by standardized clinimetrics within a new, more holistic approach of the patient using the ICF method (International Classification of Functioning, Disability and Health, WHO).
- Treatment of lymphedema can be divided in an initial and maintenance treatment phase. In all phases, compression technology is the cornerstone of treatment in combination with exercise, improvement of functionality, and weight control. In the maintenance phase, the patient should be able to use self-management to control and maintain their situation and is self-effective. When indicated, MLD should be restricted to the initial treatment phase only.
- In end-stage BCRL, stage 3 circumferential suction-assisted lipectomy (CSAL) is the therapy of choice to have a 100% volume reduction of the arm. Lifelong compression with flat knitted garments is mandatory.

42.1 Introduction

Within the realm of lymphatic disease treatment, there are many therapeutic interventions available, as highlighted in previous chapters. Treatment of lymphedema (LE) is very challenging. Therapeutic options in LE include conservative and operative modalities and should be individualized with regard to the circumstances of the patient and the lymphedema by a multidisciplinary approach. These circumstances include age, comorbidities, prognosis of (malignant) disease, psychosocial aspects, weight, and physical potential. The goals for conservative treatment are to eliminate edema by reducing interstitial fluid accumulation and to stimulate lymphatic propulsion by compression and to improve quality of life of the patient in various domains of their life as social functioning and participation, physical improvement, and psychological well-being.

The World Health Organization's taxonomy in the *International Classification of Functioning, Disability and Health* (ICF) [32] provides an appropriate framework that allows systematic categorization of clinical observations based on an integrated bio-psychosocial model. This model, which is designed for chronic conditions, focuses not

just on physical and medical aspects but takes also social functioning and personal and environmental aspects into account. The ICF framework consists of the following components:

- Body structures and functions
- Activities and participations
- Personal and environmental factors

By using the ICF method for evaluation of the results of treatment, the focus is not just on volume of the limb but includes a more holistic approach and takes the whole patient and daily practice functioning into account. Special core set for lymphedema has been developed [4] and needs further implementation.

Traditionally, many therapeutical modalities are performed in combination. The contribution of each individual treatment modality to the outcome is, therefore, still under discussion. In this chapter, we will focus on the timing of treatment, the combination of various modalities of treatment, and the phases of intervention.

Many terms are used to describe lymphatic treatments: complex decongestive therapy/treatment, complex physical therapy, or complex decongestive physiotherapy. These terms are confusing because it cannot be seen that the lymphatics are involved; «physiotherapy» is a term used too generally, and the word «complex» is unclear.

Therefore, in 1998, the term *decongestive lymphatic therapy (DLT*) was advocated to achieve uniformity of nomenclature and foster communication among the health-care professionals who administer therapy for lymphedema. DLT comprises a number of interrelated treatment modalities that are most efficacious when utilized in an interdependent fashion, as mentioned in ▶ Chap. 9.

Treatment of lymphedema consists of two phases: the initial treatment phase and the maintenance phase. The first phase gradually merges into the maintenance phase. The goal of treatment is to reduce lymphedema during the treatment phase, improve quality of life, and make the patient independent from the professional health-care worker. This provides the patient with as much knowledge as possible and with self-management skills to maintain the result with a good quality of life. The patient plays an active role in the maintenance of the therapeutic result. The role of the therapist during the second phase is more hands-off, monitoring and guiding the patient.

The various therapeutic options are listed in ◘ Table 42.1.

Physical treatment of lymphedema should not be considered as a single therapeutic modality but as a continuum that begins with informing and educating the patient, advocating awareness and self-management, objective early diagnostics by volumetry, and, at the end of the spectrum, individual specialized lymphedema treatments. A multidisciplinary approach, as suggested in many guidelines [6–8], is mandatory to the success of the treatment of upper limb lymphedema.

In the management of lymphedema, monitoring of activity of disease parameters as well as the results of treatment and follow-up is mandatory. Both health-care professionals and the patient can undertake such monitoring, using validated tools and a protocol covering all the domains of the ICF. While the clinimetric instruments provide tools for objective measuring in the various domains of function in relation to prevention, treatment, and follow-up of lymphoedema, they are not necessarily disease specific.

Table 42.1 Useful lymphedema interventions

Therapeutic option	Initial treatment phase	Maintenance phase
Manual lymph drainage	X	
Bandaging	X	(As part of self-management)
Garments/hosiery		X
Pneumatic compression	X	X
Physiotherapy	X	
Decongestive lymphatic therapy	X	
Exercise	X	X
Weight control	X	X
Skin care	X	X
Awareness	X	X
Self-management		X
Reconstructive surgery	X	
Reductive surgery	X	

For lymphedema two ICF-based questionnaires are validated in the English language for arms [33] and for legs [5]. These are very useful for monitoring of the lymphedema patient during both initial and maintenance phase based on the three ICF domains in combination with other validated clinimetrics as volumetry, circumference measurement, and weight measurements.

42.2 Lymphedema of the Arm

Lymphedema of the arm is, in most cases, due to treatment of breast cancer. Many factors influence the development of breast cancer-related lymphedema (BCRL), including obesity, [9] hypertension, [10] infection, type of cancer treatment, [11] and individual impaired lymphatic drainage [12].

Lymphedema frequently develops slowly, often with preclinical symptoms and signs, such as heaviness, transient swelling, and slight volume changes compared with preoperative values. Early detection is essential for a treatment program during the initial stages of lymphedema.

The practical issues in the approach to lymphedema in general, and to physical therapy in particular, are centered upon the organization and availability of care for the patient. In cancer-related lymphedema, and especially in BCRL, a protocolized approach is useful because lymphatic awareness can be integrated into the cancer protocol. This

gives the opportunity to start primary and secondary prevention programs on lymphedema from the outset. Much work has to be done to achieve this ambition.

42.3 Considerations in Manual Lymph Drainage

Only a few studies have been performed to study the additional effects of manual lymph drainage (MLD) over compression therapy in LE. Two controlled studies showed that compression therapy with or without additional MLD was equally effective for BCRL. Andersen et al. [13] performed a randomized controlled study in BCRL comparing MLD and compression ($n = 20$) with a control group that was treated with only compression therapy ($n = 20$). After 2 weeks, the control group actually had a greater percentage reduction in absolute edema (60%) compared with the MLD group (48%). Both groups experienced an equal reduction in the symptoms of heaviness and tightness, but the control group also had a reduction in reported discomfort. The reduction in absolute edema (66%) was maintained for 12-month follow-up (pooled data). Johansson et al. [14] studied the effect of short-stretch bandages with or without MLD in 38 female patients. Both groups showed significant improvement in volume reduction (−11% after 3 weeks) and fewer complaints.

A comparison of studies on MLD and compression therapy alone by Korpon et al. [15] found no difference in volume change.

In a systematic review, Kligman et al. [16] studied ten randomized controlled trials of treatment for BCRL. In all of these studies, the authors could not go farther than stating that there was «some suggestion» that compression and MLD «may improve» LE. The effectiveness of the use of lifelong compression garments was more obvious.

In daily practice, MLD is used in several therapeutic schemes, especially when it is combined with various forms of compression therapy, such as short-stretch multilayer bandaging applied after each MLD session [17]. Although MLD has been used widely for many decades and is assumed by many to be a panacea for the treatment of LE, there is currently no indisputable published evidence for its effectiveness or its mode of action in improving lymphatic drainage.

Controlled, comparative studies are currently not available for the effectiveness of each separate modality in the treatment of LE.

Moseley et al. [18] conducted an extensive review of the literature in 2006 for common nonoperative treatment modalities for LE and concluded that despite the identified benefits, there was still a need for large-scale, clinical trials in this area. A combination of MLD with compression therapy improved the results. In most studies reviewed by Moseley et al., there was a mix of lymphedema types, mainly BCRL, and specific outcome parameters were often not defined. Specific studies on primary lymphedema are not available.

In 2007, Hamner and Fleming [19] retrospectively studied 135 patients with BCRL who were receiving DLT. After 8 weeks, the volume reduction was about 18%. A surprisingly positive effect on pain was found: 76 patients experienced pain before treatment, and 56 were free of pain after treatment (76% reduction). It was concluded that LE continues to be a problem for patients with breast cancer. A program of lymphedema therapy can reduce the volume of edema and, in particular, reduce pain in this population.

Badger et al. [20] compared the effects of treatment for 18 days with short-stretch bandaging, followed by compression hosiery with those of compression hosiery alone for leg and arm lymphedema. They showed that initial compression therapy with subsequent use of hosiery was twice as effective as hosiery alone. Huang et al. [2] concluded in a meta-analysis that the current evidence from RCTs does not support the use of MLD in preventing or treating lymphedema. However, clinical and statistical inconsistencies between the various studies confounded our evaluation of the effect of MLD on breast cancer-related lymphedema.

Gradalski et al. [34] studied 60 patients with breast cancer-related lymphedema (≥ 20% volume difference) in two groups: CDT (bandaging and exercise) with and without Vodder II manual lymph drainage (30-min duration) with follow-up of 6 months. Results were in both groups the same and they conclude that MLD sparing CDT can be a standard procedure in moderate lymphedema and remarkably diminish time consumption and thus therapy costs.

Measurement of the undergarment pressure was performed in some studies [21, 22]. A major limitation of these studies is the discrepancy between the undergarment pressure claimed by the manufacturer and the actual interface pressure due to the large variety of types of garments and interindividual variation in measuring garments. Vignes et al. [23] studied 682 patients treated for BCRL for 4 years in the maintenance phase. Treatment failure was associated with younger age and higher weight and body mass index. Treatment with diurnal garments and nocturnal bandaging decreased the risk of treatment failure significantly (hazard ratio, 0.53 [0.34–0.82]; $p = 0.004$), whereas the addition of MLD did not.

42.4 General Considerations for Compression

Compression therapy is the cornerstone in treatment of lymphedema both during initial treatment phase as maintenance phase.

There exist many compression technologies such as multilayer bandaging, Velcro wrap devices, pressotherapy, point pressure devices, and various types and combinations of made-to-measure garments.

The pressure delivered by compression is different in the legs than in the arms. It is important to note that the hydrostatic pressure that must be overcome by external compression is much higher in the legs than in the arms. In a standing position, the venous pressure in the distal leg is equal to the weight of the blood column between the heart and the measuring point, which is about 80–100 mmHg. The high intravenous pressure in the upright body position always increases the lymphatic load by promoting increased fluid extravasation. High external pressure is necessary in order to counteract this extravasation. The venous pressure in the arm is much lower than that in the leg because of the lower weight of the blood column between the heart and the hand. Thus, less external compression will be needed to reduce extravasation into the tissue and to promote reabsorption of tissue fluid. The arm volume reduction from bandaging is probably due not only to a pressure-dependent shift in Starling's equilibrium but also to stimulation of lymphatic drainage. Besides veno-dynamic issues, lympho-dynamic issues should also be considered. In healthy arms, the distance from the arm to the

thoracic duct is short, and the intralymphatic pressure varies with the intrathoracic pressure. Lymphatic drainage is stimulated with relatively low or even negative intralymphatic pressure. In BCRL, lymphatic drainage is deficient because of damage to the major lymph collectors and lymph nodes by surgery and/or radiation, leading to lymphatic congestion [24].

42.5 Compression Therapy in the Arms

Although inelastic, multilayer, multicomponent compression bandages allow immediate reduction of volume in lymphedematous arms and are a mandatory part of treatment, studies to measure the interface pressure in arm LE have rarely been performed before. The deciding parameter of the interface pressure, which is the dosage of compression therapy, has been measured only in patients with chronic venous insufficiency [25], and there is a positive relation between pressure and volume reduction. In arm lymphedema, for example, the compression pressure required to obtain the highest volume reduction per unit of time is unknown.

Damstra and Partsch [26] showed that low sub-bandage pressures between 20 and 30 mmHg are effective and better tolerated than high-pressure bandages by the patient with arm lymphedema. In future, more research will be required to understand the therapeutic effect of types of compression therapy and materials in arm lymphedema.

Recently, published studies have shown the importance of compression therapy after circumferential suction-assisted lipectomy (the Brorson method) [27, 28] in order to achieve a 100% volume reduction in end-stage arm lymphedema. The method consists of an operative intervention to remove the complete suprafascial component of the lymphedematous arm, which consists mainly of fat [29]. Postoperatively, compression therapy is provided by short-stretch bandaging and garments, which should be worn lifelong, the same as in the conservative treatment of arm lymphedema. All garments are custom fitted and flat knitted. Long-term results are highly favorable, with sustained complete volume reduction of the preoperative volume excess, for up to 13 years of follow-up. In this procedure, manual lymph drainage is not necessary to maintain the result.

In lymphedema, intermittent pneumatic compression has been used for decades. Megens and Harris [30] reviewed the literature on physical therapy treatment of BCRL. Most studies were inappropriately designed and often lacked proper comparisons. They concluded that compression therapy should be performed with multichamber devices in combination with other therapeutic options, such as MLD and compression. Monotherapy with intermittent pneumatic compression was discouraged.

Bandaging and hosiery can provide compression. In general, hosiery is measured when the maintenance phase is reached. In this phase there is no further volume reduction despite proper LE treatment. The terms hosiery, garments, and sleeves are often used interchangeably and include gloves, gauntlets, Bermudas, and compression devices for toes. For LE, garments should always be custom fitted and flat knitted with a high-static stiffness and should be measured routinely during long-term follow-up [31].

42.6 Exercise, Breast Cancer Treatment, and Lymphedema

Longtime exercise was thought to provoke or aggravate lymphedema. Many studies show beneficial effect of exercise on recovery after breast cancer treatment. Hayes et al. [35] advised to focus on changes in the patient' exercise program to ensure that the exercise prescribed is safe and appropriate. Finally, helping women, irrespective of whether they have lymphedema, to become and stay active during and after breast cancer treatment will ultimately lead to better health outcomes. In the RESTORE trial, Anderson et al. [36] studied 82 patients prospectively during 18 months to determine the effect of a moderate exercise program on quality of life, physical functioning, and arm volume. With this early exercise intervention after breast cancer diagnosis, a significant improvement was achieved in physical function, with no decline in health-related quality of life or detrimental effect on arm volume.

Even progressive weight lifting was shown to be safe for women following breast cancer, even for those at risk or with lymphedema, irrespective of the diagnostic criteria used [37].

Dieli-Conwright et al. [3] reviewed literature about exercise and focused on well-established benefits of exercise on physical and emotional well-being, bone health, lymphedema management, and the postulated benefits of exercise on risk reduction for recurrence of breast cancer.

In patients with lymphedema, Paramanandam et al. [38] performed a systematic review of 11 eligible randomized trials. There is no evidence to suggest that high intensity weight training is harmful to the arm with or at risk of BCRL. On contrary, exercise and good mobility of the arm and shoulder support a better result in lymphedema treatment in combination with compression technology.

42.7 Weight and (Risk of) Lymphedema

Risk factors for developing lymphedema can be related to cancer treatment and/or related to patient factors. The latter one is more or less influenceable by lifestyle change of the patient or active interventions. Besides lack of exercise, a raised BMI as $\geq$25 is a main risk factor for developing or aggravating lymphedema in all incidence studies [1, 39–41]. In a review and meta-analysis in which dietary interventions were taken into account, there was evidence that exercise and weight loss as strategies improve lymphedema symptoms and reduce upper extremity lymphedema volume, respectively [42].

An integrated program for prevention or treatment of lymphedema should include active intervention for overweight reduction with dietary advices, calculating the caloric intake and burn in combination with an active caloric burn program.

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Head, Face, and Neck Lymphedema

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Summary of Basic Concepts

The predominant clinical presentation of lymphedema is characterized by the presence of regionalized edema; this problem is commonly encountered in the regions of the head and neck.

- As in other forms of this disease, lymphedema of the head and neck can be classified as either «primary» or «secondary», although hybrid forms will certainly be encountered.
- Head and neck involvement in primary lymphedema suggests a widespread developmental problem of the lymphatics.
- Localized head and neck lymphedema also occurs as a consequence of recurrent episodes of skin infection or chronic inflammation.
- Head and neck lymphedema is often iatrogenic, the consequence of surgical resection and radiotherapy.
- A compression garment is required to maintain the results achieved with manual lymph drainage and multilayered bandaging. For mild cases of facial lymphedema, a ski mask can fulfill this function, but a medical garment for facial edema may be necessary. The garment is typically worn at home.
- Treatment of head and neck cancer may trigger a variety of dysfunctional consequences beyond lymphedema. Lymphedema of the face and neck generates emotional and social dysfunction which must be assessed and addressed in a timely fashion to maximally enhance the quality of life for patients and family.

Lymphedema, the complex, regional edematous state that ensues when lymph transport is insufficient to maintain tissue homeostasis [6], appears in settings where there is a relative failure of interstitial fluid clearance in the face of normal capillary filtration [7]. The predominant clinical presentation of lymphedema is characterized by the presence of regionalized edema; this problem is commonly encountered in the regions of the head and neck. In fact, as in other forms of this disease, lymphedema of the head and neck can be classified as either «primary» or «secondary», although hybrid forms will certainly be encountered [8, 9].

Primary lymphedema of the head and neck may be associated with limb lymphedema; however, when it occurs as a manifestation of the congenital, *praecox*, or *tarda* forms of lymphedema, the presence of head and neck lymphedema will suggest to the clinician that the lymphatic insufficiency is quite widespread [10].

Localized head and neck lymphedema also occurs as a consequence of recurrent episodes of skin infection or chronic inflammation. Recurrent infections and chronic inflammation alter the structure and function of the initial lymphatics and cause obstruction of lymphatic collectors.

Head and neck lymphedema is often iatrogenic, occurring as a consequence of cancer therapeutics, typically the consequence of extensive surgical resection and radiotherapy. Prospective studies of lymphedema in head and neck cancer have been limited [11]. Beyond the initial therapeutic intervention, additional contributing factors may include either infection or recurrent neoplastic involvement [12]. Treatment of head and neck cancer typically requires interventions such as modified radical neck

dissection, total laryngectomy, and neck radiotherapy and chemotherapy. In isolation or in aggregate, these interventions can create myriad complications, including, of course, lymphedema.

Lymphedema of the head and neck is very common after radical neck dissection. A recent prospective study of 81 patients [1] suggests that 75.3% of the patients had some identifiable lymphedema, as characterized by visible swelling of skin and soft tissues, internal edema of the mucosa and soft tissue by fiberoptic endoscopy or indirect laryngoscopy, or both.

Closer examination of these data reveals that 7.4% of patients had external lymphedema, 29.6% had internal lymphedema, and 50.8% had both. Of the patients with external lymphedema, 18.5% had stage I and 27.2% had stage II lymphedema; of the patients with internal lymphedema, 34.5% were mildly edematous, 45.5% were moderately edematous, and 20% had severe lymphedema by the Patterson scale. Moderate lymphedema typically affected the interarytenoid space, valleculae, and aryepiglottic folds; severe lymphedema commonly affected the pyriform sinus and interarytenoid space [1].

With the recognition that quantitation of head and neck lymphedema and fibrosis can pose challenges, there has been recent development and early validation of a set of criteria for this purpose [2]. The Head and Neck External Lymphedema and Fibrosis (HN-LEF) Assessment Criteria allows for ultrasonographic characterization and patterning for various types of lymphedema and fibrosis, particularly in the cheek, submental, and neck regions. Early validation studies confirm that the tool demonstrates good inter-rater reliability.

Fortunately, early-onset lymphedema is often transient, improving as inflammation subsides and collateral lymphatic pathways open. However, lymphedema can also progress to the point of endangering the airway and obstructing the pharynx [12]. The condition must be assessed and treated as early as possible to minimize functional, as well as emotional, sequelae.

In addition to regionalized lymphedema, dysphagia, mucositis, dermatitis, nutritional and metabolic changes, xerostomia, dysgeusia, speech impairment, hearing loss, vestibular disorders (when radiotherapy impacts the temporal bone and the brain stem) [13], and shoulder dysfunction, when the spinal accessory nerve is injured [3, 12], commonly ensue. Verbal communication, social interaction, eating, and respiratory function may be impaired [13]. The presence of internal lymphedema correlates with the presence of subjective and objective measures of dysfunction of deglutition [4]. All of these sequelae can impact the approach to, and responsiveness of, the associated lymphedema.

43.1 Physical Treatment of Lymphedema of the Face and Neck

The physical treatment of lymphedema of the face and neck includes manual lymph drainage, multilayered bandaging, stimulation of muscular activity, use of compressive garment(s), education in the precautions that the patient should observe to avoid complications and exacerbation of symptoms, and, if appropriate, education in self-treatment techniques (Table 43.1).

Table 43.1 Treatment of Facial Edema

The treatment of lymphedema of the face includes:
1. Manual lymph drainage
2. Multilayered bandaging
3. Stimulation of muscular activity
4. Education in precautions to observe to avoid exacerbation of symptoms
5. Education in self-treatment

43.2 Manual Lymph Drainage (Leduc Method)

The superficial lymphatic collectors of the face chiefly carry lymph toward the parauricular, submandibular, and submental lymph nodes. From these nodal sites, the lymph progresses to the supraclavicular lymph nodes, from which point the treatment is initiated. However, in more complex cases, where involvement extends to the shoulder girdle, the treatment is initiated at the level of the axillary lymph nodes.

43.3 Description of the Maneuvers

- The maneuver performed on the lymph nodes consists of a slight mobilization of the skin overlying the nodes in question, in the direction of the major lymphatic drainage of the region under treatment, with manual application of a pressure equivalent to the weight of the hand. The flat hand is applied to the area, avoiding any rotation that would impart a shear force, which might generate a local inflammatory response. The maneuver is repeated ten times on each set of lymph nodes (Fig. 43.1).
- The *call-up maneuver* is applied either proximally to the lymphedematous area or after completion of the reabsorption maneuver (*v.i.*), in a distal-to-proximal direction on the lymphedematous, treated area. The radial aspect of the hand is brought into contact with the skin. The maneuver is initially intended to mobilize the skin in the direction of primary lymphatic flow, followed by the application of a gentle pressure by the full hand or several fingers, as dictated by the size of the involved area. The maneuver will be repeated five times on each section of the treated site (Fig. 43.2).
- In the *reabsorption maneuver*, the ulnar aspect of the therapist's hand is brought into contact with the skin. A mobilization of the skin is performed in the direction of the lymphatic flow. Thereafter, the full hand or several fingers, as dictated by the size of the treated area, applies a gentle pressure. This maneuver is performed in a proximal-to-distal direction on the lymphedematous area. It is repeated as many times as necessary, until a decrease in tension of the lymphedematous tissue is perceived (Fig. 43.3).

Efficacy of these maneuvers has been demonstrated through lymphoscintigraphic imaging [14].

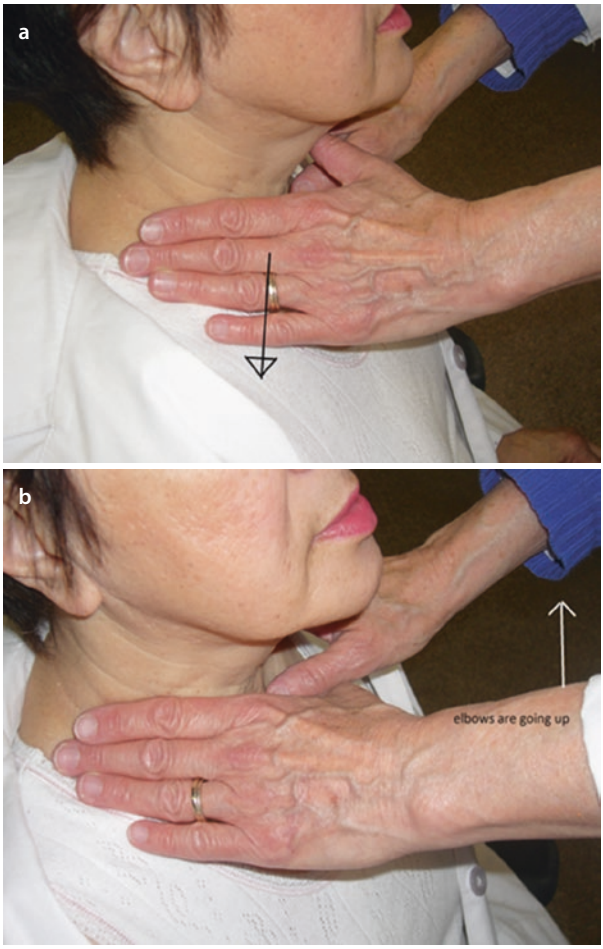

Fig. 43.1 Maneuver applied to the supraclavicular lymph nodes. **a** ascending, **b** descending

43.4 Protocol for Manual Treatment of Lymphedema of the Face and Neck

The protocol for the manual treatment of lymphedema requires the use of the described maneuvers, with application in the following order:

- 1-2 a Drainage of the *most proximal lymph nodes*. These are the nodes that receive the most proximate lymph flow derived from the involved area. In head and neck lymphedema, the proximal lymph nodes are the supraclavicular lymph nodes or, if the lymphedema extends to the shoulder region, the axillary lymph nodes.
- 1-2 b Drainage of the *intermediate lymph nodes* of the neck and face:
  1. Sternocleidomastoid lymph nodes
  2. Submental lymph nodes
  3. Submandibular lymph nodes
  4. Pre- and infra-auricular lymph nodes

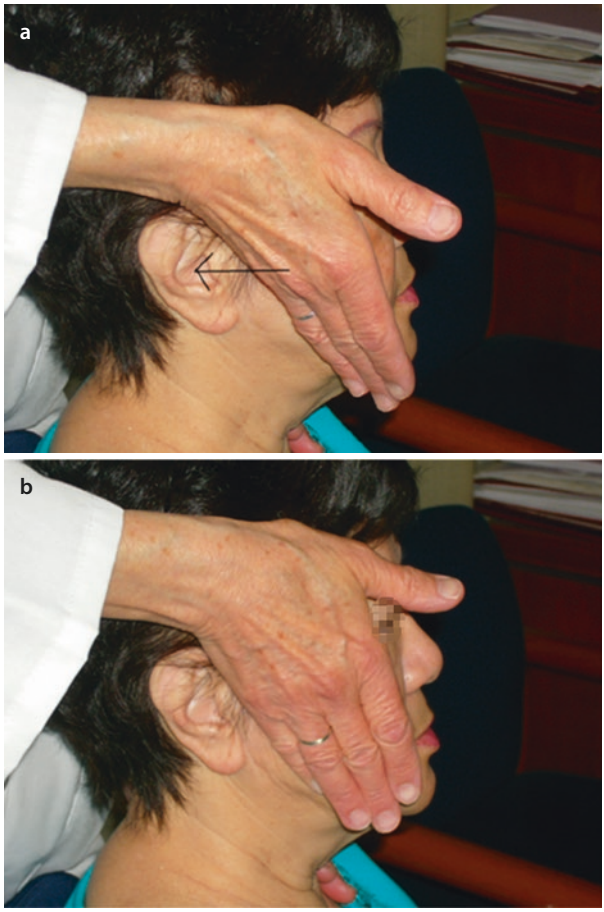

Fig. 43.2 Call-up maneuver applied proximally toward the para-auricular lymph nodes. **a** posteriorly directed, **b** anteriorly directed

- 1-2 c These lymph node maneuvers are followed by the *maneuvers on the anastomotic or substitution pathways*. Several anastomotic pathways have been described (Olivier Leduc, *unpublished observations*). Two such pathways link the two sets of auricular lymph nodes and are distributed above the upper lip and below the lower lip.
- 1-2 d Once the maneuvers on the lymph nodes and along the anastomotic pathways have been completed, the *call-up maneuver* will be applied (if there is a lymphedema-free region between the most proximal lymph nodes and the lymphedematous zone). The call-up maneuver is applied initially to the lymphedema-free area and proximal to the lymphedematous site. This maneuver has been shown experimentally to enhance the efferent lymph flow from the lymphedematous area. Efficacy of the described maneuvers has been demonstrated through lymphoscintigraphic imaging [14].

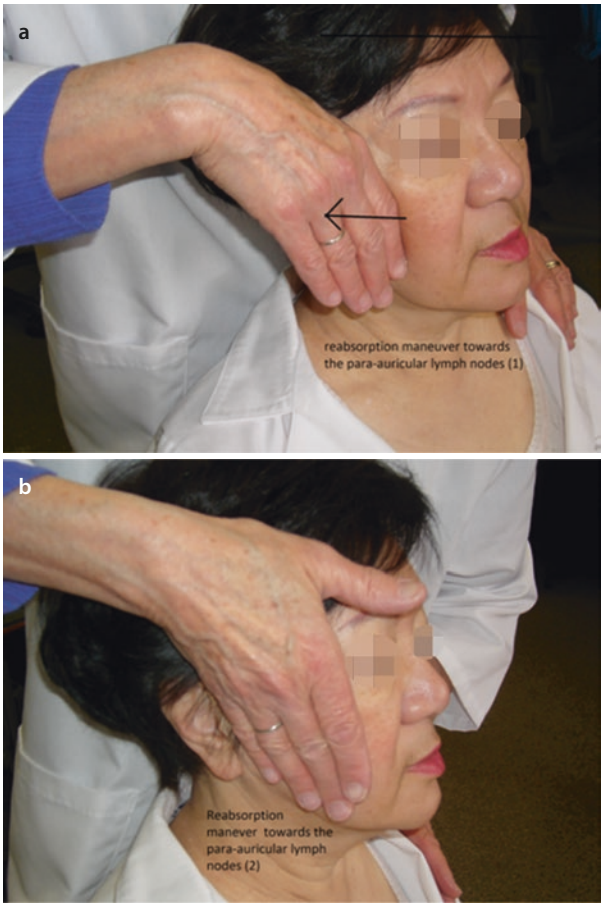

Fig. 43.3 Reabsorption maneuver applied proximally toward the para-auricular lymph nodes. **a** posteriorly directed, **b** anteriorly directed

- 1-2 e Next, the specific treatment of the lymphedematous area begins, with application of the *reabsorption maneuver*, from proximal to distal. The proximal end of the lymphedematous area is the aspect that is closest to the draining lymph nodes. The lymphedematous area will be divided into sections, each of which will be drained as previously described. The change in the consistency of tissues in the treated area is the factor that dictates when the maneuver can be considered complete, allowing the therapist to progress to the next, more distal section. The lymphedematous area will be drained toward the para-auricular lymph nodes as well as toward the submandibular lymph nodes.
- 1-2 f After all of the sections of the lymphedematous facial, neck, or scalp area have been completely addressed with the *reabsorption technique*, the *call-up technique* is applied from distal to proximal on each section.
- 1-2 g At the end of the treatment, specific lymph node maneuvers, described above, will be applied successively on each set of lymph nodes from the most distal set to the most proximal set, concluding the treatment session.

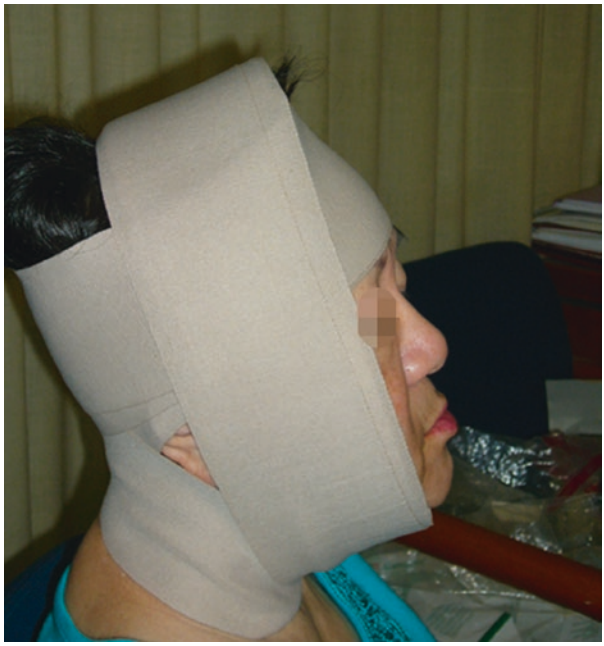

Fig. 43.4 Multilayered bandaging addressing lymphedema of the right hemiface and neck

43.5 Multilayered Bandaging (Leduc Method)

The multilayered bandaging technique requires the application of a set of semirigid bandaging materials to provide a counterpressure to the pressure generated by muscular contractions. The multilayered bandaging technique includes the application of a stockinette (to protect the skin), foam, and low-stretch bandages applied to the involved area, without exerting any tension.

This bandage is effective when the subject is active and performs muscular contractions in the lymphedematous area [15]. In the context of head and neck lymphedema, it is assumed that the patient is not isolated and has some interactions with others, utilizes facial expressions and head movements, and performs speech. To address facial lymphedema, the multilayered bandaging must be anchored in areas proximal and distal to the involved site. In between these two pieces, a bridge applies pressure to the lymphedematous area (Fig. 43.4). The treatment is best performed in the home, to minimize stress for the patient. Efficacy of the multilayered bandaging for colloidal protein reabsorption during muscular activity has been demonstrated by lymphoscintigraphy [15].

43.6 Stimulation of Muscular Activity

The patient should be educated to perform exercises of the facial musculature. These should be performed specifically while wearing the multilayered bandaging. The repetition of vowels in front of the mirror, three to four times a day, is an easily comprehended form of such exercise.

43.7 Compression Garment

A compression garment will be required to maintain the results achieved with the manual lymph drainage and multilayered bandaging. For mild cases of facial lymphedema, a ski mask can fulfill this function, but a medical garment for facial edema may be necessary. The garment is typically worn in the home.

43.8 Education in Precautions Designed to Avoid Exacerbation of Symptoms

The patient must be educated to avoid sun exposure, as well as those activities that might expose the involved regions of the skin to abrasion, laceration, or burn. The patient will be asked to practice strict hand hygiene to avoid self-contamination. Avoidance of skin scratching and eye rubbing is recommended.

Education in skin care is paramount. Strict skin and hair hygiene is recommended, with, minimally, a daily evening shower. Regular use of a skin moisturizer is also strongly recommended.

43.9 Education in Self-Treatment

Education in techniques of self-treatment becomes feasible when the patient demonstrates comprehension of the lymphedematous condition and is willing to participate in management. At times, a family member will volunteer to administer the manual techniques. In the case of a child with lymphedema, the parents will be educated. In these situations, the patient or parents will be educated to perform a simplified version of manual lymph drainage. The patient or family caregiver will be taught to initially apply the maneuver to the supraclavicular, submental, submandibular, and preauricular lymph nodes. The call-up and reabsorption maneuvers are not incorporated. Similarly, multilayered bandaging is not incorporated into the self-treatment approach, which is comprised simply of skin mobilization combined with the application of very gentle pressure. The maneuver is undertaken by the patient or caregiver, progressing from proximal to distal at the lymphedematous site. After the entire involved area has been treated, the maneuvers on the lymph nodes are repeated. The self-treatment should be closely monitored. The patient, or the parents of the patient, should be provided with a pictorial guide, including practical comments. If self-treatment education is feasible, it will be implemented early in the treatment intervention, to permit thorough training. Self-management techniques are not as effective as those applied by the trained therapist, but they do permit the patient or family caregiver to perceive changes in the consistency of tissues or in the skin temperature. The patient, or parents, should be made aware of the necessity to seek medical care if a change in tissue volume, tissue consistency, or skin temperature is detected. Erythema or pain in the involved area should also prompt medical consultation, as these symptoms may indicate the development of dermatolymphangioadenitis.

Multilayered bandaging is purposefully not incorporated into the self-treatment approach, inasmuch as there is a risk that uneven pressure application and undesired pressure gradients will be created when the bandaging materials are applied by the patient or a family member.

43.10 Rehabilitation to Address Functional Impairments

As previously mentioned, injury to the spinal accessory nerve may trigger denervation of the upper trapezius muscle and, sometimes, minor impairment of the sternocleidomastoid muscle. These nerve lesions generate shoulder drop and protracted limitations in active range of motion, especially in shoulder flexion and abduction, as well as muscle strength impairment and pain [16]. The medical literature amply documents the profound impact of shoulder dysfunction on quality of life in patients treated for head and neck cancer. Shah et al., in a study of short- and long-term quality of life after neck dissection, have documented that shoulder dysfunction and neck tightness had the greatest negative impact [5]. Thus, postsurgical evaluation, with frequent, regular assessment of shoulder function, should be implemented in these patients, in order to initiate immediate physical or occupational therapy when needed. During sessions of physical or occupational therapy, assessment of balance and strength should be implemented for early remediation or lifestyle adaptations.

43.11 Quality of Life

Treatment of head and neck cancer may trigger a variety of dysfunctional consequences beyond lymphedema. Patients receiving radiation-based therapy for locally advanced squamous carcinoma of the head and neck develop acute dysphagia related to pain, copious mucus production, xerostomia, and tissue swelling. Early evaluation and treatment by speech and language pathologists permit the identification of patients with clinically significant aspiration; in these cases, a treatment plan that includes patient education and swallowing therapy can significantly enhance quality of life. Well-monitored dietary adaptations must be implemented to address swallowing and the risk of maladaptive feeding changes [3].

Lymphedema of the face and neck generates emotional and social dysfunction which must be assessed and addressed in a timely fashion to maximally enhance the quality of life for patients and family.

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Genital Lymphedema

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Summary of Basic Concepts

Genital lymphedema is a rare entity that is frequently associated with lower limb lymphedema. Surgery, essentially based on cutaneous resection techniques, is the major symptomatic treatment in adults and children.

44.1 Definition

Genital lymphedema, defined as increased volume of the external genitals, is caused by lymphatic impairment in males (penis, foreskin, and scrotum) and females (labia minora and majora). Adjacent regions may be also involved by lymphedema: pubis (mons veneris), groin, and inner thigh(s).

44.2 Etiology

44.2.1 Primary Lymphedema

Limb lymphedema is divided into primary and secondary forms. Primary lymphedema reflects a congenital malformation of the lymphatic network, including lymphatic channels. It is essentially sporadic, sometimes familial (called Milroy's disease when present at birth or before 1 year). It may be isolated or syndromic, i.e., representing a clinical sign of a more complex and/or genetic syndrome, e.g., Turner's syndrome [6, 7].

44.2.2 Secondary Forms

Secondary lymphedemas may arise after various treatments for a wide variety of cancers (e.g., uterine, cervical, ovarian, prostate, rectum, melanomas, Hodgkin or non-Hodgkin lymphomas), including surgery with more or less extensive lymph node excision (inguinal, iliac, lumboaortic), brachytherapy, and/or external radiotherapy [8]. In developing countries, filariasis (*Wuchereria bancrofti*, *Brugia malayi*, *Brugia timori*) is the main cause of genital lymphedema [9].

Chronic inflammatory intestinal diseases (ulcerative colitis, Crohn's disease) may be associated with genital lymphedema. Pertinently, metastatic Crohn's disease is its least common dermatological manifestation, but the genitalia are its most frequent location in children [10]. In adults, genital lymphedema generally occurs after Crohn's disease has been diagnosed. In contrast, in children, genital lymphedema is most often seen prior to that diagnosis and may indeed reveal the intestinal pathology, preceding it by years, or lymphatic impairment may appear during its evolution in children and adults. In children, particularly girls, genital involvement may begin with unilateral labial hypertrophy with extension to the perianal area several weeks or months before Crohn's

disease is diagnosed. Perianal fistulas and fissures should be clinically sought. Colonoscopy is mandatory if lymphedema is the first clinical manifestation (i.e., of still covert intestinal disease) to search for chronic colitis and focal ulceration and obtain biopsies. Notably, genital lymphedema biopsies may contain giant-cell noncaseating granulomas, thereby confirming the diagnosis of metastatic cutaneous Crohn's disease. Management is difficult, with variable efficacy; it comprises oral medications (steroids, metronidazole, sulfasalazine, dapsone, tetracycline, azathioprine), topical (steroids) or infliximab, a parenterally administered antitumor necrosis factor-alpha monoclonal antibody. Surgical cutaneous excision, myocutaneous skin grafts, or circumcision should be reserved for forms resistant to standard medical treatment of Crohn's disease [1, 10].

Other rare diagnoses may be suspected in patients with genital lymphedema, for example, infections (mycobacterium, *Chlamydia trachomatis*, syphilis, actinomycosis, donovanosis) or noninfectious causes (contact dermatitis, sexual abuse, Waldmann's disease [11], sarcoidosis, pathomimia). RASopathies, due to mutations in *RAS*–/mitogen-activated protein kinase pathway genes, including Noonan's syndrome and cardiofaciocutaneous syndrome, may be associated with genital lymphedema [12].

Morbid obesity, predominantly men with body mass index >40 kg/m^2, may lead to voluminous thigh, abdomen, mons pubis, and genital (mostly the scrotum) masses, often called localized lymphedema in the literature [2], and may be confounded with neoplastic tumors, e.g., lymphosarcomas [13].

44.3 Physical Examination

Genital lymphedema is almost always associated with unilateral or bilateral lower limb lymphedema and very rarely isolated.

44.3.1 In Males

Lymphedema may involve the penis, foreskin, and/or scrotum. Lymphedema volume varies from moderate to severe, with possible discomfort walking and wearing clothing, and is possibly noticeable by others. The lymphedematous penis may assume a characteristic saxophone form (Fig. 44.1). Involvement of the foreskin may lead to urine entrapment within the pseudo-foreskin cavity and its release in multiple «spurts». Increased scrotum volume is associated with skin thickening (similar to the Stemmer sign on the second toe or on its base in lower limb lymphedema). When the scrotum volume is massive, the penis may be buried and appears smaller or is even invisible. «Buried» refers to the penile shaft engulfed within the prepubic skin, with a partially or totally hidden penis, also called trapped or concealed [3]. Trophic abnormalities may coexist with genital lymphedema: lymphatic vesicles with possible lymph oozing (representing a portal of entry for bacteria leading to cellulitis) and papillomatosis of the penis and scrotum.

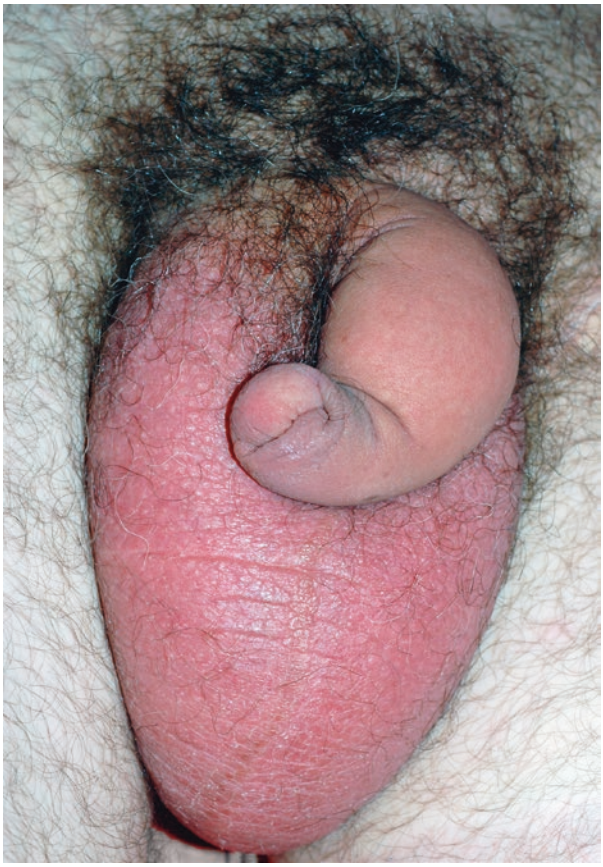

Fig. 44.1 Primary genital lymphedema in a 35-year-old man

44.3.2 In Females

Genital lymphedema, sometimes called vulvar lymphedema circumscriptum, corresponds to increased volume of labia minora and/or majora, sometimes unilateral or asymmetric. This increased volume causes spontaneous discomfort, rubbing, sometimes pruritus and lymphatic vesicles (Fig. 44.2), and can spread to the internal side of thighs, with possible lymph oozing. Cutaneous hypertrophy, sometimes very voluminous, of the labia and mons veneris occurs, giving an appearance of papillomatosis, which may be mixed with genital warts [14]. In very rare cases, genital lymphedema appears as multiple polypoid, verrucous nodules involving the vulva that frighten the patient, inciting her to consult. As for males, obesity is a risk factor. Biopsies contained dilated lymphatic channels in the papillary and reticular dermis, fibrosis, dermal edema, and hyperplastic epidermis without any sign of malignancy [15].

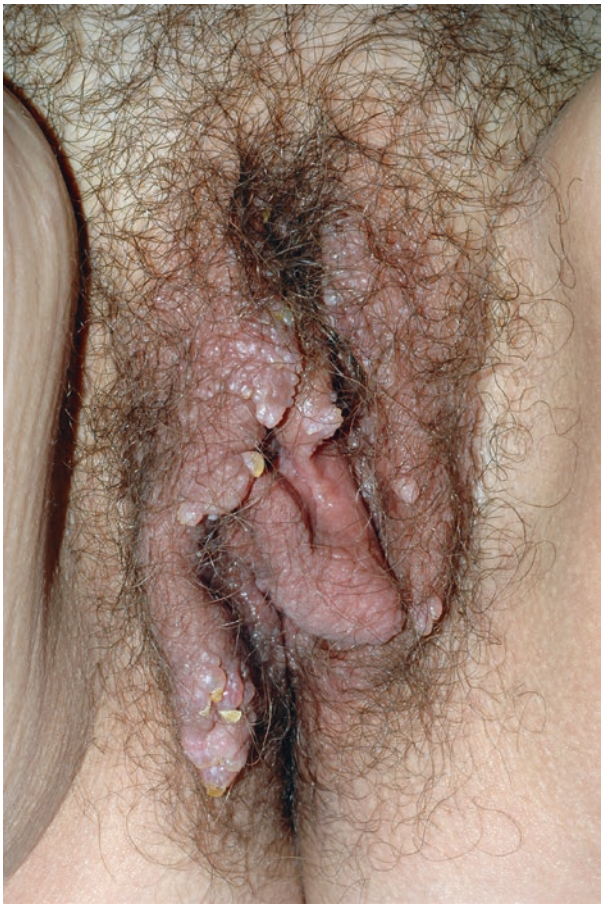

Fig. 44.2 Genital lymphedema in a 44-year-old woman long after Hodgkin lymphoma treatment. Note the increased volume of the labia associated with papillomatosis and lymphatic vesicles

44.4 Complications

Males with foreskin involvement or a buried penis may have difficulty urinating in a continuous stream. Sexual activity may be affected but is difficult to investigate, because of the frequent association with a causal pathology (such as prostate cancer or morbid obesity). For females, itching and lymph oozing represent major discomforts in everyday life. Papillomatosis and increased volume of the labia cause notable disability, have a negative cosmetic appearance, and cause discomfort and the risk of breakage and lymph oozing, hence also affecting her libido and sexual activity.

Cellulitis is the most frequent complication of lymphedema. This bacterial infection is characterized by the sudden onset of high fever and chills and redness, warmth, pain, and increased volume of the lymphedematous region. Cellulitis may begin in a lower

limb and spread to the genitalia or affect only the genitals. Patients report intense pain when cellulitis spreads to the genitals. Portals of bacterial entry include toe-web intertrigo but also folliculitis of the pubis or oozing lymphatic vesicles. Adapted antibiotic therapy is required to treat cellulitis with fever disappearing within 2–3 days and redness in 1 week. Cellulitis may recur frequently and then require long-term antibiotic prophylaxis, based on benzathine benzylpenicillin G for a prolonged but still undefined duration. Treatment of the entry site is also required: toe-web intertrigo, folliculitis, etc.

44.5 Explorations

Genital lymphedema explorations differ for primary and secondary forms.

44.5.1 Primary Forms

Diagnosis is usually easy when a primary lymphedema involves one or both lower limbs. Genital lymphedema is then associated and could appear at the same time or after lower limb lymphedema onset. Lymphatic origin is obvious and may be confirmed by lower limb lymphoscintigraphy with images obtained 40 min after injecting ^{99m}technetium-labeled colloidal albumin subcutaneously into the first web space of both feet [16]. Those images may demonstrate decreased uptake in the groin region, specifically colloid backflow in the scrotal dermis, leading to visualization of the normally invisible scrotum (Fig. 44.3). In addition, scrotum lymphedema is frequently associated with hydrocele (40%), which should be confirmed by Doppler ultrasonography. Pertinently, hydrocele

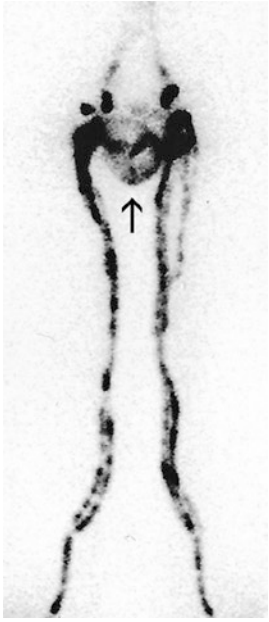

Fig. 44.3 Lymphoscintigraphy of the lower limb obtained 40 min after injecting ^{99m}technetium-labeled colloidal albumin subcutaneously into the first web space of both feet. Note the colloid uptake and dermal backflow in the scrotum

treatment is specific and differs from that of lymphedema. Doppler ultrasonography is able to confirm the increased thickness of the skin. Of course, if the diagnosis of primary lymphedema is doubtful, a specific etiology, i.e., compressive lesion, should be sought with computed tomography (CT) scan and/or magnetic resonance imaging (MRI) and, if necessary, positron emission tomography (PET) scan. Importantly, genital lymphedema may reveal and precede the diagnosis of cancer (colon, bladder, rectum, etc.).

44.5.2 Secondary Forms

For secondary forms occurring after cancer treatment, the main objective is to exclude a cancer relapse. Two situations are known: secondary lower limb lymphedema was present after cancer therapy and genital lymphedema appeared later, or genital lymphedema is the sole lymphedematous manifestation. Genital lymphedema occurs after a more or less long interval following cancer treatment and should evoke recurrent malignancy. Complementary explorations are then required, such as abdomen and pelvic CT scan or MRI and sometimes PET scan. Genital lymphedema seems to be more frequent when previous cancer treatment included radiotherapy and/or brachytherapy (cervical cancer). Other than cancer treatments, rare causes of genital lymphedema should be specifically explored: biopsies and colonoscopy for Crohn's disease and search for *Chlamydia trachomatis* (polymerase chain reaction).

44.6 Treatments

44.6.1 Nonsurgical Therapies

Compressive therapy is obviously more difficult than for limb lymphedema. Because of the shape and location of genital lymphedema, bandaging and a fitted elastic compression garment can be difficult to apply and are often impractical. Many patients use over-the-counter or custom-made expansive, elastic shorts or panties. Tolerance is frequently poor, and proximal compression enhances the risk of increasing limb lymphedema, which then requires the patient to also wear thigh-high compression stockings. Bandages may achieve volume decrease, especially for lymphedema of the penis. Patients are taught how to self-bandage at home with low-stretch bandages using bands with less than 100% elasticity [17]. Bandaging may also be useful to prepare for surgical resection, to reduce the volume and accumulated static lymph, and to soften the skin before surgery. For females, compression is more difficult to adapt, and compression therapy of the vulva is inadequate or poorly tolerated. Pneumatic compression for lower limb lymphedema is not recommended for these patients, because it might induce or aggravate genital lymphedema.

44.6.2 Surgery

Surgery objectives are numerous: to restore an acceptable cosmetic appearance close to normal, to debulk excessive lymphedematous tissue that notably increases the weight of

the scrotum and induces its descent (pendulous scrotum), and, finally, to preserve urinary and sexual functions [18]. Various procedures have been proposed for male adults and children. They include only surgical debulking to remove lymphedematous tissue by scrotoplasty, suction-assisted lipectomy, surgical lipectomy of the suprapubic region, or penis plasty. Circumcision alone may be proposed if lymphedema is essentially localized to the foreskin [4]. After cutaneous resection, reconstruction of skin defects may be achieved with local skin flaps in children or, more specifically, split-thickness skin grafts [3, 19]. In children, surgical debulking of the scrotum or penile reconstruction with adjacent skin graft is an option. Concomitant hydrocele repair or aspiration may be required. Prophylactic orchidopexy to prevent testicular torsion may also be proposed for a child [1].

For females, therapeutic objectives are to improve the cosmetic appearance, decrease lymphedema volume, and remove papillomatosis and/or lymph vesicles responsible for embarrassing lymph oozing. Lymphedematous tissue resection represents the main surgical intervention, with labia minora and/or majora resection sparing the clitoris [5]. Histological analyses of surgical specimens found dermal edema, dilated lymphatic spaces (lymphangiectasia) in the superficial dermis associated with fibrosis, and epidermal changes (papillomatous and hyperkeratotic epidermis), with no sign of malignancy.

To date, «physiological» surgical procedures, such as lymphaticovenous anastomoses, have been proposed but should be further evaluated in large cohort before they can be recommended [20]. When surgeons are experienced and trained to perform these specific techniques, surgery is very useful for genital lymphedema and has very few complications. In all cases, surgery including excisional procedures does not treat the underlying pathology, and postoperative compression is still required after resection to prevent de novo accumulation of lymph and increase of genital volume. Repeated surgical procedures may be necessary over the patient's lifetime due to recurrence [5].

44.6.3 Other Treatments

For patients with uncomfortable or even debilitating lymphatic vesicles on the vulva or scrotum not requiring skin resection, various nonsurgical treatments have been proposed, such as electrocauterization, cryosurgery, argon laser surgery, sclerosing agent (picibanil), and CO_2 laser ablation [5, 21, 22].

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Surgical Treatment: Reconstructive Surgery

Contents

Surgical Treatment - Reconstructive Surgery General Overview

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Summary of Basic Concepts

- Chronic lymphedema continues to be a challenge in management.
- Current guidelines recommend physical therapy as the first line of treatment, and at least 6 months of nonoperative compression treatment is recommended before any interventions for chronic lymphedema.
- With the development of microsurgical and supermicrosurgical techniques, a variety of lymphatic reconstructions have been performed in the past decades.
- Understanding the principles, indications, techniques, and results of each lymphatic reconstruction is important for treatment decision-making to provide the best care for the patient with chronic lymphedema.

Chronic lymphedema continues to be a challenge both in diagnosis and in management. The diagnostic dilemma remains in how to best define detailed anatomy and lymphatic function, while the problem with treatment remains our inability to cure chronic lymphedema. Still, both evaluation and treatment have greatly improved in recent years. Progress in genetics, in imaging studies, in physical therapy, and in microsurgical and supermicrosurgical techniques has sparked interest in chronic lymphedema, a disease long considered to be the stepchild of medicine. The 2nd edition of this important textbook is testimony of the increasing interest in investigation and treatment of lymphatic disorders.

The introduction of vascular microsurgery in the early 1960s by Jacobson established the possibility for surgical reconstruction of lymph vessels and lymph nodes [6]. The observations of Edwards and Kinmonth, [7] that in lymphedema, spontaneous lymphovenous shunts in lymph nodes developed, likely to decompress the high pressure lymphatic system distal to an obstruction, led to early attempts to perform microsurgical lymphovenous anastomoses (LVAs) in patients with lymphedema. Lymph vessel-to-vein [1, 2, 8–38] and lymph node-to-vein anastomoses [17, 32, 39, 40] were soon followed by lymphatic grafting to bypass the lymphatic obstructions [41–45]. Lymphovenous or lymphaticovenular bypass has gained popularity in recent years [46–49]. In patients with lymphangiectasia, vein grafts with competent valves were used to drain the lymph and also to prevent reflux of the blood into the lymphatic system [3, 46]. The technique of lymph node transfer/transplantations (LNT) as free flap was also developed; results from vascularized lymph node transfer/transplantation (VLNT) are more promising [35, 50–54].

Interest and enthusiasm for lymphatic microsurgery have waxed and waned during the last five decades mostly because only a few centers around the world have had the expertise to perform these most difficult and challenging procedures. The concept of supermicrosurgery was established in Japan in the 1980s and introduced internationally in 1997. In 2010, Koshima and colleagues defined supermicrosurgery as «a technique of microneurovascular anastomosis for smaller vessels and a single nerve fascicle, and also microneurovascular dissection for these small vessels less than 0.3–0.8 mm» [25]. This definition has also been applied to lymphatic reconstructions, and in the past decade, supermicrosurgery has been adopted for surgical treatment of lymphedema [18, 24–27, 29, 33, 36, 38]. Nowadays, the most commonly practiced procedures include LVA and

VLNT. In this section of the book, we review general guidelines only, introducing you to microsurgical and supermicrosurgical techniques, results, and potential problems of the different types of lymphatic reconstructions. The senior author's personal experience of 40 years in this field helps to focus attention to the most promising procedures.

45.1 Principles

In most patients, chronic lymphedema is the result of acquired or congenital obstruction of the lymph vessels and the lymph-conducting elements of lymph nodes. In some, valve incompetence of lymph vessels is the cause of poor lymph transport. The condition becomes clinically significant when the lymphatic collateral circulation is inadequate to drain lymph from the affected part of the body and lymph production exceeds the transport capacity of the lymphatic system. Other compensatory mechanisms such as the tissue macrophage activity and drainage through spontaneous LVA are also exhausted. The condition is aggravated by higher lymph production due to venous obstruction, venous valve incompetence, dependency of the limb, infection, or inflammation.

Surgical treatment of lymphedema includes excisional operations and lymphatic reconstructions [55, 56]. Excisional surgery involves reduction of the volume of the limb by excision of the excess lymphatic tissue. This can be performed alone or together with lymphatic reconstructions. Liposuction has been also used as an effective technique to decrease the excess volume of the affected limb [57].

The goal of microsurgical or supermicrosurgical lymphatic reconstructions is to restore or improve lymph transport in patients with chronic lymphedema. The ultimate goal is reduction of chronic swelling, decrease of the episodes of infection, and improvement of the quality of life (QoL) of these patients.

45.2 Stages of Lymphedema

Evaluation of the severity of lymphedema is important when considering an optimal treatment option [53, 58]. The International Society of Lymphology staging system, as discussed before in much more detail, classifies lymphedema into four stages [58]:

1. Stage 0: Latent lymphedema. Lymph flow impairment after injury without measurable signs of edema or swelling
2. Stage 1: Spontaneously reversible lymphedema. Measurable swelling or edema that resolves with elevation or compressive therapy
3. Stage 2: Spontaneously irreversible lymphedema. Progression of edema that does not fully respond to conservative therapies
4. Stage 3: Lymphostatic elephantiasis. The final stage in which severe irreversible swelling, fibrosis, and fatty deposition result in thickened, firm tissues in the form of hyperkeratosis

   Staging the lymphedema is important when considering microsurgical treatment, since the very best results of reconstructive microsurgery can only be expected in Stages 0 and 1. Many patients with Stage 2 benefit, although residual lymphedema is almost always present.

45.3 Indications

As discussed in ample detail in this volume previously, multimodal complex decongestive physical therapy is recommended for the first line of treatment for chronic lymphedema [55, 56, 59]. Successful therapy results in decreased volume, improved function, and improved QoL.

Considerations for surgery include: ① No response to medical management after at least 6 months of therapy in surgically fit patients without recent episodes of cellulitis or lymphangitis; ② Recurrent episodes of cellulitis and lymphangitis; ③ Intractable pain; ④ Lymphangiosarcoma; ⑤ The availability of a center with expert in lymphatic microvascular reconstructions; ⑥ Cosmetic reason when patients are unwilling to undergo more conservative treatment but even willing to proceed with experimental operations; ⑦ Preventive microsurgery after excision of major lymph nodes for malignancy, with a high likelihood of developing subsequent lymphedema.

The most suitable anatomy for lymphatic reconstructions is an acquired proximal (pelvic, axillary) lymphatic obstruction, with documented patent distal lymphatics on lymphoscintigraphy [28, 55, 56, 60, 61], magnetic resonance lymphangiography [55, 56, 62, 63], or using the technique of indocyanine green (ICG) injection and infrared scope imaging [27, 28, 34, 47, 49, 53, 55, 56].

Intrinsic contractility of the lymph vessels is one of the main factors responsible for normal lymphatic flow. Preserved contractility is ideal to assure good lymphatic flow against the higher pressure venous system. Activity and muscular contractions of the limb are also helpful and can generate intermittent pressures as high as 50 mmHg in the normal lymphatic system [64]. Unfortunately, compliance of the lymph vessels deteriorates in chronic lymphedema, and loss of contractility due to degeneration of the smooth muscle cells especially when coupled with lymphatic obstructions or valvular incompetence is an important reason why response to lymphatic reconstructions in advanced stages of chronic lymphedema is so poor. Also, patients with lymphatic fibrosis, with congenital hypoplasia or even aplasia of the lymph vessels as seen in those with primary lymphedema, are frequently poor candidates for lymphatic reconstructions.

45.4 Microsurgical/Supermicrosurgical Reconstructions

Three main techniques of lymphatic reconstructions have been developed. These include LVA, lymphatic grafting, and VLNT. LVA is usually performed in patients with confirmed open and functioning lymphatic vessels. Lymphovenous or lymph node-to-vein anastomoses can be considered in patient after excision of proximal lymph nodes for cancer treatment [47–49]. Lymphatic grafting can be attempted for the treatment of secondary lymphedema caused by localized obstruction or interruption of lymph vessels and lymph nodes and in patients with primary lymphedema if it is caused by localized lymphatic obstruction or atresia [4]. Lymphatic grafting alone is best indicated in patients with mild to moderate upper extremity lymphedema along with moderate amount of functioning lymphatics and minimal fibrosis [65]. Indications for VLNT include ① fibrosis that precludes performing lymphovenous bypass, ② evidence of total occlusion of the lymphatics on lymphoscintigraphy, and ③ Stage 2 lymphedema [58]

with a history of repeated episodes of cellulitis. In some patients, a combined procedure of VLNT and lymphovenous bypass may be considered [65]. Patel et al. recommended VLNT for grades II–IV lymphedema patients [53].

For surgical treatment of primary lymphedema, according to the consensus document of the International Union of Phlebology (IUP), LVA is best utilized in the early stages of lymphedema (stages I and II); VLNT is best utilized in patients with lymphadenodysplasia (stages II and III) [55].

Although surgical treatment of lymphedema should be reserved for cases refractory to conservative therapy, there has been a paradigm shift toward earlier intervention for physiologic procedures such as lymphovenous bypass and VLNT [66].

45.5 Lymphovenous Anastomosis

LVA has been performed to drain lymph into the venous system in an area distal to the lymphatic obstruction [1, 2, 8–40, 46–49]. Most patients have acquired or primary iliac lymphatic obstruction. Occasionally the operation is performed for congenital lymphangiectasia [3, 46] or filariasis [13, 40]. Two techniques have been introduced, lymph vessel-to-vein and lymph node-to-vein anastomoses (Fig. 45.1a, b). Lymphovenous or lymphaticovenular bypass is discussed in lymph vessel-to-vein anastomosis.

45.5.1 Lymph Vessel-to-Vein Anastomosis

Microsurgical Technique

Earlier techniques of lymph vessel-to-vein anastomosis involved simple invagination of transected lymph vessels into large veins, like the saphenous, femoral, basilic, or brachial veins. This technique was popularized first in Brazil by Degni [9] and Cordeiro and used in large number of patients by Campisi's group in Italy [2, 19, 20, 37] (Fig. 45.2 a, b). The same method of lymphatic reconstruction was also used in a prospective study by Damstra [23]. Variations of the invagination technique include pulling of the lymphatics into a vein graft and fixing there with one or two sutures. Additional lymphatics distal to the obstruction can be pulled into the vein graft in an attempt to improve lymphatic drainage and using the vein graft as a large lymphatic conduit to bypass the obstruction (Fig. 45.2b).

Most microsurgeons perform direct end-to-end or end-to-side LVAs, using high-power magnification and 8–11/0 microsutures [10, 14, 15] (Fig. 45.1b). The latest techniques of supermicroscopic surgery use very high-power magnification [18, 24, 26, 27, 29, 33]. A side-to-end LVA is preferred when a lymphatic vessel is not too sclerotic to create a lateral window for the anastomosis [33–35, 48, 54]. LVA configurations such as the end-to-end, end-to-side, and side-to-end allow to establish unidirectional lymph flow from the distal limb of the lymphatic collector [5, 18, 24, 27, 29, 34, 38, 47, 48]. To establish bidirectional lymph flow in cases with lymphatic retrograde flow, LVAs with end-to-end coupled with side-to-end, side-to-side, and pi-shaped anastomosis have been reported [5, 29]. When a recipient venule is far from a lymphatic vessel, the half notching method in lambda-shaped anastomosis has been used to

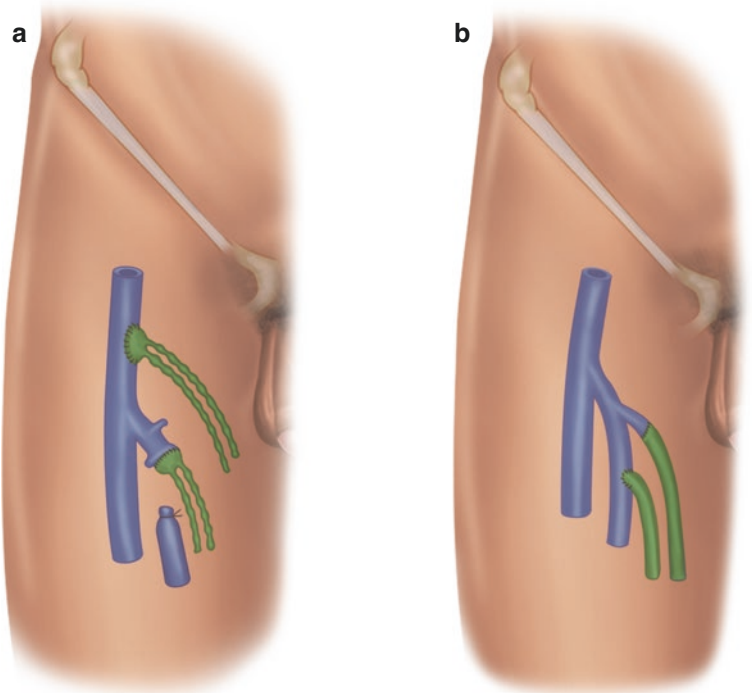

Fig. 45.1 **a** End-to-end and end-to-side lymph node-to-vein anastomosis at the groin. **b** End-to-end and end-to-side microsurgical lymph vessel-to-vein anastomosis (By permission of Mayo Foundation)

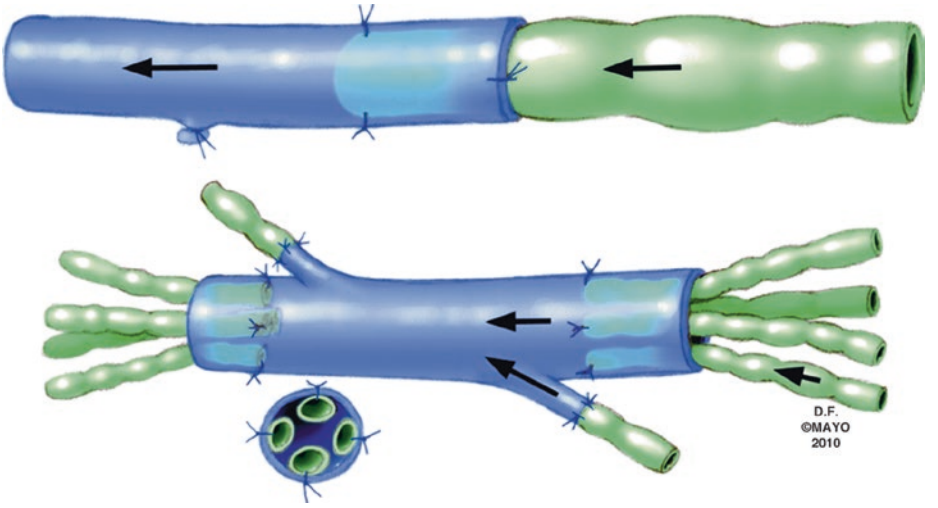

Fig. 45.2 Invagination techniques of Campisi: **a** Lymphovenous anastomosis. **b** Lymphatic-venous-lymphatic anastomoses, performed using invagination of multiple lymphatics into an interposition vein graft (By permission of Mayo Foundation)

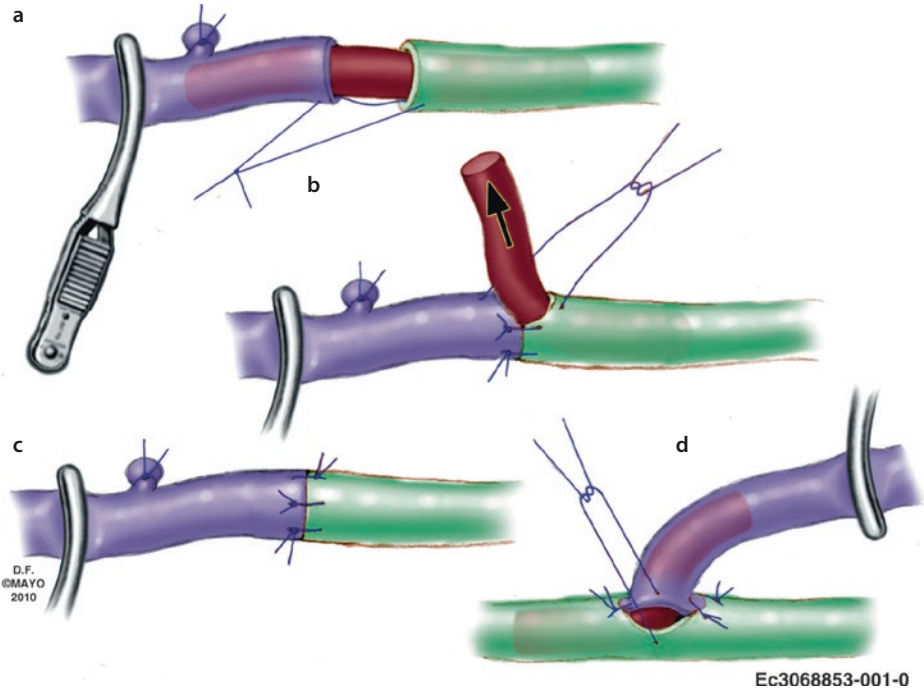

Fig. 45.3 Lymphovenous anastomoses performed with supermicroscopic technique, high-power magnification, and intravascular stents, according to Narushima. **a**–**c** endo-to-end anastomoses. **d** end-to-side anastomosis (By permission of Mayo Foundation)

facilitate the procedure [36]. Recently, the T-shaped LVA which maximizes the lymphatic collector spatial configuration, emerging the same concept of branched-type [27] and lambda-shaped anastomosis, [29] has been reported [38]. The introduction of intravascular temporary stents and multiple configuration anastomoses, using both the proximal and distal ends of the transected lymph vessel (Figs. 45.3 and 45.4), enables better anastomosis of smaller (<1.0 mm) lymph vessels and likely contributes to improved patency rates and durable efficacy [27]. Lymphovenous or lymphaticovenular bypass is performed with anastomoses between subdermal lymphatic vessels and adjacent venules (<0.8 mm) or vein grafts to create new channels to excess lymph fluid; this procedure is effective in reducing lymphedema [46–49]. Reconstruction of larger lymph collectors and of the thoracic duct has also been reported [22, 67].

Significant progress in supermicroscopic surgical techniques has been documented in the past decade in publications of Koshima, [18, 25] Demirtas, [24, 26] Narushima, [27] Yamamoto, [29, 33, 36] and others [38]. These authors have used high-power magnifications for direct LVA and lymphovenous implantations.

Results

Technically, LVA can be performed by experienced microsurgeons, and in experiments, anastomoses between normal femoral lymph vessels and a tributary of the femoral vein yielded a patency rate of 50% at 3–8 months after surgery [15]. The clinical effectiveness

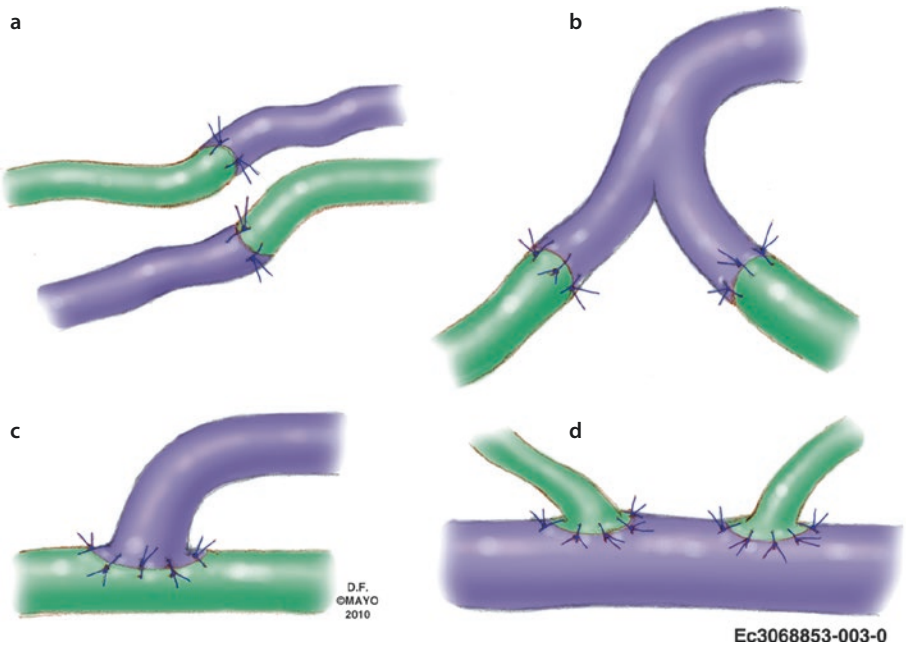

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Fig. 45.4 Techniques of Narushima for multiconfigurational lymphovenous anastomoses, with reconstruction of both the proximal and the distal ends of the transected lymph channels. **a**, **b** end-to-end anastomoses. **c**, **d** end-to-side anastomoses (By permission of Mayo Foundation)

of this operation is more difficult to prove in humans, since almost all studies were uncontrolled and adjuvant compression therapy was used in most published series. Only 5 patients out of 14 that we operated in an earlier series maintained the initial improvement at an average of 46 months after surgery [16]. Patients with secondary lymphedema did better than those with primary.

Experiences in large numbers of operated patients, however, suggest that clinical improvement can be achieved with lymphatic drainage procedures [12, 14, 16, 18]. In O'Brien's series from Australia, 73% of the patients had subjective improvement and 42% experienced long-term efficacy [11]. Campisi in Italy has currently the largest experience with lymphatic microsurgery [2, 19, 20, 37]. His team reported results in 665 patients with obstructive lymphedema using microsurgical LVAs, with subjective improvement in 87% of the patients [19, 20]. Four hundred forty-six patients were available for long-term follow-up: volume of the limb was reduced in 69%, and conservative treatment was discontinued in surprisingly high number of patients (85%). In 1500 operated patients, using a variety of microsurgical reconstructions (Fig. 45.2), Campisi reported a diminished volume of the operated limbs in 83% of the patients and decreased number of cellulitis in 87% [2]. His most recent study including more than 2600 patients showed that LVA or lymphatic reconstruction using interpositioned vein-grafted shunts provided excellent outcomes in both pri-

mary and secondary lymphedemas, during an average follow-up of at least 10 years, over 84% of the patients had significant reductions in excess limb volume (ELV), over 86% of stages IB and IIA patients progressively discontinued conservative therapies, and 42% of stages IIB and III patients decreased the frequency of physical therapies [37].

Narushima et al. [27] reported the use of temporary intravascular stents in 14 patients to assure patency of 39 multiconfiguration lymphaticovenous anastomoses capable of decompressing both proximal, refluxing, and distal, antegrade lymphatic system. These authors observed significant reduction in limb girth at a mean follow-up of 8.9 months and found a greater decrease in cross-sectional area with increasing number of lymphaticovenous anastomoses per limb. Demirtas et al. [24, 26] performed microlymphatic surgery in 80 lower extremities with primary and 21 with secondary lymphedema. Reduction of the edema occurred earlier in the secondary lymphedema group, but the mean change in the edema volume was comparable between the two groups. Although these results need confirmation by other investigators, this is the first promising study of using microsurgery with good results in patients with primary lymphedema.

According to a meta-analysis including 22 studies that have reported outcomes after LVA, pooled results have shown 89% of patients report a subjective improvement, 88% experience a quantitative improvement, and 56% of patients were able to discontinue compression therapy [5].

Concerning surgical treatment of lymphedema secondary to cancer, Damstra et al. [23] in a small cohort of 10 operated breast cancer patients with 11 procedures did not find durable benefit of the invagination technique of LVA as described by Degni [9]. However, Takeishi [21] suggested that LVA could prevent lymphedema in patients who undergo pelvic lymphadenectomy for cancer. Improvement of lymphedema symptoms after LVA in cancer patients has also been reported in other studies [27, 29, 34, 37]. In a prospective study including 100 patients with lymphovenous bypass, 96% of the patients had symptom improved and 74% had quantitative improvement. The overall mean volume differential reduction at 12-month follow-up was 42%; this reduction was significantly larger in patients with Stage 1 or 2 versus Stage 3 or 4 lymphedema [47]. In addition to symptom improvement, lymphovenous bypass could also induce pathologic changes in the skin of the lymphedematous limb, resulting in decreased inflammation, and fibrosis, reported in a case series of six patients [49].

45.5.2 Lymph Node-to-Vein Anastomosis

Technique

Lymph node-to-vein anastomoses were first performed by Nielubowicz and Olszewski in Poland in 1968 [39]. During the operation, transected inguinal lymph nodes are anastomosed end-to-end or end-to-side to the saphenous or the femoral veins (◘ Fig. 45.1a).

Results

Clinical improvement after lymph node-to-vein anastomoses has been reported in a few uncontrolled studies [17, 39] but concerns about scarring over the cut surface of the lymph nodes leading to failure prevented widespread application of this technique in most types of secondary lymphedema. In filariasis, however, lymphatics are frequently enlarged even within the lymph nodes and lymph flow is high. Jamal from India reported good results in 90% of patients with parasitic lymphatic infections [13]. Jamal also found that patients with congenital lymphangiectasia, who underwent lymph node venous shunts constructed in the inguinal area, improved following the procedure [13, 40].

In a study including 1176 patients with lymph node-saphenous vein (LNSV) or lymphatic vessel-saphenous vein (LVSV) anastomosis, at 5 years, improvement of lymphedema was achieved between 30% and 80%, depending on the type of lymphedema, and the most satisfactory results were obtained in the congenital nonhereditary hyperplastic lymphedema group, reaching 80–100% improvement. Results were also satisfactory in cancer patients after iliac lymphadenectomy, reaching 80%. A less satisfactory outcome was observed in the postinflammatory group, not exceeding 30–40%. Results in idiopathic lymphedema were the worst [32].

45.6 Lymphatic Grafting

45.6.1 Technique

Baumeister [41] developed the technique of bypass with lymphatic grafts, harvested from the unaffected lower limb. Two to three lymph vessels of the peri-saphenous superficial lymphatic bundle are harvested under magnification and used either as a free graft for postmastectomy lymphedema to bypass the axillary lymphatic obstruction (Fig. 45.5a) or as a suprapubic cross-femoral transposition graft to treat unilateral lower limb lymphedema in patients with iliac or iliofemoral lymphatic obstruction (Fig. 45.5b).

45.6.2 Results

In a comprehensive review of the subject, Baumeister, an experienced lymphatic microsurgeon, detailed long-term results of these tedious operations [4]. In a group of 55 patients undergoing lymphatic grafting, improvement in limb volume after a mean follow-up of 3 years was documented in 80% of the patients [42]. In a series of 127 patients suffering from arm edema, a significant volume reduction was achieved with this technique both at 8 days and at a mean of 2.6 years after surgery. In 81 patients with unilateral lower limb edema, volume reduction after suprapubic transposition was significant both early after surgery and at 1.7 years [43]. Patency of a transposed

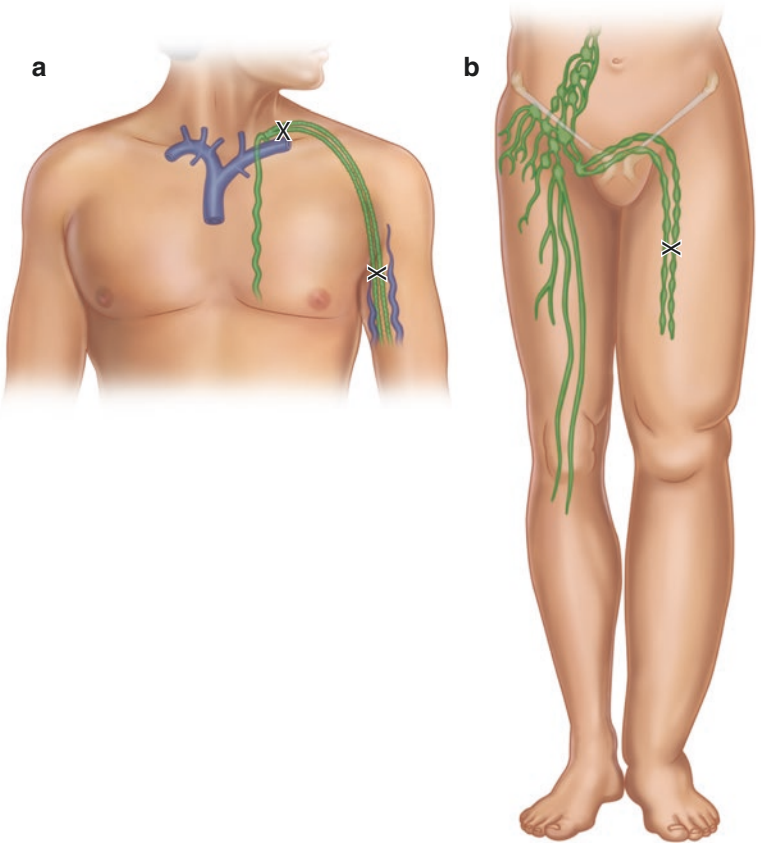

Fig. 45.5 Techniques of Baumeister: **a** Treatment of postmastectomy lymphedema with transplantation of two lymph channels from the lower to the upper extremity to bypass the axillary lymphatic obstruction. **b** Cross-femoral lymph vessel transposition for unilateral lower extremity lymphedema (By permission of Mayo Foundation)

suprapubic lymph vessel can be documented with lymphoscintigraphy (Fig. 45.6). Using semiquantitative lymphoscintigraphy, significant improvement in lymphatic function could be demonstrated in 17 of 20 patients at 8 years after the operation [44]. Baumeister and colleagues recently reported results of 352 patients treated with transposition of lymphatic grafts (arm edema, 199; edema of lower extremities, 143; penis and scrotum edema, 10). Lymphedema was significantly improved both in patients with arm edema and in patients with lower limb edema postoperatively and at 3.1 years for arm edema patients and 2.0 years for lower limb edema patients. This benefit persisted at least 10 years for arm edema patients [45] (Fig. 45.5).

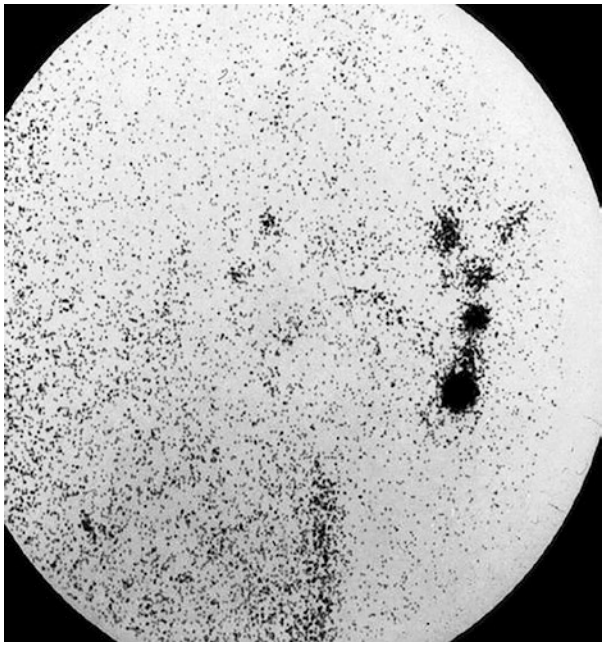

Fig. 45.6 Lymphoscintigraphy 3 months after cross-femoral lymphatic transposition. Note visualization of the left inguinal nodes following injection of isotope into the right edematous foot. There was no uptake prior to operation (By permission of Mayo Foundation)

45.7 Lymph Node Transplantation

45.7.1 Technique

Becker et al. [50, 51] reported on the technique of lymph node transplantation, harvested from the groin as a free flap, to bridge the lymphatic obstruction in patients with postmastectomy lymphedema. The feeding artery and the draining vein of the flap are anastomosed to the appropriate vessels in the axillary fossa using standard microsurgical technique. Three main donor sites for VLNT have been described, with the groin flap being the most popular [66].

45.7.2 Results

In 22 of 24 patients, the volume of the limb either decreased or returned to normal at 5 years or more after lymph node transplantation [50, 51]. However, only 5 of 16 (31%) isotopic lymphoscintigraphy demonstrated activity of the transplanted nodes. Still, physiotherapy was discontinued in 15 patients (62.5%) and cure was demonstrated in 10 (41.6%) [51]. The authors noted most improvement in patients with early stages of lymphedema. Results from the early use of VLNT for lymphedema have been appealing, and later on, the efficacy of this procedure has been reported by other independent microsurgical groups.

Saaristo and colleagues reported favorable outcomes after combined VLNT with autologous breast reconstruction in nine patients with breast cancer, the upper limb perimeter decreased in seven patients, three no longer needed compression therapy, and there was evidence of improved lymphatic flow on lymphoscintigraphy in five of six cases [52]. In a meta-analysis including five quantitative studies reporting outcomes after VLNT, 100% of the patients reported subjective improvement, 91% had a quantitative improvement, and 78% were able to discontinue compression therapy [5]. In a recent published prospective study of 25 patients undergoing VLNT for upper or lower extremity lymphedema, decreased limb circumference and increased QoL have been observed throughout the study period up to 12 months [53].

Akita and colleagues conducted a retrospective study comparing the vascularized supraclavicular lymph node transfer (VSLNT) with LVA. Patients with Stage 2 or worse lower extremity lymphedema were included. VSLNT was performed in 13 limbs of 13 patients and LVA in 43 limbs of 33 patients. Both mean operative time and hospital stay were shorter in the LVA group than in the VSLNT group (213 vs 414 min, $P < 0.01$; 8.9 vs 15 days, $P < 0.01$), and complications were lower in the LVA group (0 vs 3 cases, $P < .01$). Compared with preoperative conditions, improvement in lymphatic function was significant in both groups. The authors concluded that VSLNT and LVA were both effective techniques for the treatment of advanced lymphedema, with LVA to a lesser degree than VSLNT. LVA was less invasive and required a shorter hospital stay [35].

45.8 Problems with Microvascular Lymphatic Reconstructions

During the past decades, concerns and comments on reasons for failures of lymphatic reconstructions have been voiced. Basta et al. [5] first published a meta-analysis regarding lymphovenous microsurgery and tissue transplantation for treatment of lymphedema in 2014. Results have shown that these treatments appeared to provide consistent quantitative improvements with a relatively wide safety margin and VLNT might provide better outcomes compared with LVA in patients with lymphedema. However, of the 27 studies included, 24 offer level IV evidence and three offer level III evidence; evidence on efficacy of surgery is of low or very low quality. In 2015, Raju and Chang published a comprehensive review of VLNT for treatment of lymphedema, although the results had been largely positive, the authors called for a further exploration into standardized protocols for diagnosis, treatment optimization, and patient outcomes assessment in this field [66]. Most recently, Silva and Chang reviewed VLNT and lymphovenous bypass for treatment of symptomatic lymphedema; all these treatment modalities have shown great promise. However, concerns about donor site lymphedema, a less common, but serious complication after VLNT, have been expressed by Chang and colleagues [65, 66].

One concern raised by critiques of LVA has been the lack of documented late patency. While lymphoscintigraphy is suitable to show patent lymphatic grafts [44] or transplanted lymph nodes, [51] this test can provide only indirect evidence of patency

Table 45.1 Guidelines of the American Venous Forum on surgical treatment of chronic lymphedema

No. of Guideline	Guideline	Grade of recommendation 1. Strong 2. Weak	Grade of evidence A: High quality B: Moderate quality C: Low or very low quality
6.4.1.	All interventions for chronic lymphedema should be preceded by at least 6 months of nonoperative compression treatment	1	C
6.4.2.	We recommend excisional operations or liposuction only to patients with late-stage non-pitting lymphedema, who fail conservative measures	2	C
6.4.3.	We recommend microsurgical lymphatic reconstructions in centers of excellence for selected patients with secondary lymphedema, if performed early in the course of the disease	2	C

of LVA by showing improved lymph transport of the limb. Such improvement, however, can also be achieved by conservative measures. Observing contrast during lymphangiography as it passes through the anastomosis is the only current way to document patency of lymphovenous shunts. Also, the droplets of the lipid soluble contrast are taken away immediately by the venous blood stream, so the technique of cinelymphangiography is essential to document patency. In experiments, our group could demonstrate this, [12, 15] but in patients, no firm data are available [56]. In addition, assessment of efficacy of microsurgical reconstructions is also hampered by the fact the reported studies are uncontrolled, almost all are retrospective, and, as pointed out by Damstra, [23] they lack a validated method of outcome evaluation. Damstra, disappointed by the negative results of his prospective study of ten patients who underwent the Degni technique of lymphatic invagination, concluded that there was no convincing evidence of the success of LVA [23]. Based on the available literature and consensus of experts, the American Venous Forum formulated recommendations for surgical treatment of lymphedema (Table 45.1).

Finally, an observation on the clinical ineffectiveness of lymphovenous shunts in some patients deserves attention. In chronic lymphedema inflammatory tissue changes occur that frequently will not reverse to even complete reconstruction of lymph vessels or the lymph-conducting elements of lymph nodes. Under such circumstances, lymphatic grafting or VLNT might be an option in selected patients.

Conclusions

Conservative management with compression garments, decongestive lymphatic therapy, manual lymphatic drainage, bandaging, lifestyle modification, skin care, and treatment of infectious complications continues to be the mainstay of therapy of chronic lymphedema. Scientific evidence for efficacy of lymphatic reconstructions to decrease limb swelling and improve QoL of patients with chronic lymphedema remains of very low quality. Most studies are uncontrolled and retrospective. Current recommendations for lymphatic microsurgery in patients with chronic lymphedema, nonresponding to at least 6 months of intensive physical therapy, are weak. We suggest performing lymphatic reconstructions only in microsurgical centers of excellence in selected patients with obstructive, secondary lymphedema, early in the course of the disease [56]. In cases with advanced lymphedema, VLNT can be performed in selected patients [65]. Progress in the field of lymphatic microsurgery, however, has been noticeable, and improvement in technique has been substantial. Interest in lymphatic microsurgery is increasing, and supermicroscopic surgical techniques permit more reliable reconstructions of lymph vessels <1.0 mm in size. As noninvasive imaging techniques of the lymphatic system have also progressed, patient's selection will likely be better, and clinical improvement attributed solely to surgery can be documented in larger number of patients, in multiple centers. The subsequent chapter will discuss in much more detail the indications and current results of lymphatic reconstructions. The authors present good reasons for optimism to treat effectively chronic lymphedema. Patient's selection, individualized treatment modality, and compliance with physical therapy following surgery are important to treatment success. However, until controlled prospective trials prove clinical efficacy and durable function of lymphatic reconstructions, lymphatic microsurgery continues to remain an unfulfilled promise. In addition, standardized protocols for diagnosis, grading system, treatment, and outcomes assessment are needed to better understand the effects and potential benefits of these procedures.

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Principles of Patient Selection for Surgical Management of Lymphedema

Joseph H. Dayan

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Summary of Basic Concepts

- Imaging of the lymphatic system using ICG or MR lymphangiography uncovers pathology that may impact the type of surgery
- Assess the degree of fat hypertrophy and fluid accumulation
- Physiologic procedures for earlier fluid-dominant limbs and liposuction for fat hypertrophy
- Evaluate the venous system.

The topic of patient selection for lymphatic surgery has evolved dramatically in recent years largely because of advances in lymphatic imaging. Patient work-up for lymphedema has historically been reduced to two physical exam findings: presence or absence of pitting edema and presence or absence of advanced skin changes. While these are important components of the work-up, they are inadequate in the modern era of lymphatic surgery. Greater fidelity is required to accurately assess the nature of lymphatic dysfunction and fibrofatty proliferation in order to apply the most appropriate surgical technique to the patient's disease [6, 7]. Techniques such as indocyanine green (ICG) lymphangiography and magnetic resonance lymphangiography (MRL) have provided surgeons with a more complete picture of the patient's physiology [1–9]. This is particularly important for physiologic procedures such as vascularized lymph node transfer (VLNT), supermicrosurgical lymphaticovenular anastomosis (LVA), and proximal lymphovenous bypass (LVB). Similar to the way ultrasound and angiography fundamentally changed the assessment and treatment of heart disease, lymphatic imaging has opened a new world to surgeons and their patients. While there are still many unknowns, the purpose of this chapter is to provide a framework for patient selection using the current tools available.

Perhaps the most important component in patient selection is deciding who *not* to operate on. While practices vary, we avoid offering physiologic procedures to patients with a body mass index greater than 30 given the correlation between obesity and impaired lymphatic function [9]. We have observed poor results in this group, in addition to the increased risk of DVT and pulmonary embolus. Another relative contraindication is patients with lower extremity lymphedema who have significant venous insufficiency because venous hypertension may impair the lymphovenous shunting effect of certain physiologic procedures. Additionally, all patients are referred to a certified lymphedema therapist with the understanding that they will require therapy postoperatively. Patients who are noncompliant with the time demands of compression therapy may also not be tolerant of the patience required for lymphatic surgery which can sometimes take 1 or 2 years to work. A transparent discussion of the surgeon's data on successes as well as failures is central to the informed decision-making process for the patient and allows the surgeon to identify unrealistic expectations. Finally, many patients with lymphedema were treated for locally advanced cancers, and rapidly increased swelling occasionally with weakness or altered sensation may indicate a local recurrence which should prompt further evaluation.

The patient work-up is designed to assess the degree of lymphatic disease from the early fluid-dominant state to the more advanced fibrofatty dominant limb. Earlier fluid-

dominant states are most appropriately treated with a physiologic procedure, while liposuction can be used to address the fat hypertrophy component in selected cases. Improved results are likely seen with physiologic procedures in patients who have intact lymphatic pumping function as opposed to sclerotic and nearly obliterated lymphatic vessels [10, 11]. In some cases of early intervention, the need for compression can even be averted. This has led to a trend in earlier surgical intervention as opposed to historically offering surgery as a last resort. Once the limb does become dominated by fat, most of the lymphatics are likely nonfunctional, and liposuction may be the primary treatment in patients already committed to continuous compression [12, 13].

While the timing of surgery is still a matter of debate, patient evaluation is focused on four dimensions of the patient's disease: the degree of lymphatic disease, immunologic dysfunction, fat hypertrophy, and the state of the venous system. A focused history and physical provides a rough idea of the state of the limb, but requires imaging for complete assessment. A loss of responsiveness to decongestive therapy and limb elevation suggest advanced compromise of the superficial collectors. A rough estimation of the relative contribution of fat hypertrophy to the volume of the limb is assessed by the degree of pitting. Lack of pitting is consistent with a fat-dominant limb where physiologic procedures are unlikely to significantly reduce limb volume. Finally, evidence of venous hypertension such as varicosities and brawny edema is relative contraindications to LVA and VLNT. Palpation of the distal pulses is also routine for surgery of any extremity and has uncovered rare but potentially limb-threatening pathology in the author's practice [3].

46.1 Assessing Lymphatic Disease

Fortunately, a variety of tests are now available to visualize the anatomy and functional status of the lymphatic system including lymphoscintigraphy, ICG lymphangiography, and MR lymphangiography. While long-term data is not yet available, the results of these tests may influence which techniques or combination of techniques are used, such as LVA, LVB, VLNT, and liposuction.

In the author's practice, patients undergo ICG lymphangiography in the clinic preoperatively which demonstrates not only the anatomy but also the pumping function of the superficial lymphatic collectors. Intradermal injections into the first and third web spaces are performed with 0.5 ml of 1% plain lidocaine followed by 0.1 ml of indocyanine green which yields a complete view of both dorsal and volar lymphatic collectors with a near-infrared camera [14]. ICG is currently limited by its depth of visualization of approximately 1 cm.

Patients with similar limb volume differences may have significantly different degrees of lymphatic disease on ICG study (Figs. 46.1 and 46.2). The patient in Fig. 46.1 has moderate pitting edema with areas of patent lymphatic collectors as well as patchy areas of dermal backflow. This patient would be a potential candidate for LVA and/or VLNT. In contrast, the patient in Fig. 46.2 has moderate pitting edema but with widespread dermal backflow throughout the limb without any visible lymphatic collectors. This ICG finding is consistent with leaky and sclerotic lymphatic vessels where the outcome following LVA may not be as promising. VLNT may be more appropriate in this circum-

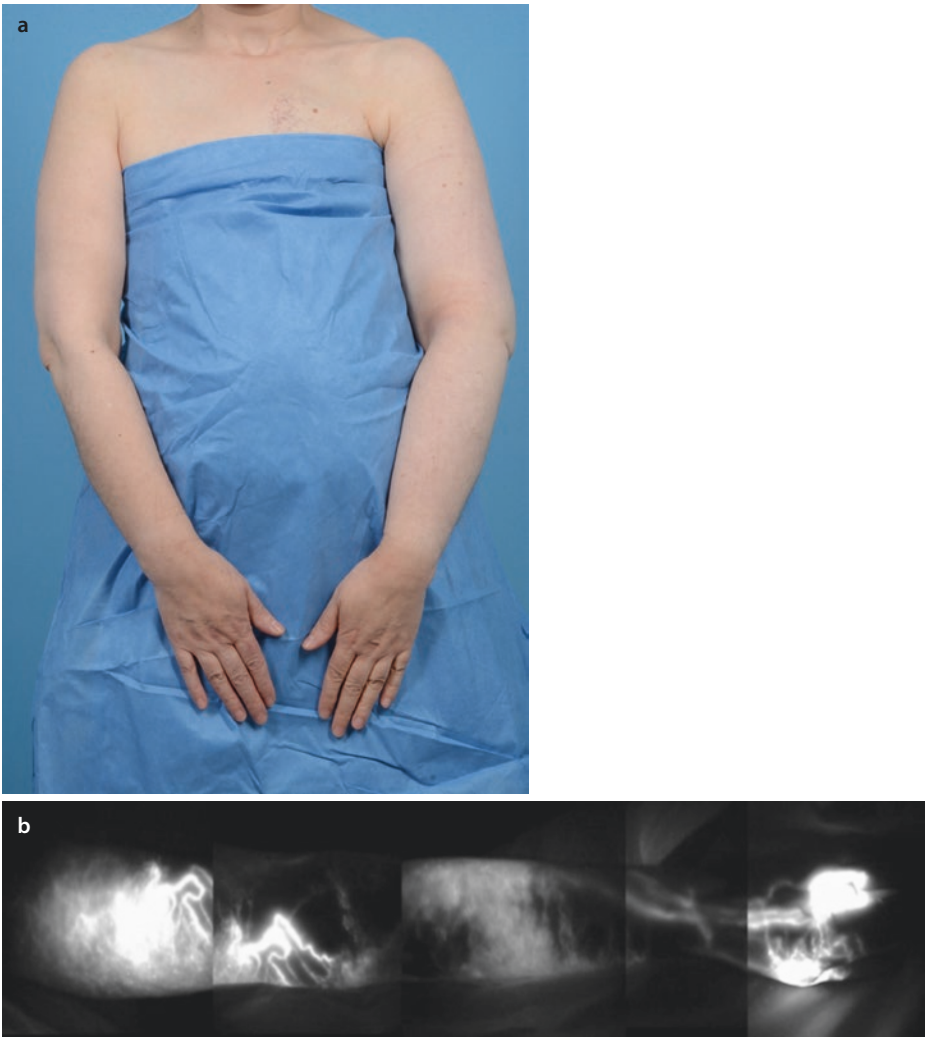

Fig. 46.1 **a** Clinical image of patient with moderate pitting edema. **b** ICG lymphangiography of this patient's left upper limb demonstrating patent lymphatic vessels and patches of dermal backflow (Published with kind permission of © Joseph Dayan 2017. All Rights Reserved)

stance, but the practical question becomes where to place it [4]. In the author's practice, if only one lymph node transfer is possible and there is no ICG flow above the elbow, the lymph nodes are buried in the forearm using the radial recurrent vessels. If there is flow above the elbow into the axillary region, then lymph nodes are placed in the axilla. In the case of a vascularized free omentum transfer which can be divided into two flaps, one is placed in the axilla, and the other is placed in the forearm for patients with globally dif-

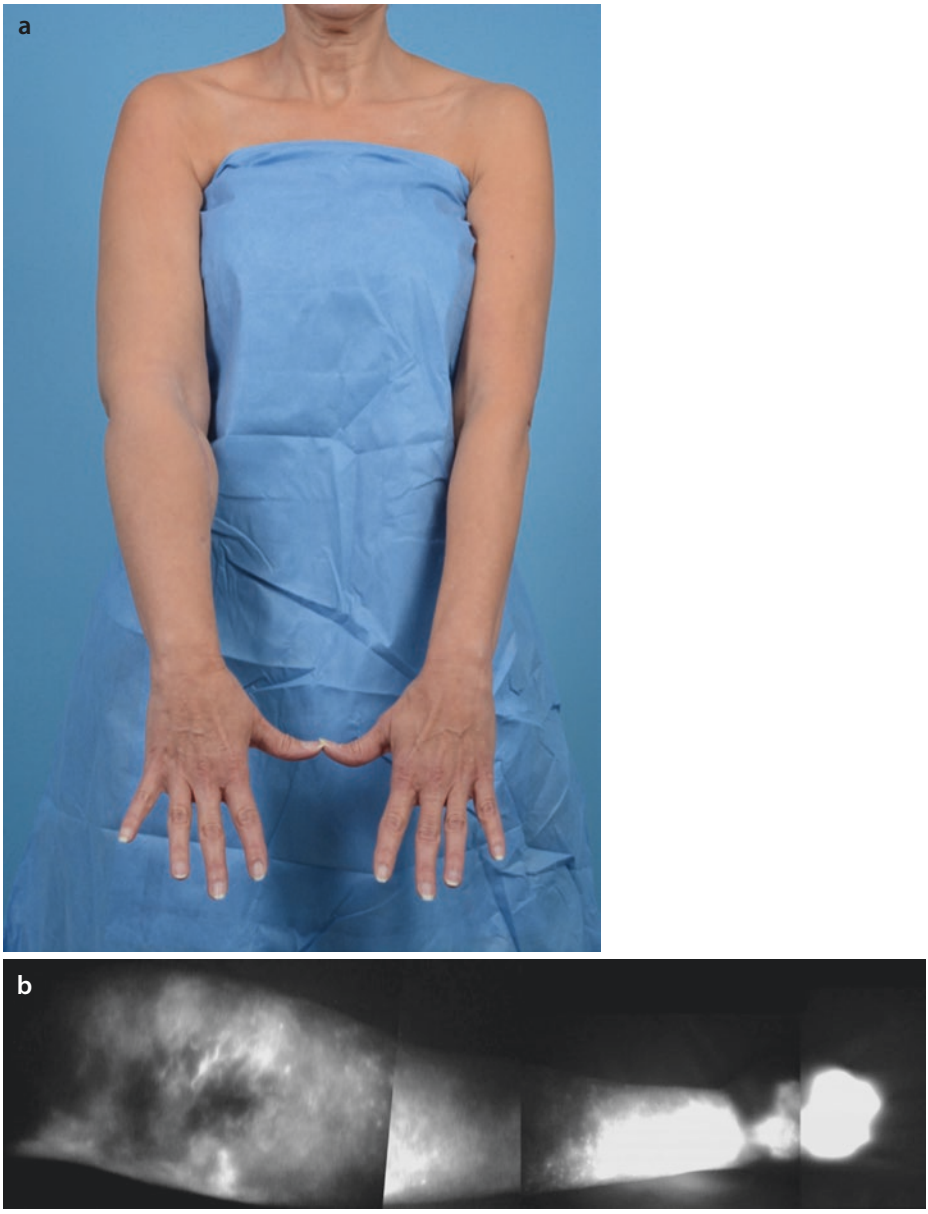

Fig. 46.2 **a** Clinical image of another patient with similar clinical findings. **b** However, ICG lymphangiography reveals significantly more advance disease with dermal backflow throughout the limb and no visible lymphatic collectors (Published with kind permission of © Joseph Dayan 2017. All Rights Reserved)

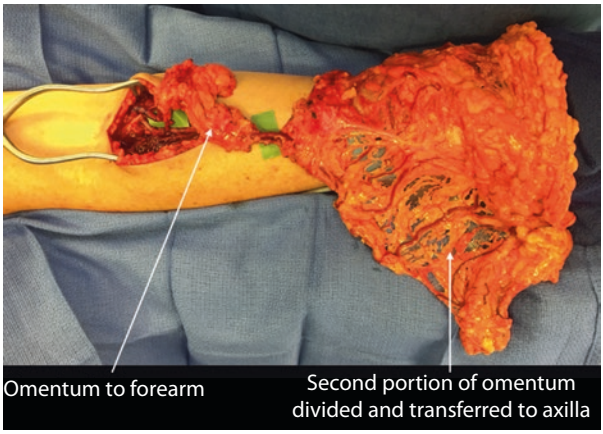

Fig. 46.3 Double omentum transfer for patient with diffuse dermal backflow on ICG. One portion of the omentum based on the right gastroepiploic vessels is anastomosed to the radial recurrent vessels in the forearm with the remainder of the flap divided and transferred to the axilla using the thoracodorsal vessels (Published with kind permission of © Joseph Dayan 2017. All Rights Reserved)

Pre-op limb volumes:
Left: 2007
Right: 1844
Difference: 163
% Dif.: 8.84% BIS score: 9

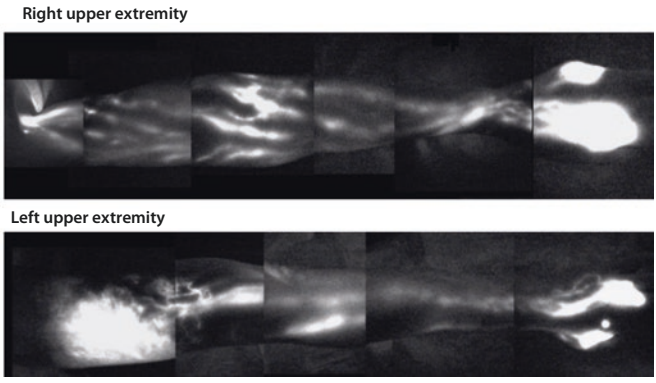

Fig. 46.4 Patient with a normal bioimpedance score and a limb volume difference of less than 10%. While clinical swelling is equivocal, ICG lymphangiography reveals significant lymphatic disease with a dermal backflow pattern in the upper arm (Published with kind permission of © Joseph Dayan 2017. All Rights Reserved)

fuse disease (Fig. 46.3). Alternatively, Neligan uses MR lymphangiography preoperatively to decide between LVA and VLNT (or a combination of both) [1].

Not only has ICG become useful in clinically obvious lymphedema, but it has also uncovered subclinical pathology. In recently presented but yet unpublished work by the author, patients who had transient swelling with equivocal limb volume differences and a normal bioimpedance score were found to have significant abnormalities on ICG lymphangiography (Fig. 46.4) [14]. While long-term study is needed, this opens up the potential to surgically intervene when most of the lymphatic system is functional in order to avoid chronic lymphedema [15]. The LVA versus VLNT debate has yet to be resolved, but these imaging techniques provide a tool by which we can stratify patients and study our outcomes.

Finally, lymphoscintigraphy has been routinely used in our practice as a baseline to confirm whether or not there is uptake into the transferred lymph nodes 1 year follow-

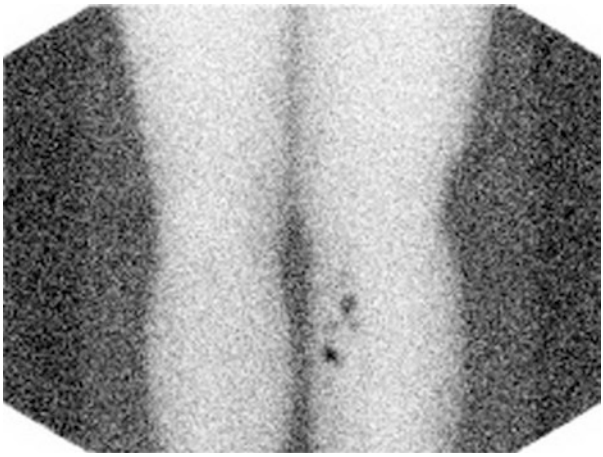

Fig. 46.5 One-year postoperative lymphoscintigraphy of the lower extremity following vascularized thoracodorsal artery-based lymph node transfer to the calf. Technetium uptake seen in the transplanted lymph nodes following injection into the foot confirming lymphangiogenesis into the nodes (Published with kind permission of © Joseph Dayan 2017. All Rights Reserved)

ing VLNT (Fig. 46.5) [16]. In patients who have had axillary lymphadenectomy, there is occasional technetium uptake in the axilla, and a less aggressive scar excision is performed to avoid disrupting functional lymphatics.

46.2 Assessing Immunologic Dysfunction

It is still unclear why some patients have intractable cellulitis despite strict compliance, while others never have a single episode. We do not yet have more sophisticated clinical tools to assess their immunologic impairment at this time. From an admittedly simplified surgical perspective, the location of the cellulitis may be significant. When using VLNT, the lymph nodes are often transferred to the epicenter of infection.

46.3 Assessing Fat Hypertrophy

Magnetic resonance angiography (MRA) has become our primary method for assessing the degree of fibrofatty proliferation and fluid accumulation [17]. Using the venous phase, this technique also uncovers areas of stenosis in the venous system and has also identified occult tumor recurrence in several cases. The MRA provides a clear image of the fluid-fat balance of the limb as seen in Fig. 46.6 where the patient has significant fluid accumulation and almost no fat hypertrophy. In contrast, Fig. 46.7 shows a patient with both significant lymph accumulation and abundant fat hypertrophy. The patient can appreciate from seeing the image that even if all lymph was removed from the extremity it would still be much larger than the unaffected limb. Adjuvant liposuction may be appropriate if the physiologic intervention is successful [5]. Alternatively, the fluid-fat balance can be evaluated with ultrasound or other imaging modalities.

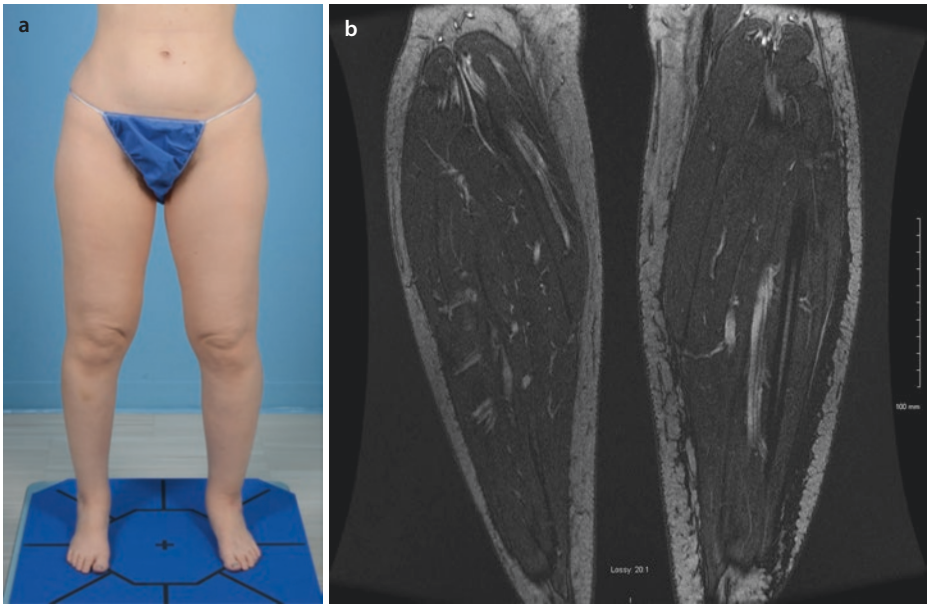

Fig. 46.6 **a** Clinical image of patient with left lower limb lymphedema—how much of this volume is fluid and how much is fat? **b** Coronal section on MRA demonstrating nearly total fluid dominance (fluid is *black*; fat is *gray*) (Published with kind permission of © Joseph Dayan 2017. All Rights Reserved)

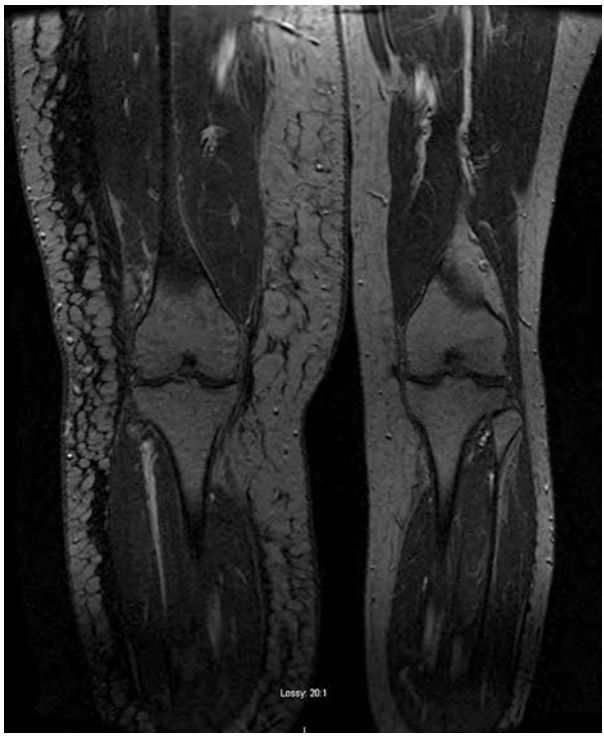

Fig. 46.7 Coronal section of lower limbs on MRA in a patient with both significant fluid and fat accumulation (Published with kind permission of © Joseph Dayan 2017. All Rights Reserved)

46.4 Assessing the Venous System

Evaluation of the venous system is fundamental to a thorough investigation of limb swelling. Lower extremity venous insufficiency is very common and, if significant, may be a contraindication to physiologic procedures which require a low-pressure venous outflow to work. A duplex ultrasound is commonly used to evaluate reflux as well as the presence of a deep vein thrombosis. Rare causes of limb swelling such as May-Thurner syndrome resulting from compression of the left iliac vein by the overlying iliac artery may be amenable to stenting [18]. It is best to collaborate with a vascular surgeon or interventional radiologist specializing in vein disorders.

Conclusions

A thorough evaluation of the patient is essential to arriving at a logical surgical approach. Lymphatic imaging has become central in uncovering significant pathologic differences among patients who appear to have clinically similar findings. This will likely lead to more consistently positive outcomes following surgery in the future. There are many questions that remain, but long-term studies stratifying patients based on imaging and further research into the immunologic and proliferative nature of lymphedema will guide surgical approaches that best match the patient's diagnosis.

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Lymphatic-Venous Derivative and Reconstructive Microsurgery

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Summary of Basic Concepts

Microsurgical methods included derivative multiple lymphatic-venous anastomoses (MLVA) and lymphatic reconstruction by interpositioned vein-grafted shunts (LVLA). In advanced stages, the technique of fibro-lipo-lymph-aspiration with a lymph vessel sparing procedure (FLLA-LVSP) is performed to improve the outcome of microsurgical procedures. Lymphatic-venous anastomoses are also used to prevent peripheral lymphedema following lymph nodal dissection (LYMPHA technique).

47.1 General Considerations

Lymphedema that is refractory to nonoperative methods may be managed by surgical treatment. Indications include insufficient lymphedema reduction by well-performed medical and physical therapy (less than 50%), recurrent episodes of lymphangitis, intractable pain, worsening limb function, patients who are unsatisfied with the result obtained by nonoperative methods, and patients who are willing to proceed with surgical options.

The first microsurgical derivative operations were those using lymph nodal-venous shunts. These have been largely abandoned, except in endemic areas of lymphatic filariasis such as India, where thousands of these procedures have been performed. Lymphatic channels in lymph nodal-venous anastomoses are often widely dilated because of the high rate of anastomotic closures caused by the thrombogenic effect of lymph nodal pulp on the venous blood and the frequent re-endothelialization of the lymph node surface [6]. Because of the difficulties encountered with lymph nodal-venous shunts by surgeons worldwide, the next approach was to use lymphatic vessels directly anastomosed to veins [7].

The technique consists of anastomosing lymphatic vessels to a collateral branch of the main vein with competent valvular function to secure the proper continence of the vein segment used for the anastomosis with no reflux. Valvular competence warrants the mandated condition of lymph flow alone and not the blood within the venous segment, avoiding any risk of thrombosis of the anastomosis [1, 3].

47.2 Clinical Experience and Surgical Techniques

The operations consisted of multiple microsurgical lymphovenous anastomoses. Healthy-appearing lymphatics found at the operation site are directly introduced together into the vein segment by a U-shaped stitch and then further secured to the vein's cut end by means of additional stitches between the vein border and the perilymphatic adipose tissue. With the use of the Patent Blue dye, properly functioning lymphatics appear blue, and the passage of blue lymph into the vein branch verifies the patency of the lymphovenous anastomosis under the operating microscope when the anastomosis is completed (Fig. 47.1).

For patients with lower limb lymphedema, anastomoses are performed at the subinguinal region. Superficial lymphatic-lymph nodal structures are isolated, and all afferent

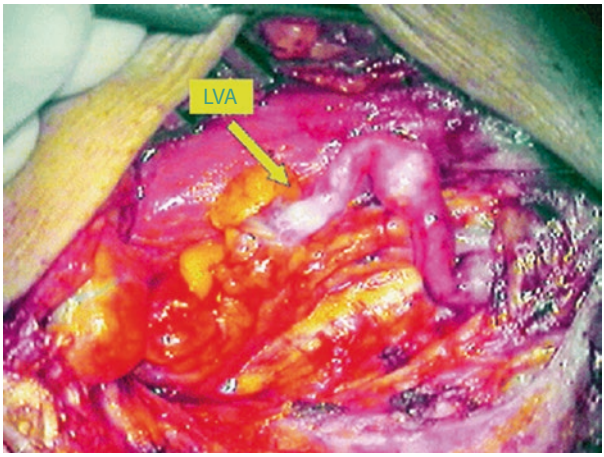

Fig. 47.1 Lymphatic-venous multiple anastomosis: several lymphatics are introduced inside a valved vein. The blue dye flowing into the vein demonstrates the patency of the vein. The well-functioning valve ensures the continence of the vein, avoiding blood reflux toward the lymphatics. This technical trick is important for the long-term patency of the anastomosis

lymphatics are used for the operation. Lymph nodes are subjected to histopathological examination. The usual finding in primary lower limb lymphedemas is a varying grade of nodal fibrosclerosis and thickening of the nodal capsule, but with normal afferent lymphatic vessels.

For upper limb lymphedema, lymphovenous anastomoses are performed at the middle third of the volar surface of the arm, using both superficial and deep lymphatic collectors, as demonstrated by the blue dye. Deep lymphatics are found among the humeral artery, vein, and the median nerve. The vein used for anastomoses is a patent branch of one of the humeral veins, and the technique most frequently performed is the end-to-end telescopic microsurgical procedure (Fig. 47.2).

Primary lymphedemas largely include lymph node dysplasias (LAD II, according to Papendieck's classification [8]) consisting of hypoplastic lymph nodes with sinus histiocytosis and a thick and fibrous capsule with microlymphangioadenomyomatosis. In these cases, lymph flow obstruction is apparent, as seen by alterations of the afferent lymphatics, which appear dilated and swollen with thickened walls and where smooth muscle cells are reduced in number and appear fragmented by associated fibrous elements.

Secondary lymphedemas are largely due to lymphadenectomy and radiotherapy performed for oncological reasons (carcinoma of the breast, uterus, penis, bladder, prostate gland, rectum and seminoma of the epididymis, etc.), as well as for complications of minor operations for varicose veins, crural and inguinal hernias, lipomas, tendinous cysts, or axillary and inguinal lymph node biopsies. Most of the lymphedemas treated by the microsurgery in our experience were at stages II (39%) and III (52%), whereas 3% of the patients were stage Ib and 6% were stages IV and V.

Lymphoscintigraphy, performed with 99mTc-labeled antimony sulfur colloid, is employed in the diagnostic work-up of patients with lymphedema and as a test for

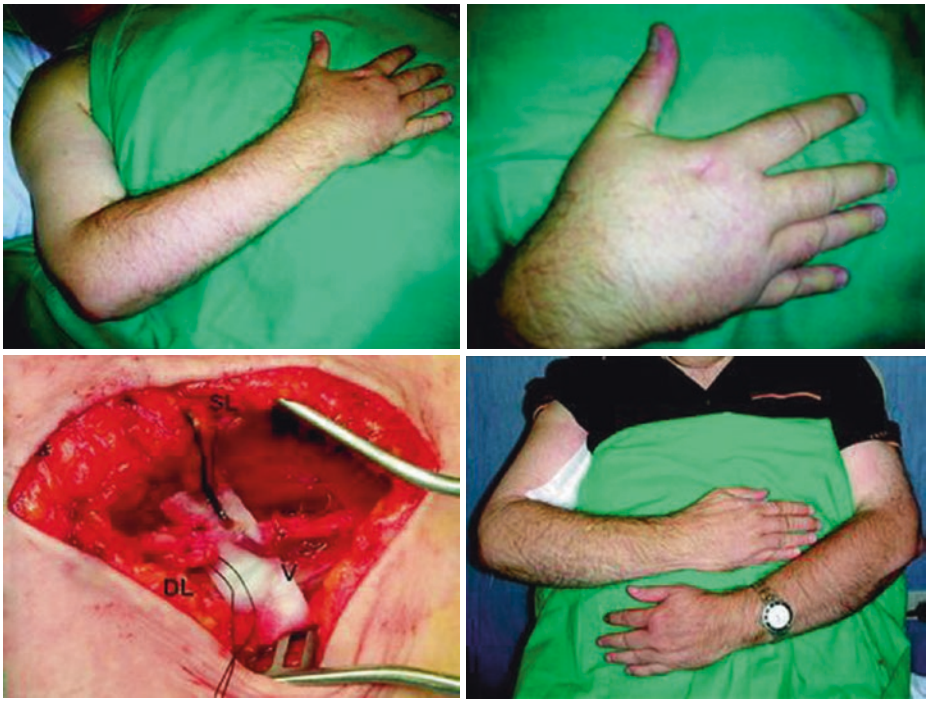

Fig. 47.2 Primary right upper limb lymphedema in a man treated with derivative lymphatic-venous anastomosis at the volar surface of the upper third of the arm. Superficial (SL) and deep (DL) lymphatics are prepared together with a vein (V) branch of one of the brachial veins with well-functioning valves. The result of the operation is immediate and the technique allowed stable results to be obtained at long-term follow-up

selecting patients for derivative microsurgical operations. Lymphoscintigraphy clearly determines whether or not edema was of lymphatic origin and also provides important data about the etiologic and pathophysiologic aspects of the lymphedema.

Echo Doppler is performed in all patients to identify any venous disorders possibly associated with lymphedema. In most patients, venous dysfunction is corrected at the same time as microlymphatico-venous anastomoses (i.e., valvuloplasty in the case of venous insufficiency) are performed. In other cases, the finding of venous dysfunction contraindicates derivative lymphovenous shunts, but at the same time facilitates referral of the patient for reconstructive microsurgical operations.

In those cases involving the lower limbs, where surgically uncorrectable venous disease exists, it is not advisable to use derivative lymphatic-venous techniques, and, accordingly, reconstructive methods are used. The most commonly used technique is the interposition of an autologous vein graft between the lymphatics above and below the obstacle to lymph flow. Competent venous segments can be obtained from the same operative site or from the forearm (mostly the cephalic vein). The length of the graft is

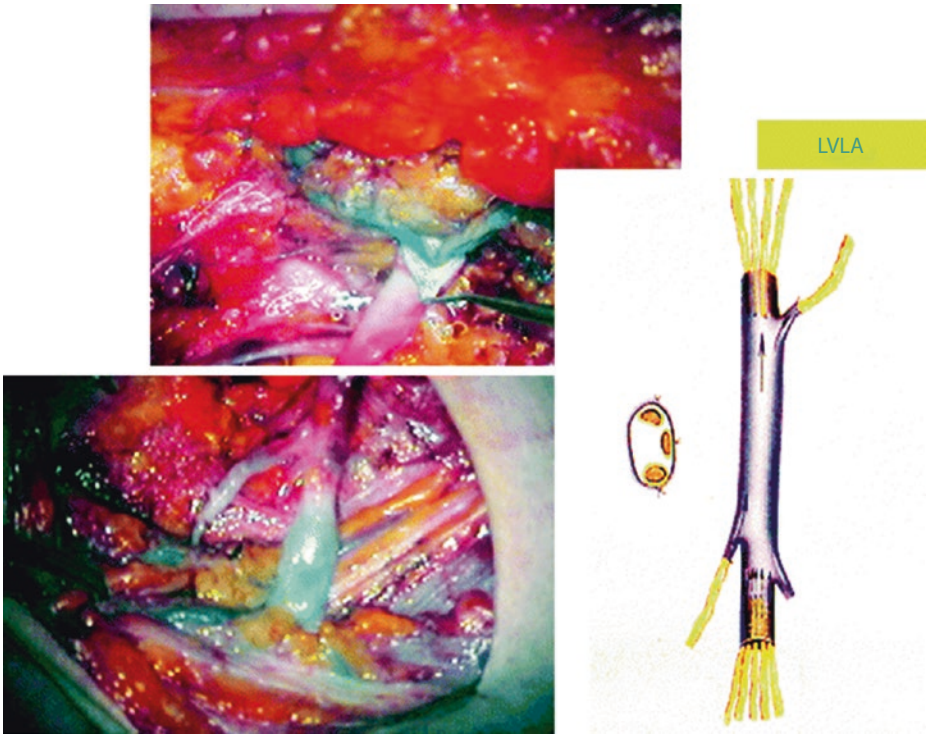

Fig. 47.3 Lymphatic-venous-lymphatic anastomoses used in those cases in which, owing to venous dysfunction, derivative technique is contraindicated. The technique consists in interposing a vein segment in between lymphatics above and below the obstacle to lymph flow [11]

variable from 7 to 15 cm, and it is important to collect several lymphatics to connect to the distal cut end of the vein so as to ensure that the segment is filled with enough lymph and to avoid closure due to subsequent development of the fibrosis. The competent valves of the vein segments are essential for the correct direction of the lymphatic flow and to avoid gravitational backflow, or reflux. The technique of anastomosis is the microsurgical procedure with introduction of the lymphatics inside the vein cut ends by a U-shaped stitch, which is then secured by additional peripheral stitches (Fig. 47.3).

47.3 Indications and Results

Clinical outcome improves the earlier microsurgery is performed, owing to absent or minimal fibrosclerotic alterations of the lymphatic walls and surrounding tissues. Subjective improvement in our experience was noted in 87% of patients. Objectively,

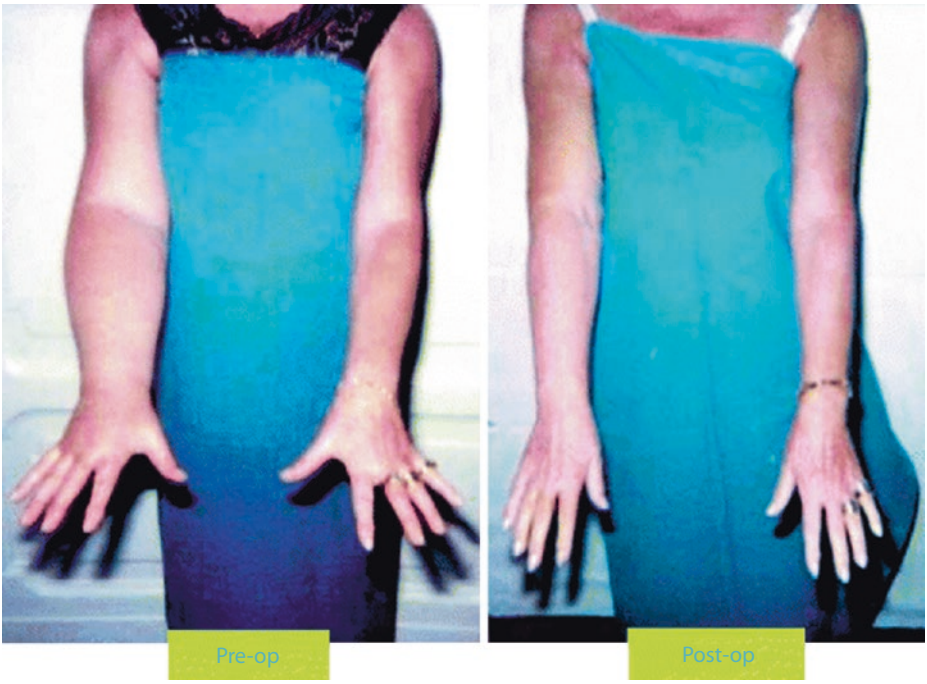

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Fig. 47.4 Right upper limb lymphedema due to breast cancer treatment, managed by derivative lymphatic-venous microsurgical anastomoses at the arm (long-term follow-up)

volume changes showed a significant improvement in 83%, with an average reduction of 69% of the excess volume. Of those patients followed up, 85% have been able to discontinue the use of conservative measures, with an average follow-up of more than 15 years and average reduction in excess volume of 69% (Figs. 47.4, 47.5, 47.6, 47.7 and 47.8). There was an 87% reduction in the incidence of cellulitis after microsurgery.

Lymphoscintigraphy helped in verifying the patency of microanastomoses long term after operation by direct and indirect findings: reduction of dermal backflow together with the appearance of preferential lymphatic pathways not visible before microsurgery, disappearance of the tracer at the site of lymphatic-venous anastomoses because of direct tracer passage into the bloodstream, and earlier liver uptake compared with preoperative parameters (indirect patency test; Figs. 47.9 and 47.10).

Lymphatic microsurgery represents a means of bypassing the obstacle to lymph flow through lymphatic-venous drainage (lymphatic-venous anastomoses) or by using venous grafts between lymphatic collectors below and above the obstruction (lymphatic-venous-lymphatic plasty). Combined physical therapy nonetheless represents the initial treatment of patients affected by peripheral lymphedema, and it is best performed in specialized centers. The surgical timing follows completion of conservative treatment

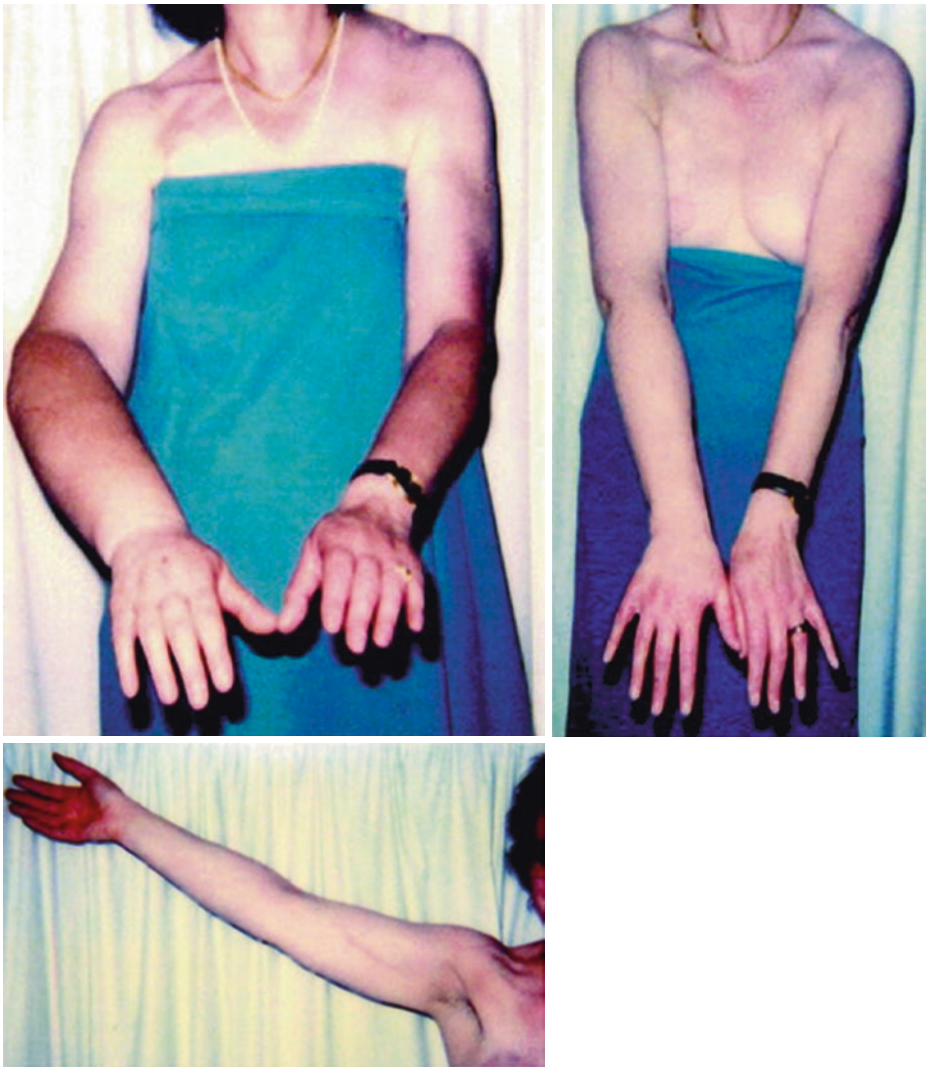

Fig. 47.5 Another case of secondary upper limb lymphedema. Of note is the good result at the hand and the favorable result from a cosmetic point of view

when further clinical improvement can no longer be achieved and/or recurrent lymphangitic attacks are not further reduced [9]. Microsurgical operations can then be performed and provide further improvement in the condition [10, 11].

The optimal indications for lymphatic microsurgery are represented by early stages (I and II), lymphoscintigraphy showing a low inguinal or axillary lymph nodal uptake

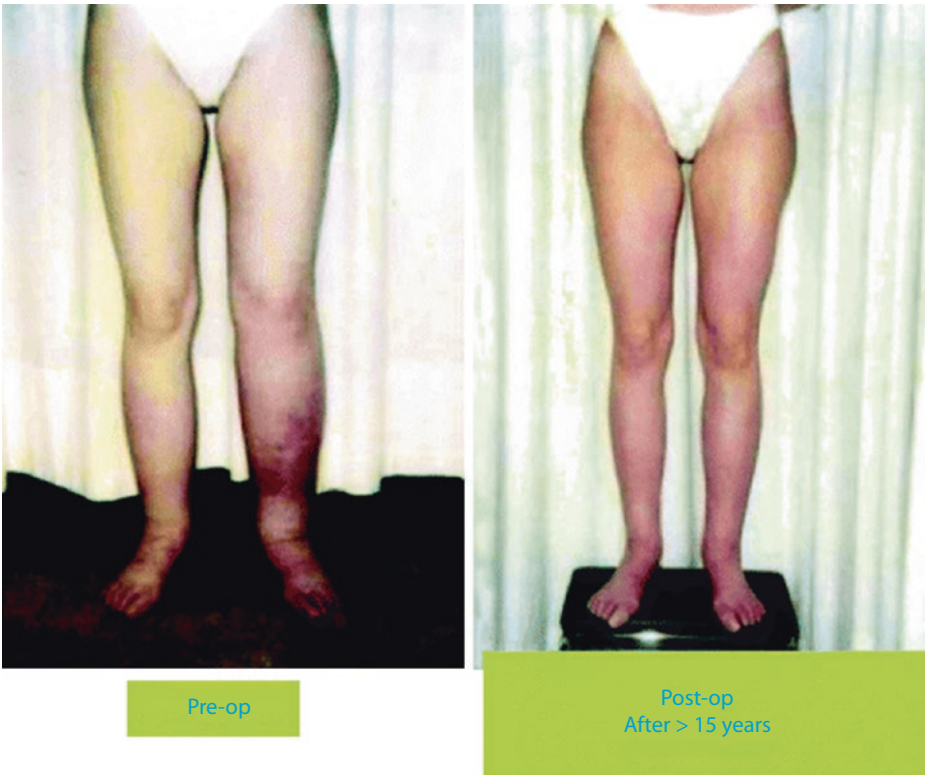

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Fig. 47.6 Bilateral lower limb primary lymphedema before and after 15 years from microsurgical derivative operation at the groin. The technique of lymphatic-venous anastomoses, if performed in the proper manner, represents a physiological, long-lasting repair of the lymphatic drainage of the extremity

and minimal or absent passage of the tracer beyond this proximal nodal area, excellent patient compliance, and a well-organized lymphedema center where the patient can be easily referred for additional care to a Center of Lymphatic Surgery to receive this specialized surgery.

At later stages (stage III), with absent visualization of lymphatic channels and regional lymph nodes, it is necessary to reduce the stage of the lymphedema by nonoperative methods before microsurgery. After the operation, it is particularly important for these patients to be kept under close follow-up with the regimen of complete lymphedema functional therapy – CLyFT [12]; such an approach is essential to improve the clinical outcome and maintain the short-term operative results for the long term (Fig. 47.11). In the case of poor patient compliance, the results may be unsatisfactory. Relative contraindications to lymphatic microsurgery are represented by cases of lymphatic-lymph nodal aplasia (extremely rare), diffuse metastatic disease, and advanced stage not responsive to conservative therapy.

In recent years, both primary and secondary peripheral lymphedemas have become better understood and more manageable problems, with increased awareness and early

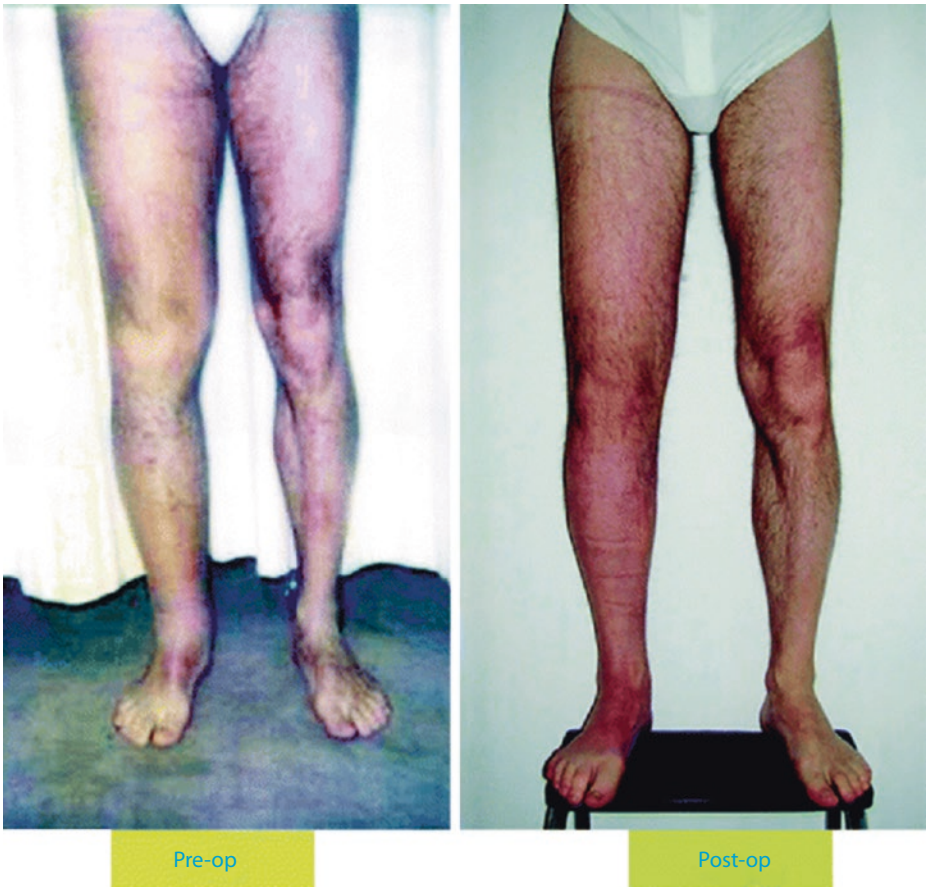


Fig. 47.7 Right lower limb lymphedema treated with derivative lymphatic-venous anastomoses at the inguino-crural region. These techniques allow the compression garments to be used irregularly, thanks to the formation of preferential lymphatic pathways and to the positive lymphatic-venous pressure gradient

detection [13–17]. Nonetheless, nonoperative measures are aimed at minimizing morbidity without removing the cause of the underlying disturbance [2, 18, 19]. Microsurgical derivative and reconstructive operations can restore lymphatic drainage, both in the short and long term, and the best results are obtained when these surgical procedures are combined with physical rehabilitative methods.

Traditional debulking operations are presently less frequently utilized to treat lymphedema except in cases of late-stage lymphedema to reduce skin folds after marked edema reduction obtained by conservative physical and microsurgical methods, in body regions relatively inaccessible to effective compression such as the genitalia, in advanced lymphatic filariasis at times combined with lymphatic-venous or nodal-venous anastomosis in the setting of widely dilated lymphatic channels, and in localized lipolymphedema associated with massive obesity and forced immobility.

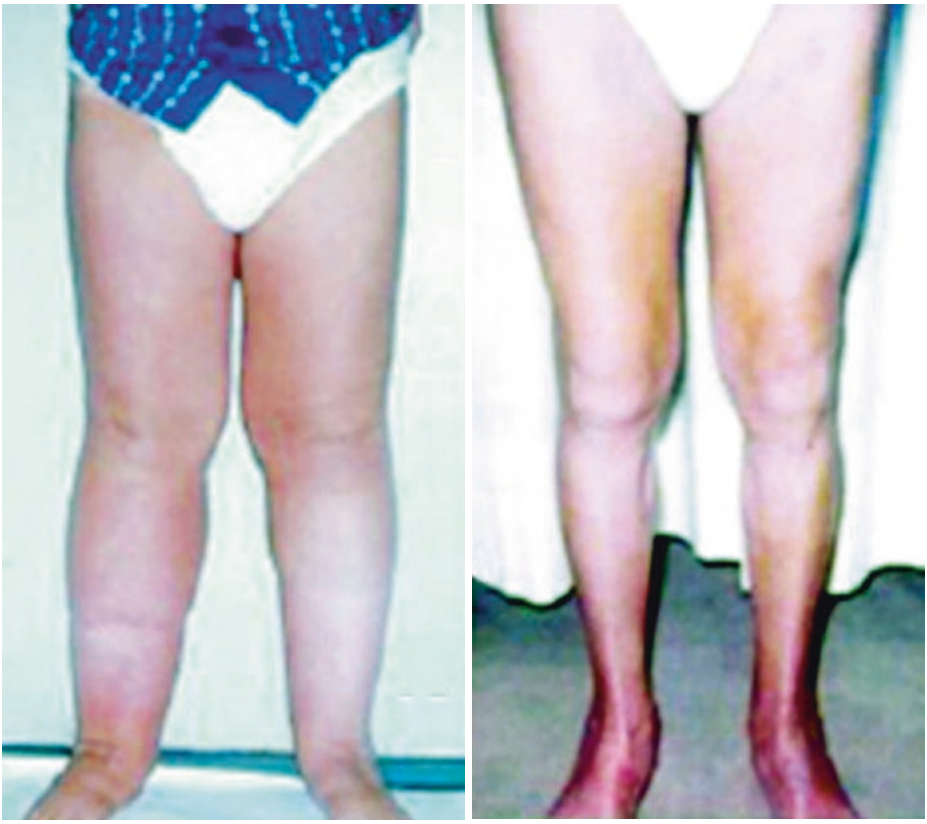
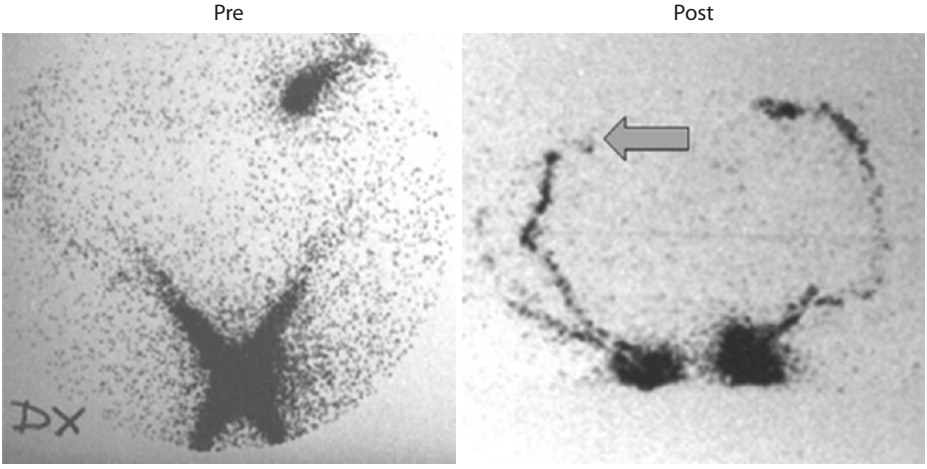


Fig. 47.8 Bilateral primary lower limb lymphedema with associated important venous dysfunction. In this case, reconstructive lymphatic-venous anastomoses were used bilaterally with a good long-term result. This technique can also be used in bilateral lymphedemas and does not determine any risk of secondary lymphedema at the harvesting site



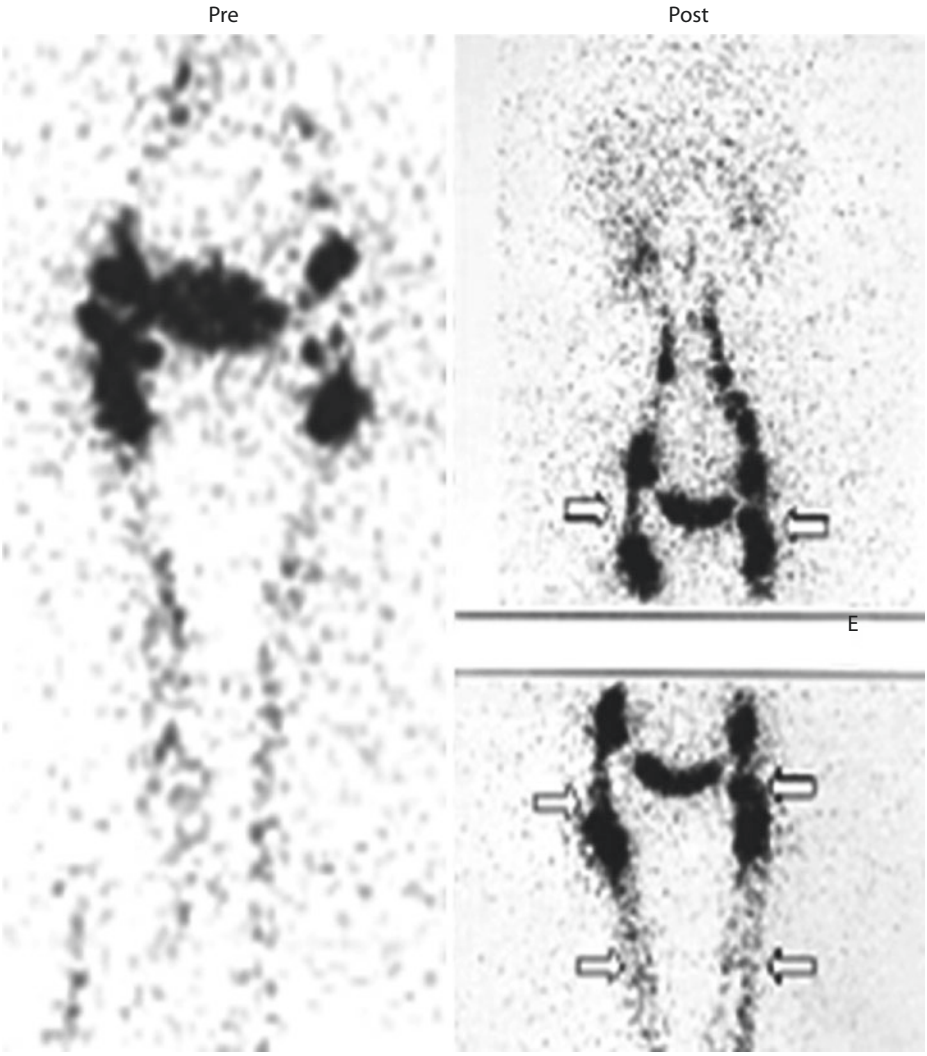


Fig. 47.10 Lymphoscintigraphy before and after reconstructive microsurgical lymphatic-venous technique performed in a bilateral lower limb lymphedema. Postoperatively, venous grafts are visualized in between lymphatic pathways below and above the inguinal region

Fig. 47.9 Lymphoscintigraphic follow-up of an upper limb secondary lymphedema treated by derivative lymphatic microsurgery. Postoperatively, preferential lymphatic ways are evident and the tracer disappears at the site of anastomosis because of passage into the bloodstream

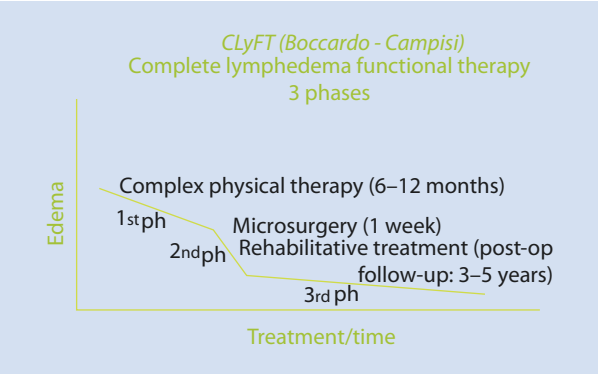


Fig. 47.11 Scheme of the complete lymphedema functional therapy (CLyFT) proposed for the combined nonoperative and microsurgical treatment of lymphedema. This therapeutic association proved to supply the best and longest-lasting results, combining the efficacy of nonoperative methods with the results of microsurgical procedures and giving the patient the possibility of wearing compression garments irregularly at the beginning, and also to avoid the use of stockings and sleeves in the long run

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47.4 Fibro-Lipo-Lymph-Aspiration Lymph Vessel Sparing [FLLA-LVSP]

Currently, the technique of fibro-lipo-lymph-aspiration with a lymph vessel sparing procedure [FLLA-LVSP] for the treatment of advanced chronic primary or secondary peripheral lymphedema has been developed [20–23]. In lymphedema, excess adipose tissue occurs with progression of the disease because of chronic lymph stasis, impeding lymphatic flow. Recently, liposuction has been used as a less invasive procedure to remove this excess tissue. Given the existing poor lymph drainage in patients with lymphatic diseases, extra caution should be taken to avoid damaging lymphatic vessels during liposuction [24–27]. We developed a new technique (fibro-lipo-lymph-aspiration with a lymph vessel sparing procedure [FLLA-LVSP]) to improve chronic swelling in patients with advanced lymphedema. The FLLA-LSVP highlights the superficial lymphatic pathways in the treated limb. This visibility allows surgeons to avoid these pathways while removing the maximum amount of excess tissue. One hundred forty-six patients with primary or secondary lymphedema that had already been treated by lymphatic microsurgery, in Genoa, Italy, were included in this retrospective study. All patients had residual fibrotic/adipose tissue, resistant to conservative treatments. Indocyanine green (ICG) fluorescent dye and blue patent violet (BPV) dye were injected laterally/medially to the main superficial veins at the wrist/ankle of the limb to be treated. Using a photodynamic camera (PDE test), the superficial lymphatic network was made visible and sketched onto the skin in indelible ink. After the microlymphography, the excess adipose tissue was carefully aspirated [28–30]. Preoperative and postoperative excess limb volume was calculated using circumferential measurements and the formula of a frustum. For the upper limb, 0.80 L, on average, and 2.42 L for the lower limb were removed with the FLLA-LVSP. For the upper limb, there was an average pre-surgery excess volume of 20.19%, which reduced to 2.68% after the FLLA-

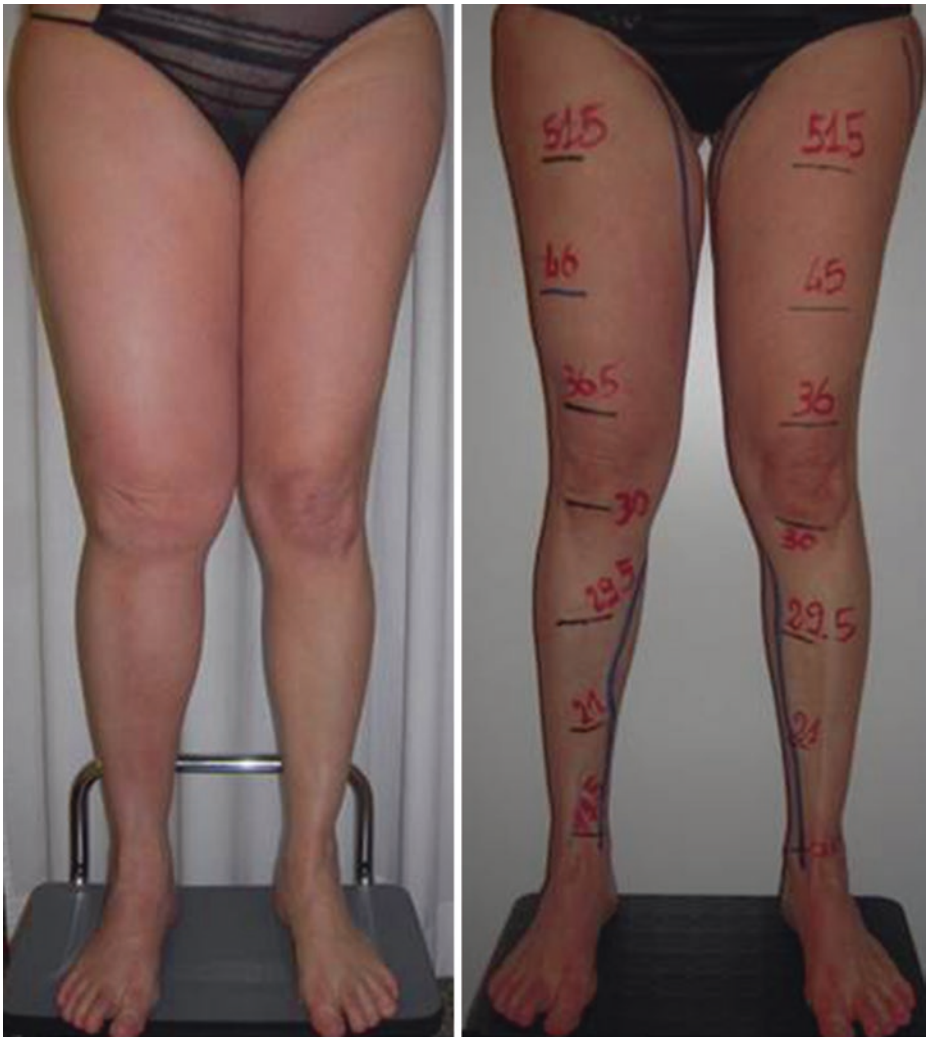

Fig. 47.12 Pre- and postoperative – lower limb secondary lymphedema

LVSP (Z score = −6.90, $P < 0.001$). Similarly, for the lower limb, there was an average pre-surgery excess limb volume of 21.24% and a reduction to 2.64% postoperatively (Z score = −3.57, $P < 0.01$). Immediate postoperative PDE/BPV test confirmed no lymphatic complications. No episodes of postoperative infection occurred. The FLLA-LVSP is efficient. An entire leg can be completed within 90 min. Recovery time is short, and cosmetic results are immediate. More importantly, the removal of excess tissue is completed without further damage to lymphatic vessels [31–34]. When used after microsurgery, FLLA-LVSP offers the possibility of removing almost all obstacles to lymphatic flow (Figs. 47.12 and 47.13).

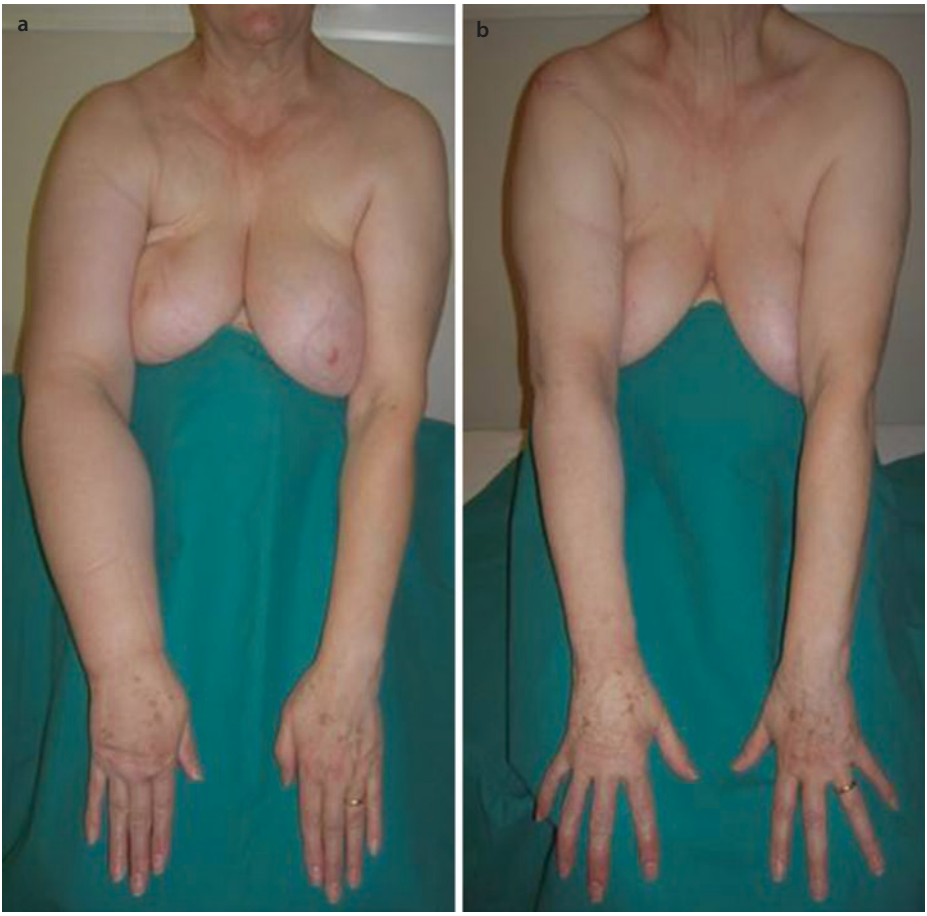

Fig. 47.13 Pre- and postoperative – upper limb secondary lymphedema

47.5 LYMPHA Preventive Technique

We recently proposed the use of lymphatic-venous anastomoses for primary prevention of secondary lymphedema, performing anastomoses at the same time as axillary and inguinal lymph nodal dissection for the treatment of malignant tumors. Axillary and inguinofemoral lymphadenectomy carries a high risk of lymphedema of extremities. We assessed the feasibility of performing multiple lymphatic-venous anastomoses after axillary and inguinofemoral lymph node completion (lymphatic microsurgical preventive healing approach – LYMPHA technique) and the possible benefit of LYMPHA for preventing lymphedema [35, 4, 5]. Between July 2008 and October 2014, 82 patients with breast cancer (BC), 11 with vulvar cancer (VC), and 16 with melanoma of the trunk (TM) requiring axillary or inguinofemoral lymphadenectomy underwent lymph node dissection and LYMPHA technique. Blue dye was injected into the arm or the thigh 10 min prior to surgery. Lymphatics afferent to the blue nodes were used to per-

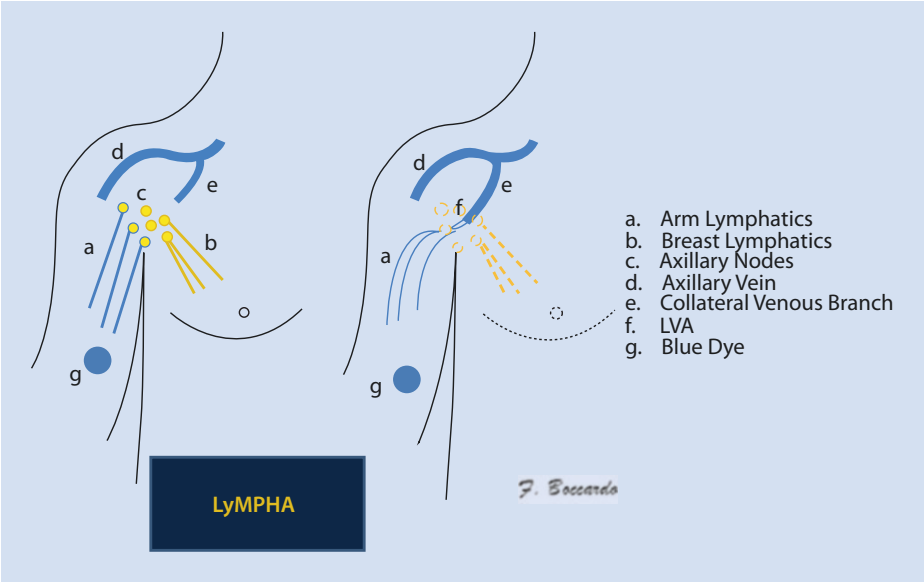

Fig. 47.14 Schematic drawing of LYMPHA technique at the axilla

form multiple lymphatic-venous anastomoses (MLVA) using a collateral branch of the axillary or great saphenous vein. Volumetry was performed pre- and postoperatively in all patients. Lymphoscintigraphy was performed pre- and postoperatively after at least 6 months, comparing pre-op and post-op lymph transport index (TI – normal below 10). Mean follow-up was 36 months (6–60 months) [36–38]. In BC group, patients with BMI higher than 30 were candidates for LYMPHA (Figs. 47.14 and 47.15); patients with normal BMI were studied with lymphoscintigraphy which was able to point out latent lymphatic impairment, still not evident clinically. Five patients with VC underwent bilateral inguinofemoral lymphadenectomy, while the other 6 VC patients and all 16 patients with TM had unilateral node dissection. All patients were treated by the LYMPHA technique (Figs. 47.16 and 47.17). No lymphocele or infectious complications occurred. Seventy-nine BC patients had no sign of lymphedema and volumetry was coincident to preoperative condition. In three patients (3, 6%), belonging to the initial clinical experience, arm lymphedema occurred after 8–12 months postoperatively, usually with the appearance of lymphangitic attacks. Transient lower extremity edema occurred in one TM patient (6.25%) which resolved after 2 months, and permanent lower extremity edema occurred in one VC patient (9%). Lymphoscintigraphy in BG group showed the patency of lymphatic-venous anastomoses at 1–4 years after operation and an improvement of lymphatic TI compared to preoperative conditions in all patients except in three with clinical arm lymphedema. In VC and TM groups, lymphoscintigraphy demonstrated a postoperative TI below 10 in 8 VC and in 13 TM patients, between 10 and 14 in 2 VC and 3 TM patients (without clinical lymphedema), and 29 in 1 VC patient (with lymphedema) [39–40]. The LYMPHA technique appears feasible, safe, and effective for the prevention of upper and lower limb lymphedema, thereby improving the patient's quality of life and decreasing healthcare costs.

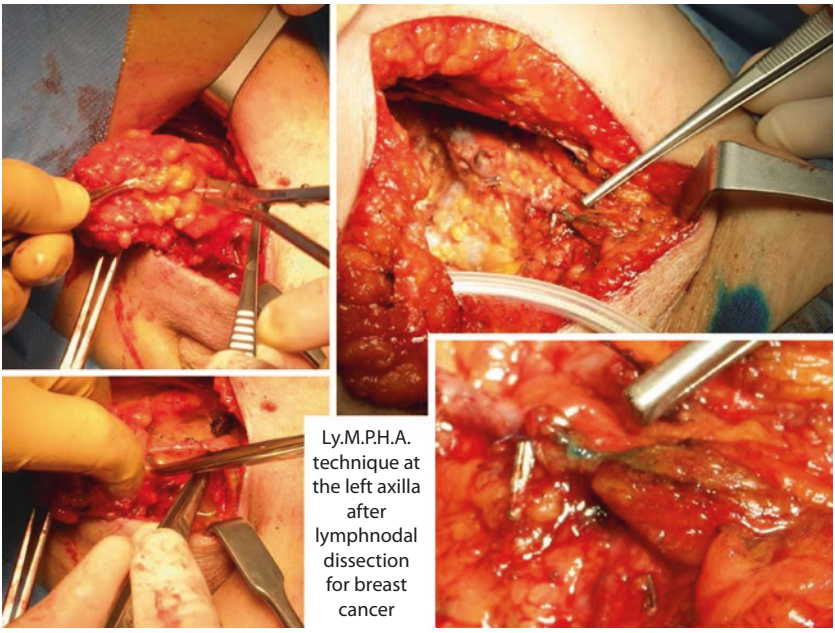

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Fig. 47.15 LYMPHA technique at the left axilla after lymph nodal dissection for breast cancer

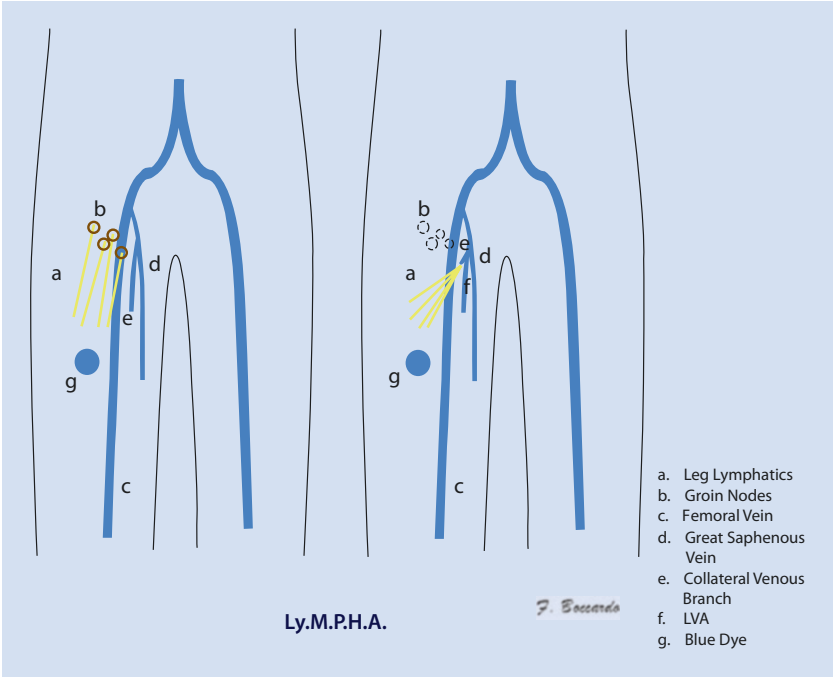

Fig. 47.16 Schematic drawing of LYMPHA technique at the groin

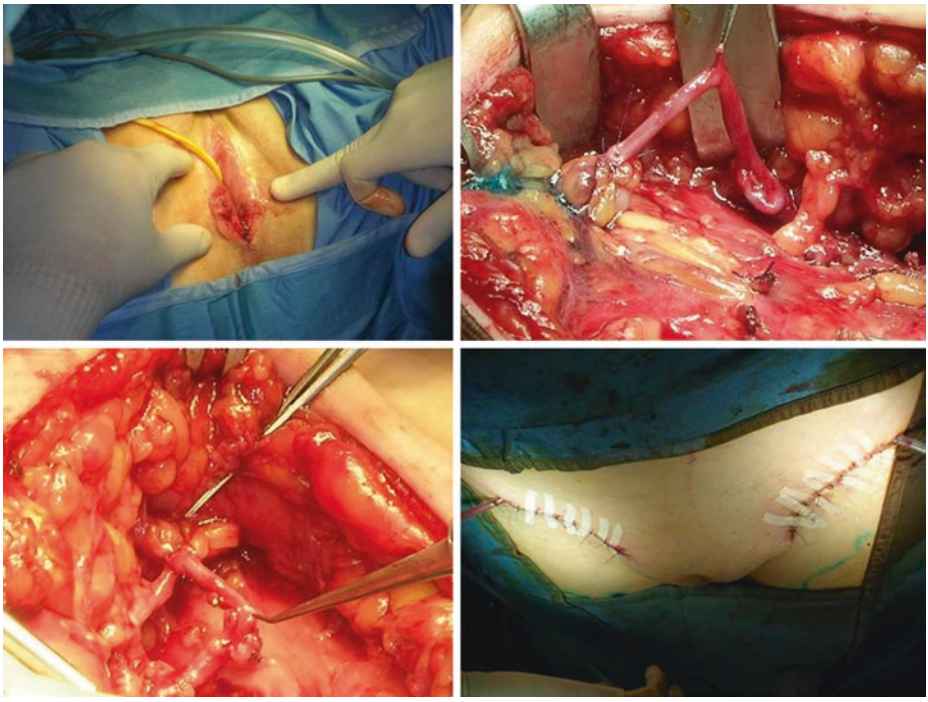

Fig. 47.17 LYMPHA technique at the right and left groin after bilateral lymph nodal dissection for vulvar cancer

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Lymphatic-Lymphatic Reconstructive Microsurgery

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B.-B. Lee et al. (eds.), *Lymphedema*, https://doi.org/10.1007/978-3-319-52423-8_48

Summary of Basic Concepts

Lymphatic vascular transporting system is considered as consisting of microsurgical treatable vessels.

Local interruptions or impairments of the lymphatic transporting system are treated by a bypass procedure.

2–3 Lymphatic vessel grafts are harvested out of the ventromedial bundle at the thigh which consists of about 16 lymphatic vessels without touching the lymphatic narrowings, the inguinal region with the lymph nodes, and the knee area after a preoperative lymphoscintigraphic screening.

In arm edema due to axillary revision, lymphatic grafts are anastomosed to lymphatic main collectors at the upper arm and lymphatic vessels or lymph nodes at the neck.

In unilateral leg edema and penile and scrotal edema, the grafts remain attached to the inguinal lymph nodes and are transposed either to the thigh of the edematous leg or the root of the penis and the scrotum and anastomosed to lymphatic collectors.

Performing the procedure within the lymphatic system has multiple advantages:

- The correct pressure gradient is respected.
- Mayor lymphatic collectors within the edematous area are connected to the grafts.
- Danger of thrombosis at the anastomosis is low because of the low coagulability of lymphatic fluid.
- The known self-connecting ability of lymphatic vessels may assist additionally.
- The known autonomous pumping activity of lymphatic vessels is of advantage.

48.1 Introduction

A direct approach to the lymphatic vessels was considered unthinkable for a long time. However, on the basis of high-power operating microscopes and increasing ability to anastomose small arteries and veins, the lymphatic vessels also became possibly suturable vessels.

Lympho-lymphatic anastomoses and microsurgically performed lymphovenous anastomoses using grafts were described by Cordeiro et al. [6].

In extensive experimental studies, the use of lymphatic grafts for reconstruction purposes within the lymphatic vascular system and their patency could be demonstrated as well [7].

Subsequently, lymphatic grafting was introduced into the treatment protocol for the patients with localized lymphatic interruptions and was performed for the first time in June 1980 in Munich [1].

48.2 Correlation with the Pathophysiology of Lymphedemas

The origin of the development of lymphedemas can be described as an imbalance between the lymphatic load and the lymphatic transport capacity [8, 9]. In western countries, most jeopardized lymph transport capacity is due to surgical and/or radiation injuries. Therefore, the obstruction of the lymphatic system is limited to a localized area, mostly at the root of an extremity, e.g., in the axilla or the groin.

For such limited interruption of the lymphatic vessels, a bypass has been considered as an option that could lead to full recovery of the reduced transport capacity because the bypass surgery has been well accepted as a viable treatment in other vascular systems with obstruction.

However, especially in advanced lymphedemas, secondary tissue damages/changes have a serious impact on the outcome of the therapy. Therefore, preferably at an early stage, after maximum conservative treatment, a reconstruction should be offered to the patient as an optional treatment to provide further improvement of the condition. Because edemas also can subside spontaneously within approximately 6 months, this time period should be used for this kind of treatment.

If the early interventional option was missed and the lymphedema accompanied heavy tissue change with fat and connective tissue deposits, an improvement in the transport capacity by reconstruction of the lymphatic interruption should be attempted first. Thereafter, further treatment to restore the original volume and shape of the extremity may be added with various invasive methods/resections including the suctioning out of the surplus tissue when indicated.

However, a great concern regarding suction is the potential risk of lymphatic tissue damage, and, therefore, it should be performed with great care to spare the lymphatics as much as possible [2]. In addition, lymphedematous tissue is quite different from normal fatty tissue, which can be sucked out in aesthetic indications. Therefore, this procedure should be named properly, with consideration of the underlying lymphatic problem, and should not be called just liposuction [10] but rather «lipo-lymphosuction» at best.

In this way, the surgical procedure follows the pathophysiology. The reconstruction of the interrupted lymphatic system is attempted first, and thereafter the sequelae of the primary cause are dealt with the deposit of fat and connective tissue when indicated.

48.3 Experimental Basis

Reconstruction of lymphatics is based on extensive experimental investigations [1, 7].

Anastomosing procedures were tested in the rat model at the abdominal thoracic duct.

Lymphatic vessels are relatively resistant against longitudinal traction, but most fragile under oblique tension. Therefore, the «tension-free anastomosing technique» was developed. The ends of the lymphatic vessel remain in place to maintain a tension-free condition. First, the corner stitch opposite the surgeon is performed. Then, for the

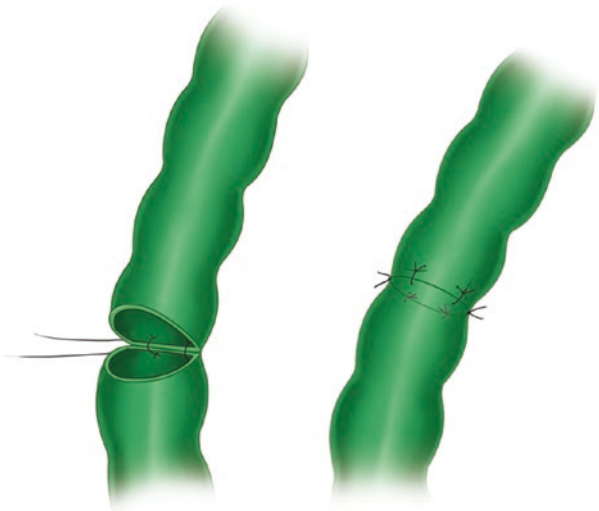

Fig. 48.1 Lympho-lymphatic end-to-end anastomoses under tension-free anastomosing technique without turning the vessel

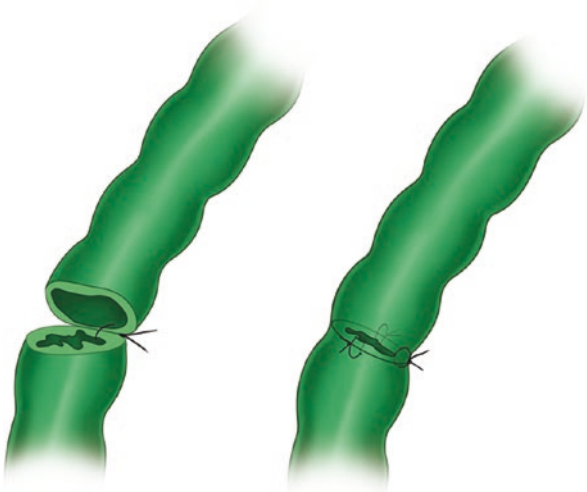

Fig. 48.2 Lympho-lymphatic end-to-end anastomoses between the graft with a thin wall and the lymph vessel with long-standing lymphedema with heavy fibrosis using three stitches

back wall stitches, the vessel is minimally lifted as necessary to handle the needle. The second corner stitch and the front wall are made subsequently without moving the vessel. In small lymphatic vessels, only three stitches can be applied in the same manner (Figs. 48.1, 48.2 and 48.3).

Absorbable suture material seemed to be of advantage. Histological studies showed within several weeks almost no foreign body reactions using this material, whereas nonabsorbable suture material remained long after the intervention with a remarkable foreign body reaction close to the small lymphatic vessels. Therefore, we prefer absorbable suture material for the anastomoses, even though it is available only in a larger size compared with nonabsorbable material.

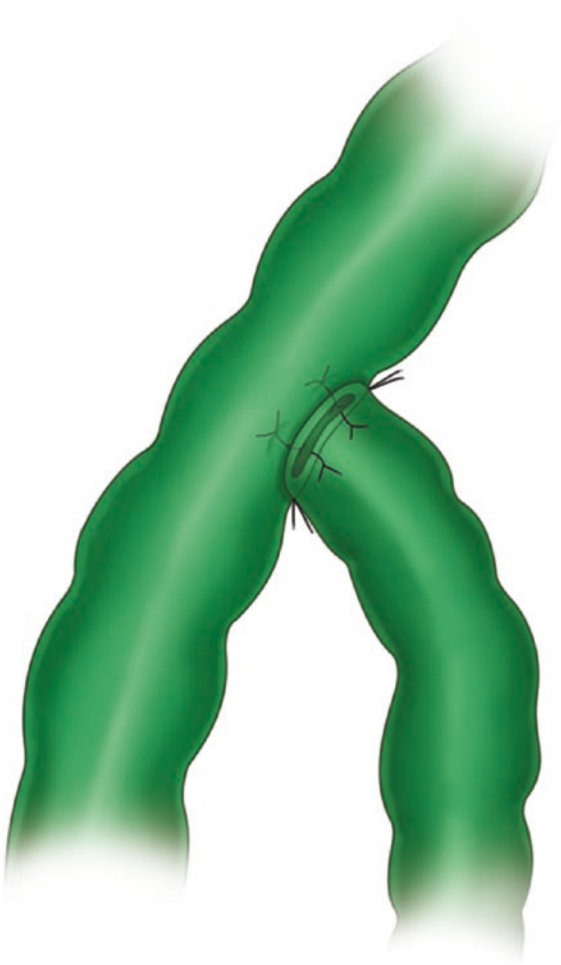

Fig. 48.3 Lympho-lymphatic end-to-side anastomoses

The patency of the lympho-lymphatic anastomoses has been proved by surgical reinterventions, direct lymphographies, Patent Blue injections, and electron microscopy.

The rate of patency reached 100% checked by histological examinations, which indirectly reflects that the lymphatic collectors are able to help to maintain patency following microsurgery. The findings of the Danese et al., who only approximated lymphatic vessels and found spontaneous communication, also support this impression [11].

The patency and effect of lymphatic transplants were checked in the rat as well as in the dog model using surgical reinterventions, direct lymphography, dye injections, isotopic tracers, volume estimations, and intralymphatic pressure measurements. Thereby, high patency rates and high functional benefits could be demonstrated. After removal of the lymphatic transplant, as a control study, the opposite effect was seen. The volume of the affected extremity immediately increased again.

By measuring the intralymphatic pressure, we investigated the effect of low molecular dextran as well. We documented an increase in the pressure and assumed it to be an effect of flushing through the newly created anastomoses. Therefore, we also administer

this or similar drugs to the patients for several days after the intervention to keep increased lymph flow through the anastomoses.

Also, we compared different materials like autogenic veins, allogeneic lymphatics, and small PTFE grafts, together with autogenous lymphatic grafts. This showed the clear superiority of autologous lymphatic grafts. This was confirmed in a study of the canine model by Yuwono [12].

48.4 Indications for Lymphatic Reconstruction Using Lymphatic Grafts

Secondary lymphedemas due to a locally interrupted lymphatic system are the main indication for lymphatic grafting [3, 13].

Arm edemas after axillary node dissection are a predominant form of chronic lymphedema in the countries outside the tropical region and are those mostly treated in our series.

Leg edema after the interventions in the inguinal or pelvic region is also common in developed countries generally as unilateral lymphedema. This iatrogenic condition can also be treated by transposing the lymphatic vessels from the healthy to the affected side. One leg has to serve as the harvesting side.

In primary lymphedemas, a selected group with unilateral atresias of the inguinal and/or pelvic region can be treated by lymphatic grafting as well.

In cases with a history of malignancies, the patient must be tested to be tumor-free.

Since the burden of surgery is comparable to that of venous interventions in the subcutaneous tissue, there is almost no known general restriction for this type of surgery.

Each patient should report adequate conservative treatment before the surgery of at least 6 months' duration. During that time period, spontaneous regression of the edema is also reported.

Therefore, before the reconstructive surgery is performed, the patient has to get a complete set of lymphatic decongestion therapy, including manual lymphatic drainage, elastic stockings, and compression bandage therapy for at least half a year.

48.5 Operative Technique

The grafts are harvested from the medial aspect of the thigh (Fig. 48.4). As many as 16 lymphatic vessels can be found within the ventromedial bundle. About one to three vessels are used as grafts, but should be harvested with caution avoiding the narrowing portions of the lymphatic system at the groin and at the knee region.

The lymph nodes at the knee region as well as the groin are not touched or removed to spare the lymphatic system as much as possible.

The number of lymphatic collectors, used for grafting, is sufficient for reconstructive purposes, since anatomical studies also showed that only one preserved lymphatic collector of the long lateral bundle of the upper arm is able to prevent a patient after axillary node dissection from developing arm edema [14].

To facilitate the preparation, about 15 min before the incision, Patent Blue® is injected subdermally into the first to second web space. The joints are moved to improve the transport of the dye.

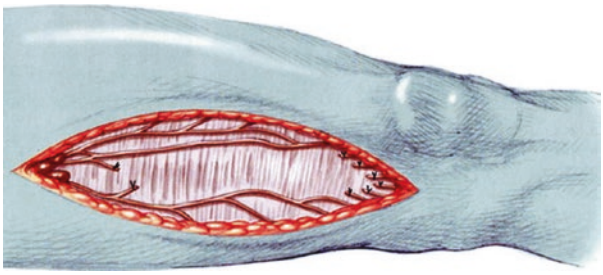

Fig. 48.4 Harvesting lymphatic vessels from the patient's thigh

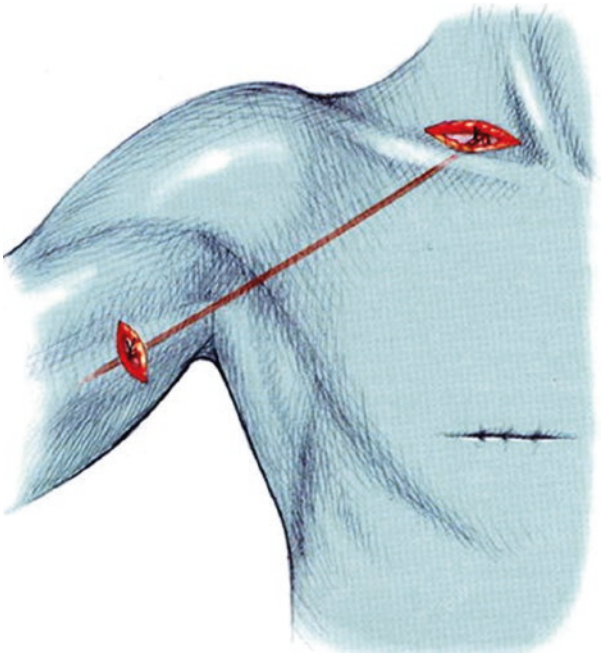

Fig. 48.5 Bridging a lymphatic gap at the axilla with autogenous lymphatic vessels by lympho-lymphatic anastomoses at the upper arm and the neck

The incision is started medial to the palpable vessels beneath the inguinal ligament. The incision is extended distally step-by-step following the direction of the stained vessels.

Also, the ramifications of the main lymphatic collectors can be saved to use for anastomosing purposes. Therefore, more lympho-lymphatic anastomoses can be performed at the affected extremity as the equivalent of the number of the harvested main collectors. For safety reasons, it is necessary that stained lymphatic vessels also remain untouched.

Depending on the length of the thigh, the grafts can be harvested up to a length of about 30 cm. The grafts are secured at the proximal end with 6-0 sutures and transected proximally and distally. Distally on the transected side, the proximal ends of incoming lymphatic vessels are ligated to avoid lymphatic leakages.

In arm edemas (Fig. 48.5), an oblique incision is performed at the inner aspect of the upper arm. Under the microscope, the tissue is searched for lymphatic vessels. Since the transport of dye is disturbed in lymphedema, no staining is performed.

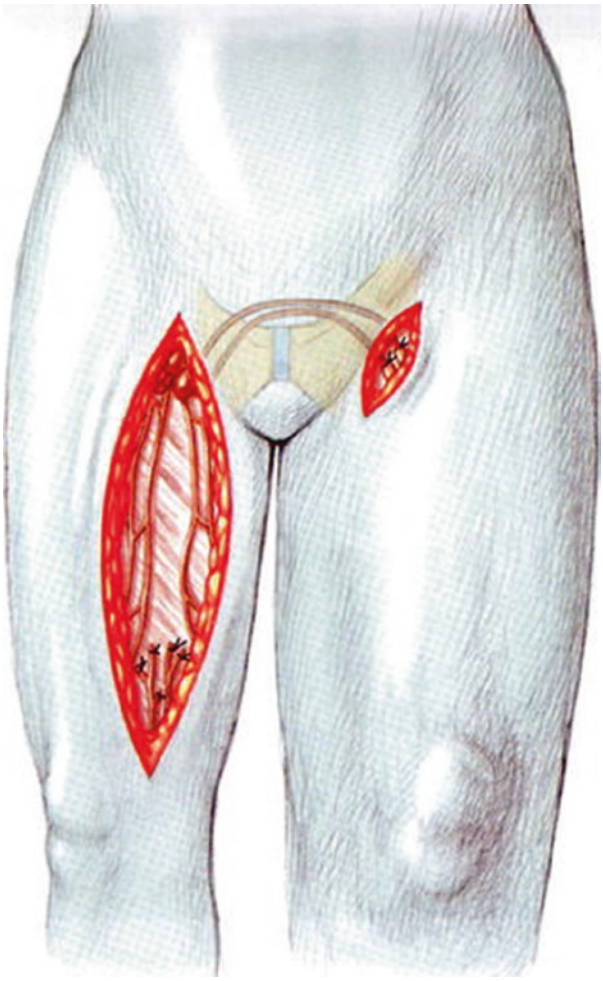

Fig. 48.6 Lymphatic grafting in unilateral lymphedema of lower extremities; the grafts remain attached to the inguinal lymph nodes

At the neck, an oblique incision is made at the dorsal rim of the sternocleidomastoid muscle. Prior to this step, a dye injection is performed cranial to the ear to enhance the chance of dyeing the lymphatic vessels at the neck. Behind the muscle up to the lateral border of the internal jugular vein, thin-walled lymphatic vessels can be found. Often, it is easier to prepare several lymph nodes.

In between the incisions at the upper arm and the neck, a tunnel is created by blunt dissection, and a silicon tube is temporarily inserted, and with its help, the grafts are pulled through. Finally, the tube is removed, and the grafts lie in the subcutaneous tissue without friction.

The anastomoses are performed under the «tension-free» anastomosing technique in an end-to-end or end-to-side fashion with 10-0 absorbable suture material. In the neck region lympho-lymphonodular anastomoses can also be performed.

In unilateral lymphedema of the lower extremities (Fig. 48.6), the grafts remain attached to the inguinal lymph nodes on the harvesting side. Ascending lymphatics are

dissected via an incision below the inguinal ligament on the affected side. The grafts are placed in a technique similar to that in arm edemas. After microsurgical lympho-lymphatic anastomosing, the lymph flows via the grafts to the healthy side.

In penile and scrotal edemas with at least one edema-free leg, short lymphatic collectors, remaining attached to the inguinal lymph nodes, can be anastomosed with draining lymphatic vessels at the route of the penis and the scrotum.

48.6 Postoperative Procedures

The limbs are elevated, and bed rest is recommended for 3 days. For about 5 days, antibiotics are given. Elastic bandaging is applied, and elastic stockings should be worn for 6 months. In addition, a prophylaxis against erysipelas is recommended for the same time period. Thereafter, we try to discontinue the additional therapy.

48.7 Results

In patients, follow-up studies included volume measurement of the affected extremity as well as of the harvesting area, lymphoscintigraphic studies, and quality of life interrogations; more invasive procedures like indirect lymphographies using water-soluble contrast medium and MRI lymphographies using gadolinium are undertaken among selected patients [13, 15].

As complications, one patient developed a lymph cyst at the groin that was treated with puncture drainage. One patient developed a swelling of the lower leg due to the venous thrombosis, and two patients showed postoperative erysipelas in the first series of our patients prior to the routine postoperative administration of antibiotics.

Starting in June 1980 and continuing until January 2009, a total of 329 patients were treated: 187 suffered from arm edemas, 132 from leg edemas, and 10 from scrotal and penile lymphedema.

In arm edemas as well as in leg edemas, more than 60% of the patients showed a reduction in volume difference to the healthy side of more than 50% after a mean follow-up period of more than 2 years.

In 100 arm edemas after a follow-up of more than 1 year, a significant reduction in volume from 3234 ± 78 cm^3 to 2597 ± 66 cm^3 compared with a volume of the healthy contralateral arm of 2181 ± 46 ($p < 0.001$) was demonstrated.

Follow-up in arm edemas up to at least 10 years also showed a significant reduction after this long period of time (mean volumes: 2918 ± 141–2243 ± 147 cm^3 compared with 1890 ± 88 cm^3 in the healthy arm).

The patency of the graft was confirmed in an indirect way via lymphoscintigraphy [15]. In arm edemas, the route of the grafts was able to track down along the visible tracts of the tracer activity, whereas no such activity has been found prior to the transplantation. In edemas of the lower extremities, the radioactive tracer activity was able to be tracked toward the contralateral groin where the transposed crossover grafts remained attached to the nodes following the injection of radiotracer only to the affected limb.

The proof of long-term patency was also possible after more than 10 years with indirect lymphography in the upper and lower extremities and more than 7 years with MRI lymphoscintigraphies in the lower extremities.

Lymphoscintigraphy also enabled us to calculate the overall function of the lymphatic system of an extremity [4, 16].

The lymphatic transport index was also feasible to estimate the function of the graft [15]. Hereby, the investigators of the department of nuclear medicine summarized the findings as a score between 0 and 45:0 for the best and 45 for the worst outflow. The difference between normal and pathological status is calculated based on the transport index of 10.

A follow-up study within 7 years showed a score of 10 in the group with a clearly visible activity of the transplants, which means it reached the value of a normal lymphatic outflow. Since the decrease in limb volume runs parallel to the improvement shown on lymphoscintigraphy, it suggests a potential chance for a cure and freedom from further additional treatment [4].

A recent study compared the results in volume measurement and lymphoscintigraphic follow-up studies in 177 patients suffering from arm edemas and treated by autologous lymph vessel transplantation. The different follow-up periods, 6–12 months, 32–38 months, and more than 8 years, showed a persistently improved lymph drainage and good correlation to the findings in volume measurement [5].

Regarding possible negative effects on the harvesting side, nuclear medical controls have been performed at the donor leg in 19 consecutive patients at a mean follow-up period of 49 months. The lymphatic transport index, a measure for the lymphatic transport, was very close to the preoperative value and always in the normal range [17].

This is coincident with the low complication rate. In one patient we had to treat a lymphatic cyst by puncture on the harvesting side. In two early patients, prior to our regular perioperative administration of antibiotics, we saw erysipelas. In one patient we had to stop a venous bleeding in the subcutaneous tunnel which was created for the graft. And in one patient we saw a swelling of the lower leg together with a venous thrombosis.

In long-standing lymphedemas with excess accumulation of adipose and fibrous tissue, additional removal of surplus tissue with lymphatic sparing suction might be added to get closer to the condition and shape of the healthy extremity without continuous treatment.

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Lymph Node-Venous Microvascular Reconstructive Surgery: Filariasis Lymphedema

Gurusamy Manokaran

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Summary of Basic Concepts

- Lymphatic filariasis should be treated different from other lymphoedemas.
- Excisional surgery alone has a high rate of recurrence and produce bad scars.
- Physiological operations are a must along with MLD + Bandaging.

Lymphatic filariasis is one of the most chronic, incapacitating diseases; once it was believed that there was no treatment. Ancient sculptures and scriptures depict lymphatic filariasis of the lower limb and still can be seen in many temples in India. According to Manusmrithi's 300 BC written in Hindu mythology, it was mentioned, and some native treatments also have been mentioned. It was considered to be caused by karma (result of sins from a previous life), but through science and technology, we have been able to identify the organism and its transmission to human beings from one person to another person by mosquito. Initially, a lot of medical and surgical treatments were done unsuccessfully, and this disease was classified as «neglected tropical disease.» Because excisional surgery has not given good results, during the era of microvascular reconstructive surgery in 1963 Niclubowicz, Olszewski developed this nodovenal anastomosis in artificial lymphedema produced in dogs; subsequently this procedure was tried in various parts of the world in human beings with lymphedema. This procedure is a surgery of choice for treatment of early lymphedema in some centers and in cases of elephantiasis before performing cyto-reductive/debulking procedures. This nodovenal anastomosis is more of a physiological procedure [1–5, 7–11] and is very useful when there is a deformity or disease of the afferent lymphatics to connect to the efferent lymphatics (e.g., lymphatic filariasis, posttraumatic lymphedema, postinflammatory lymphedema). This is not useful in disease for which there is no lymphatics or lymph node (e.g., after mastectomy, after irradiation, and congenital lymphedemas). Thus, in developed countries, where lymphedema is mainly due to mastectomy, irradiation, and congenital etiology, this procedure is not very popular, although it has been introduced in Europe.

49.1 Nodovenal Shunt

49.1.1 Indications

1. Patients with competent saphenofemoral junction.
2. Patients without inguinal abscess or sepsis.
3. All grades of lymphedema.
4. There should be a healthy and functioning lymph node (lymphoscintigraphy or ICG Lymphangiography (Indocyanine green) ultrasound finding).

49.1.2 Surgical Techniques

There are two methods of anastomosis: end to end or end to side (Fig. 49.1).

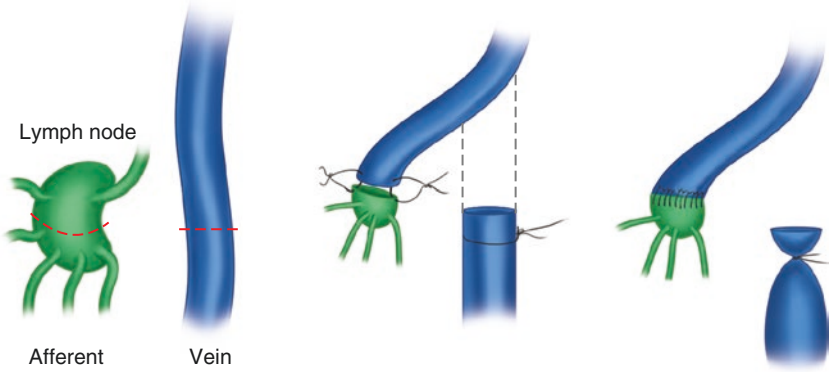

Fig. 49.1 Diagrammatic representation of a nodo-venous bypass (microvascular anastomosis): **a** vein and node showing (*red dotted lines*) the area to be shaved, **b** anastomosis of node-vein end to end, **c** completion of anastomosis (This technique which we modified from the original following)

End-to-End Anastomosis

Nodovenal shunting for lower limb lymphedema is carried out with the patient in a supine position under general or regional anesthesia. A vertical incision of 3 cm is made, in the upper part of the thigh just medial to the femoral pulsations, and the long saphenous vein or a good caliber vein is exposed. Ligate the distal end with chromic catgut and the upper end is cut open like a fish mouth. There should not be any retrograde flow in the proximal segment, proving that there is no saphenofemoral incompetence. Identify a vertical group of inguinal lymph nodes; these nodes must be reasonably big (at least 1 cm in diameter) and pink in color. No dissection is performed around the lymph node so that both afferent and efferent lymphatics are preserved. Shave the upper capsule of the lymph node and you can see the lymph ooze from the cut surface. Avoid using diathermy; if it is urgently needed, use bipolar diathermy, so that it causes less damage to the surroundings. Anastomose the proximally cut long saphenous vein to the cut surface of the capsule of the node using 6-0 or 7-0 nylon continuous suture. Then the wound is closed in layers after perfect hemostasis. No drain is required. This is the one which we practice now and found it to be very useful and functioning well.

End-to-Side Anastomosis

A nodovenal shunt can be placed end to side also. In this method a vertical stab incision of 0.5–1 cm is made, depending upon the vein caliber, with an 11-sized blade. The stab incision is made after applying vascular clamps proximally and distally, and the cut surface of the node is anastomosed with the vertical stab incision into the vein using 8-0 nylon, interrupted sutures. Clamps are released and observed for filling of the vein. Continuous irrigation of the anastomosis site with heparinized saline should be performed because clot formation is common with this technique. When there is no healthy or reasonable sized lymph node in the inguinal region, multiple lymphatic channels can be buried into the continuous vein at three or four places. The open end of the lymphatics is left in the venous lumen to float (use an 18-gauge needle to stab); lymphatic vessels are anchored with 8-0 nylon as a single suture. This technique is known as lymphatic venous anastomosis.

This nodovenal shunt can be done bilaterally for genital involvement of LF (lymphatic Filariasis) in the surgical management along with scrotal reduction and penile skin reduction surgery [6]

49.1.3 Contraindications

1. No visible lymph node in lymphoscintigraphy or in ultrasound or ICG lymphangiography
2. Associated varicose veins or saphenofemoral incompetence
3. No reduction of circumferential measurements of the leg at any given point, even after 6 days of MLD (manual lymph drainage)
4. Acute ADL (adeno-dermo-lymphangitis)
5. Elderly patients with incompetant veins
6. Associated medical diseases

49.1.4 Complications

1. Seroma
2. Lymphorrhea
3. Lymphocele
4. Wound dehiscence

49.2 Free Omental Transfer [12, 13]

This procedure is carried out in lymphatic filariasis and posttraumatic and postsurgical lymphedemas. In lymphatic filariasis with lower limb lymphedemas, through a vertical, upper thigh midline incision, the GSV, superficial circumflex iliac artery, and the inguinal lymph nodes or lymphatics are exposed and prepared for microvascular anastomosis. The abdomen is opened with a lower transverse incision, and the omentum is dissected with its artery, vein, and lymphatics, which can be anastomosed with the respective artery, vein, and lymphatics. *A small window during the closure of the thigh incision is left open for assessment of the viability of the omentum, which can be closed secondarily after 48 hrs*. The abdomen is closed in layers after perfect hemostasis. Both abdominal and thigh wounds are closed separately, leaving no communication between the two. The tunneling of the omentum into the inguinal region (omentoplasty) was initially popular with Russian surgeons in the management of various types of lymphedemas but was subsequently abandoned, because of the increased incidence of lymphangitis of the leg, leading to peritonitis as the omentum was kept in continuity. Surgery for lymphedema should not cause mortality, although a certain amount of morbidity is acceptable.

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Vascularized Lymph Node Transfer for the Treatment of Lymphedema

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Summary of Basic Concepts

- Select lymphedema patients who have failed conservative therapy may be candidates for physiologic surgical procedures, which include vascularized lymph node transfer (VLNT).
- There are two prevailing hypotheses to explain the functional mechanisms of VLNT: the lymphatic «wick» and lymphatic «pump» theories.
- Lymph node donor sites for free transfer include superficial groin, submental, supraclavicular, thoracic, and omental.
- VLNT recipient sites include may be either anatomic (groin, axilla) or non-anatomic (upper inner arm, wrist, upper posterior calf, ankle).
- Reverse lymphatic mapping is a physiologic technique used to identify and delineate lymphatic drainage patterns to a given lymph node donor site to facilitate flap dissection and minimize risk of iatrogenic lymphedema.

50.1 Introduction

Lymphedema is classified as either primary or secondary. It is a worldwide problem associated with significant morbidity, including pain, disfigurement, recurrent infections, physical disability, and overall reductions in quality of life. In the developed world, it typically arises as a consequence of breast and gynecological cancer-related treatments (tumor resection, lymphadenectomy, lymph node biopsy/dissection, and radiation therapy). Approximately 5% of patients undergoing sentinel lymph node biopsy (SLNB) go on to develop lymphedema. When an axillary lymph node dissection (ALND) is performed as part of breast cancer treatment, this risk is estimated to be over 15% [6]; with the addition of postoperative radiotherapy, the incidence can be as high as 40%. Less commonly, lymphedema may originate from hereditary developmental defects of the lymphatic system. Complex decongestive therapy (CDT) aims to minimize the soft tissue accumulation of lymph fluid and is currently the baseline treatment of choice regardless of disease severity. Surgical options include both reductive and physiologic approaches. Reductive approaches, including direct excision and liposuction, aim to decrease morbidity by removing varying amounts of fibrofatty tissue in patients with chronic lymph stasis. On the other hand, physiologic surgical procedures such as lymphovenous anastomosis (LVA) and VLNT aim to improve lymph drainage of the affected extremity. There is increasing evidence that VLNT can reverse the disease process, thereby obviating the need for lifelong massage therapy, compressive garments, and other supportive measures.

50.2 Background and Mechanisms of Action

In 1979, Shesol et al. reported the successful restoration of lymph function with free lymph node transfer in rats [7]. Subsequent authors would demonstrate similar findings in both rat and canine models [8, 9]. Becker et al. reported the first clinical series with long-term results of microsurgical lymph node transfer to the axillary region in 24 female patients with upper extremity lymphedema and demonstrated positive results [1]. Two main hypotheses that explain the functional mechanisms of VLNT have been

advanced [2, 3]. The first theory is that of a lymphatic «wick.» The transferred flap, which contains a rich supply of vascularized lymph nodes, bridges the zone of obstruction and forms lympholymphatic connections with proximal and distal lymphatic channels at the recipient bed. The second theory proposes that the transferred lymphatic tissue acts as a «pump»; excess interstitial lymph fluid is absorbed into the flap, which then shunts this fluid into the systemic circulation.

50.3 Preoperative Assessment

Proper patient selection is a crucial element in lymphedema surgery. Only patients that have demonstrated compliance with conservative therapy and that have proven refractory to further CDT should be considered; in order to maximize results following VLNT, postoperative instructions must be reliably followed. Furthermore, all candidates should optimize weight loss preoperatively, possess a patent and competent venous system in the extremity of interest, and be free of active infection at the time of surgery.

At the initial visit, a full history and physical exam should be performed. Careful and precise measurements of limb circumferences (normal vs. abnormal) are documented. Patients then undergo Tc^{99} lymphoscintigraphy to assess the baseline extent of lymphatic flow obstruction (partial vs. total). Other imaging modalities that may be used include computed tomography (CT) and magnetic resonance imaging (MRI). Both modalities are able to provide both anatomic and volumetric information of a given limb and can evaluate honeycombing of the soft tissues. MRI provides superior contrast between the different soft tissue components. More recently, MR lymphography has gained popularity for the noninvasive diagnosis of lymphedema and assessment of disease severity [10]. Lastly, a venous duplex ultrasound to rule out venous thrombosis and insufficiency is also performed.

Indications for VLNT include [4, 11]:

- Stage I–II (International Society of Lymphology Classification) lymphedema patients that are not candidates for LVA (lack suitable lymphatic channels) with or without history of repeated episodes of cellulitis
- Fibrosis that precludes LVA
- Total occlusion of lymph drainage on lymphoscintigraphy
- Stage III lymphedema patients (VLNT may be offered in combination with partial wedge excision or as a second stage procedure after liposuction)
- As part of a combined approach in patients undergoing LVA
- Treatment of brachial plexus neuropathy complicating breast cancer treatment

50.4 Treatment: Principles and Operative Technique

50.4.1 Secondary Lymphedema

In developed countries, the etiology of chronic upper extremity lymphedema is mostly secondary to the lymphadenectomy as a part of breast cancer management. Surgical excision of these axillary lymph nodes is often combined with postoperative radiation therapy to the lymphadenectomy site, which may damage the function of the lymph nodes and channels that remain.

Lymphadenectomy and radiotherapy in the inguinal and iliac regions can induce either unilateral or bilateral lower limb lymphedema. Common scenarios leading to lower extremity lymphedema include:

- Pelvic surgery combined with radiotherapy in the context of extended hysterectomies or prostatectomies
- Lymph node resections in the inguinal region for melanoma
- Radiotherapy and inguinal lymph node biopsy for Hodgkin's disease

VLNT, which aims to reverse the process of lymphedema by replacing what has been lost, therefore appears to be a logical approach. The fatty flap containing lymph nodes may provide various potential benefits in lymphedematous upper and lower limbs:

- Established interconnections between the nodes and the body's venous circulation
- Enhanced immune system in a given limb due to the germinal cells found within the transplanted lymph nodes
- Promotion of lymphangiogenesis by the abundant cytokines found within the fatty tissue around the nodes

50.4.2 Primary Lymphedema

The principles of VLNT in cases of primary lymphedema are akin to those in secondary lymphedema [12–14]. However, congenital abnormalities of lymphatic channels (e.g., aplasia, hypoplasia, and hyperplasia) have extremely variable clinical and anatomical presentations and are particularly difficult to manage; surgical outcomes are generally poorer and less predictable than in cases of secondary lymphedema. Depending upon the nature, extent, and severity of the lymphatic system abnormalities, VLNT potentially provides the best existing solution for disease improvement. Furthermore, the transplanted lymph nodes and their surrounding fatty tissues are a source of vascular endothelial growth factor C (VEGF-C) and other cytokines that induce and regulate lymphangiogenesis. The transplantation of lymph nodes into the lymphedematous limb not only can improve lymphatic drainage but also regional immunological function and resistance to infection.

When lymphedema appears at birth or in the first years of life, physiotherapy is an important component of the treatment approach. However, it is particularly challenging to effectively apply compressive bandages in the growing child, and conservative treatments often fail to adequately slow disease progression to fibrosis. Therefore, if a donor lymph node flap is technically feasible and there are no significant medical comorbidities, VLNT must be carried out as soon as possible [15]. If the lymphedema occurs in puberty and is resistant to conventional physiotherapy treatments, VLNT should also be considered as soon as possible in order to avoid rapid disease progression and to avoid recurrent infections. In select cases, a combined approach of VLNT with reductive techniques may be indicated.

The recipient site for the transferred lymph node flap should be chosen based on lymphoscintigraphy findings and type/distribution of lymphedema. If the entire lower extremity is affected, the inguinal region is the preferred recipient site. The superficial circumflex iliac vessels are most commonly chosen for arterial and venous microanastomoses. If the

lymphedema is limited to the calf, the lymph node flap may be inserted into the popliteal region, and a branch of the lesser saphenous vein may be used for the venous anastomosis. The thoracic and supraclavicular lymph nodes may be selected as donors in cases of primary lymphedema; however, as in cases of secondary lymphedema, the ultimate decision will be largely based on surgeon preference and patient characteristics.

50.4.3 Lymph Node Donor Sites

Lymph node flaps may be harvested from several donor sites. Selection depends on planned recipient site, previous history of surgery or radiation therapy, as well as both surgeon and patient preference. The number of nodes typically available for harvest varies by location; on average, between three and six nodes are included in the flap (possibly more in the omental flap).

Superficial Groin Lymph Nodes

The groin lymph node flap is based off branches of the superficial circumflex iliac artery (SCIA) or a small medial branch of the femoral artery. Preoperatively, the course of the SCIA and landmarks for flap elevation are marked; these landmarks include the inguinal ligament, sartorius muscle, and femoral vessels [16]. Target lymph nodes are found within a 3 cm radius of a point one third the distance from the pubic tubercle to the anterior superior iliac spine (Fig. 50.1) [17]. An elliptical skin paddle (5 × 10 cm) is designed along the inferior border of the inguinal ligament. A superior skin incision is made and dissection is performed from lateral to medial above the sartorius muscle fascia. The superficial circumflex iliac vessels are explored from distal to proximal until their origins. The flap (which includes the skin, subcutaneous tissue, and superficial inguinal lymph nodes) is then raised. Careful attention is taken to keep the dissection above the groin crease in order to avoid injuring the deep inguinal lymph nodes that drain the lower extremity. Advantages include predictable anatomy, presence of multiple lymph nodes, ability to harvest in conjunction with abdominal flap for breast reconstruction, and hidden scar. Disadvantages include small size and length of donor artery as well as risk of iatrogenic lymphedema [11].

Submental Lymph Nodes

The submental lymph node flap is based off the submental artery, a branch of the facial artery. Preoperatively, the course of the facial artery and location of its perforators are marked. Landmarks for flap design include the lower border of the mandible, mandibular angle and symphysis, as well as the anterior border of the sternocleidomastoid muscle (SCM) [18]. An elliptical skin paddle (10 × 5cm) from the mandibular angle to the symphysis is designed. The distal facial artery is identified above the mandible at its junction with the submental artery and mobilized fully with careful preservation of the septocutaneous perforators. Soft tissue around the junction of the submental artery and the facial artery are included to maximize the number of lymph nodes. The anterior digastric muscle belly can be taken to ensure perforator and lymph node preservation within the flap. During dissection, the marginal mandibular nerve is identified and protected. The advantages of the submental flap include reliable anatomy, good vascular

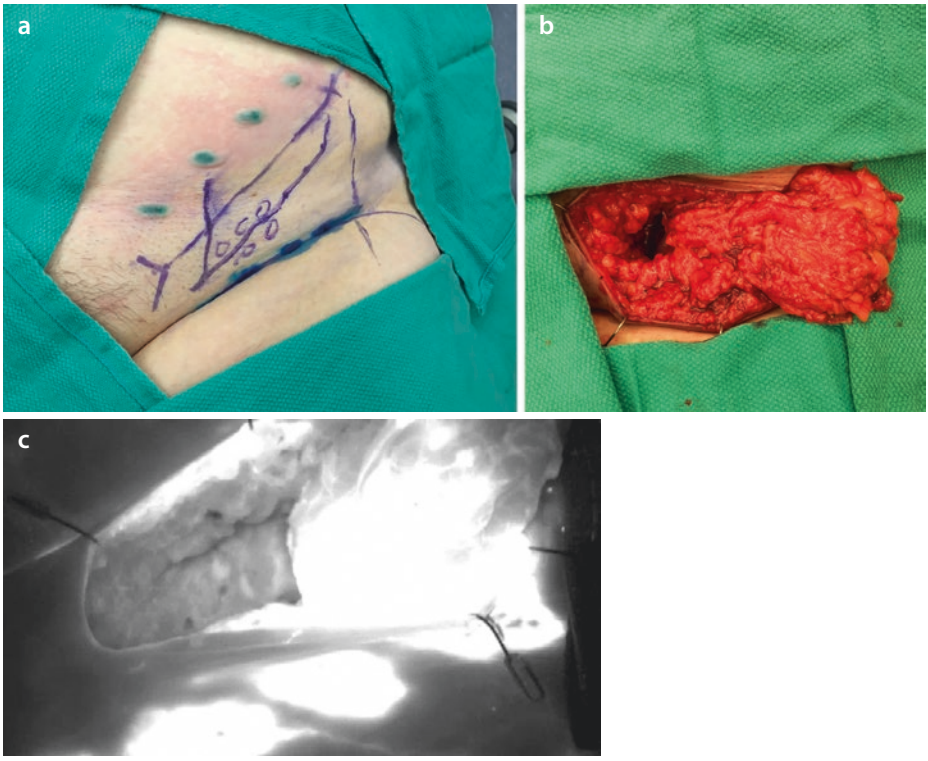

Fig. 50.1 **a** Markings of left groin lymph node flap illustrating localization of target lymph nodes within junction of superficial circumflex iliac vessels and superficial inferior epigastric vessels, approximately one third the distance from the pubic tubercle to the anterior superior iliac spine. **b** Completed dissection of superficial groin lymph node flap. **c** Intraoperative indocyanine green (ICG) fluorescence angiography imaging with SPY Elite (Novadaq Technologies Inc., Mississauga, ON, Canada) demonstrating intense uptake into lymph node flap

pedicle caliber, relative ease of harvest, and limited risk of iatrogenic lymphedema. The disadvantages include potential damage to the marginal mandibular nerve, platysma palsy, and visible scarring on the upper neck [11].

Supraclavicular Lymph Nodes

The supraclavicular lymph node flap is supplied by the transverse cervical artery. Flap harvest from the left side of the neck should be avoided when possible in order to avoid potential iatrogenic injury to the thoracic duct. The target flap and its lymph nodes are found within the boundaries of the posterior triangle of the neck. A skin island centered over the posterior triangle, located just above the clavicle, and oblique to the SCM may be designed [19, 20]. Alternatively, the lymph nodes and the surrounding fatty tissue may be taken alone. Deep dissection from lateral to medial reveals the transverse cervical artery and vein, which run posterolaterally toward the trapezius muscle. Care should be taken to preserve the accessory nerve. The external jugular vein may sometimes be taken along with the lymph nodes, which are located deep in close proximity to the internal jugular

vein (Fig. 50.2). Advantages include inconspicuous donor site and negligible risk of ipsilateral upper limb lymphedema. Disadvantages include lower density and number of lymph nodes, potential damage to the thoracic duct (when donor site is on the left), variable location of vascular pedicle, and injury to the supraclavicular nerves [11, 21].

Thoracic Lymph Nodes

The thoracic lymph node flap harvests lymph nodes at the lower axilla based on either the thoracodorsal or lateral thoracic vascular bundles (Fig. 50.3). An incision is made anterior to the latissimus dorsi muscle and lateral to the breast. The lateral thoracic and/or thoracodorsal vessels are identified. If the lateral thoracic artery caliber is sufficient, it is preferable to use this as the pedicle, leaving the thoracodorsal vessels intact. In order to avoid causing or exacerbating ipsilateral upper extremity lymphedema, harvest should be limited to the level 1 lymph nodes, which are located inferior to the lateral border of the pectoralis minor muscle. For similar reasons, nodes surrounding the axillary vein are preserved [22]. This flap may be approached in combination with surgeries aimed at removing scar caused by previous ALND, and the candidate vessels are typically of adequate caliber. Risks of this flap include potential for iatrogenic lymphedema in the ipsilateral upper extremity as well as potential damage to the thoracodorsal, intercostobrachial, and long thoracic nerves.

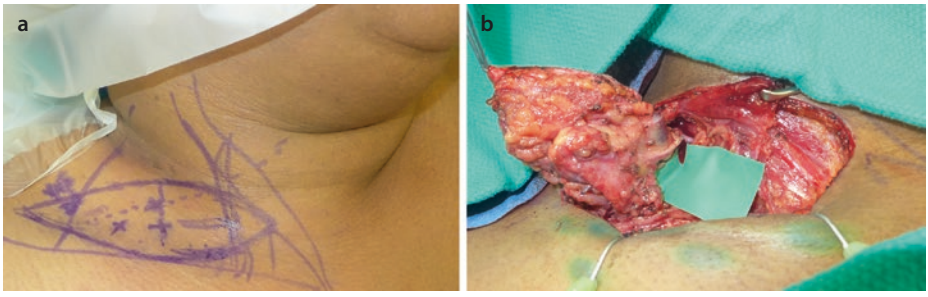

Fig. 50.2 **a** The supraclavicular lymph node flap is centered over the posterior triangle of the neck. **b** The flap is based on the transverse cervical artery and, when a skin island is included, its perforators

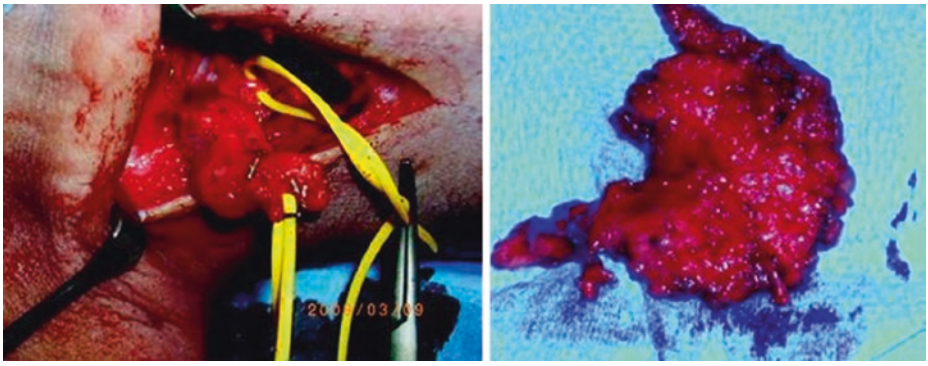

Fig. 50.3 Thoracic lymph node flap based on branches of the thoracodorsal vessels

Omental Lymph Nodes

The omental lymph node flap is supplied by the gastroepiploic vessels and can be harvested laparoscopically or via midline laparotomy. The greater omentum is located by identifying the greater curvature of the stomach and the transverse colon. Although less commonly used for the treatment of lymphedema, this flap offers a large number of potential nodes for transfer. The main drawbacks of this flap are the need for entry into the abdominal cavity and the risk of damage to visceral structures.

50.4.4 Reverse Lymphatic Mapping

Reverse lymphatic mapping is a technique that may be employed in concert with VLNT in order to guide selection of lymph nodes to harvest and thereby augment the safety of the procedure. This technique is similar in concept to the axillary reverse mapping technique that is used by surgical oncologists for ALND and SLNB in order to reduce the risk of secondary lymphedema in the ipsilateral upper limb [23, 24]. Critically, reverse lymphatic mapping aims to guide the surgeon in avoiding lymph nodes that strongly drain either the ipsilateral lower limb (during harvest from groin donor site) or the ipsilateral upper limb (during harvest from thoracic or supraclavicular donor sites). Technetium is injected distally into the extremity of interest preoperatively. Indocyanine green (ICG) is subsequently injected into the trunk at the beginning of the procedure in the region adjacent to the planned donor site; the ICG migrates along lymphatic channels toward the nodes located within the region of the donor site. Once the donor site area and its lymph nodes are exposed, a gamma probe is used to detect (and thereby avoid) those nodes providing significant drainage of the ipsilateral limb. Concomitantly, an ICG fluorescence imaging system such as SPY Elite (Novadaq Technologies Inc., Mississauga, ON, Canada) is applied, yielding lymphangiographic visualization of the nodes draining the trunk; these lymph nodes are subsequently targeted for harvest. For a more detailed description of this technique and its specific applications, readers may refer to Dayan et al.'s original paper on reverse lymphatic mapping [5].

50.4.5 Lymph Node Recipient Sites

Recipient site selection at the affected extremity is as important as donor site selection; each recipient site has its own set of advantages and disadvantages. Recipient sites are classified as either anatomic (groin and axilla) or non-anatomic (upper inner arm, elbow, wrist, upper posterior calf, and ankle). Anatomic placement is largely inspired by the «lymphatic pump» theory in which the pulsations from the anastomosis act as a pump providing hydrostatic force into the flap, while the low-pressure vein acts as a suction drawing lymph fluid into the capillaries. One of the concepts supporting non-anatomic placement is the «catchment» effect where distal flap placement promotes gravitational drainage of the limb, normalizing interstitial pressure of old lymphatic channels and improving lymphatic flow [4].

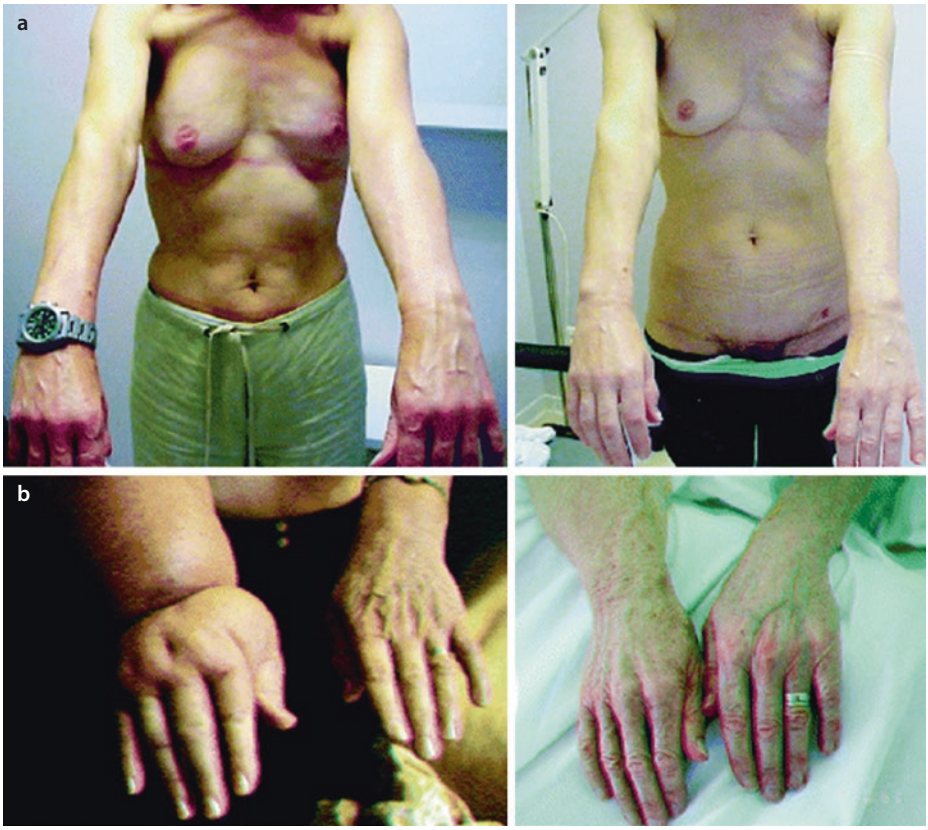

Fig. 50.4 Vascularized lymph node transfer to axilla. **a** Moderate lymphedema involving the left upper limb: preoperatively (*left*) and 2 years postoperatively following VLNT (*right*). **b** Preoperative finding of advanced lymphedema along the right upper limb (*left*) and 4 years postoperatively following VLNT showing near-complete relief

Anatomic placement has the advantage of allowing concurrent excision of scar tissue which may be contributing to the patient's existing lymphedema by obstructing lymph flow and interfering with lymphangiogenesis. Furthermore, these sites frequently have sufficient soft tissue for primary closure, obviating the need for a skin paddle with the flap. For the axilla, the same incision that was used for previous axillary lymph node dissection is generally sufficient to prepare the lymph node graft recipient site. In certain cases, especially when severe fibrosis is present, the incision may require extension for additional exposure (Fig. 50.4). The groin is ideal when the pelvis and lower abdomen are affected by lymphedema and is located near a plethora of familiar recipient vessels (Fig. 50.5). Naturally, great care in dissection and tissue mobilization at these anatomic sites is crucial as any inadvertent injury to residual lymphatic tissue risks exacerbating preexisting lymphedema in the ipsilateral limb.

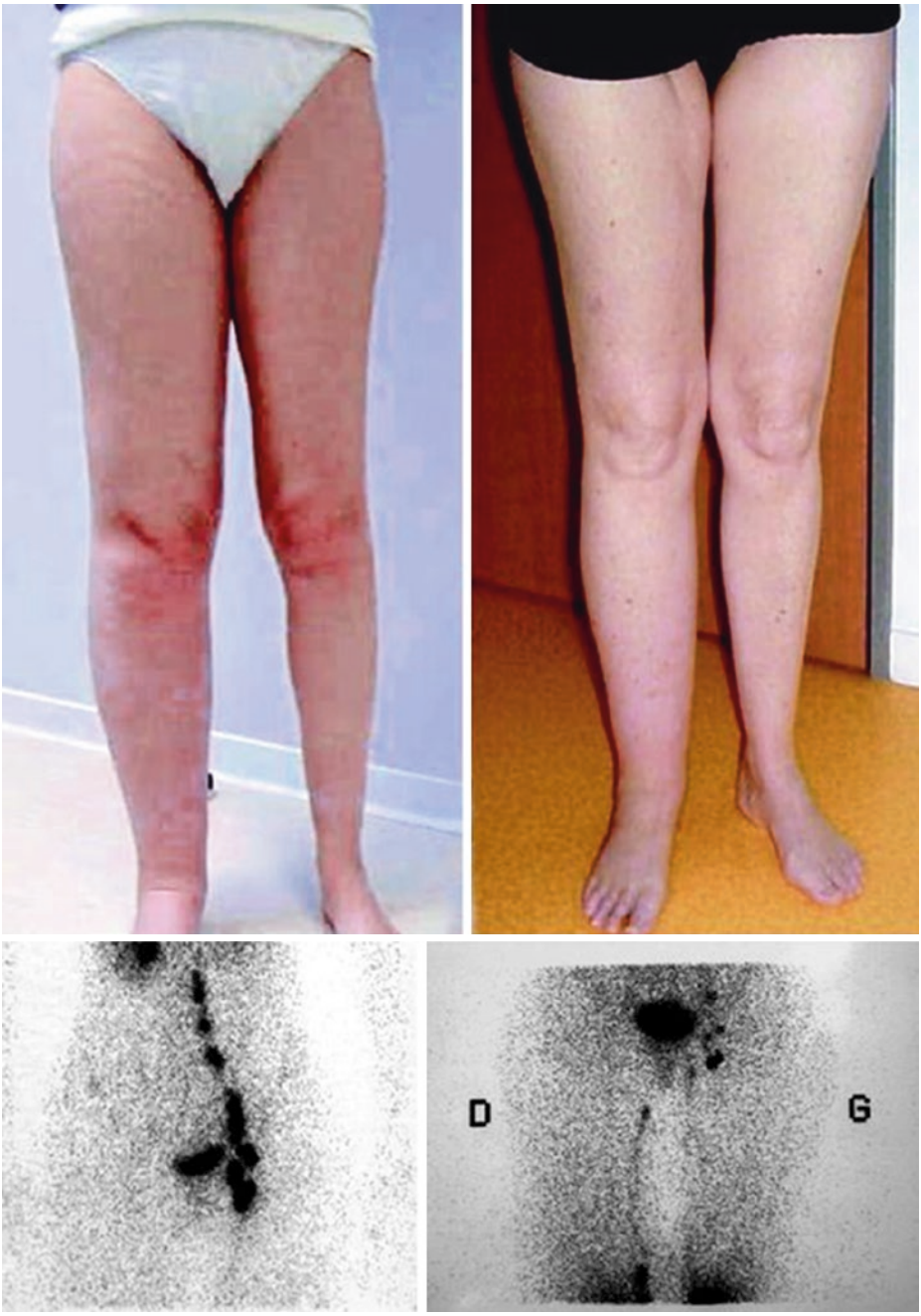

Fig. 50.5 Vascularized lymph node transfer to groin. Secondary (post-hysterectomy) lymphedema: preoperative clinical and corresponding lymphoscintigraphic findings (*left*). One-year postoperative clinical and lymphoscintigraphic findings following the lymph node transplant to the groin region (*right*)

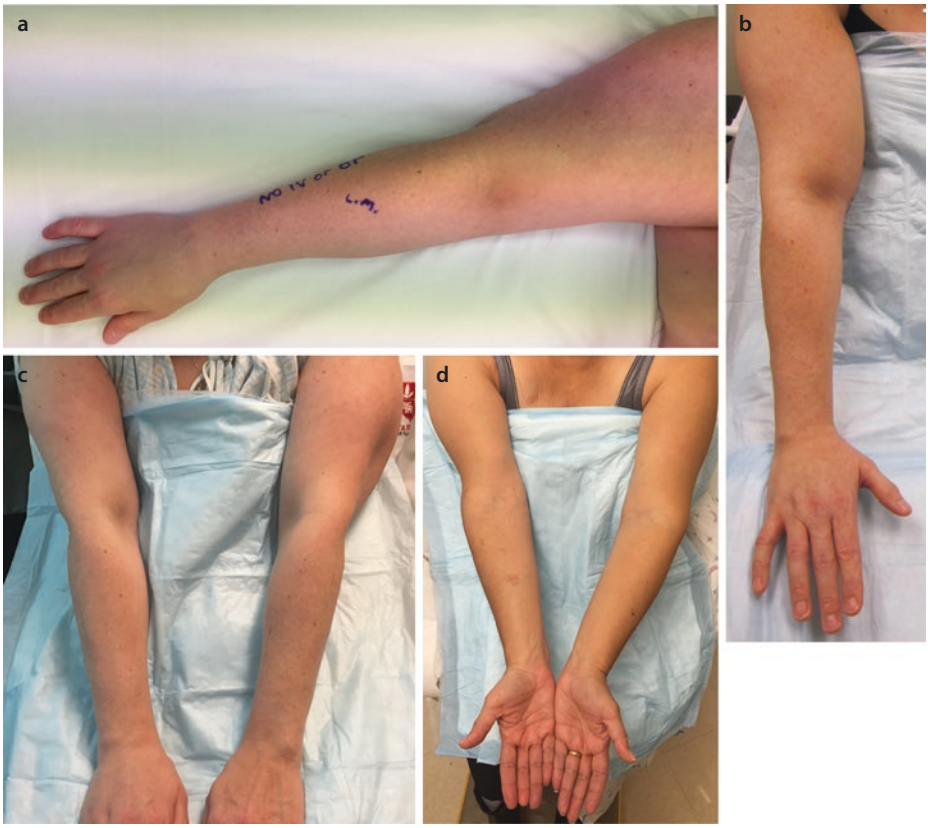

Fig. 50.6 Vascularized lymph node transfer to upper inner arm. Superficial groin lymph node flap transfer to Stage II right arm lymphedema preoperatively **a** and postoperatively **b**. The upper inner arm recipient site scar is well hidden as seen postoperatively in this patient who had a right upper inner arm recipient site **c** and another patient who had a left upper inner arm recipient site **d**

On the other hand, non-anatomic sites provide a more hospitable well-vascularized bed for flap inset that is free of scar. The dependent location of the more distal non-anatomic sites (wrist and ankle) has the theoretical advantage of leveraging the natural effects of gravity on lymph fluid; hence, some authors believe that the wrist and ankle donor sites have a faster effect on lymph drainage [16]. However, these distal sites have limited space to accommodate lymph node inset and thereby require the inclusion of a skin paddle with the flap, which may be cosmetically displeasing. Also, they may make wearing standard gloves or certain shoes difficult due to the bulkiness of the flaps in places that are normally relatively tapered areas of the body. More proximal non-anatomic recipient sites, such as the upper inner arm (Fig. 50.6) and posterior calf (Fig. 50.7), may provide superior cosmesis since primary closure over the lymph node flap is usually possible, thereby obviating the need for a skin paddle. Furthermore, any scarring is more easily hidden in these proximal locations.

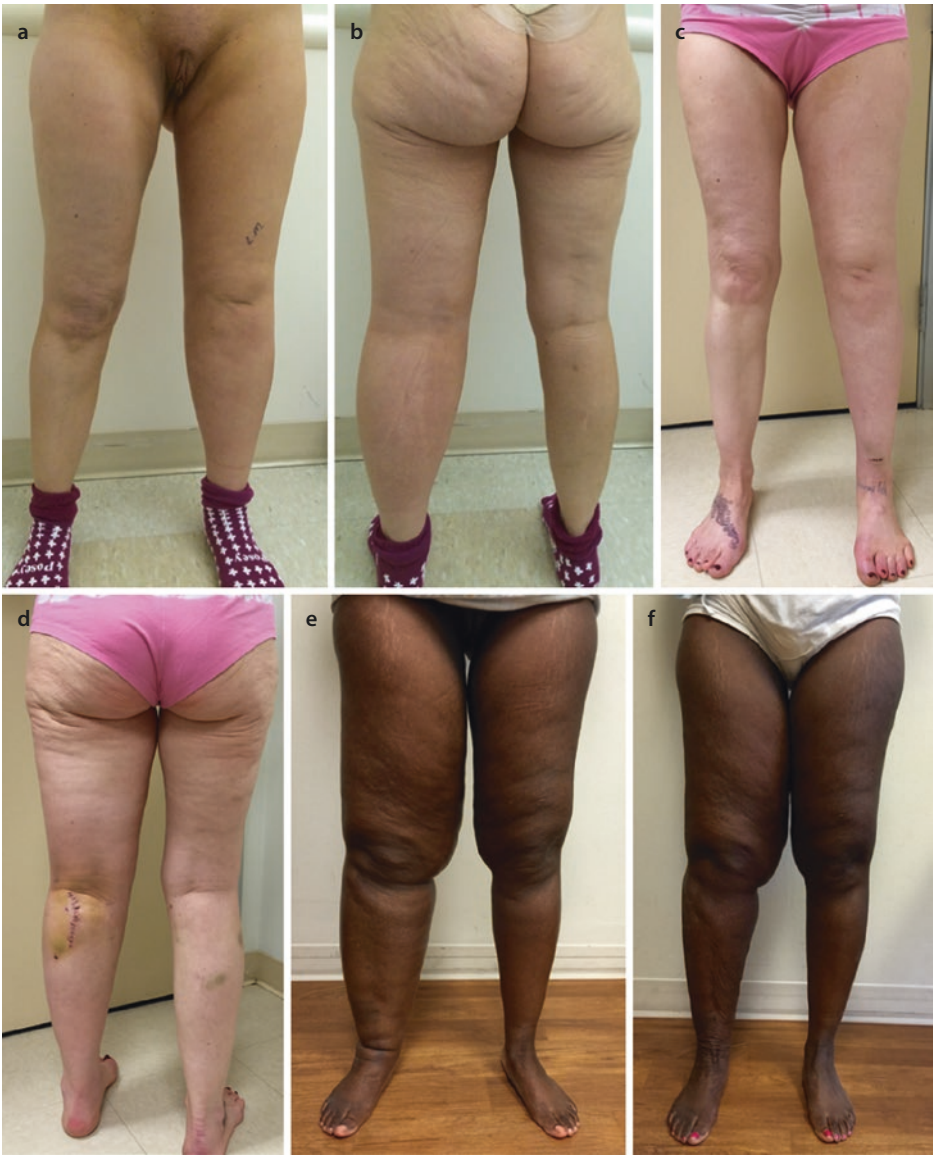

Fig. 50.7 Vascularized lymph node transfer to upper posterior calf **a** secondary Stage II left leg lymphedema preoperatively **a**–**b** and postoperatively 1 month after supraclavicular lymph node flap transfer to left posterior calf **c**–**d**. Congenital lymphedema of right and left lower extremities preoperatively **e** and 1 year postoperatively following supraclavicular lymph node flap to right upper posterior calf **f**

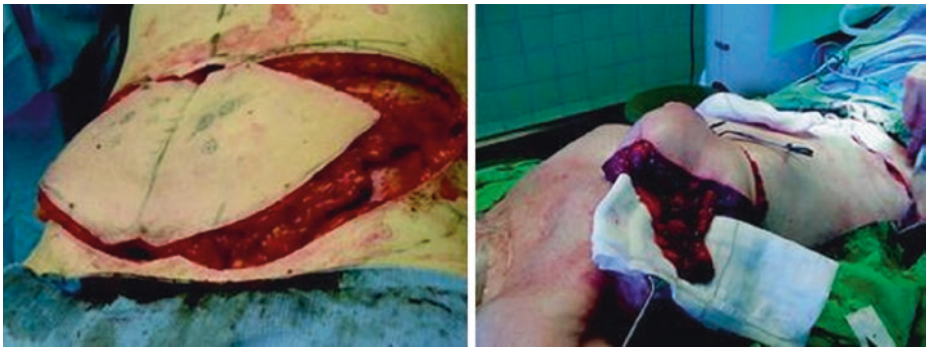

Fig. 50.8 Deep inferior epigastric perforator (DIEP) flaps being elevated along with superficial groin nodes (*left*). The lymph node component of the flap to be implanted is depicted (*right*)

50.4.6 Other Applications of Vascularized Lymph Node Transfer

Treatment of Upper Extremity Secondary Lymphedema in Combination with Ipsilateral Breast Reconstruction

Abdominal-based flaps for breast reconstruction (deep inferior epigastric perforator [DIEP], transverse rectus abdominis muscle [TRAM], muscle-sparing TRAM [ms-TRAM], and superficial inferior epigastric artery [SIEA] flaps) can be elevated in combination with the superficial groin lymph nodes [25].

The lymph node component of the flap is inserted into the previous lymphadenectomy site, while the abdominal soft tissue is shaped to rebuild the breast. The flap pedicle (deep or superficial inferior epigastric vessels) may be anastomosed to either the thoracodorsal vessels in the axillary region or to the internal mammary vessels. Importantly, the fibrosis in the axillary region must be dissected before implanting the lymph nodes. Neurolysis of the brachial plexus can also be performed if indicated (Fig. 50.8). The effect on the lymphedematous extremity is similar to that obtained with the more conventional VLNT from the superficial groin.

Treatment of Brachial Plexus Neuropathy

An additional benefit of the free fatty lymph node flap is that it can improve radiotherapy-induced pain and progressive palsy by neovascularization of the nerves. Younger patients may recover within 2 years, while older patients may experience stabilization of their palsy. When the lymphedema reduces significantly, tendon transfers may be employed to reinforce some upper extremity movements as deemed necessary. Additionally, pain symptoms in the breast and thoracic region cause by previous surgery subside following neurolysis [26].

50.5 Postoperative Management

Postoperative admission for flap monitoring is indicated. Typical hospital stay is 1–2 days for upper extremity cases and 2–3 days for lower extremity cases. The operated limb should be elevated above the level of the heart to prevent venous congestion. At

3 weeks postoperatively, compression garments are started. Class I compression garments are used for the upper extremities and Class II for the lower extremities. An intensive manual lymphatic drainage is also resumed at 3 weeks postoperatively and is performed daily in advanced cases or every other day in mild cases for a minimum of 3 months to prevent lymph stasis along the graft site. At 6 months postoperatively, gradual weaning of the garment as tolerated is permitted.

50.6 Complications

Donor site complications include lymphorrea, lymphocele, seroma, donor site pain, delayed wound healing, and infection. One of the most dreaded complications is iatrogenic lymphedema to the limb ipsilateral to the donor site; the literature currently cites a rate of 1.5% [27]. Iatrogenic injury to structures unique to each donor site may also occur as previously discussed.

Recipient site complications include wound infection, delayed wound closure, partial loss of skin graft (when applicable), and prolonged flap edema. As in any microsurgical flap procedure, lymph node flaps are at risk for thrombotic complications and total flap loss.

50.7 Outcomes

A recent comprehensive review of 24 VLNT studies, involving 271 VLNT procedures, further demonstrated this surgery's promising benefits. The overall response rate was better in upper extremity cases (74.2%) compared to lower extremity cases (53.2%). No significant differences in outcome were found between donor sites [27]. Another recent meta-analysis, which included quantitative data from 85 VLNT patients in five studies (level III and IV evidence), showed that 100% of patients reported subjective improvement, 90.7% had quantitative improvement, and 78% were able to discontinue compression therapy. Only 4 of the studies (total 51 patients) had information on excess circumference reduction, yielding a pooled mean of 48.5% excess circumference reduction [28]. Aside from subjective and volumetric improvements, patients may also benefit from decreased rates of cellulitis in the affected limb following VLNT. The underlying heterogeneity of current studies in the literature and inherent variability of the disease and treatment approaches make it difficult to more precisely quantify the effects of VLNT in lymphedema patients.

Conclusion

Lymphedema is a debilitating disease and one that is extremely challenging to treat effectively. Conservative therapy should constitute the baseline of any treatment approach. However, VLNT can provide substantial benefits in either primary or secondary lymphedema cases. When the disease has not progressed to severe fibrosis, significant resolution of the lymphedema can be expected with surgery. Several lymph node donor site options exist, and VLNT may also be raised in

combination with abdominal-based free flaps to concomitantly treat mastectomy defects and lymphedematous limbs in select cases. The role of surgery in lymphedema is still in its nascent phase and continues to evolve.

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A Combined Microsurgical Reconstruction Approach for Lymphedema

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Summary of Basic Concepts

- Combination of microsurgical lymphatic surgery and preoperative using medical device which enables more precise and efficient microsurgery of lymphedema
- Selection of lymphatic surgical technique or combination of them according to acuity of lymphedema.

51.1 Lymphatic Network

Lymphatic system is a complex network of structures which are responsible of two main functions: fluid homeostasis and immunologic response. The lymphatic network is anatomically divided into primary or central lymphoid organs, peripheral or secondary lymphoid organs, and the transporting network of lymphatic vessels.

Primary lymphoid organs (bone marrow and thymus) are responsible for production and maturation of lymphocytes from early clonal selection to lymphocytes T and B. These organs are not structurally interconnected with the lymphatic circulatory network. Mature B lymphocytes from the bone marrow and T lymphocytes from the thymus usually join the lymphatic network via blood circulatory system. Secondary lymphoid organs (lymph nodes, spleen, and other peripheral lymphoid tissue such as tonsils, GALT) are responsible for activation, mature lymphocytes clone expansion, and adaptive immunoresponse. In these organs, lymphocytes are activated by specific antigens. By circulating between lymphatic network and blood circulatory system, activated lymphocytes work as sentinel until they recognize the specific antigen for which they have been activated. Primary and secondary lymphoid organs account for the immunoresponse of the lymphatic system, against different antigens from infective to tumoral ones.

Lymphatic circulatory system is anatomically interconnected with lymph nodes which represent stations for peripheral immunoresponse. In fact, lymph nodes are located along lymphatic collectors, and there are afferent lymphatics which enter the subcapsular sinus of the lymph nodes and efferent lymphatic vessels which exit from lymph node through the hilum.

Lymphatic networks account directly for fluid homeostasis by draining around 3 liters/day of interstitial fluid that cannot be drained back by venous system. The fluid drained by lymphatic network is called lymph, and it is mainly constituted by cellular debris, bacteria, antigens, lymphocytes, and medium-to-high molecular weight molecules which cannot be resorbed by filtration or diffusion by vein capillaries because of their molecular weight and/or low liposolubility.

The main focus of medical research and development has been directed mainly to the immunologic function of lymphatic system because infectious disease and cancer are the most common diseases affecting human body worldwide. In this perspective, primary and secondary lymphoid organs received higher attention than lymphatic network in medical research. Lymph nodes are the main target of modern diagnostic because their enlargement and structural modifications are directly related to infectious and cancer diseases.

CT and MRI are powerful anatomical diagnostic tools to detect which nodal station is enlarged and shows atypical three-dimensional structure in cancer staging. However, these findings are not specific because micrometastasis usually does not alter the node structure as well as enlarged nodes may be related to temporary hyperplasia rather than metastatic disease. For these reasons, functional imaging such us color Doppler ultrasound (CDUS), positron emission tomography (PET), dynamic contrast enhancement MRI (DCE-MRI), ultrasmall particles of iron oxide MRI (USPIO-MRI), and optical imaging have come into help. However, these methods are not helpful in studying the lymphatic vessel network and lymph fluid dynamics.

The other main disease of lymphatic system, lymphedema, needs specific imaging on lymphatic system and lymphatic flow to better understand the etiopathogenesis as well as its acuity. Lymphatic network is a unidirectional, dead-end, low pressure system which starts from cellular interstitium with the network of origin where the lymph fluid is absorbed by lymphatic capillaries from interstitial space. The lymph is then directed toward central venous system (subclavian-jugular vein trunk) through precollectors, collectors, and main lymphatic trunks. In order to easily describe the imaging method available to visualize lymphatic network, a brief detailed description of lymphatic network anatomy and physiology is beneficial.

Lymphatic capillaries are the dead-end portion of the lymphatic network. These capillaries can be found closely to vascular capillaries in the cell interstitium. Their caliber (30–60 μm) is slightly larger than vascular capillaries. They show a unique structure constituted by two peculiar components:

- Anchoring ligaments with surrounding connective tissue
- Overlapping of endothelial cells which allows the formation of wall gaps that creates a direct communication between lymphatic capillaries lumen and interstitium

The anchoring ligaments are made of elastic fibers that are stretched by swelling into interstitium. Their stretch favors the formation of endothelial gaps. Besides the role of anchoring ligaments, the endothelial gaps usually form when the interstitial pressure becomes higher than pressure within the lymphatic capillary. These two phenomena allow the lymph to progress from interstitium to capillaries and not the opposite way. As for extremity lymphedema, lymphatic capillaries can be found in the cellular interstitium of soft tissues. However, their maximal distribution can be found at the level of dermis.

Precollectors represent the connecting channels between the capillaries and collectors. Differently from capillaries, precollectors do not show endothelial gaps. Their wall is made of endothelium, thin smooth muscular layer, and adventitia. Few valvular structures are present, and this sometimes may be responsible of a physiologic temporary reverse of flow.

Collectors are the lymphatic vessels by definition. Their structure is made of endothelial layer, smooth muscle cell layer with muscular fibers showing a spiral trend, and adventitia layer. The collectors are also called contractile lymphatics. Their caliber is variable (usually from 0.10 to 0.60 mm), and they can be appreciated at the operating

microscope. Collectors allow the lymph to propel toward intercalating lymph nodes and major lymphatic trunk. Their structures allow unidirectional propulsion of lymph through three mechanisms:

- Intrinsic (neurological reflex valve-related): numerous and constant unidirectional valves are present along collectors. The segment between valves is called lymphangion or microlymphatic heart, which is the smallest functional portion of the lymphatic system. Between two valves, the lymph fluid is retained. When the intraluminal pressure comes up to 0.25 mmHg, wall stretching induces reflex neurologic stimuli which activate the contraction of smooth muscle cells and allow the lymph propulsion. The lymph reflux is counteracted by the valves. They have been estimated around 10–12 contractions per min within each lymphangion.
- Intrinsic (musculature-related): due to recurrent propulsive contraction of smooth muscle cells under adrenergic, cholinergic, and peptidergic stimuli.
- Extrinsic: due to external pressure on collectors, mainly from muscles.
- Extremity lymphedema is a chronic, progressive, and debilitating disease characterized by imbalance of lymphatic flow dynamics as follows:
- High-output lymphedema, a pathological status due to overaccumulation of lymph in the interstitial spaces for osmotic/oncotic alteration which exceeds the ability of healthy lymphatic network to properly drain it. This is a common clinical picture of patients suffering chronic heart, kidney, or liver failure. Lymphatic network is not impaired.
- Low-output lymphedema, a pathological status due to inability of lymphatic network to drain a normal production of lymph. The etiology of this pathological status is a primary or secondary damage of components of the lymphatic network such as lymphatic vessels and/or lymph nodes.

51.2 Preoperative Lymphatic Imaging for Lymphedema Microsurgery

Lymphedema is not a rare disease, affecting over 140 million patients worldwide. With advances in cancer early diagnosis and improvement in cancer treatment, the number of cancer survivors is rapidly growing, and it is expected to continue with this trend. As a consequence, the number of patients affected by lymphedema is expected to increase in the next years/decades making this disease one of the most common debilitating outcomes affecting quality of life of cancer survivors.

Since a decade, the surgical treatment of lymphedema has expanded in breadth and scope with the introduction of physiologic procedures such as lymphaticovenous anastomosis (LVA) and lymph node flap (LNF) transfer [1]. Both procedures have been demonstrated to be effective in the treatment of not fibrotic lymphedema. However, outcomes are still very operator dependent; thus, level of evidence remains low and standardized surgical protocol is lacking.

Preoperative imaging becomes mandatory in order to understand the functional status of lymphatic collectors and the acuity of lymphedema. These informations are helpful in choosing the indication for the physiologic procedure to be performed as well as may help in predicting the outcome. Lymphatic network imaging has been underde-

veloped as lymphedema has usually been neglected as pathology of medical interest and its treatment has been delegated to physiotherapist. However, physiotherapy may offer symptomatic and transient amelioration, but it cannot be curative as it does not interfere with the spiral of decline of the disease.

In the last decade, many advances have been made in lymphatic network imaging, and nowadays the lymphatic microsurgeon can take advantage on the preoperative imaging. Based on the concept behind each diagnostic method, today we can group the lymphatic imaging for the lymphatic microsurgery in the following three categories: direct method, physiologic method, and indirect method.

51.2.1 Direct Method (Intraluminal)

Direct method refers to the technique of visualization of lymphatic network by intralymphatic injection of contrast substance. However, differently from peripheral vein cannulation, peripheral lymphatic cannulation is a technically difficult procedure because of three main reasons:

1. Dimension: peripheral lymphatics are the collectors, which have a caliber ranging from 0.2 to 0.6 mm; this requires microscopic instrumentations.
2. Percutaneous visualization: lymphatic collectors are small and transparent and thus they are not percutaneously visible as veins are; differently from arteries, they have no pulsation, and thus they are even not palpable.
3. Fragility: differently from peripheral arteries and veins, lymphatic collectors are very fragile structure which can be easily disrupted by small trauma such as cannulation.

Nevertheless all these difficulties, the first reported imaging method for lymphatic network visualization has been the oil-contrast lymphography. This method has been used in the assessment of nodal metastases in lymphoma and other cancers before the introduction of CT and MRI which have completely replaced it. It has been reported also to study lymphatic network in patients suffering lymphedema.

Oil-Contrast Lymphography

In oil-contrast lymphography, the limitations described above are overcome as follows:

1. Dimension: use of 30-gauge needle cannula.
2. Visualization: blue dye is injected intradermally at the interdigital spaces. An incision is then made to locate collectors large enough to be cannulated.
3. Fragility: the trauma is reduced by open wound control of the procedure and choosing a large collector.

After cannulation, iodinated oil is injected at graded pressure for 60–90 min time, and fluoroscopy or CT scan is used to visualize the lymphatic network anatomy. Node visualization may take up to 24 h to be visualized. Oil contrast has been demonstrated to take several years to be cleared from human body.

This procedure has been abandoned for several reasons. It is an invasive procedure that places a scar and exposes patients to high dosage of radiation; it is time-consuming

and highly expensive. The oil-contrast medium has also been demonstrated to be toxic on lymphatic endothelium (oil-injured lymphangiopathy). Moreover, life-threatening complications have been reported with oil-contrast lymphography such as pulmonary embolism and respiratory distress syndrome. Finally, major indications for which lymphography had been developed are now largely covered by CT and MRI. According to Campisi and Boccardo, oil-contrast lymphography should be limited for patients with chylous reflux syndrome, where more precise visualization of retroperitoneal collectors may be required.

51.2.2 Physiologic Methods

Nowadays, physiologic methods represent the mainstay of lymphatic network anatomy imaging and functionality evaluation. The concept behind these methods is to inject the contrast in the interstitial space so that the tracer can be picked up by lymphatic capillaries and be drained by the lymphatic network. So far, these methods are less invasive than oil-contrast lymphography because the tracer can be introduced by intradermic/subcutaneous injection. However, in order to be drained specifically by the lymphatic system, the contrast material should have pharmacological features that allow it not to take the blood absorption route via the blood capillaries. In this perspective, the contrast material should be a colloid (high molecular weight) or should manifest high binding affinity with high molecular weight interstitial components, such as indocyanine green which has high binding affinity (95%) with apolipoprotein B so that the contrast cannot be absorbed by the blood capillaries but only by lymphatic capillaries. Moreover, the contrast material should have specific physical properties that allow to be visualized by the imaging technology chosen. There are different physiologic methods available, each with its own advantages and limits. These methods can be combined in the surgical planning of lymphatic microsurgery.

Lymphoscintigraphy

Lymphoscintigraphy with radioisotope-labeled colloids for the clinical study of lymphatic network has been introduced in the 1960s. However, it has been officially recognized as valid imaging method in the diagnosis and evaluation of lymphedema only in 2004 by the ISL Consensus Document as it was considered still experimental.

The main issues with lymphoscintigraphy during the past decades have been (1) the radioisotope colloid to be used, (2) amount of injected radioactivity, (3) amount of injected volume, (4) particle concentration, and (5) administration route.

The radioisotope colloid used varies in different countries worldwide. In Europe, a new radioisotope with favorable characteristics introduced in the 1990s and approved by EMEA, the 99mTC-nanocolloids, is largely used [6]. This radioisotope is characterized by particle size <80 nm which allows a fast visualization of lymphatic network. Moreover, it does not require an acidic pH to maintain radiolabeling stability as for Tc-sulfur colloids, so that 99mTC-nanocolloids are diluted with a saline solution with neutral pH which allows a painless injection compared to that of acidic solutions. The administration route and technical methodologies are also very important in defining the subtype of lymphoscintigraphy performed and consequently the timing and infor-

mations that each technique can provide. The standard lymphoscintigraphy method that is usually performed to study the lymphatic network is represented by the rest subcutaneous lymphoscintigraphy.

Subcutaneous Rest Lymphoscintigraphy (SubQ-RL)

This method is not yet standardized and may vary among different centers for choice of injection site, for using dynamic rather than static acquisition, and for choice of acquisition time. However, this method is usually performed by injecting 0.1–0.3 cc of radiocolloid diluted solution in the first interdigital space of foot or hands with particular care to avoid any intravascular injection. After injection, two imagings are usually acquired: early and late scans. Early scans may take up to 30–60 min, whereas late scans are acquired from 3 to 6 h from injection. In this timing, patient is asked to avoid strenuous activity in order to obtain information at rest.

The evaluation of the findings is made based on clearance rate of the colloid from injection site, percentage of uptake by locoregional lymph node, delay in lymphatic drainage, asymmetric or absence visualization of locoregional nodes, presence of collateral collectors, and dermal backflow. Moreover, transport index (TI) is a quantitative method used to classify the severity of lymphatic drainage impairment as proposed by Weiss and Baumeister.

Although SubQ-RL is the most diffused method, it shows several limitations especially in the preoperative planning of physiologic microsurgical treatment for lymphedema. RSL is a time-consuming exam, with poor image resolution due to high background activity from injection sites, the blood, liver, and bladder, which makes very difficult also a univocal interpretation of result and TI evaluation.

In experience with RSL, this method is not useful for a detailed quantitative and qualitative analysis of lymphedema acuity and of residual collector function, especially for advanced lymphedema stage. We believe that both parameters are very important either in choosing the physiologic treatment to propose to patient (LVA vs LNF) or in planning the surgery. Intradermal rest-stress lymphoscintigraphy according to Tartaglione G is able to overcome limitations of standard RSL.

Intradermal Rest-Stress Lymphoscintigraphy (IDI-RSL)

IDI-RSL represents preferred method to preoperatively study patient with lymphedema. This method gives us clear quantitative and qualitative data for lymphedema staging and surgical planning. As for surgical protocol, we combine data from IDI-RSL with that coming from ICG-lymphography in order to plan the microsurgical treatment. Early experience with this combined (IDI-RSL + ICG-lymphography) preoperative imaging approach on more than 50 patients seems very promising (Figs. 51.1 and 51.2).

IDI-RSL has been introduced by Tartaglione G in 2010 [7, 8]. Briefly, diluted 99mTC-nanocolloids in neutral pH solution are intradermally injected into first interdigital space of the hand or feet. The acquisition protocol takes less than 1 h only, and it is differentiated in rest scan (within the first 10 min), stress scan (after 2 min of exercise), and late scan (30–60 min after injection). This acquisition protocol is based on the evidence that a healthy, not lymphedematous limb shows symmetric visualization of locoregional nodes (axillary or inguinal) within stress scan (within 10–12 min after injection) compared to a lymphedematous limb where the tracer appearance time (TAT) is delayed or absent.

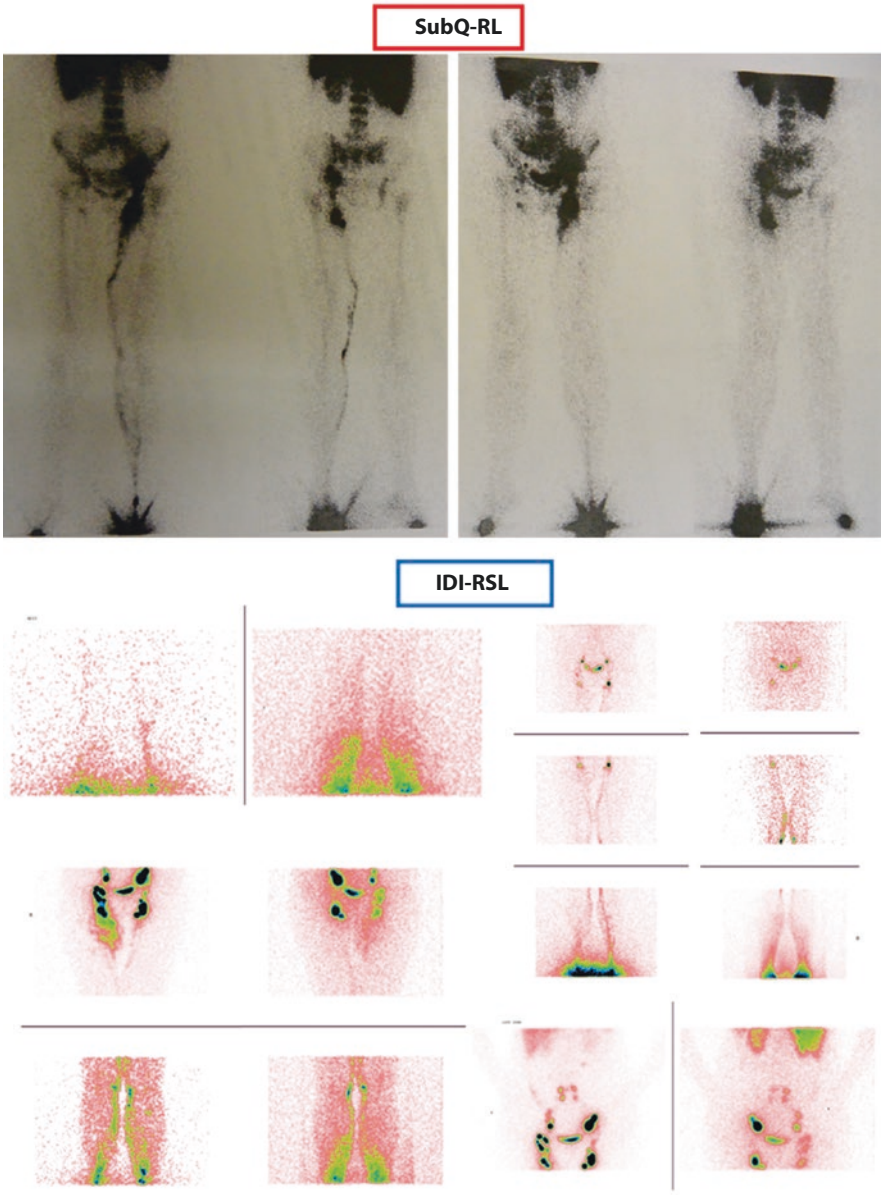


Fig. 51.1 Head-to-head comparison of traditional SubQ-RL with IDI-RSL performed on the same patient with a history of prostatectomy for prostate cancer, obturator and iliac node clearance, and adjuvant radiotherapy. This patient developed an ISL stage 3 lymphedema on the left lower limb. Lymphedema occurs 2 months after end of radiotherapy. The SubQ-RL method showed clearly main lymphatic collector on the contralateral healthy limb and no activity on the affected limb either at 30 min (above, right) or late (above, left).The IDI-RSL was able to show no visualization of collector (as SubQ-RL), but it also depicted severe dermal backflow and the presence of a weak inguinal node on affected side in late scans (1 h later than injection). Moreover, it showed the main collector of the contralateral healthy limb in rest and presence of secondary collectors activated by exercise (stress). The image quality is more detailed with much lesser background activity compared to SubQ-RL

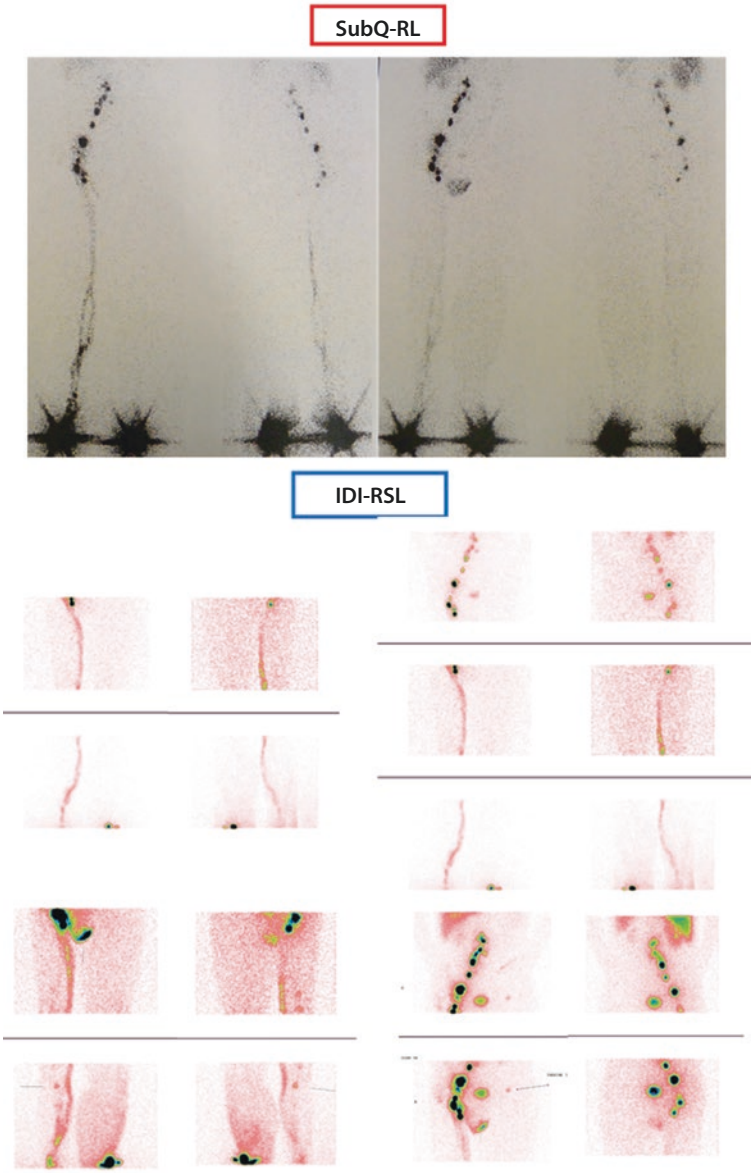


Fig. 51.2 Head-to-head comparison of traditional SubQ-RL with IDI-RSL performed on the same patient with a history of prostatectomy for prostate cancer, obturator and iliac node clearance, and adjuvant radiotherapy. This patient developed an ISL stage 3 lymphedema on the left lower limb. Lymphedema occurs 2 months after end of radiotherapy.The SubQ-RL method showed clearly main lymphatic collector on the contralateral healthy limb and no activity on the affected limb either at 30 min (above, right) or late (above, left).The IDI-RSL was able to show no visualization of collector (as SubQ-RL), but it also depicted severe dermal backflow and the presence of a weak inguinal node on affected side in late scans (1 h later than injection). Moreover, it showed the main collector of the contralateral healthy limb in rest and presence of secondary collectors activated by exercise (stress). The image quality is more detailed with much lesser background activity compared to SubQ-RL

These velocity findings are comparable to ICG-lymphography data. Besides TAT, lymphedematous limb shows different IDI-RSL patterns which correlate with lymphedema acuity. We believe that IDI-RSL is methodologically superior to SubQ-RL, both in lymphedema diagnosis and in preoperative planning for the following reasons:

1. Not time-consuming exam (takes less than 1 h)
2. Higher-resolution images with minimal background activity.
3. Univocal and easier to analyze quantitative data (drainage velocity, transit time, TAT, etc.)
4. Qualitative data such as stagnation points, more precise visualization of dermal backflow areas, and compensation phenomena
5. Dynamic data such as intrinsic lymphatic pump function (rest), combined intrinsic and extrinsic function (stress) and lymphedema diffusion (late)

MRI Lymphangiography

Although lymphoscintigraphy, especially if performed with IDI-RS method, allows to obtain very valuable quantitative data, the quality of image resolution remains poor, and it is not possible to have an anatomical detailed map of the lymphatic network.

In this perspective, high-resolution imaging methods such as CT and MRI have been explored in the last decade [9–11]. MRI has been the preferred method investigated as it does not expose the patient to ionizing radiation, it provides high-resolution three-dimensional imaging of the superficial and deep lymphatic network as well as functional information, it allows to map percutaneously the site of interest, and it can be used to evaluate other informations such as subcutaneous fat thickness, amount of lymph stasis, and limb volumetry.

The reported contrast medium used to perform MR lymphangiography has been gadolinium-labeled diethylenetriaminepentaacetic acid (Gd-DTPA), gadolinium dendrimers or liposomes, and iron oxide particles. Although few reports are available with MR lymphangiography in the diagnosis of lymphedema, this methodology seems promising.

MRI lymphangiography may be very useful to depict lymphatic collector degeneration patterns as well as may be very useful in the assessment of lymphatic collector and/or lymph node malformation in patients with primary lymphedema.

At the best of our knowledge, none have yet explored this method as preoperative tool for physiologic microsurgery for the treatment of lymphedema. As this method is rapidly evolving in the diagnosis of lymphedema, we believe that this imaging tool may be very promising in microsurgical planning for the treatment of lymphedema.

Fluorescence ICG-Lymphography

(See ▶ Chap. 26).

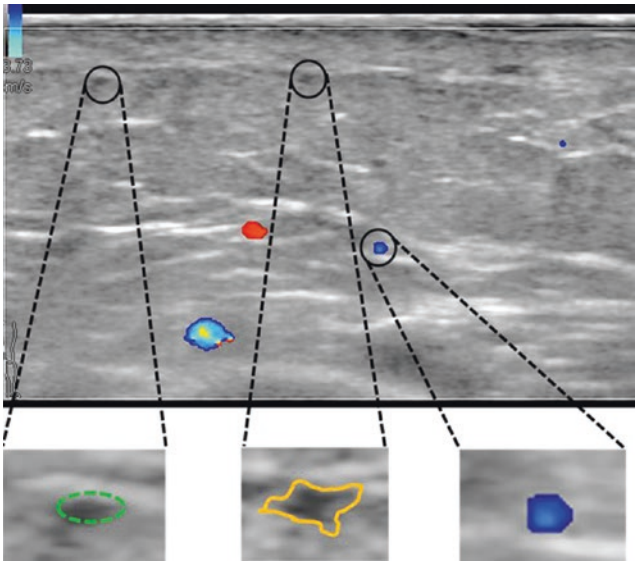
51.2.3 Indirect Method

Among the surgical procedures, lymphaticovenular anastomosis can be performed under local anesthesia and is an effective, minimally invasive treatment for refractory lymphedema. These advantages have made lymphaticovenular anastomosis a progressively common surgical treatment for secondary lymphedema. Lymphaticovenular anastomosis has developed from supermicrosurgery, microsurgical techniques that allow anastomoses of vessels less than 0.5 mm in diameter.

A positive correlation between the number of lymphaticovenular anastomoses performed and therapeutic effectiveness has been reported. The establishment of as many bypasses as possible is important in performing lymphaticovenular anastomoses. For the successful performance of lymphaticovenular anastomosis in a limited time duration, it is important to identify functional lymphatic vessels and determine the location of lymphatic vessels and venules preoperatively.

Ultrasound

For detection of lymphatic vessels in the site where dermal backflow pattern was shown in indocyanine green lymphography or indocyanine green is not able to be used, the ultrasound, which is more common and simple, could be a substitute for indocyanine green lymphography. It was reported that lymphatic vessels were identified as intermittent homogeneous, hypoechoic, and specular misshapen images using ultrasonography in the lower extremity [2]. The most important thing for the detection of lymphatic vessels is distinguishment from blood vessels and nerves. Each has its own characteristics such as shape, echogenic texture, and color Doppler mode (Fig. 51.3). However, when lymphatic vessels were too small (smaller than 0.3 mm), they were mistaken for subcutaneous vein and nerve, because it was hard to judge the shape of small vessels even if used with color Doppler mode.



	Shape	Echogenic texture	Color Doppler mode
Lymphatic vessel (Yellow)	Spicular missshapen	Hypoechoic	Not colored
Blood vessel (Blue)	Round	Hypoechoic	Colored/ Not colored
Nerve (Green)	Honey comb Oval (Superficial nerve)	Bright with hypoechoic fascicles One hypoechoic fascicle (Superficial nerve)	Not colored

Fig. 51.3 Characteristics findings of lymphatic vessel, blood vessel and nerve in ultrasound images

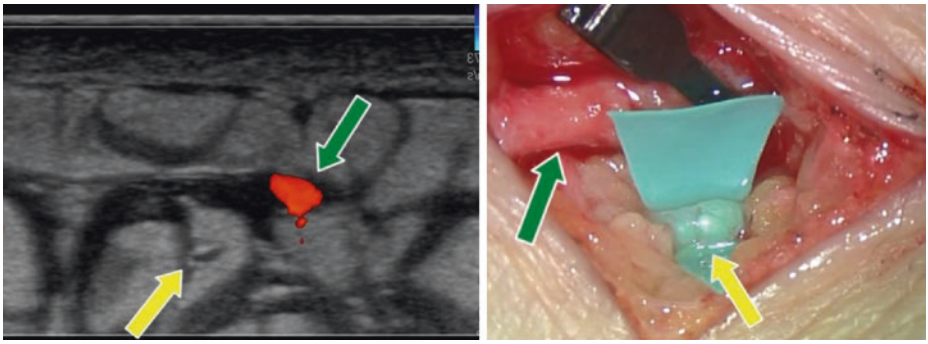


Fig. 51.4 (*Left*) Ultrasound image of lymphatic vessel (*Yellow arrow*) and vein (*Green arrow*) in the knee resided in rich fatty tissue in the deep layer. (*Right*) Lymphatic vessel in rich fatty tissue (*Yellow arrow*) and vein (*Green arrow*) were dissected as ultrasound indicated in the incision site of knee

Indocyanine green lymphography has a depth limit, detecting lymphatic vessels only within 1.5–2 cm of the body surface. Some lymphatic vessels in the thigh region and knee region exist 1.5 – 3 cm from the skin. Thus, detection of lymphatic vessel in the thigh region and knee is difficult with indocyanine green lymphography. Lymphatic vessels in the thigh region and knee reside in rich fatty tissue in the deep layer, making their detection consistently challenging for surgeon. Because lymphaticovenular anastomosis incisions in the thigh region and knee are placed mainly according to the experience of surgeons, nondetection of lymphatic vessels in some incisions is a common occurrence. Preoperative ultrasound detection of lymphatic vessels resolves this uncertainty and tells surgeon exact location of lymphatic vessels even in the deep layer where they reside in the rich fatty tissue (Fig. 51.4).

Finding venules appropriate for anastomosis to the detected lymphatic vessels intraoperatively is also difficult and demanding. Surgeons face a situation in which there is a suitable lymphatic vessel but no suitable venule for lymphaticovenular anastomosis frequently. In such cases, surgeons attempt to extend the incision to find a suitable vein, and this leaves a long scar with no contribution to the therapeutic outcome. Ultrasound can detect not only lymphatic vessels but also venules. Surgeons can select the venule which has suitable size for the diameter of lymphatic vessels easily from among subcutaneous veins and a branch of the greater saphenous vein and know also the location of venules. Surgeons can select also the venule which has less backflow using push and release technique in ultrasound color Doppler mode for prevention of venous reflux at the lymphaticovenular shunt preoperatively. These advantages of preoperative ultrasound detection technique reduce required time for dissecting vessels using lymphaticovenular anastomosis and also increase the postoperative reduction change rate of the limbs.

The presence of large lymphatic vessels with abundant lymph flow is an important factor determining the therapeutic effect of lymphaticovenular anastomosis in patients with lower extremity lymphedema. Using ultrasound, surgeons can detect and select the lymphatic vessels which have expanded lumen preoperatively. Lymphatic vessels which have expanded lumen in ultrasound express the lymphatic vessels which have still valve function and high flow. Preoperative ultrasound detection technique of lymphatic vessels has a therapeutic advantage that is independent of lymphatic diameter or lymphatic flow.

Ultrasonography can detect lymphatic vessels in dermal backflow pattern of indocyanine green lymphography and where indocyanine green lymphography hardly visualizes lymphatic vessels. However, indocyanine green lymphography can detect whole lymphatic flows of the lower limbs and evaluate and diagnose lymphedema. Taking each characteristic into consideration, detecting of lymphatic vessels using ultrasonography technique would complement indocyanine green lymphography technique for lymphedema patients.

Nowadays, elastography which is performed by ultrasonography could be a useful alternative evaluation for lymphedema severity when indocyanine green lymphography is not available. Elastography is a relatively new ultrasonographic technique to evaluate tissue elasticity, which visualizes fluid retention as a red region in lymphedema patients. This technique has been used to identify and differentiate mammary tumors, prostate tumors, malignant liver lesions, pancreas, and lymph nodes [12–21]. Ultrasound elastography is an objective quantitative measurement for the diagnosis and evaluation of edema. Elastography has the correlation to ICG lymphology [3]. As ICG pattern progressed, red region area was likely to increase. Elastography can determine whether a leg is physiologically normal or lymphedematous to a certain degree (moderate to severe). Elastography is useful to indicate surgery for lymphedema patients. Since elastography is performed by ultrasonography which is available in most institutions, elastography could be a useful alternative evaluation for lymphedema severity (Fig. 51.5).

In conclusion, ultrasonography has a higher possibility of usefulness for diagnosis and treatment of lymphedema.

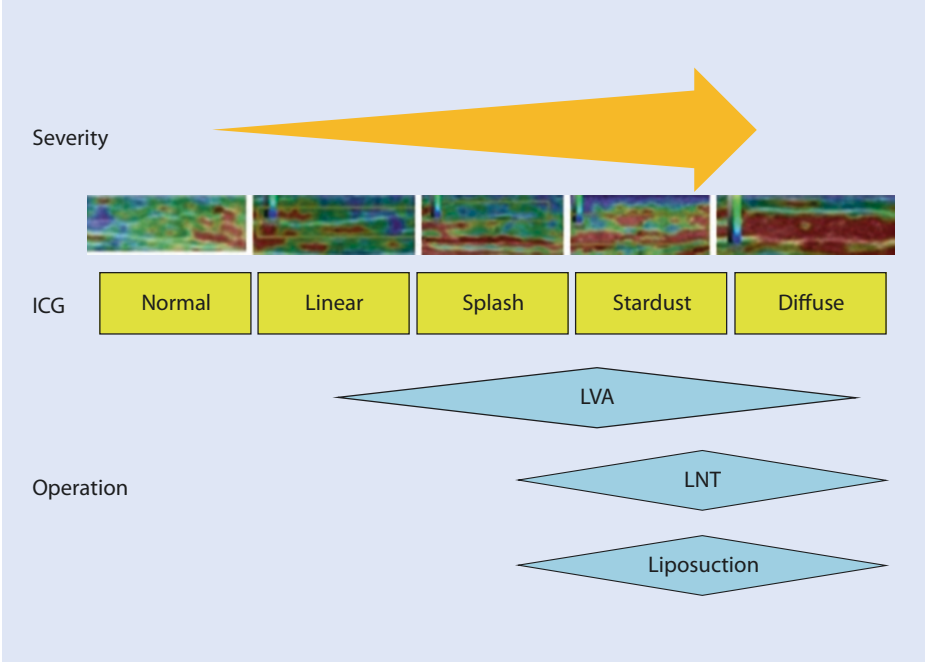


Fig. 51.5 Elastography performed by ultrasonography could be a useful alternative evaluation for lymphedema severity and suggest appropriate operative option

51.3 Selection and Combination of Lymphatic Microsurgery and Novel Technique

Lymphedema is a chronic progressive disease affecting not only the lymphatic system but also the interstitial space and skin. The functionality of the lymphatic system is based on the contractility of the lymphatic musculature and sustained by the vascularization of lymphatics through the vasa vasorum (small artery and vein running on the surface of the lymphatics).

The strategy of the surgical approach is based on the level of degeneration of the lymphatic smooth cells: reversible or irreversible. Distinct surgical strategies, according to the severity of lymphedema, should be applied in order to achieve the best therapeutic result. The mechanism of degeneration of the lymphatic system is based on the paradigm of «lymphatic hypertension» caused by the interruption of normal lymphatic pathways (after surgery/radiotherapy) which hamper the efflux of lymph out of the lymphatic system. This consequential retention of lymph fluid causes a stretching of the lymphatic musculature resulting both in an alteration of frequency of contraction and in an increased contractility of the lymphatics, in an effort to regain the normal intra-lymphatic pressure. However, the inefficient lymphatic pumping results in global deterioration of the lymphatics.

In the case of reversible smooth cell degeneration (mild edema), the best approach is lymphaticovenular anastomosis. In the case of irreversible smooth cell degeneration (severe edema), lymphaticovenular anastomosis is not so effective given the loss of functionality of the lymphatics and not enough. Recurrent infections (erysipelas) determine ischemic changes in the feeding vessels of the lymphatics with lymphangiosclerosis (loss of functionality of lymphatics and progressive occlusion of the lumen) with total loss of the lymphatic function and secondary causing progressive irreversible alteration of the subcutaneous tissue.

The popular method to evaluate the condition/status of lymphatic functioning is performing a lymph fluoroscopy (observation of spreading of ICG with NIR): mild edema is characterized by a «stardust» pattern and severe edema by a «diffuse» pattern. The displayed patterns will determine the feasible surgical treatment options. In the case of a stardust pattern, lymphaticovenular anastomosis is recommended at first. However, when lymphedema is refractory to lymphaticovenular anastomosis, lymphatic tissue transfer is the second option. In the case of a diffuse pattern, the first therapeutic option is combination of lymphaticovenular anastomosis and lymphatic tissue transfer. Two approaches are available for lymphatic tissue transfer typically: (1) Lymphatic adipofascial flap in the first web space of foot, (2) Vascularized functional lymph nodes in the lateral thoracic area, inguinal area, submandibular area, and supraclavicular area. Eventually, for the case which patient complained about thickness of limbs, only the liposuction can satisfy their demand after performance of lymphaticovenular anastomosis and lymphatic tissue transfer (Fig. 51.5).

51.4 The Superior-Edge-of-the-Knee Incision Method

The Superior-Edge-of-the-Knee Incision (SEKI) method is the effective lymphaticovenular anastomosis procedure for lower extremity lymphedema based on the kinetic theory of lymph flow in which mechanical movement of the knee joint during walking promotes to propel lymph to the site of lymphaticovenular anastomosis in the specific area, the SEKI point [4]. The area of the SEKI point is defined as the intersection of a

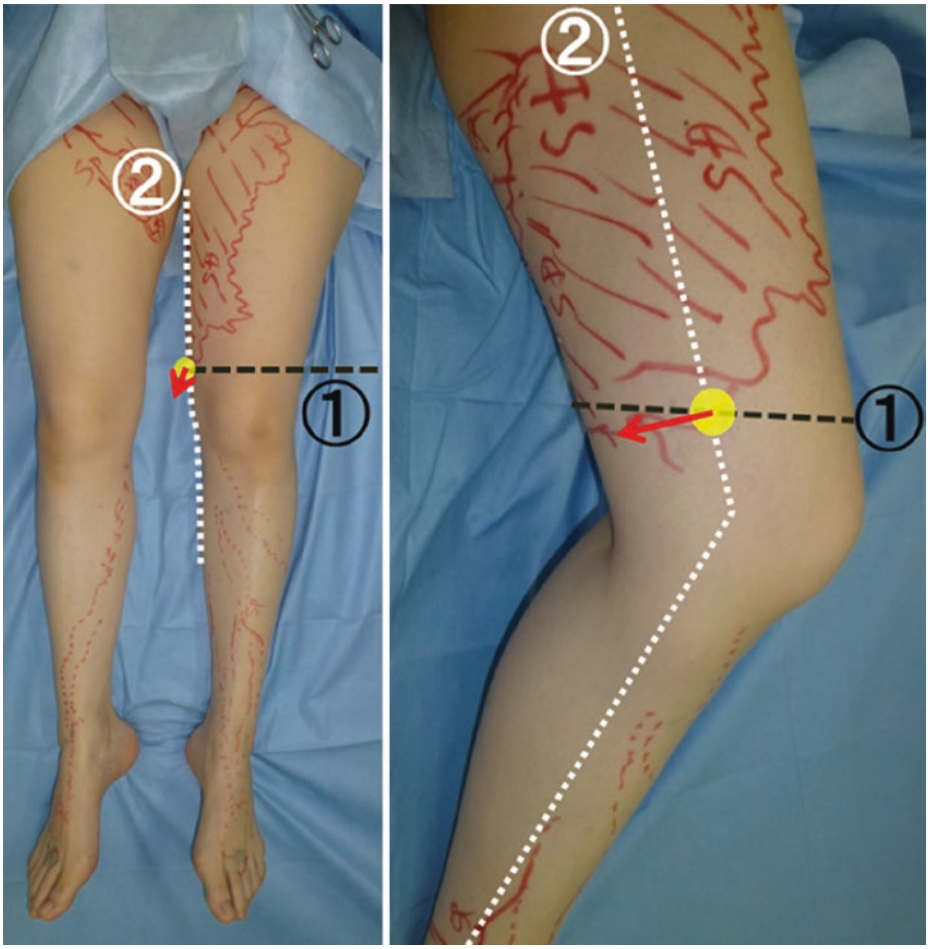


Fig. 51.6 (*Left*) The SEKI point is defined as the intersection of a transverse line drawn at the superior edge of the patella and a longitudinal line drawn along the medial axis of the distal thigh with the patient in the supine position. (*Right*) From the point of intersection, a 2.5-cm-long transverse incision was made posteriorly

transverse line drawn at the superior edge of the patella and a longitudinal line drawn along the medial axis of the distal thigh with the patient in the supine position. From the point of intersection, a 2.5-cm-long transverse incision was made posteriorly (Fig. 51.6).

At the SEKI point, only lymphatic vessels under the superficial fascia layer are selected for lymphaticovenular anastomosis, because the movement of the knee joint works as the power source for propulsion of lymph within lymphatic vessels between the deep and superficial fascia layers. Although many lymphatic vessels are easy to be identified technically over the superficial fascia layer at the SEKI point, these lymphatic vessels cannot utilize kinetic advantages of the knee joint movement at the SEKI point (Fig. 51.7).

One of the most important anatomical landmarks of the SEKI point is the great saphenous vein. A second to third branch of the greater saphenous vein is always found in the

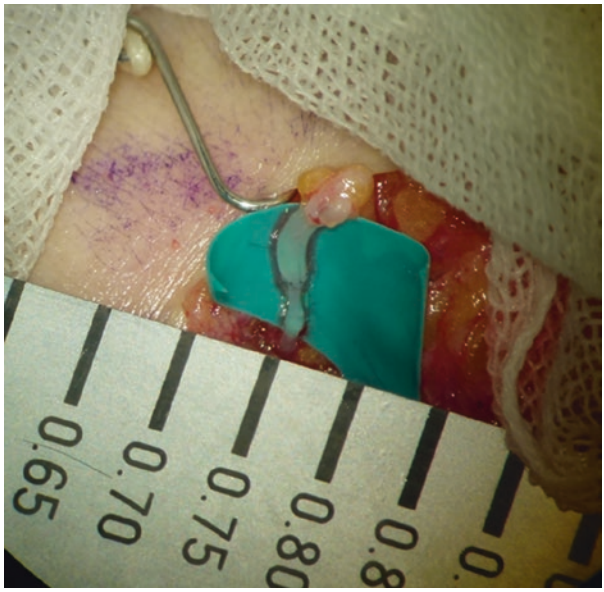


Fig. 51.7 Only lymphatic vessels under the superficial fascia layer are selected for lymphaticovenular anastomosis at the SEKI point

SEKI point; however, the great saphenous vein itself should not appear in the incision. The great saphenous vein is always located in the posterior area from the SEKI point. If the great saphenous vein is found in the SEKI site, dissection under the superficial fascia should be done more anteriorly to detect the large and high-flow lymphatic vessels.

Although detection of the large and high-flow lymphatic vessels under the superficial fascia is still difficult surgical procedure for beginners, dissection of the superficial fascia should be limited within narrow area (2.5 cm or less) for the clinical efficacy of the SEKI method. A large incision with wide area dissection of the superficial fascia at the SEKI point will make the detection of the lymphatic vessels easy, but it also will weaken the strength of the pressure by muscle pumping to the lymphatic vessels under the superficial fascia. Because the upward propulsion of lymphatic fluid to the site of lymphaticovenular anastomosis is derived from compression of the lymphatic vessels between the deep and superficial fascia layers, lack of the superficial fascia continuity in large area which is made by the wide dissection might diminish the power of compression and lymph propulsion during walking. Then clinical efficacy of the SEKI method cannot be obtained properly.

The SEKI method facilitates the treatment of lower extremity lymphedema by lymphaticovenular anastomosis with a detection of the large and high-flow lymphatic vessels based on the kinetic lymphatic fluid propulsion to the site of lymphaticovenular anastomosis.

51.5 The Guide Wire Method

In lymphaticovenular anastomosis, a lymphatic vessel is anastomosed to a small vein to circumvent the obstructed section of the lymphatic flow. Among several types of anastomosis, side-to-end (S-E) anastomosis, in which a window is made on the wall of a lymphatic vessel, is considered to be one of the most effective methods; it creates retrograde lymphatic bypass as well as normograde lymphatic bypass. While intravascular

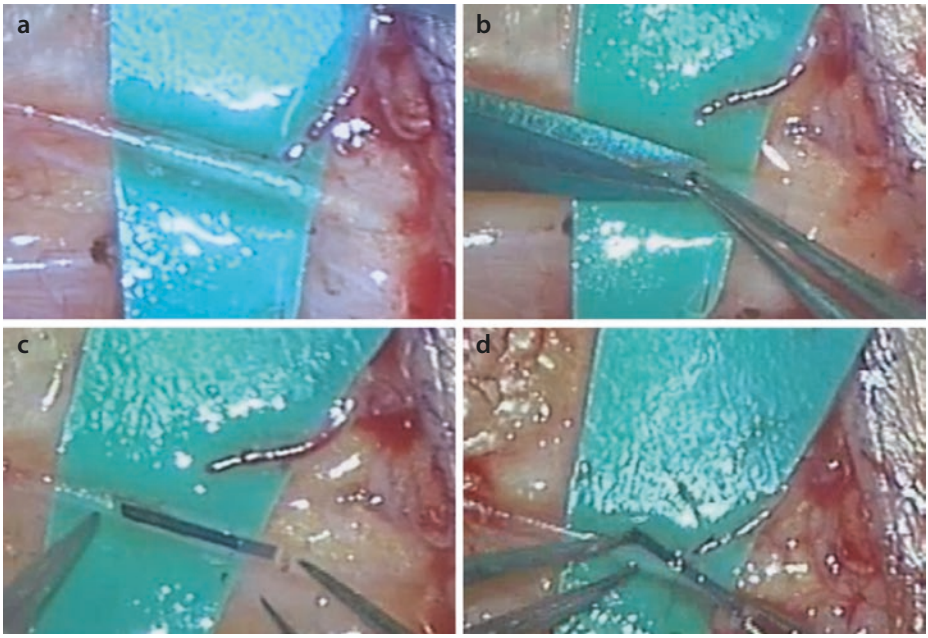


Fig. 51.8 In procedure of lymphaticovenular anastomosis , (**a**) first, care should be taken to choose a venule with a valve to prevent backflow of the venous blood into the lymphatic. (**b**) Next, using microscissors, a small window is made on the wall of the lymphatic vessel. (**c**) A piece of 5–0 or 6–0 nylon suture is inserted from this window into the lumen of the lymphatic vessel. (**d**) The last suture is left untied for removal of the nylon suture. The nylon suture is pulled out from the window with no effort

stenting (IVaS) method can facilitate end-to-end anastomosis between the lymphatics and the veins, S-E anastomosis still remains a great challenge for many microsurgeons [5, 22–24]. For safe and reliable S-E lymphaticovenular anastomosis, the following technique can be useful.

A lymphatic vessel and a small vein are identified and dissected for anastomosis. The vein is transected, leaving the proximal end long enough for anastomosis. In lymphaticovenular anastomosis, care should be taken to choose a venule with a valve to prevent backflow of the venous blood into the lymphatic (Fig. 51.8a). Next, using microscissors, a small window is made on the wall of the lymphatic vessel (Fig. 51.8b). Abundant lymphatic outflow from the window can be seen from functional but obstructive lymphatics, appropriate for lymphaticovenular anastomosis. A piece of 5–0 or 6–0 nylon suture is inserted from this window into the lumen of the lymphatic vessel (Fig. 51.8c). Once the tip of the nylon suture is inserted into the lumen, further insertion is very smooth, similar to insertion of a guide wire into the blood vessel. After the nylon suture is completely inserted into the lymphatic vessel, it is slid back for a short distance along the lumen. The color contrast between the nylon suture and the lymphatic wall makes the window apparent. During anastomosis, needle insertion is significantly facilitated since the nylon suture keeps the lumen open. The last suture is left untied for removal of the nylon suture. The nylon suture is pulled out from the window with no effort (Fig. 51.8d), and the suture is tied to complete the anastomosis. Patency and efficacy of the anastomosis are confirmed by the flow of lymphatic fluid into the venule.

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Current Dilemmas and Controversies in Reconstructive Surgery for Lymphedema

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Summary of Basic Concepts

- Reconstructive lymphatic surgery remains controversial mainly because of poor reproducibility and a wide variety of mixed outcomes.
- The optimal timing of the surgical procedure has been recognized as the most critical factor for its long-term durability.
- Long-term patient compliance with decongestive lymphatic therapy and compression therapy is critical following surgical therapy.

Restoration and maintenance of normal limb function and normal cosmetic appearance are the main goals of treatment of the lymphedematous limb [1, 2, 6, 7].

Manual lymphatic drainage (MLD)-based complex decongestive therapy (CDT) [8–11] has long been the mainstay of treatment in the contemporary management of chronic lymphedema. Its clinical validity as well as its legitimacy is thoroughly reviewed in the two previous sections: Section VI (Physical and Medical Management) and Section VII (Practical issues in the Physiotherapeutic Approach to Lymphedema).

Because of the ease of availability and accessibility, in addition to having no risk to add «harm» to an already deranged lymphatic system, its value has been overestimated as the sole treatment modality for long-term management. Unfortunately, one crucial aspect of DLT has been neglected: «DLT is neither a panacea nor a curative method.» It is only effective in slowing progression at best and never restores the lost function. This remains its Achilles heel. When DLT is discontinued, the lymphedematous condition deteriorates often at a faster rate, requiring a lifetime commitment that, again, only slows progression.

Such reliance on DLT-based therapy was partly due to the old concept that chronic lymphedema is a simple «static» condition characterized by soft tissue swelling of the affected limb/region after blockage of the lymph-transporting/collecting system. Chronic lymphedema is *not* a static condition but is actually a *steadily progressing* condition independent of the efficacy of DLT [12–15].

Chronic lymphedema is a «continuously changing» condition of degenerative and inflammatory processes involving the skin and soft tissue in addition to the lymphatic vessels and lymph nodes. This condition is characterized clinically by recurrent episodes of dermatolymphoadenitis, resulting in diffuse, irreversible tissue fibrosis. What began as a simple phenomenon of accumulation of lymph fluid eventually becomes a disabling and distressing limb condition affecting the entire surrounding soft tissue beyond the lymphatic system.

With a better understanding of the disease process, contemporary treatment of lymphedema has evolved into an approach that is focused on strategies aimed at preserving and improving quality of life for better social, functional, and psychological adaptation in addition to the control of the lymphatic disorder [3–5, 16].

Various surgical treatments introduced throughout the last century, especially for curative and reconstructive purposes, were revisited with different points of view in order to improve patient quality of life [17–20]. The role of reconstructive lymphatic surgery has also changed in that its new, different role is focused more to provide improvement of patient quality of life as a whole [21–24]. Detailed information regarding these reconstructive surgical treatments is further reviewed through eight other chapters in Section VIII.

Despite reconstructive surgery having been known to be the ideal treatment to restore normal lymphatic function with a chance of a «cure» for decades, this unique treatment modality still remains controversial mainly because of poor reproducibility and a wide variety of mixed outcomes. The mixed outcomes are most likely due to the variation in the selection of patients and variability in the indications for treatment by different surgical teams in different countries [2, 24, 25].

Among the various criteria required for successful outcome, the «optimal timing» of the surgical procedure has been recognized as the most critical factor not only for immediate success but also for its long-term durability. New knowledge of lymphodynamics and autonomous peristaltic propulsion by the «lymphangion» system once again confirmed how critical the «optimal timing» of surgery is in order to relieve the lymphatic obstruction before permanent damage occurs [2, 25].

Reconstructive surgery is only successful when performed at the «earlier» stage of chronic lymphedema, *before* residual lymphatic vessels are damaged by *prolonged* lymphatic hypertension. Injured lymphatic vessels (not yet destroyed) can be effectively rejuvenated and restored to normal function by continuous MLD-based DLT postoperatively.

Reconstructive surgery is, therefore, most effective when performed in the earlier stage of lymphedema, when residual lymphatic vessels remain functionally intact with the ability to relieve lymphatic obstruction and lymph stasis after successful lymphatic reconstruction.

Nevertheless, in reality, the majority of «ideal» lymphatic reconstruction candidates are never offered timely intervention when the residual lymphatic system is still salvageable and are, instead, treated with DLT. When reconstructive lymphatic surgery is belatedly considered, it is often after the window of opportunity has already passed and the patient is left with an unsalvageable condition with damaged and paralyzed lymphatic vessels.

Furthermore, reconstructive surgery requires a commitment by a multidisciplinary team in order to achieve and maintain successful long-term results. Reconstructive lymphatic surgery requires a dedicated and experienced microsurgical team (e.g., lymphovenous and lympho-lymphatic anastomosis). Such an undertaking requires significant resources that are often far beyond what is available at the majority of many capable medical institutes.

Assessment of lymphatic function in lymphedema patients who are potential reconstructive candidates relies heavily on radionuclide lymphoscintigraphy. The current status of lymphoscintigraphy is far from perfect in providing adequate data to allow determination of the feasibility and subsequent planning of lymphatic reconstruction [10, 26–28]. Lately, MR lymphangiography and indocyanine green lymphangiography may provide high-resolution imaging required for planning lymphatic reconstruction [29–32].

This ideal treatment has been extremely limited to a few select patients. Although there is no doubt that it is more theoretically sound than DLT, with a definite chance of a «cure,» it is still far from being a practical treatment in the day-to-day management of chronic lymphedema. Nevertheless, through the last decade, many consider a new role of reconstructive surgery to serve as a *supplemental* therapy to augment DLT-based physical therapy in lymphedema patients described as poor responders [1, 2, 7].

Lately, reconstructive surgery is limited to lymphedema patients who are determined to be poor to nonresponders to conventional DLT-based treatment. Since DLT-based treatment is invariably effective in the majority of chronic lymphedema patients, the recommendation has been to delay surgical therapy until DLT-based therapy has been maximized with no further improvement. In reality, however, reconstructive surgery is often recommended by a multidisciplinary care team *only after* properly documenting that the patient has failed extensive DLT, is determined to be a «treatment failure,» and has experienced steady progression of the disease for at least 2 years.

Lymphedema patients where maximal DLT-based therapy has failed are then considered for additional reconstructive surgical therapy. These patients are typically clinical stage II or III, based on our experience. This stage of lymphedema is generally too advanced and is long after the ideal time period for reconstructive surgery to be curative [1, 2, 7].

Therefore reconstructive surgery, when limited to a «supplemental role» in the management of lymphedema in the poor to nonresponding group of DLT patients, is often doomed to fail from the outset. Lymphatic reconstructive surgery is now offered as an *adjunctive* treatment in the management of lymphedema along with DLT-based treatment since both treatment modalities have mutually complementary effects.

Reconstructive surgical therapy requires maintenance DLT to allow the treated lymphatic vessels to regain its function after being in a «paralyzed» condition. The success of reconstructive surgical therapy in this situation is totally dependent on patient compliance with postoperative DLT [1, 2, 7].

Patient compliance with lifelong maintenance DLT is the single most important factor that directly influences the long-term results of reconstructive surgical therapy. A comprehensive treatment plan incorporating both surgical and postoperative maintenance treatment modalities as part of a multidisciplinary approach will produce the most effective results. The various modes of surgical therapy have recently been found to be more effective when combined with DLT.

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52.1 Clinical Experiences (Personal)

Among 1065 lymphedema patients (131 males and 934 females, 259 primary and 806 secondary, age range 2 months to 82 years), a total of 32 patients were selected for lymphovenous anastomotic surgery (LVAS; $n = 19$ patients) and free lymph node transplant surgery (FLTS; $n = 13$ patients), during a 10-year period (January 1995 to December 2004) [1, 7, 21, 22].

All 32 patients were selected due to failure of DLT alone to relieve intractable symptoms with various indications. Various noninvasive tests including lymphoscintigraphy were performed to determine clinical and laboratory staging in all surgical candidates.

The inclusion criteria and indications for reconstructive surgery were:

- Failure to respond to therapy at clinical stage I or II
- Progression of the disease to an advanced stage (e.g., stage I to stage II, or stage II to stage III) in the setting of DLT-based treatment

- Chylo-reflux combined extremity lymphedema
- High recurrence of local and systemic infection
- Poor tolerance to DLT-based conservative treatment

We *never* initiated the surgery as the primary mode of therapy. We selected various reconstructive surgical therapies as a supplemental treatment to DLT.

For lymphovenous anastomotic surgery (LVAS), the candidates were offered the surgery when DLT-based treatment failed or when it was not sufficient to prevent the rapid progression of the disease: clinical stages I to II, or early stage II to late stage II.

All patients selected met all the inclusion criteria for this additional treatment, particularly among the «secondary» lymphedema patients. Nineteen patients (mean age 49 years; female =18, male =1; primary =4, secondary =15) underwent a minimum of 3–4 anastomoses between healthy, well-functioning collecting lymph vessels and competent branches of the saphenous vein.

At 6 months, 16 out of 19 LVAS patients with good compliance to maintain postoperative MLD/compression therapy had clinically satisfactory improvement, while the other noncompliant 3 failed. At 24 months, 8 out of 16 were compliant and 8 were not. The noncompliant patients showed progressive deterioration, while the compliant patients maintained their improvement.

At 48 months, 2 out of the 8 compliant patients dropped out. Three of the remaining 6 maintained satisfactory clinical and lymphoscintigraphic improvement.

For free lymph node transplant surgery (FLTS), candidates were selected based on the same indications as for LVAS but the priority for «primary» lymphedema with progress from clinical stages II to III. Thirteen patients (mean age 34 years; female = 10, male = 3; primary =6, secondary =7) at clinical stages II or III underwent FLTS using a microsurgical free grafting technique when LVAS could not be performed.

At 12 months, 10 of the 13 FLTS patients with good compliance to MLD showed clinical improvement with a successful graft, but the remaining 2 with poor compliance with the MLD failed.

At 24 months, 8 patients were compliant and 5 were not. Compliant patients maintained clinical improvement while the remaining noncompliant patients showed progressive deterioration.

Conclusion

Reconstructive lymphatic surgery is the best option for the treatment of chronic lymphedema when performed at the optimal time. It is also a viable treatment option for lymphedema patients who have failed to respond to DLT alone. Postoperative DLT and compression therapy are required as supplemental therapy in the group of poor responders to DLT. Postoperative DLT is even more important when performing lymphatic surgery at a less ideal, later stage of lymphedema.

Long-term patient compliance with DLT and compression therapy is absolutely essential for satisfactory clinical improvement and maintenance following reconstructive lymphatic surgery. This is especially true in the group of patients who are poor responders to DLT therapy alone.

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Future Prospects in Lymphatic Reconstructive Surgery

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Summary of Basic Concepts

- Lymphedema can be extremely morbid for those who are affected.
- Primary lymphedema generally develops as a result of a hereditary condition, whereas secondary lymphedema can develop as a sequela of numerous acquired conditions.
- The most common etiology of lymphedema in the United States is cancer and related therapy.
- Although treatment for lymphedema has improved in recent years, a cure still has yet to be found.
- Promising treatment approaches include strategies aimed at prevention as well as options to reconstruct and regenerate the lymphatic system.
- While lymphatic reconstructive surgery is likely to remain as the cornerstone of advanced lymphedema treatment, it is crucial that we continue to investigate adjunctive therapies such as tissue engineering, nanotechnology, and lymphangiogenesis.

53.1 Introduction

Disorders of the lymphatic system, which affect millions of people across the world, are increasingly recognized as a significant source of morbidity. Lymphedema can develop as a result of a hereditary condition (primary lymphedema) or as a sequela of numerous acquired etiologies (secondary lymphedema). Most commonly, secondary lymphedema presents as a complication of cancer treatment. With respect to breast cancer, which is the most common cancer afflicting women, lymphedema may occur in up to 28% of patients after lumpectomy and 49% of patients after mastectomy [6]. Symptoms include increased volume and weight of an affected extremity and a subjective feeling that the affected limb is heavy compared to the normal limb. Patients may report difficulty performing activities with the affected limb or wearing normal clothing. Left untreated, the condition will progress to include skin changes, induration and fibrosis, and bouts of cellulitis and/or lymphangitis. Lymphedema also has implications on emotional well-being, as patients are often left embarrassed by an enlarged, disfigured limb and the need to wear specialized garments.

Currently, there is no cure for lymphedema. The available treatments, therefore, attempt to palliate the condition. Nevertheless, there has been a rapid evolution of surgical and microsurgical treatments in recent years. This is the result of a better understanding of the lymphatic system and the pathophysiology of lymphedema, advances in technology, and improved reporting in the literature of outcomes and effective surgical techniques. As interest in lymphedema continues to increase, so too will effective treatment protocols. In this chapter, we provide a brief review of current treatment options and their limitations, detail emerging technologies that will inform

and improve developing treatment strategies, and discuss future prospects in lymphedema surgery.

53.2 Current Treatment Options

53.2.1 Medical

The cornerstone of early lymphedema treatment includes conservative approaches such as limb compression and elevation, weight reduction in obese patients, and complex decongestive therapy (CDT). CDT encompasses several phases of intensive lymphatic massage and skin care combined with continuous bandaging and compression garments. Although some patients do respond favorably to CDT, with reported volume reductions of 40–60% [7], many will fail treatment due to advanced disease, poor compliance, a shortage of trained lymphedema therapists, and other cost-related barriers. In addition, several pharmacologic agents have been used to treat lymphedema. Results have been inconsistent as to how effective various agents are at reducing symptoms. Generally, pharmacologic approaches are offered in adjunct fashion and are not used as a primary treatment option.

53.2.2 Surgical: Debulking

In patients who fail conservative management, various surgical methods may be employed in an attempt to ameliorate the condition. At the present time, there is no consensus regarding the optimal choice of procedure or timing of intervention. Surgical management can be broadly categorized into debulking techniques and physiologic techniques (Table 53.1).

Debulking or reductive procedures aim to reduce the amount of affected tissue. Indeed, the earliest surgical procedures for lymphedema involved the direct excision of excess tissue. Charles first reported radical debulking of the skin and subcutaneous fat of affected scrotal and lower extremity tissue in 1912 [8]. For many years thereafter, modifications of these procedures dominated the surgical treatment of lymphedema [9]. Today such techniques are rarely employed due to their associated morbidity and are reserved only for the most debilitating of cases.

Originally developed for cosmetic body contouring, liposuction is an additional debulking technique that has proven effective in treating lymphedema. This technique utilizes cannulas attached to vacuum suction to aspirate subcutaneous tissue in the lymphadematous extremity. It is less invasive than other debulking methods and has been shown to facilitate significant long-term volume reduction [10]. Drawbacks to liposuction include the need for lifelong compression garments to prevent recurrence and the potential to exacerbate symptoms by damaging residual functioning lymphatic channels [11].

Table 53.1 Summary of surgical techniques used for lymphedema treatment

Category	Procedure	Mechanism	Current uses	Reference
Debulking	Skin/ subcutaneous tissue excision	Direct excision of lymphedematous tissues	Severe disease (infrequently used)	[9]
	Liposuction	Suction-assisted excision of lymph-edematous tissues	Moderate to severe disease when conservative treatment has failed and microsurgical options are unavailable	[10]
Physiologic	Lymphatic-lymphatic bypass	Obstructed lymphatic channels are connected to healthy lymphatic channels	Used infrequently when LVB is technically not feasible	[13]
	LVB	Obstructed lymphatic channels are drained into venous circulation	Primarily used in early-stage disease[a]	[14]
	VLNT	Healthy lymph nodes transferred to affected area	Primarily used in early-stage disease[a]	[16]

LVB lymphovenous bypass, *VLNT* vascularized lymph node transfer
[a]Supermicrosurgery and microsurgery procedures gaining popularity

53.2.3 Surgical: Physiologic

The goal of physiologic procedures is to restore lymphatic drainage by creating new lymphatic channels. Examples include flap interposition, vascularized lymph node transfer, and lymphatic bypass procedures [1]. Early attempts at these techniques involved the rotation of lymphatic vessel-containing tissues (e.g., greater omentum, local skin, and musculocutaneous flaps) from the donor site to the affected area with an intact vascular pedicle [12]. High morbidity and sparse data substantiating efficacy led to the phasing out of many of these procedures.

Proving more effective are procedures that involve the use of microsurgical techniques. Two of the most common microsurgical procedures offered today are lymphatic bypass and lymph node transplantation. In lymphatic-lymphatic bypass, obstructed lymphatic channels within the lymphadematous region are connected to healthy lymphatic channels outside the affected region using a transplanted lymphatic vessel or vein as an interposition graft [13]. Another effective strategy is lymphovenous bypass (LVB), in which obstructed lymphatic channels are drained into the venous circulation in order to improve lymph drainage [14]. Lymphovenous shunts are created by microsurgically anastomosing

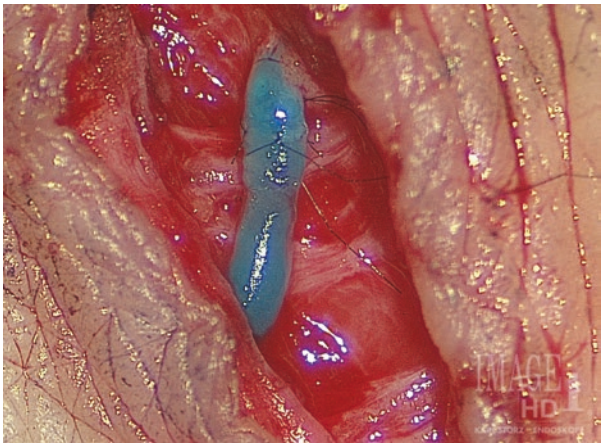

Fig. 53.1 Lymphovenous bypass with isosulfan *blue* within the lumen to confirm patency of the bypass

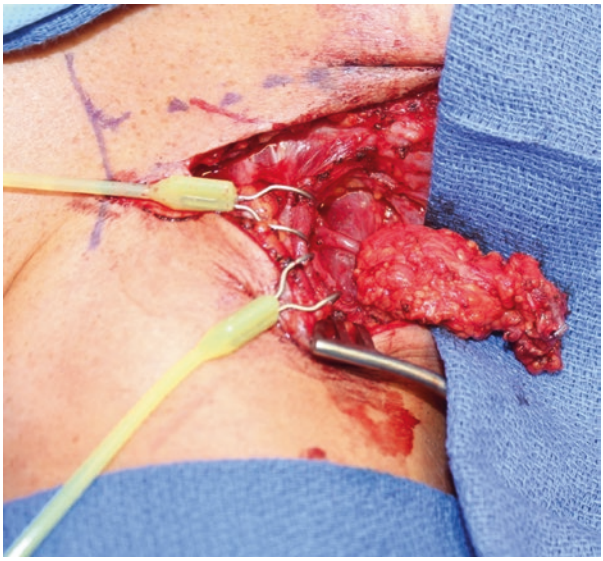

Fig. 53.2 Supraclavicular lymph node transfer

a patent lymphatic located within a diseased region to a regional vein (Fig. 53.1). Prospective studies of LVB have demonstrated symptomatic improvement in 96% of patients, quantitative improvement in 74% of patients, and a 12-month mean volume differential reduction of 42% [2]. Intraoperative mapping of lymphatic vessels using fluorescence lymphangiography may further improve outcomes by identifying potential sites of bypass, objectively assessing lymphedema severity, and optimizing patient selection.

Lymph node transfer consists of transplanting healthy nodes from one region (e.g., supraclavicular region) to the affected area (Fig. 53.2). Originally, lymph nodes were transferred as an avascular graft [15]. It is now the preferred method to transfer nodes and surrounding fat as part of a vascularized tissue flap by microsurgically repairing the blood supply to recipient vessels at the intended location (Tables 53.2 and 53.3).

Table 53.2 Common donor sites for vascularized lymph node transfer

Site	Artery	Vein	Notes
Groin	SCI	SCI	Avoid harvest of sentinel LN to prevent lymphedema of the leg
Submental	Submental	Submental	Care must be taken to avoid injury to marginal mandibular nerve
Supraclavicular	Transverse cervical	Transverse cervical	Vascular anatomy may vary; external jugular vein may be used
Thoracic	Lateral thoracic	Lateral thoracic	LN harvest limited to level 1 nodes to avoid damage to draining arm lymphatics[a]

[a]Level 1 denotes inferior to lateral border of pectoralis minor
SCI superficial circumflex iliac, *LN* lymph node

Table 53.3 Common recipient sites for vascularized lymph node transfer

	Site	Artery	Vein	Notes
Upper extremity	Axilla	Axillary or TD	Axillary or TD	Wide scar removal is key to successful transfer and symptom resolution
	Elbow	Anterior recurrent ulnar	Basilic	Radial artery and venae comitantes may be used
	Wrist	Radial (superficial branch)	Cephalic	May improve proximal arm lymphedema due to «pumping» action [3]
Lower extremity	Ankle	AT or DP	AT or DP	STSG may be required for side coverage of flap is skin pocket tight
	Groin	SCI	SCI	Often heavily scarred and fibrotic
	Knee	Medial genicular	Medical genicular	Saphenous vein may be used

AT anterior tibial, *DP* dorsalis pedis, *SCI* superficial circumflex iliac, *STSG* split-thickness skin graft, *TD* thoracodorsal

Several authors have reported successful outcomes in treating lymphedema with this approach [16], and it has become a standard surgical option at centers with appropriate expertise [17]. The mechanism underlying the success of vascularized lymph node transfer (VLNT) is still under investigation, but it is hypothesized that transferred nodes promote lymphangiogenesis and may also act as a lymphatic pump [3]. A potential and feared complication of VLNT is the development of lymphedema at the donor site.

53.3 Limitations in Lymphedema Management

No cure for lymphedema exists at the present time. Indeed, despite making significant strides since the early days of radical excision, many issues still exist with respect to our current understanding of lymphedema and its treatment. One significant shortcoming is the lack of a standard protocol for the measurement of lymphedema. Comparison of the affected extremity to the normal side as well as pre- and postoperative comparisons can be made in an objective way. At many centers quantitative assessment involves circumferential measurements at several places on the limb or by measuring the volume of water displaced. These methods are imprecise and limited, however, because they cannot account for extrinsic factors that alter limb volume such as time of day, patient diet and activity level, and time since removal of compression garments [12].

Imaging techniques (e.g., ultrasonography, computed tomography, and magnetic resonance imaging) can reliably show volume differences between extremities. However, similar limitations are present due to factors that affect limb volume as well as issues with cost and availability. Perhaps the most useful imaging technique used today to assess lymphatic function is lymphoscintigraphy. However, lymphoscintigraphy mostly provides qualitative data regarding lymphatic function of the limb. Another useful tool is indocyanine green (ICGN) lymphography, which gives information about the location of functioning lymphatic vessels and the severity of lymphedema.

An additional limitation is the lack of consensus in outcome measures when evaluating treatment protocols. Methodology between studies often varies, making comparison difficult. Similarly, aspects of patient care are approached differently from center to center due to a dearth of data evaluating the timing of surgical procedures, the optimal surgical approach, and the ideal algorithm for pre- and postoperative adjunctive therapies. This largely stems from a lack of consensus on assessing disease grade and optimal patient selection. Large prospective trials focusing on these issues are warranted.

There are many limitations to medical or surgical approaches to treat lymphedema. Most of these treatments, including physiologic procedures such as LVB, focus on reducing the fluid volume load of the lymphedema but do not address the existing fat hypertrophy and tissue fibrosis. Even in the case of VLNT, where lymphatic function is improved, complete reversal of tissue damage that has already developed cannot be expected. Furthermore, debulking procedures such as liposuction remove excess fat but do not address underlying lymphatic function, and patients must continue to wear compression garments indefinitely.

53.4 Emerging Technologies in Lymphedema Surgery

The treatment for lymphedema will continue to improve as technology in the field advances. A recent example of this is lymphodynamic evaluation using fluorescence lymphography [18]. With this technique, a near-infrared light detection system detects light emitted by a dye that has been injected into the affected limb called indocyanine green (ICG). Preoperatively, this facilitates improved evaluation of lymphatic vessels and real-time lymph flow. Therefore, disease severity can be accurately gauged and optimal surgical candidates can be selected. Perioperatively, this system enables the surgeon to map the lymphatic system and identify functional channels prior to incision

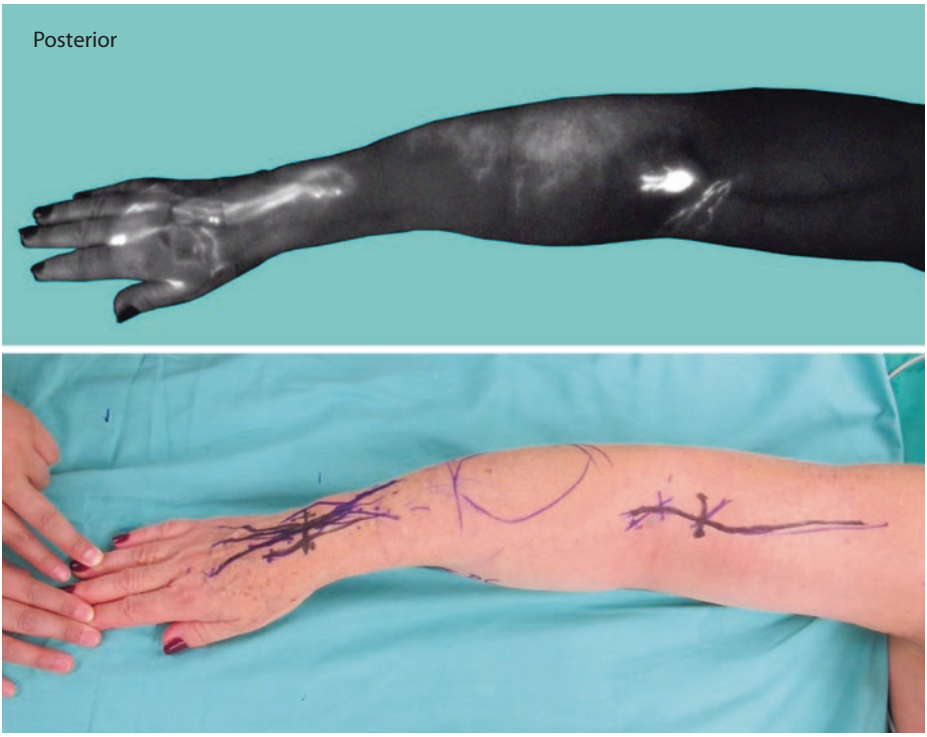

Fig. 53.3 Indocyanine *green* lymphangiography

(Fig. 53.3). As a result, operative time is saved and outcomes may be improved [12]. Formal evaluation of this and other developments that improve clarity and imaging will determine which technologies prove to be useful.

Treatment options will also improve with advancements in surgical technique as well as the instruments used. Lymphovenous bypass, for example, is particularly challenging to surgeons due to the extraordinarily small anatomic structures involved. These technical limitations can be overcome, however, with practice and mastery of supermicrosurgical technique. Advances with high-resolution microscopy, superfine instruments, and suture have been instrumental in improved success with supermicrosurgical techniques.

53.5 Future Prospects in Lymphedema Management

Presently there is no ideal treatment for lymphedema Whether medical or surgical, current treatment options do not completely restore lymphatic function and cannot reverse tissue damage that has occurred secondary to lymphedema. Future prospects in lymphedema management must focus on prevention and early restoration of lymphatic function before significant and permanent tissue damage occurs.

In recent years, a better understanding of lymphatic system physiology and pathophysiology as well as advances in technology have led to improved treatment options.

Nevertheless, despite this improvement in our ability to treat the symptoms of lymphedema, prevention of the condition would be ideal. With improved understanding of cancer biology as well as the lymphatic system, it is plausible that cancer treatment options can be developed that avoid removal or radiation of lymph nodes. This would significantly decrease the risk of lymphedema due to cancer treatment. Until then, a possible solution is prophylactic surgery for secondary lymphedema following oncologic resection Before the widespread adoption of this treatment algorithm, however, several factors must be considered. First, prophylactic surgery must be oncologically safe and should not significantly increase the risk of donor site lymphedema. Further, an analysis of the cost involved in prophylactic surgery relative to the cost of managing lymphedema must be performed. Finally, it is crucial to identify appropriate candidates and to offer them suitable surgical or microsurgical options. Therefore, rigorous and well-designed trials are necessary prior to the implementation of prophylactic procedures.

In addition, to more fully understand how our treatment options can be optimally used, it is crucial to elucidate how the lymphatic system functions. Traditional in vitro experiments that rely on migration and transmigration assays do not recapitulate the multiple factors that affect lymphatic function. In an effort to better match the size dimensions, mechanical forces, and fluid forces in the lymphatic microenvironment, Swartz and colleagues at the University of Chicago have designed a novel flow chamber that combines traditional constructs with controlled microfluidics to simulate in vivo lymphatic biomechanics [4]. Initially designed to study tumor invasion of lymphatics, this technology has also provided insights into flow dynamics of the lymphatic system under different conditions.

Tissue engineering is another strategy that may facilitate enhanced study of the lymphatic system as well as the development of lymphatic grafts that can be surgically implanted. Tissue engineering involves cell-based, growth factor-based, and/or scaffold-based methods for the regeneration of desired tissue [19]. Biodegradable synthetic scaffolds, nonbiodegradable synthetic scaffolds, and decellularized scaffolds have each been used successfully for lymphatic tissue regeneration [20]. Examples of cell-based methods include the isolation of lymphatic endothelial cells from human dermis for in vitro expansion, the differentiation of embryonic stem cells into lymphatic cells in vitro in the presence of vascular endothelial growth factor-C (VEGF-C) and Ang1 [21], and improved lymphatic function after injection of adipose-derived mesenchymal stem cells into animal limb and tail models [22]. In addition, strategies that involve the use of growth factors to facilitate lymphatic development are largely based on factors that have been found to be important in normal lymphatic development and function. Growth factor-based therapy, as well as gene therapy, which entails genetic and recombinant protein strategies, may be used as adjuncts to engineered biomaterials to enhance lymphangiogenesis and to provide greater biocompatibility for the biomaterial. Tissue engineering strategies are still evolving and further study of their use in animal and human models is necessary.

Several authors have also demonstrated that specific biologic factors promote lymphangiogenesis. In one study aimed at finding targets for cancer therapy, the metalloprotease ADAM17 was shown to promote motility, invasion, and sprouting of lymphatic endothelial cells. It was further shown that silencing of ADAM17 had antilymphangiogenic effects [23]. It is therefore plausible that ADAM17 would have a role in the generation of new lymphatics in cases where the lymphatic system has been damaged. In addition, transfer of the VEGF-C gene to the skin of lymphadematous mice promotes generation of cutaneous lymphatic vessels but also results in an untoward vascular

response consisting of angiogenesis, blood vessel leakiness, and associated edema [24]. Saaristo and colleagues therefore conducted a clever experiment in which a mutant form of VEGF-C (VEGF-C156S) was shown to strongly induce lymphangiogenesis while avoiding unwanted vascular side effects in normal and lymphedema mice [5]. While these strategies appear promising, they must be carefully evaluated for potential adverse effects. Some forms of angiogenic gene therapy, for example, may promote dormant tumor growth. Similarly, substances secreted by cancer cells that promote lymphangiogenesis are associated with enhanced tumor spread through lymphatic channels [25]. Therefore, whether the administration of lymphangiogenic substances increased the risk of tumorigenesis would require thorough investigation.

Finally, an alternative approach that is beginning to show promise is the development of lymphedema-reversing pharmacology. Targeted anti-inflammatory therapy [26] and retinoic acids have demonstrated improvements in lymphedema in animal models [27]. Though much work has yet to be done, studies are underway that test whether specific agents improve lymphedema in humans.

53.6 Summary

As we gain a deeper understanding of lymphedema pathophysiology and diagnosis, we will be better able to adequately treat the condition. To that end, the future of lymphatic reconstructive surgery is bright. Global awareness is at an all-time high as research on effective procedures and treatment protocols is being conducted around the world. Each year, lymphedema experts and thought leaders have the opportunity to present the results of their work and discuss the latest developments at international meetings. This increased awareness and growth of the field will undoubtedly lead to a more formalized consensus on how to best select surgical candidates, report outcomes in a way that facilitates improved data comparison, and which procedures and associated techniques have shown the best results. Finally, while lymphatic reconstructive surgery is likely to remain as the cornerstone of advanced lymphedema treatment, it is crucial that we continue to investigate adjunctive therapies such as tissue engineering, nanotechnology, and lymphangiogenesis. Indeed, advancements in these complementary treatment approaches will allow for surgeons to optimize outcomes after surgery.

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Surgical Treatment: Excisional and Debulking Techniques

Contents

Contemporary Indications and Controversies in Excisional Surgery

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Summary of Basic Concepts

- Excisional surgery is a viable option as supplemental therapy in the treatment of end-stage, intractable lymphedema by improving the efficacy of decongestive lymphatic therapy.
- Long-term maintenance following the excisional surgery is dependent on patient compliance with decongestive lymphatic therapy and compression therapy.

Chronic lymphedema was once considered to be a relatively benign condition of limb swelling associated with minimal morbidity. This condition is a steadily progressive condition that not only affects the lymphatic system but all of the surrounding soft tissue, resulting in the development of dermato-lipo-fibrosclerosis (e.g., elephantiasis) [1–7].

When the condition progresses to end-stage chronic lymphedema (stages IV–V, equivalent to International Society of Lymphology (ISL) stage III) [8–11], the effectiveness of DLT [12–15] is significantly reduced. The dermato-lipo-fibrosclerosis of the tissues reduces the efficacy of DLT, and the resulting massively swollen limb becomes increasingly difficult to apply compression therapy with garments and/or bandaging. The extremity is often grotesquely disfigured (Fig. 54.1).

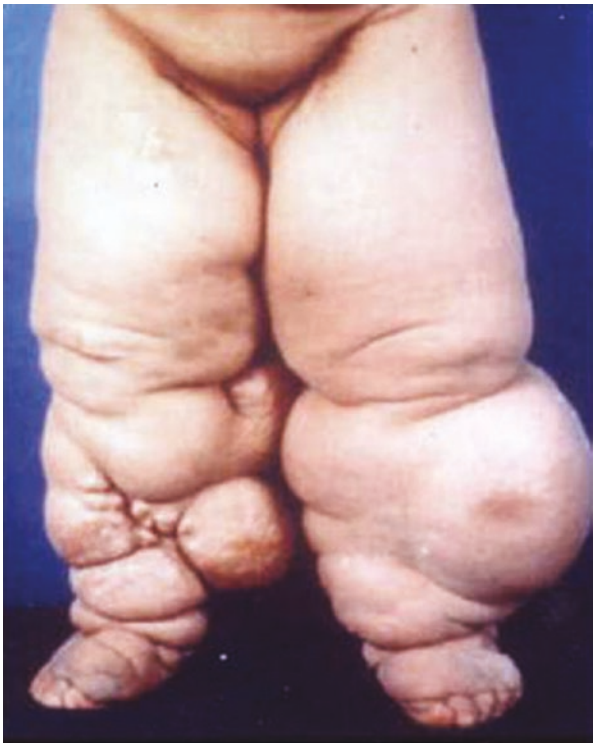

Fig. 54.1 Clinical appearance of the bilateral lower limbs with chronic lymphedema at its end stage (clinical stages III to IV) before the excisional surgery. The resection of grotesquely disfigured fibro-edematous tissue was mandated to improve decongestive lymphatic therapy (DLT)-based management

Untreated chronic lymphedema progresses to a disabling and distressing condition that is unresponsive to DLT. Chronic lymphedema is further complicated with frequent bacterial and fungal infections resulting in chronic inflammation of the affected limb/tissues [6, 16–18].

Once the local infection sets in, the risk of systemic sepsis is significantly increased and may progress to a potentially life-threatening condition. The chronic inflammation associated with lymphedema also predisposes patients to an immunodeficient condition resulting in the malignant transformation of the affected tissues and development of Kaposi sarcoma or lymphangiosarcoma [1, 2].

The associated morbidity of advanced-stage, chronic lymphedema produces significant physical, psychological, social, and financial burdens on the patient, resulting in poor quality of life [8, 19–22]. Additional lymphedema treatments were desperately needed in addition to DLT.

As part of a new approach to the treatment of chronic lymphedema, various excisional surgical procedures were revisited during the past decade in order to define their potential role in the treatment of this condition, especially in end-stage lymphedema [3, 23–25].

Several debulking operations described by Dellon (1977), Sistrunk (1918), Homans (1936), Thompson (1962), etc. [26–29] were introduced during the last century, where the goal of treatment was to remove disfiguring, scarred, lymphedematous tissue from the affected limb.The indiscriminate use of these procedures resulted in generally poor outcomes [3, 23–25]. Over time, the debulking operations were abandoned due to the associated morbidity and questionable efficacy.

Careful review of data determined that the poor outcomes associated with excisional surgery throughout the last century was mostly due to a cavalier approach by surgeons, the lack of appropriate knowledge about lymphedema and lymphatic function, and unclear indications for the surgical procedures.

Excisional surgery for the treatment of lymphedema has been carefully resurrected with limited application in patients with end-stage chronic lymphedema [3–5, 23–29]. Many clinicians remain skeptical and biased against excisional surgery due to previous outcomes and its use as sole independent therapy in lymphedema patients throughout the last century.

An emerging role for excisional surgery in the treatment of chronic lymphedema is as a supplemental treatment in patients who are «failing» DLT. The surgical excision of fibrosclerotic, overgrown soft tissue improves the efficacy of subsequent DLT and compression bandaging [3, 30].

In addition, there is no additional risk of injury to the remaining lymphatic vessels by the excision procedure at this advanced stage [3, 30]. Excisional surgery may be performed in a patient with end-stage lymphedema associated with recurrent local and systemic sepsis that is refractory to maximum DLT combined with compression therapy. The outcome of excisional surgery is, however, dependent on the appropriate postoperative DLT and patient compliance [14, 15].

54.1 Clinical Experience

A total of 1065 patients (131 men and 934 women; 259 primary lymphedemas and 806 secondary lymphedemas; age range, 2 months to 82 years) were evaluated with various

noninvasive tests, including lymphoscintigraphy, to determine proper clinical and laboratory staging between January 1995 and December 2004 [3, 25].

Twenty-two patients (mean age, 46 years; three men, 19 women; five primary lymphedemas and 17 secondary lymphedemas) at stage IV or advanced stage III underwent excisional surgery on 33 limbs (11 unilateral, 22 bilateral) as supplemental therapy; indications were for palliation, to reinforce failing DLT, to improve the local condition to facilitate proper DLT and/or compression therapy, and to reduce the incidence of sepsis.

Indications for excisional surgery as an additional/supplemental therapy [3, 25] included:

- Failure to implement proper care with the DLT at clinical stage III or IV (end stage)
- Progression of the disease to end stage, despite maximal treatment for a minimum of 2 years and declared a «treatment failure» by a multidisciplinary care team
- Increased frequency and/or severity of local and/or systemic sepsis
- Properly declared treatment failure and subsequent progression of the disease to become a candidate for excisional surgery per recommendation by IRB

Evaluation confirmed end-stage chronic lymphedema (stage IV or late stage III) in all 33 limbs with increased technical difficulty in providing effective DLT with proper compression due to a morbidly enlarged extremity and subsequent deterioration of limb function and quality of life. Besides, increased frequency and severity of local and/or systemic sepsis (3–4 episodes per year) despite prophylactic antibiotic administration were also confirmed in its majority.

A modification of Auchincloss-Homans' operation [23, 27] was used to excise a generous amount of grotesquely disfigured tissue with advanced dermato-lipo-fibrosclerotic change, including the whole skin layer, subcutaneous tissue, and muscle fascia in order to reestablish the normal limb contour and to allow proper postoperative compression therapy (Fig. 54.2)

Postoperative MLD and compression therapy were instituted in all patients. Pre- and postoperative evaluation was based on clinical improvement (patient satisfaction index), four-level limb circumference measurements, infrared optical limb volume determination, and lymphoscintigraphy [3, 14, 15].

Follow-up assessment was made every 6 months for a mean of 4 years. An additional clinical evaluation was performed during each episode of local and/or systemic sepsis.

At 12 months, 28 out of the 33 limbs in 22 patients with good compliance in maintaining postoperative compression therapy reported satisfactory improvement.

At 24 months, 18 out of 28 limbs with good compliance were able to maintain successful results, while 10 with poor compliance failed.

At 48 months, 8 limbs in 6 patients were compliant and maintained satisfactory improvement. Among the remaining 25 out of total 33 limbs, 9 were lost to follow-up and 16 noncompliant patients experienced further deterioration.

Our own experience limited to 33 limbs has shown that excisional surgery is a very effective method of establishing optimal conditions for DLT. Patients reported satisfactory improvement initially, but most did not experience long-term improvement without postoperative DLT and/or compression therapy.

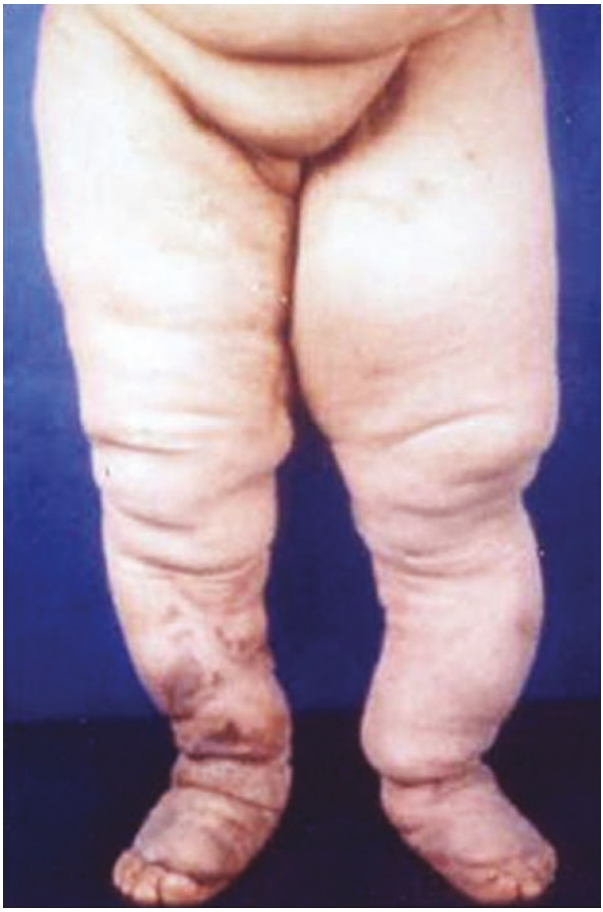

Fig. 54.2 Clinical appearance of the bilateral lower limbs with fully restored normal contour following excisional surgery. The efficacy of DLT was markedly improved postoperatively

Follow-up data of surgical excision patients showed that patient compliance with postoperative DLT was once again confirmed as the single most important factor that determined long-term outcome. Compliant patients maintained successful results, whereas noncompliant patients experienced further deterioration.

Compliance of the patient and the commitment to lifelong DLT are critical in order to achieve satisfactory long-term results. Full integration with DLT-based therapy as a part of a multidisciplinary team approach following surgical therapy is the only means of achieving the most effective control of chronic lymphedema.

Excisional surgery can play a new supplemental role in the non- to poorly responding DLT group of chronic lymphedema patients. As adjunctive therapy in most situations, it plays a critical role in the management of chronic lymphedema together with DLT. Surgery and DLT have mutually complementary effects.

However, at the present time, DLT-oriented treatment is still first-line therapy, although it is not curative. It effectively prevents disease progression and produces a satisfactory outcome in the majority of chronic lymphedema patients who are compliant and maintain self-motivated home treatment following hospital-initiated care [13, 31–33].

Patient compliance with maintenance DLT is the most important factor in the treatment of chronic lymphedema [2, 22]. Prevention and treatment of systemic and/or local infection (e.g., cellulitis, erysipelas) is the next most important factor in the successful management of chronic lymphedema with this combined approach, with excisional surgery reserved for end-stage disease [2, 6, 16–18, 22].

Based on the same principle, percutaneous liposuction was introduced as a less radical surgical approach to avoid the complications and morbidity associated with the traditional excisional technique [34–37].

Instead of resecting all soft tissue with fibrosclerotic overgrowth using a conventional open surgical method, liposuction aims to remove excessive adipose tissue alone in order to obliterate the epifascial compartment by «circumferential» suction-assisted lipectomy. This technique, however, requires more vigorous compression therapy following the procedure to maintain the reduced limb volume.

Initial results of liposuction to remove excessive adipose tissue in the early stage of lymphedema have been reported. Despite excellent efficacy, long-term results, durability, and safety, many hold lingering doubt regarding the risk of collateral damage to the viable lymph vessels system when done in early stage while the remaining lymphatic system still holds substantial lymphatic function on contrary to the end stage [2, 22].

54.2 Conclusion

Excisional surgery is a viable option as supplemental therapy in the treatment of end-stage, intractable lymphedema by improving the efficacy of DLT. Long-term maintenance of satisfactory clinical improvement following the excisional surgery is dependent on patient compliance with DLT/compression therapy.

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Debulking Surgery for Lymphatic Filariasis

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Summary of Basic Concepts

- Lymphatic filariasis is the single largest lymphedema producing disease.
- World's two-third of lymphedemas are due to lymphatic filariasis.
- Multimodality treatment only can give a good result.
- Posttreatment follow-up is a must.
- Avoid reinfection.

The debulking surgical procedure in lymphatic filariasis – lymphedema – is carried out in grade IV lymphedemas with nodules, warty growths, and ulcers. The basic principles in lymphedema surgery are (a) augment the lymphatic drainage using a physiological procedure and (b) reduce the lymphatic load by debulking the lymphedematous, lymph-producing surface. In this chapter, we will be talking about our strategy for lymphedema surgery, followed by a review of the existing forms of debulking surgery [1–16].

Our strategy for debulking is always done after establishing a lymphatic drainage procedure, namely, complete decongestive therapy (CDT) for 1 week, followed by a permanent drainage surgical procedure, such as nodovenal shunt, lymphovenous shunt (LVA), free omental transfer, or *supramicrovascular surgery* of transplanting a myocutaneous flap with arterial, venous, and lymphaticolymphatic anastomosis. Once permanent lymphatic drainage is established, the huge grade IV lymphedema with or without skin changes shrinks, leaving only the subcutaneous fat, fibrous tissue, and the soft tissues like muscle and fascia. We wait for 10–14 days and then debulk the excess skin, fat, and subcutaneous tissue up to the level of the deep fascia under tourniquet control. This debulking surgery may have to be done periodically at a minimum interval of 6 weeks to 3 months, depending upon the entire size of the limb, until near normal shape and size are achieved. We try to use the same skin to resurface without using a split-thickness skin graft (STSG). The same remaining skin with subcutaneous tissues containing the subdermal lymphatics drains the reshaped limb and maintains the contour for a long time with a pressure garment, leg elevation, elimination of the focus of sepsis, and prevention of secondary infection by periodic, cyclic antibiotics like penicillin, doxycycline, and quinolones (ciprofloxacin, ofloxacin, etc.), depending upon the sensitivity pattern of the drug and patient.

The entire outcome of debulking surgery depends upon the methodical preoperative preparation and postoperative follow-up with the abovementioned recommendations. If the patient does not follow the postoperative instructions meticulously, secondary infection can occur. Secondary infection leading to lymphangitis and cellulitis is the main cause of recurrence and progress of lymphedemas. This abovementioned technique has been followed by us for the last 25 years, and we have been able to achieve very good results and maintain the shape and size of the limb in our long-term follow-ups. If any patient comes to us with recurrence or progress of the lymphedema, we repeat a lymphoscintigram and find out the status of the lymphatics, lymph nodes, and drainage. Most were found to have had repeated attacks of lymphangitis due to their negligence and experienced recurrence. We motivate these people again to meticulously follow the conservative, nonsurgical methods like manual lymphatic drainage and CDT, by which most of the patients get better and get back the original shape and size of the limb, and

we maintain it with a pressure garment or bandaging techniques. Very few patients (approximately 5–6%) need a revision surgical procedure, like redoing a nodovenal or lymphaticovenous shunt.

This debulking procedure is always done under tourniquet control to avoid blood loss, hematoma, and infection. The tourniquet can be used safely for 2 h in the lower limb and 1 h in the upper limb. Once the excision is made, the tourniquet is released and perfect hemostasis secured before retaining the suction drain and closing the wound in layers. The incision is always made as a reverse hockey stick on the medial side of the limb. The edges of the skin surface are examined for viability after the excess skin has been trimmed. We always try to go through the same scar for any subsequent reduction surgeries so that patient does not have multiple unsightly scars on the limbs. The excision always stops short of the deep fascia. We never open the deep fascia because it allows the muscle to bulge into the subcutaneous plane and makes wound closure difficult, causing a lot of pain during the postoperative period and even blocking the drains.

The other debulking procedure that has been practiced for a long time is Charles excisional surgery, wherein the lymphedematous tissue (skin, subcutaneous tissue up to the fascia) is excised circumferentially and then STSG is done to cover the raw area. As there is no subdermal plexus for drainage and the STSG is stuck to the fascia, it produces much worse edema distal to the excision, usually in the foot. Because of the unaesthetic outcome and a *bottleneck deformity*, this procedure has almost been abandoned these days. The Kondoleon excision is also technically similar to the Charles procedure; therefore, this technique has also almost been abandoned due to the cobblestone appearance of the operated leg (unaesthetic appearance).

Thomson's procedure was claimed to be a physiological procedure as the de-epithelialized dermal flap is buried under the opposite skin flap and sutured in two layers. The disadvantage of this procedure is that if the dermal flap sutured as a deeper layer becomes necrosed, then the skin closure will not heal. Thus, we have to reopen the flaps and salvage the necrosed skin flap and then provide skin cover. This causes morbidity to the affected limb and it takes a longer time for the leg wound to get settled.

The older techniques of debulking surgeries such as the Thomson, Kondoleon and Charles procedures have been abandoned because of poor outcome. Many patients are scared to undergo surgery after seeing these unsightly results. In many of the centers where debulking surgery is performed for lymphedema, it is always carried out as a secondary procedure, following lymphatic drainage. These days simple elliptical excisions of multiple stages, following a microvascular lymphatic drainage procedure and maintained by conservative multimodality therapies like periodic antibiotics to prevent secondary infections, regular foot hygiene, CDT, and elimination of focal sepsis like caries teeth and intertrigo, followed by pressure garments, provide the most acceptable long-term results.

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From Lymph to Fat: Liposuction as a Treatment for Complete Reduction of Lymphedema

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Summary of Basic Concepts

There need be no tension between those who favor conservative treatment and proponents of liposuction. Accumulated lymph should be removed using the well-documented conservative regimens until minimal or no pitting is seen. If there is still significant excess volume, it can be removed by the use of liposuction. Continuous wearing of a compression garment prevents recurrence.

To date, the author has trained and approved several teams from several countries. Several publications have recently been published showing the same favorable outcome as from our clinic [5, 38–40].

- Excess volume without pitting means that adipose tissue is responsible for the swelling.
- Adipose tissue can be removed with liposuction. Conservative treatment and microsurgical reconstructions cannot do this.
- As in conservative treatment, the lifelong use (24 h a day) of compression garments is mandatory for maintaining the effect of treatment.

56.1 Excess Subcutaneous Adiposity and Chronic Lymphedema

There are various possible explanations for adipose tissue hypertrophy in lymphedema. There is a physiological imbalance of blood flow and lymphatic drainage, resulting in the impaired clearance of lipids and their uptake by macrophages [6, 7]. There is increasing support, however, for the view that the fat cell is an endocrine organ and a cytokine-activated cell [8, 9] and chronic inflammation plays a role here [10–13].

For more information about relationship between slow lymph flow and adiposity, as well as that between structural changes in the lymphatic system and adiposity, see Harvey et al. [14] and Schneider et al. [15].

Other indications for adipose tissue hypertrophy include:

- The findings of increased adipose tissue in intestinal segments in patients with inflammatory bowel disease (Crohn's disease), known as «fat wrapping,» have clearly shown that inflammation plays an important role [10, 16, 17].
- Consecutive analyses of the content of the aspirate removed under bloodless conditions using a tourniquet showed a high content of adipose tissue (mean 90%) [18].
- In Graves' ophthalmopathy with exophthalmos, adipocyte-related immediate early genes are overexpressed, and cysteine-rich, angiogenic inducer 61 may play a role in both orbital inflammation and adipogenesis [19].
- Tonometry can distinguish if a lymphedematous arm is harder or softer than the normal one. Patients with a harder arm compared with the healthy one have excess adipose tissue [20].
- Volume-rendered computed tomography and dual X-ray absorptiometry have shown adipose tissue excess of 81% and 73%, respectively, in the swollen arm and that the deposition starts when the lymphedema appears or soon thereafter [1, 2, 21].

The common misunderstanding among clinicians is that the swelling of a lymphedematous extremity is purely due to the accumulation of lymph fluid, which can be removed by use of noninvasive conservative regimens, such as complete decongestive therapy and controlled

compression therapy (CCT). These therapies work well when the excess swelling consists of accumulated lymph, but do not work when the excess volume is dominated by adipose tissue [22]. The same may apply to microsurgical procedures using lymphovenous shunts and lymph vessel transplantation [23–25], which do not remove adipose tissue.

56.2 The Outcome of Liposuction

Today, chronic non-pitting arm lymphedema of up to 4 L in excess can be effectively removed by use of liposuction without any further reduction in lymph transport [3, 4]. Complete reduction is mostly achieved in between 1 and 3 months. Long-term results have not shown any recurrence of the arm swelling (Fig. 56.1a, b) [22, 26–28]. Promising results also can be achieved for leg lymphedema (Fig. 56.2a, b), for which complete reduction is usually reached at around 6 months [29, 30].

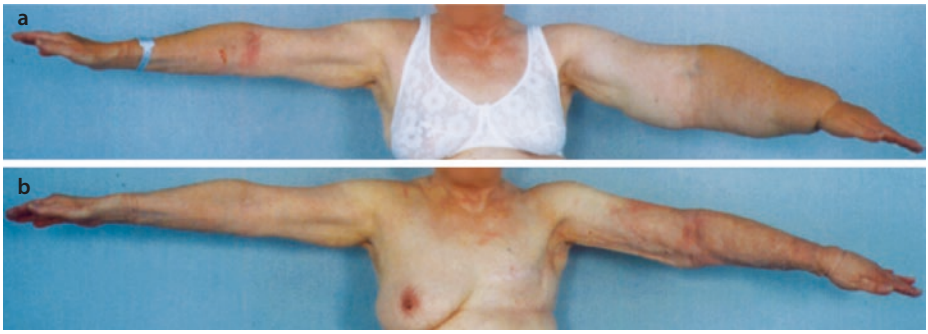

Fig. 56.1 **a** A 74-year-old woman with non-pitting arm lymphedema lasting for 15 years. Preoperative excess volume was 3090 mL. **b** Postoperative result

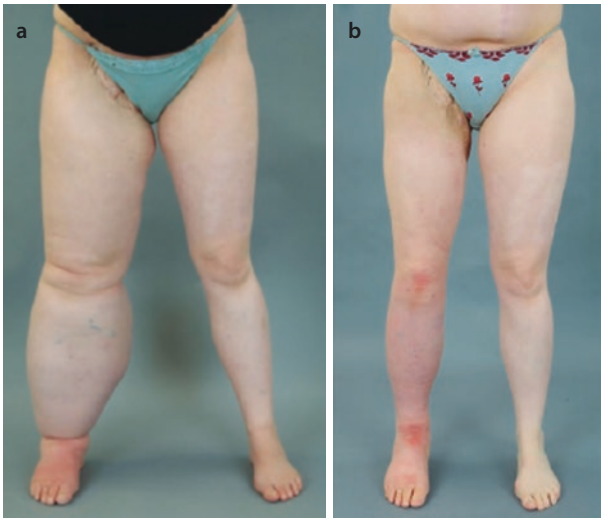

Fig. 56.2 **a** Secondary lymphedema: preoperative excess volume 7070 mL. **b** Postoperative result after 6 months where excess volume is −445 mL, i.e., the treated leg is somewhat smaller than the normal one

56.3 How to Perform Liposuction for Lymphedema

56.3.1 Surgical Technique

Made-to-measure compression garments (two sleeves and two gloves) are measured and ordered 2 weeks before surgery, using the healthy arm and hand as a template.

Nowadays we use power-assisted liposuction because the vibrating cannula facilitates the liposuction, especially in the leg, which is more demanding to treat.

Initially the «dry technique» was used [31]. Later, to minimize blood loss, a tourniquet was utilized in combination with tumescence, which involves infiltration of 1–2 L of saline containing low-dose adrenaline and lignocaine [32, 33].

Through approximately 15–20, 3-mm-long incisions, liposuction is performed using 15- and 25-cm-long cannulas with diameters of 3 and 4 mm (Fig. 56.3). When the arm distal to the tourniquet has been treated, a sterilized made-to-measure compression sleeve is applied (JOBST® Elvarex, BSN medical, compression class 2) to the arm to stem bleeding and reduce postoperative edema. A sterilized, standard interim glove (Cicatrex interim, Thuasne®, France), in which the tips of the fingers have been cut to facilitate gripping, is put on the hand.

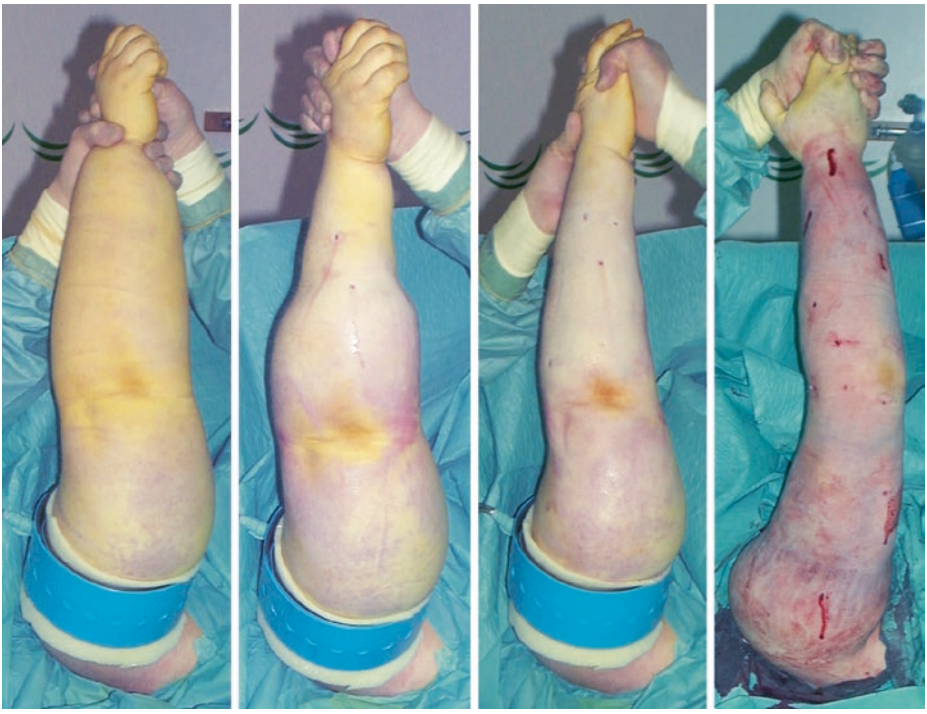

Fig. 56.3 Liposuction of arm lymphedema. The procedure takes about 2 h. From preoperative to postoperative state (*left to right*). Note the tourniquet, which has been removed at the right to show the concomitant reactive hyperemia. Normally the compression garment is put on before release of the tourniquet. Then liposuction is performed on the most proximal part of the upper arm is using the tumescent technique

The tourniquet is removed, and the most proximal part of the upper arm is treated using the tumescent technique [32, 33]. Finally, the proximal part of the compression sleeve is pulled up to compress the proximal part of the upper arm. The incisions are left open to drain through the sleeve. The arm is lightly wrapped with a large absorbent compress covering the whole arm (60 × 60 cm, Cover-Dri, ► www.attends.co.uk). The arm is kept at heart level on a large pillow. The compress is changed when needed.

The following day, a standard gauntlet (a glove without fingers but with a thumb) (JOBST® Elvarex, BSN medical, compression class 2) is put over the interim glove after the thumb of the gauntlet has been cut off to ease the pressure on the thumb. Operating time is, on average, 2 h.

56.3.2 Postoperative Care

Garments are removed 2 days postoperatively so that the patient can take a shower. Then, the other set of garments is put on and the used set is washed and dried. The patient repeats this after another 2 days before discharge. The standard glove and gauntlet are usually changed to the made-to-measure glove at the end of the hospital stay.

The patient alternates between the three sets of garments (two sleeves and two gloves) during the 2 weeks postoperatively, changing them daily or every other day so that a clean set is always put on after showering and lubricating the arm. After the 2-week control, the garments are changed every day after being washed. Washing «activates» the garment by increasing the compression due to shrinkage.

56.3.3 Controlled Compression Therapy

A prerequisite to maintaining the effect of liposuction and, for that matter, conservative treatment is the continuous use of a compression garment [22, 26]. After initiating compression therapy, the custom-made garment is taken in at each visit using a sewing machine to compensate for reduced elasticity and reduced arm volume. This is most important during the first 3 months when the most notable changes in volume occur, but even later it is important to adapt the garment to compensate for wear and tear. This can often be managed by the patient himself or herself. At the 1- and 3-month visits, the arm is measured for new custom-made garments.

This procedure is repeated at 6, 9, and 12 months. If complete reduction has been achieved at 6 months, the 9-month control may be omitted. If this is the case, garments are prescribed for the next 6 months, which normally means double the amount that would be needed for 3 months.

When the excess volume has decreased as much as possible – usually the treated arm becomes somewhat smaller than the normal arm – and a steady state is achieved, new garments can be prescribed using the latest measurements. In this way, the garments are renewed three or four times during the first year. Two sets of sleeve and glove garments are always at the patient's disposal: one is worn while the other is washed. Thus, a garment is worn permanently, and treatment is interrupted only briefly when showering and, possibly, for formal social occasions.

The life span of two garments worn alternately is usually 4–6 months. Complete reduction is usually achieved after 3–6 months, often earlier. After the first year, the patient is seen again after 6 months (1.5 years after surgery) and then at 2 years after surgery. Then the patient is seen once a year only, when new garments are prescribed for the coming year, usually four garments and four gloves (or four gauntlets). For active patients, 6–8 garments and the same amount of gauntlets/gloves a year are needed. Patients without preoperative swelling of the hand can usually stop using the glove/gauntlet after 6–12 months postoperatively.

For legs, the author's team often uses up to two or three compression garments on top of each other, depending on what is needed to prevent pitting. A typical example is Elvarex® compression class 3 (or 3 Forte), JOBST Bellavar® compression class 2 (or Elvarex® compression class 2), and Elvarex® compression class 2 (BSN medical), the latter being a below-the-knee garment.

Thus, such a patient needs two sets of 2–3 garments. One set is worn while the other is washed. Depending on the age and activity of the patient, two such sets can last for 2–4 months. That means that they must be prescribed 3–6 times during the first year. After complete reduction has been achieved, the patient is seen once a year when all new garments are prescribed for the coming year.

56.3.4 Volume Measurements

Volumes of both extremities are always measured at each visit using water plethysmography, and the difference in volumes is designated as the excess volume [22, 26].

56.4 When to Use Liposuction to Treat Lymphedema

A surgical approach, removing the hypertrophied adipose tissue, seems logical when conservative treatment has not achieved satisfactory reduction of the excess volume and the patient has subjective discomfort of a heavy arm or leg.

Liposuction should never be performed in a patient with a pitting edema, as it is dominated by accumulated lymph, which can be removed by conservative treatment.

The first and most important goal is to transform a pitting edema into a non-pitting one by conservative regimens like complete decongestive therapy or CCT. «Pitting» means that a depression is formed after pressure on the edematous tissue by the fingertip, resulting in lymph being squeezed into the surroundings (Fig. 56.4a). To standardize the pitting test, one presses as hard as possible with the thumb on the region to be investigated for 1 min, the amount of depression being estimated in millimeters. A swelling, which is dominated by hypertrophied adipose tissue, shows little or no pitting (Fig. 56.4b) [27].

Around 4–5 mm of pitting in an arm lymphedema and 6–8 mm in a leg lymphedema can be accepted. The reason for not performing liposuction for a pitting edema is that liposuction is a method to remove fat, not fluid, even if theoretically it could remove all the accumulated fluid in a pitting lymphedema without excess adipose tissue formation.

Liposuction improves patients' quality of life [22, 34, 35] and reduces the incidence of erysipelas [36].

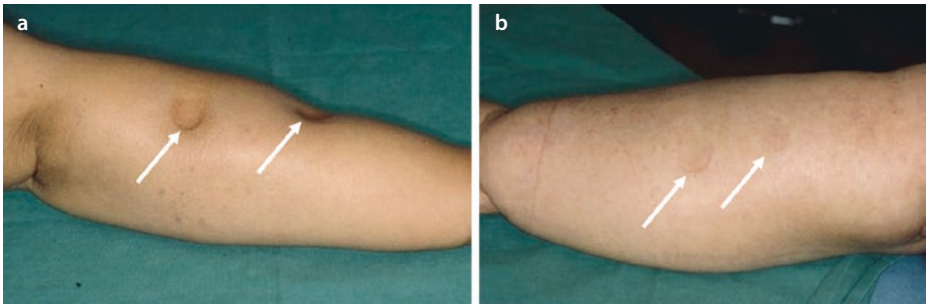

Fig. 56.4 **a** Marked lymphedema of the arm after breast cancer treatment, showing pitting several centimeters in depth (grade I edema). The arm swelling is dominated by the presence of fluid, i.e., the accumulation of lymph. **b** Pronounced arm lymphedema after breast cancer treatment (grade II edema). There is no pitting in spite of hard pressure by the thumb for 1 min. A slight reddening is seen at the two spots where pressure has been exerted. The «edema» is completely dominated by adipose tissue. The term «edema» is unsuitable at this stage since the swelling is dominated by hypertrophied adipose tissue and not by lymph. At this stage, the aspirate contains either no or a minimal amount of lymph

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Surgical Management of Lipedema

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Summary of Basic Concepts

- Liposuction is the primary surgical treatment option for lower extremity lipedema.
- There are various liposuction techniques that can be used in lipedema patients. Most use some form of tumescent anesthesia to decrease blood loss and pain after surgery.
- Patients often require several rounds of liposuction to address all involved areas.
- Compression is used after liposuction to decrease bleeding, maintain intravascular volume, support skin and tissues, improve contour, prevent fluid collections, and facilitate resolution of edema. The duration of compression used postoperatively is variable.
- Potential complications of liposuction include bleeding, infection, prolonged edema or lymphedema, contour irregularities, and anesthetic-related complications.
- Durable improvements in pain, sensitivity to pressure, edema, mobility, cosmetic appearance, and overall quality of life can be achieved with liposuction.

57.1 Introduction

Lipedema is a disorder predominantly affecting females that results in disproportional accumulation of fat in the lower extremities. Most striking are the large cuffs of fat that can be present above the ankles that may mimic the appearance of lymphedema, except that the feet are usually unaffected. Although its cause is unknown, there is empiric evidence suggesting that hormone levels are involved, as onset and exacerbations of lipedema often coincide with puberty, pregnancy, or menopause. Symptoms of lipedema include orthostatic swelling (typically without significant pitting), increased sensitivity to touch or pressure in the affected region, easy bruisability, and gait disturbance secondary to large medial fat pads. Progression of lipedema can lead to immobility, weight gain, and secondary lymphedema (i.e., lipolymphedema) [6–9].

Conservative treatment typically involves compression therapy and manual lymph drainage to minimize symptoms of swelling that most patients experience. However, many patients find little benefit with compression or are unable to tolerate it due to discomfort from the pressure of the garments. Surgical management for lipedema has focused on suction-assisted lipectomy (i.e., liposuction) [10–12]. Liposuction does not reverse the underlying pathophysiology of lipedema, but it does relieve symptoms of tenderness and can improve gait and overall appearance of the legs [1, 10, 13–15].

Liposuction has been reported to decrease the sensitivity of affected tissues in patients with lipedema. The mechanism of this is unknown but may be mechanical in nature as non-lipedema patients typically experience temporary numbness and decreased sensitivity after liposuction in the treated areas. Some authors believe that debulking of medial thigh fat may improve gait and may decrease strain on the knees in patients with valgus deformities, while others feel that overall weight is the main determinant of knee strain leading to osteoarthritis [16].

57.2 Liposuction Techniques

There are numerous forms of liposuction that incorporate different technologies to dislodge and remove fat from subcutaneous tissues. Some of the more popular forms currently in use are listed below:

- *Manual suction-assisted lipectomy (SAL)* – The surgeon manually moves a suction cannula back and forth through the adipose tissue to dislodge and remove the fat.
- *Power-assisted liposuction (PAL)* (e.g., MicroAire®) – The cannula used to aspirate the fat is attached to a reciprocating handle that increases the frequency of the back-and-forth movement of the cannula and facilitates mechanical dislodgment of the fat [1, 17, 18].
- *Ultrasound-assisted liposuction (UAL)* (e.g., Vaser®) – Ultrasonic energy is emitted from the tip of a probe that is passed through the subcutaneous tissue to liquefy fat through vibration and heat. The fat is then removed using a suction cannula. Some surgeons believe that the heat results in some tightening of the overlying skin.
- *Laser-assisted liposuction (LAL)* (e.g., SmartLipo™) – Laser energy is emitted from the tip of a probe that is passed through the subcutaneous tissue to liquefy fat through heat. The fat is then removed using standard suctioning. Like UAL, some surgeons believe LAL can help tighten the skin during liposuction through its thermal effect on collagen [19–21].
- *Water-assisted liposuction (WAL)* (e.g., body-jet® evo) – A pulsating jet of water is ejected from the tip of an irrigation-aspiration cannula to locally tumesce and loosen the fat while simultaneously suctioning. Larger volumes of fluid may be injected because the solution is immediately suctioned out with the fat, which minimizes the distention and distortion of the tissue by the tumescent fluid. This facilitates monitoring the contour of the tissue during surgery to avoid over- or under-suctioning. Some surgeons believe that this technique is less traumatic to lymphatics due to the lack of thermal energy emitted and the greater reliance on water jets, rather than mechanical force from the cannula to dislodge fat [2, 16].

57.3 Tumescent Solution in Liposuction

Liposuction may be done under local anesthesia (with or without sedation) or under general anesthesia. Regardless of which type of anesthesia is used, most surgeons will use some form of tumescent anesthetic solution during liposuction. This has been referred to as the «wet» technique, as opposed to the «dry» technique that does not involve any tumescent fluid injection. Tumescent solution consists of a dilute mixture of a local anesthetic and adrenalin that provides pain relief and vasoconstriction and mechanically facilitates suction of the tissue by distending the tissue with fluid [1, 17, 18, 22, 23].

Different mixtures have been used for tumescent anesthesia. The most commonly used mixtures incorporate a local anesthetic such as lidocaine or prilocaine. These are mixed with normal saline or Ringer's lactate at a dilute concentration of 0.05–0.1%. Adrenalin is added to the mixture in a 1:1,000,000 ratio to provide vasoconstriction, which has the threefold effect of decreasing bleeding, prolonging analgesia, and decreasing toxicity. Normally, when giving prepackaged lidocaine or prilocaine

(at 1–2% concentration mixed with adrenalin at 1:100,000), a total dose of 7 mg/kg is the upper limit for injection. But in the dilute formulation described above, up to 35 mg/kg has been deemed safe to inject. Some surgeons have reported injecting levels up to 50–60 mg/kg without complications [3]. It should be noted that peak serum levels of the local anesthetics may not occur until 12–18 h after administration, and surgeons and patients should be aware of symptoms of toxicity (discussed below).

Additional ingredients may also be added to the solution. Sodium bicarbonate 8.4% is often added in a 1:10 ratio to the local anesthetic to lower the pH. This has the dual effect of decreasing pain of injection and prolonging the anesthetic effect. Some surgeons will also add a small amount of triamcinolone at 10 mg/L to decrease inflammation.

Once injected, the solution increases the tissue turgor (i.e., tumescence), which facilitates lipoaspiration. The main drawback of tumescent anesthesia is the potential for anesthetic toxicity if large amounts are used. This also limits the total volume of lipoaspirate that can be removed when using solely tumescent anesthesia. Lipoaspirate is the mixture of fat along with tumescent solution and blood that is removed through suction. It is generally considered safe to remove five liters of lipoaspirate in the outpatient setting using standard tumescent anesthesia. Certain techniques, such as water-assisted liposuction, may involve injecting and aspirating more fluid because of how suctioning is performed (i.e., simultaneous tumescent injection and suctioning), which decreases the amount of anesthetic absorbed. Regardless of technique, this usually equates to 2–4 liters of actual fat being removed. The addition of intravenous sedation or general anesthesia may allow greater volumes to be removed; however, when larger volumes of fat are removed, internal fluid shifts may require intravenous fluid hydration and inpatient monitoring to ensure adequate fluid resuscitation [1, 18, 23].

Typically, two to four sessions of tumescent liposuction are required to adequately treat multiple areas.

57.4 Dry Technique

Dry liposuction involves liposuction without the use of tumescent solution. It has been associated with greater blood loss, postoperative pain, and complications. Greater lymphatic injury may occur, especially when performed in a horizontal manner compared to longitudinal [2, 24]. Additionally, there have been accounts of long-term pain and numbness at the surgical site associated with the dry technique [25]. The dry technique is used in some patients with advanced lymphedema by implementing a tourniquet to decrease bleeding [26]. However, this technique is not applicable to the proximal extremities or trunk [4]. This technique is not usually used for treating lipedema.

57.5 Skin Excision

Selective skin excision may be helpful in addressing excess skin after liposuction. Care should be taken to avoid excising the major lymphatic collectors in the medial thigh and inguinal region and the medial upper arm [27–34].

57.6 Perioperative Management

Complications after liposuction are rare. Most common are minor contour irregularities. Deep vein thrombosis (DVT) or pulmonary embolus after large-volume liposuction has been reported at rates between 0 and 1.1%. Many surgeons give DVT prophylaxis during and after surgery, especially if there is a history of venous insufficiency or if liposuction is being performed under general anesthesia. Infection rates are low and overall mortality has been reported as 1 in 47,415 [35]. Despite low infection rates, many liposuction surgeons will still give antibiotic prophylaxis after surgery until incisions stop draining. Early ambulation should be encouraged to avoid venous stasis and to encourage resolution of edema. Patients should remain well hydrated and encouraged to drink fluids postoperatively.

57.7 Postoperative Compression

Compression is used postoperatively in liposuction to decrease bleeding, maintain intravascular volume, support skin and tissues, improve contour, prevent seromas (fluid collections), and facilitate resolution of edema. Due to the dependent location of the lower extremities, swelling can be prolonged, especially after suctioning in the calf and ankle region. Manual lymph drainage can be helpful in mobilizing edema from the lower extremities and may commence once tenderness resolves, usually within 2–3 weeks of surgery. Prolonged compression, often for several months, may be required, and patients should be counseled to continue compression therapy and manual lymph drainage until edema has resolved [1, 5]. Proper garment fit is also important, and patients should be measured and fitted prior to surgery.

57.8 Patient Selection and Surgical Planning

Patient selection is important for any surgical procedure. Patients should understand the goals of surgical management. Liposuction should decrease the sensitivity of fat in the regions treated and can result in an improvement in contour. Liposuction will not take care of excess skin, and patients with poor skin elasticity should expect that skin irregularities or excess may be more apparent after liposuction. Excess skin may be amenable to excision; however, this should be done with caution, as indiscriminate excision of skin and soft tissue may damage lymphatic pathways and lead to prolonged swelling or permanent lymphedema. Patients should be reminded that weight loss is not a prime objective of liposuction [33].

57.8.1 Venous Stasis Disease

Varicose vein disease can be associated with lipedema, though treatment guidelines for varicosities in these patients are not well established. Preoperative evaluation involves assessment of the venous system with duplex ultrasound examination to rule out venous

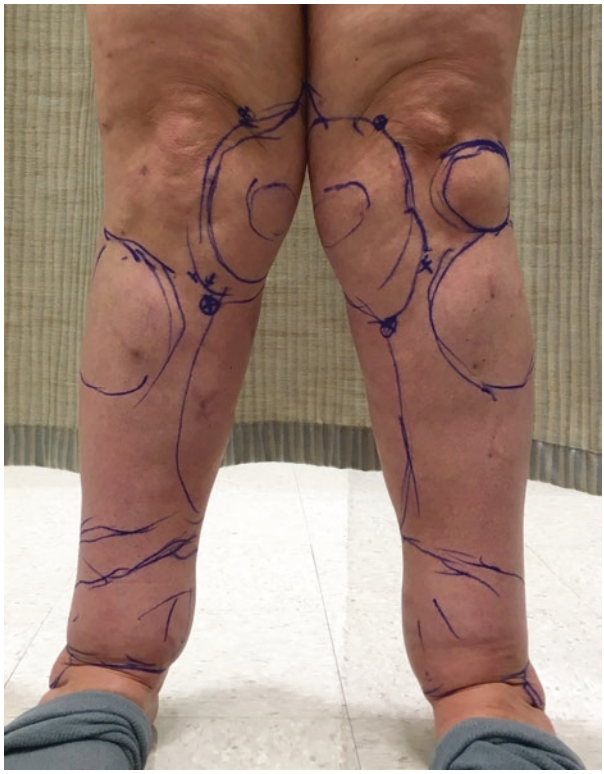

Fig. 57.1 Preoperative markings for liposuction

insufficiency, which may contribute to prolonged swelling and a risk of bleeding during or after surgery. Mild venous insufficiency can be treated with endovascular techniques and surgical ligation of venous perforators. Moderate-to-severe venous insufficiency with edema is a relative contraindication to liposuction in the lower leg as swelling can be prolonged or permanent after surgery [36, 37]. A study by the Földi Clinic showed that treatment of varicose veins did not help most patients with lymphedema or lipedema; however, many surgeons still prefer to treat superficial venous insufficiency prior to performing liposuction [37]. Guidelines for liposuction in the presence of lymphedema are different, and one should refer to the chapter in this textbook by Brorson that describes liposuction for lymphedema (Fig. 57.1).

57.9 Contraindications

The main contraindications for surgery are unmanaged medical conditions, limb ischemia, cardiovascular or pulmonary insufficiency, active smoking, bleeding disorders, and anticoagulation therapy. Patients with lymphedema should be counseled on the fact that liposuction will not reverse lymphedema, and lifelong compression will be required to maintain any improvement after suctioning. Patients with congenital methemoglo-

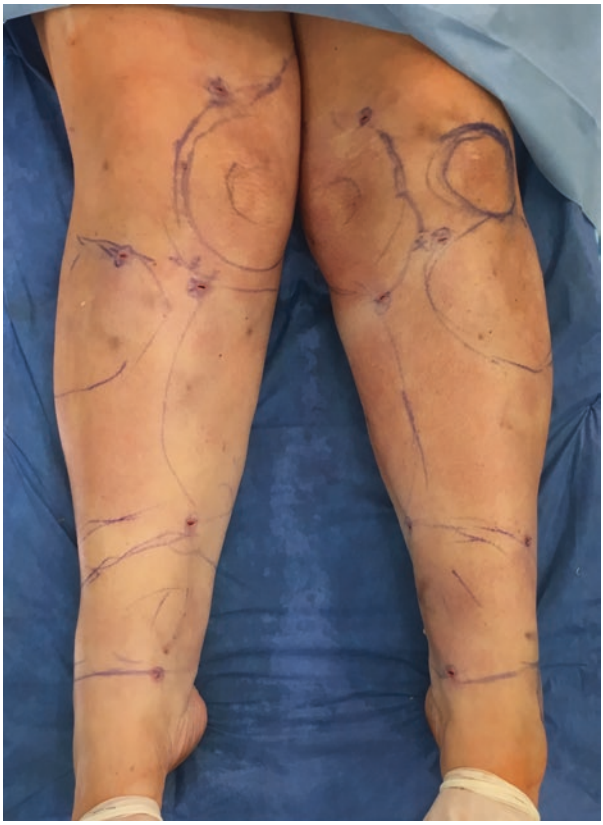

Fig. 57.2 Intraoperative view after suctioning under local anesthesia with WAL

binemia or taking known oxidative medications, such as trimethoprim-sulfamethoxazole, are at increased risk for methemoglobinemia, especially when using prilocaine, and should be carefully monitored during and after surgery for at least 24 h. Methylene blue can reduce methemoglobin and should be available if needed [3, 38] (Fig. 57.2).

57.10 Complications

Complications after liposuction can be classified as surgical or medical. Surgical complications include bleeding, infection, seroma, DVT, pulmonary embolus, organ perforation, and contour irregularities [22, 39]. Medical complications may be secondary to fluid shifts or anesthetic levels. Anesthetic reactions include CNS depression, seizures, cardiac arrhythmias, methemoglobinemia, and allergic reactions [3, 20, 38] (Fig. 57.3).

All liposuction techniques can result in lymphatic injury, especially when performing liposuction along major lymphatic pathways such as the inner knee and thigh. Compromise of lymphatic vessels can be especially problematic in patients with advanced lipedema or lipolymphedema [40].

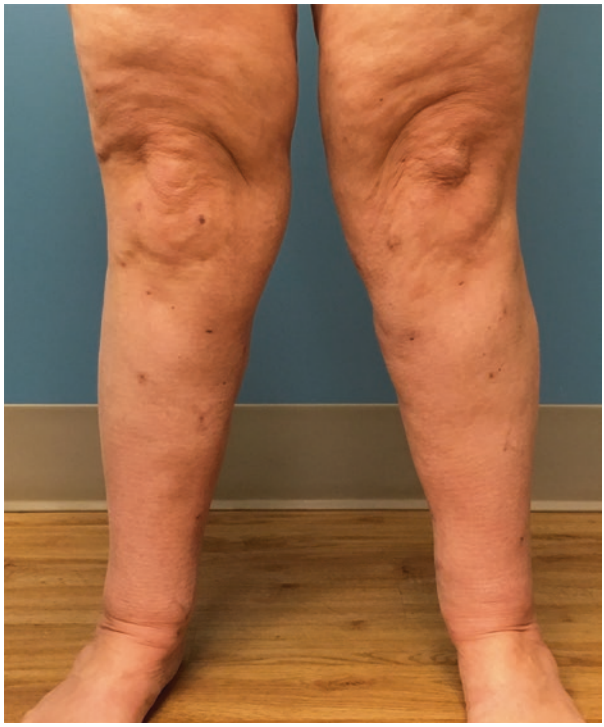

Fig. 57.3 Four weeks postoperatively with resolving edema

57.11 Long-Term Expectations After Surgical Treatment

Although there have only been limited reports of long-term outcomes postoperatively after treatment of lipedema with suction-assisted lipectomy and/or excisional procedures, most patients and surgeons report sustained improvement after surgery. Specifically with liposuction, durable improvements in pain, sensitivity to pressure, edema, mobility, cosmetic appearance, and overall quality of life can be achieved in lipedema patients. No correlations have been demonstrated between degree and durability of symptom improvement and amount of adipose tissue removed, age, duration of disease, and length of conservative therapy [5, 40, 41]. There has been reported correlation of symptomatic improvement based on stage of lipedema, with greater improvements seen in those with more severe stage lipedema [5].

57.12 Closing Comments

It is important for surgeons treating lipedema patients to have appropriate training prior to undertaking surgical intervention. In particular, they should be familiar with the condition, its conservative and surgical management, and the indications and contraindications for surgery.

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Congenital Vascular Malformation with Lymphatic Involvement

Contents

General Overview

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Summary of Basic Concepts

- Congenital vascular malformations are structural anomalies that develop during vascular morphogenesis.
- Combined vascular malformations may present as single component lesions or mixed component lesions with capillary, lymphatic, venous, or arterial malformations.
- The hemolymphatic malformation is a combined vascular malformation that has both venous malformation and lymphatic malformation components.
- The treatment strategy for hemolymphatic malformations can be classified in three major categories: conservative therapy, endovascular therapy, and surgical excision.
- A retrospective review by Byung-Boong Lee, who discusses various diagnostic testing and treatment strategies in managing congenital vascular malformations: 1007 patients were retrospectively reviewed, of which 333 patients underwent embolosclerotherapy with very favorable results. These patients were selected for treatment based on their institutional guidelines for indication for treatment. They report immediate success rate of 96.2% and failure rate of 3.8%. However, they also report a high complication rate of 34%. Two thirds of the complications were minor complications such as skin bullae, necrosis, and erythema.
- Klippel-Trenaunay syndrome is a rare, sporadic, vascular malformation characterized by capillary malformations, soft tissue and bone hypertrophy, and venous varicosities. This review article by Gloviczki outlines the etiology of the disease, variations in clinical presentation, diagnostic methodology, and treatment modalities and highlights the importance of multidisciplinary approach to management of this rare condition.
- This article discusses the changing practice in management of congenital vascular malformations over the years. This article highlights the importance of multidisciplinary approach to the management of congenital vascular malformations and the integration of traditional surgical therapy with endovascular therapy.
- This is a systematic review of current date on percutaneous sclerotherapy for patients with congenital vascular malformations. Excluding the two comparative studies, the data reviewed are mostly case series. The article concludes that ethanol sclerotherapy is effective but has 16% major complication rate including deep tissue injury, deep venous thrombosis, and nerve injury. Most common complications seen are skin necrosis, hematuria, skin lesions, and edema. The data on OK-432 as a sclerosant is promising for lymphatic malformations but needs more data.
- This is a recent evaluation of surgical outcome of patients with Klippel-Trenaunay syndrome. All the patients in the study underwent open venous surgery, which was then compared to endovascula r therapy. Seventy-five percent of the patients remained free of disabling pain at 5 years. Twenty-five percent of patients required secondary procedures. The outcome was comparable to the patients who underwent endovascular surgery during the same time period.

58.1 Introduction

Congenital vascular malformations (CVMs) are structural anomalies that occur during vascular morphogenesis. As defined by Mulliken and Glowacki, they are collection of structurally anomalous vessels [6]. Vascular malformations are subcategorized on the basis of architectural anomaly as slow-flow anomaly (capillary, lymphatic, or venous) and fast-flow (arterial) [7]. Often times these structural anomalies can contain combined elements, further complicating the management of these lesions. Though it may not always be apparent, CVMs are always present at birth. CVM is a rare entity with reportedly less than 1% of the babies born worldwide are affected. Worldwide incidence of lymphatic malformations is 0.5% [8].

58.2 Classification

Under the umbrella of fast-flow and slow-flow anomalies, CVMs are further classified by vessel type according to the Hamburg classification (Table 58.1a, b) [1, 9–12]. Combined vascular defects can contain any components of capillary, lymphatic, venous,

Table 58.1a Hamburg classification[a] of congenital vascular malformations (CVMs): Types

Arterial defects
Venous defects
AV (arteriovenous) shunting defects
Lymphatic defects
Capillary defects
Combined vascular defects

[a]The modified classification of the original classification, which was established based on the consensus on CVM through the international workshop in Hamburg, Germany, 1988.

Table 58.1b Hamburg classification of CVMs[a]: Forms – Embryological subtypes

1. Extratruncular forms Diffuse, infiltrating Limited, localized
2. Truncular forms Stenosis or obstruction Hypoplasia; aplasia; hyperplasia Membrane; congenital spur Dilatation Localized (aneurysm) Diffuse (ectasia)

[a]Represents developmental arrest at the different stages of embryonic life:
Earlier stage – Extratruncular form
Later stage – Truncular form. And both forms may exist together.

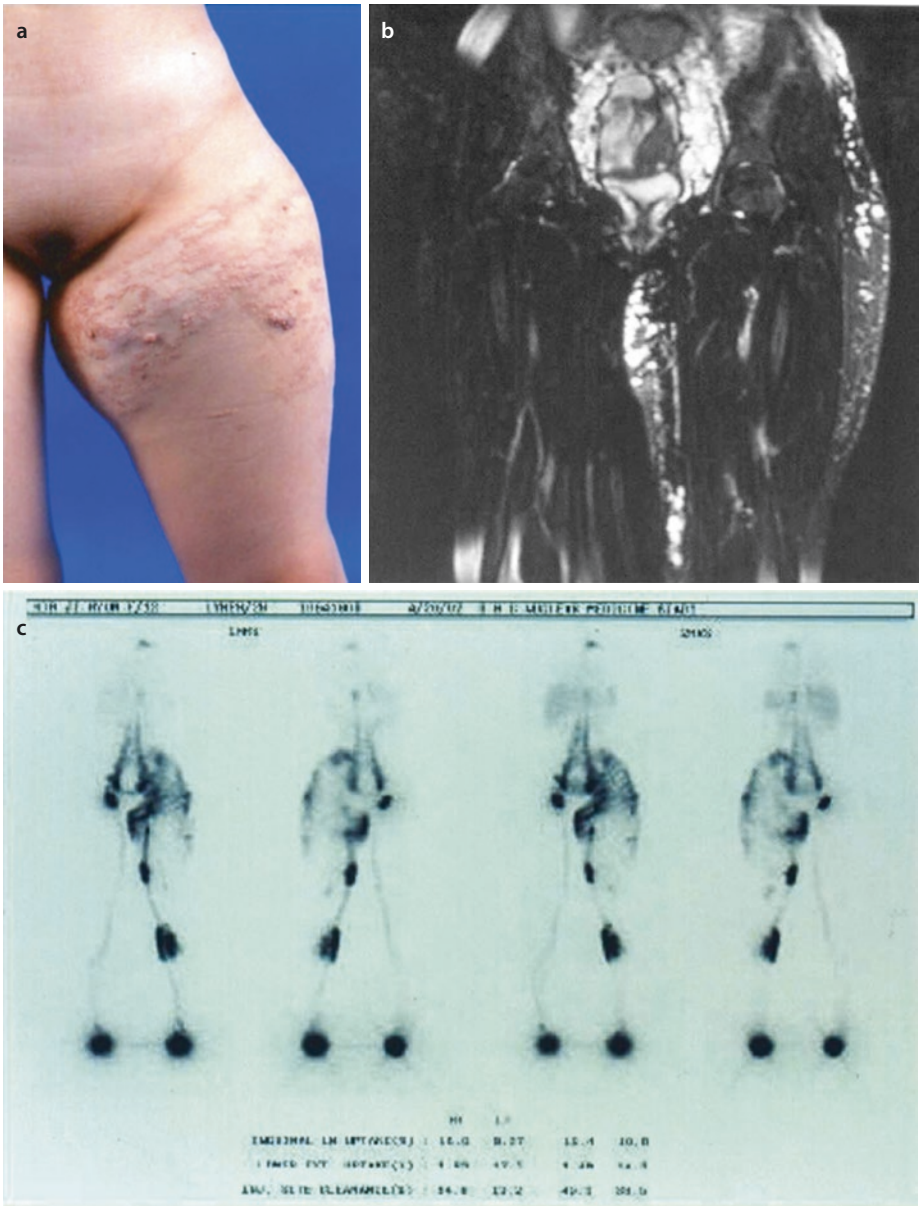

Fig. 58.1 **a** shows a typical infiltrating «extratruncular» lymphatic malformation (LM) lesion affecting the left groin and left upper leg as a diffuse swelling. This visible lesion involving the groin as a boggy soft mass is actually the tip of the iceberg of quite extensive deep-seated lesion extended into the pelvic/retroperitoneal soft tissue structure. **b** (MRI findings) depicts its extent of the involvement throughout the intrapelvic as well as upper part of the left lower extremity. **c** (radionuclide lymphoscintigraphy) delineates not only the extratruncular LM lesion shown in **b** but also shows abnormal condition of lymph vessels of the lower extremity as a mild form of dysplastic development (truncular lesion)

or arterial malformations. Each class of vascular can be divided in subtypes of «extratruncular» and «truncular» malformations. Extratruncular vascular malformations arise when developmental arrest has occurred during the reticular stage of embryonic development [8, 9].

Truncular vascular malformations arise when developmental arrest has occurred during vascular trunk formation at the later stage of embryologic development [8, 9]

The hemolymphatic malformation (HLM) is a combined CVM that has both venous malformation (VM) and lymphatic malformation (LM) components [9]. Some of these diseases include Klippel-Trenaunay syndrome (KTS), Parkes Weber syndrome, and Maffucci syndrome (Fig. 58.1a–c).

58.3 Embryology

Formation of the vascular system consists of two phases: vasculogenesis and angiogenesis. Vasculogenesis starts with a primitive vascular plexus formed from endothelial precursors, which is attached to the developing heart. The primary circulation is then formed by the end of the third gestational week. This is then followed by angiogenesis, where new vessels are formed by propagation and proliferation of endothelial cells [13].

The lymphatic system begins to develop at the end of the fifth week as an endothelial outgrowth from the venous system [12]. Extratruncular lesions arise when developmental arrest occurs while the vascular system is in the reticular stage. Extratruncular lesions are, therefore, embryonic tissue remnants of mesodermal origin that retain the characteristics of the mesenchymal cells. It retains the potential to grow and proliferate when stimulated internally (e.g., menarche, pregnancy, and hormone) or externally (e.g., trauma, surgery). These lesions, therefore, continue to grow at a rate that is proportional to the growth rate of the body and carry a significant risk of a recurrence, especially after suboptimal treatment [14–17]. Extratruncular lesions remain amorphous clusters of lymphatic tissues independently with no direct involvement of matured vessels. They often present as either a diffuse infiltrating lesion or a limited lesion causing mechanical compression to surrounding tissues and organs (Fig. 58.1a–c).

Truncular lesions arise during vascular trunk formation, later in the embryonic development. These lesions lost the embryonic characteristics of the mesenchymal cells along with the potential to grow and proliferate unlike extratruncular lesions. However, truncular lesions often produce more serious lymphodynamic consequences since all truncular lesions present as a part of «formed» vessel with varying degrees of developmental defects ranging from incomplete or immature lesions (aplasia or hypoplasia) to overdeveloped lesions (hyperplasia) [13–16]. All truncular lesions are, therefore, associated with varying degrees of involvement of the systemic circulation often involving the native vasculature, lymphatic system, and lymph nodes (Fig. 58.2a–c).

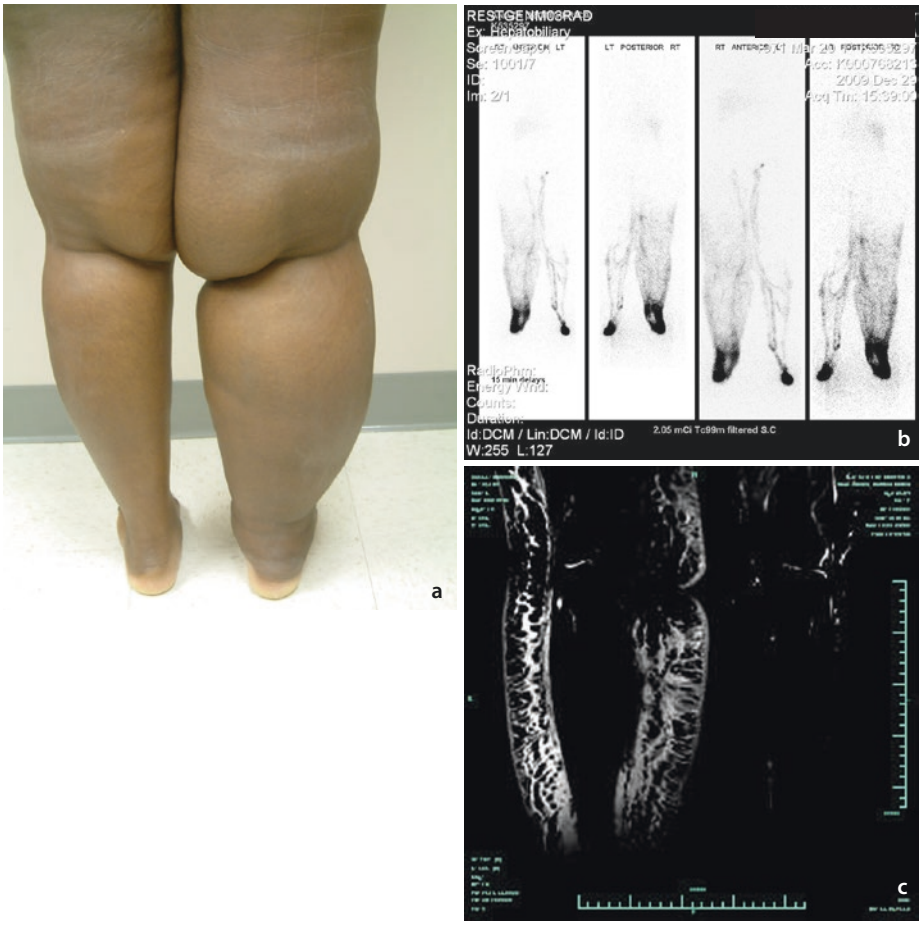

Fig. 58.2 **a** shows diffusely swollen right lower extremity as a clinical manifestation of primary lymphedema. It is the outcome of truncular lymphatic malformation (LM) as hypoplasia of the lymph-transporting vessel. **b** (radionuclide lymphoscintigraphy) depicts abnormal/poorly compensated lymph-transporting status affecting entire right lower extremity; it shows a diffuse dermal backflow due to the lymphatic obstruction/stasis secondary to the truncular LM. **c** (MRI findings) renders typical MR findings of lymphedematous fluid accumulation throughout entire soft tissue of the extremity. Such honeycomb-type image of the soft tissue is the hallmark of chronic lymphedema to confirm clinically observed diffuse swelling of the limb as lymphedema

58.4 Presentation and Diagnosis

Diagnosis of CVMs can be made based on history and physical examination alone; however imaging does have a key role in identification of the lesion [18]. Lymphaticovenous malformations are noted as most common bases for craniofacial abnormalities such as macrocheilia, macroglossia, macrotia, and macromelia [18]. Physical exam should be followed by duplex ultrasound imaging to help delineate the patency of the venous system and identify the underlying aberrant anatomy such as hypoplasia, atresia, aneurysms, or persistent embryonic veins.

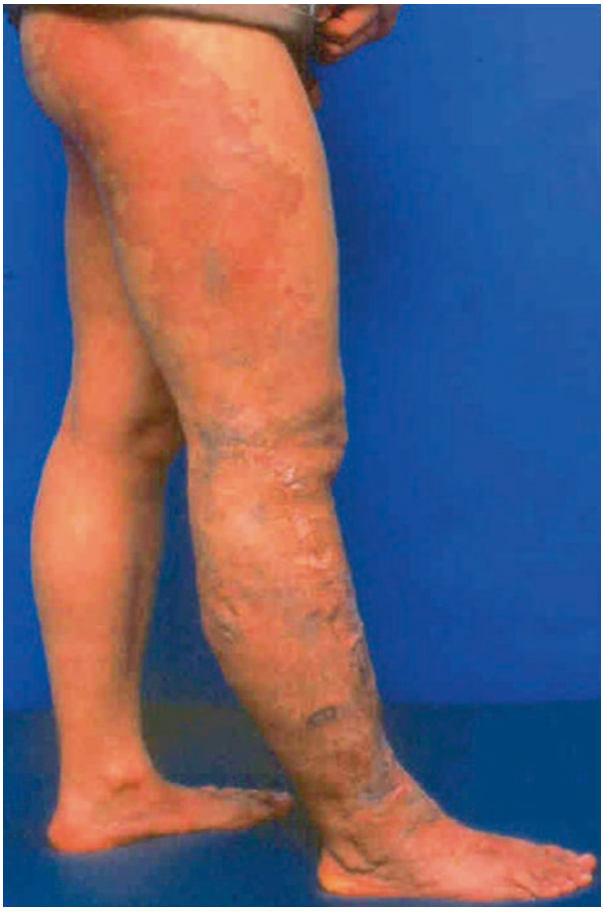

Fig. 58.3 **a** shows a clinical condition of diffusely swollen right lower extremity representing Klippel-Trenaunay syndrome (KTS); its vascular malformation component is a mixed clinical condition of the VM (*venous malformation*), LM, and CM (*capillary malformation*), classified to «hemolymphatic malformation»

Magnetic resonance imaging (MRI) is a valuable tool in characterizing various vascular malformations. MRI allows assessment of lesion extent, severity, and anatomic relationship with the surrounding tissues and organs [1, 9]. It can differentiate between the muscle, bone, fat, and vascular tissue without the need of radiation or nephrotoxic intravenous contrast. Axial, coronal, and sagittal images can be generated and gadolinium enhancement produces high-resolution angiography (Fig. 58.3a).

Computed tomography (CT) imaging with high-resolution three-dimensional reconstruction allows assessment of vascular lesion extent, severity, and anatomic relationship with the surrounding tissues and organs. The quality of the imaging is usually adequate for planning treatment.

Contrast venography of the lower extremity allows complete evaluation of the venous system and assessment of patency, venous stenosis, occlusion, aberrant anatomy, and presence of collateral venous circulation [1, 9]. Direct puncture phlebography of the malformation allows the diagnosis or exclusion of an AVM and assessment of the lesion and its relationship to the lower extremity venous and arterial vasculature. When treatment is indicated, endovascular therapy can also be performed at the time of venography and direct puncture phlebography [1, 9].

Other imaging modalities that may be helpful are whole body blood pool scan (WBBPS), radionuclide lymphoscintigraphy, and ultrasound studies.

58.5 Klippel-Trenaunay Syndrome

Klippel-Trenaunay syndrome (KTS), also known as capillary-lymphaticovenous malformation, was originally described by French physicians, Maurice Klippel and Paul Trenaunay in 1900, based on observations in two patients with hemangiomatous lesions of the skin associated with asymmetric soft tissue and bone hypertrophy – «naevus variqueux osteohypertrophique» [19]. KTS occurs spontaneously, and there is no known genetic or familial linkage with equal gender distribution [18].

Patients present with its classic triad of port-wine stains, lower extremity soft tissue and bone hypertrophy, and lower extremity varicose veins. Patients with at least two of the three cardinal features have been classified as having an incomplete form of KTS [18]. Limb hypertrophy observed at birth progressively worsens with growth [20].

LM lesions observed in KTS patients include primary lymphedema and lymphangectasia (truncular LMs), as well as skin vesicles draining lymph fluid and cystic hygromas (extratruncular LMs) [20–22].

The severity of vascular lesions and symptoms observed in KTS patients can vary widely from those with an incomplete form of KTS with mild, asymptomatic port-wine stains and few varicose veins causing only minor cosmetic problems to patients with severe disability associated with massive limb overgrowth, chronic pain syndrome, skin infections, thromboembolism, and life-threatening pelvic or recurrent rectal bleeding from symptomatic VMs [18, 20, 21].

58.6 Maffucci Syndrome

Maffucci syndrome is an extremely rare disorder characterized by cutaneous VMs and long bone enchondromas [23]. It is associated with IDH1/IDH2 gene mutation. The progression of enchondromas can cause bony deformities, and these patients often present with pathologic fractures [25]. The cutaneous vascular malformation occurs in childhood as compressible, bluish venous malformations. These lesions can give rise to spindle cell hemangioma over time. These patients are also at risk for developing chondrosarcoma and other malignancies [24].

58.7 Parkes Weber Syndrome

Parkes Weber syndrome is a fast-flow capillary-lymphatico-arteriovenous malformation involving lower limbs and proximal trunk. It is associated with RASA-1 mutation, and patients present with multiple cutaneous staining with underlying microarteriovenous fistulas with or without lymphedema [25].

58.8 Other Associated Conditions

PTEN hamartoma syndrome, also known as Bannayan-Riley-Ruvalcaba syndrome, is characterized by macrocephaly, multiple lipomas, hamartomatous polyps of distal ileum and colon, Hashimoto thyroiditis, pigmented penile macules, and vascular anomalies [26]. It is an autosomal dominant condition with a mutation in tumor suppressor gene PTEN. Cowden syndrome is a spectrum of disease seen under the same genetic mutation.

CLOVES syndrome (congenital, lipomatous, overgrowth, vascular malformations, epidermal nevi, and spinal/skeletal anomalies) presents with trunk, retroperitoneal, pelvic, and extremity fatty masses with lymphatic involvement [27]. Patients also present with capillary and arteriovenous malformations in the trunk, extremities, and paraspinal region [28].

58.9 Treatment of Hemolymphatic Malformation Lesions

Treatment strategy for HLMs can be classified in three major categories: conservative therapy, endovascular therapy, and surgical excision. Incomplete lesion excision is usually followed by recurrence and may become a potential source of significant complication and morbidity [3]. Treatment should be approached in multidisciplinary fashion and often combining multiple elements of treatment modalities. Multidisciplinary team often involves some combination of a vascular surgeon, orthopedic surgeon, plastic surgeon, head and neck surgeon, interventional radiologist, physiatrist, and physical therapist.

Absolute surgical indications for treatment of HLM lesions include hemorrhage, infection, acute thromboembolism, and refractory venous ulcers [21, 30]. Relative indications for treatment include pain, functional impairment, chronic venous insufficiency, limb asymmetry due to vascular bone syndrome, or cosmetic reasons [21, 30].

58.10 Conservative Treatment

Options are limited in terms of conservative management, which usually involves observation and some level of compression therapy if the patient has a truncular lesion [30]. Compression therapy is beneficial in treating both lymphedema and chronic venous insufficiency associated with LM and VM lesions. Compression garments should be initiated at an early age to improve later compliance and should be tailored for the patient by an experienced practitioner, with close attention to areas of the malformation that are symptomatic [20, 21, 23]. Patients require new garments at least twice per year to ensure adequate fit and therapeutic benefit. Garments are also an important adjunct postsclerotherapy. In addition, compression bandaging, manual lymphatic drainage, and intermittent pneumatic compression therapy have all been shown to be

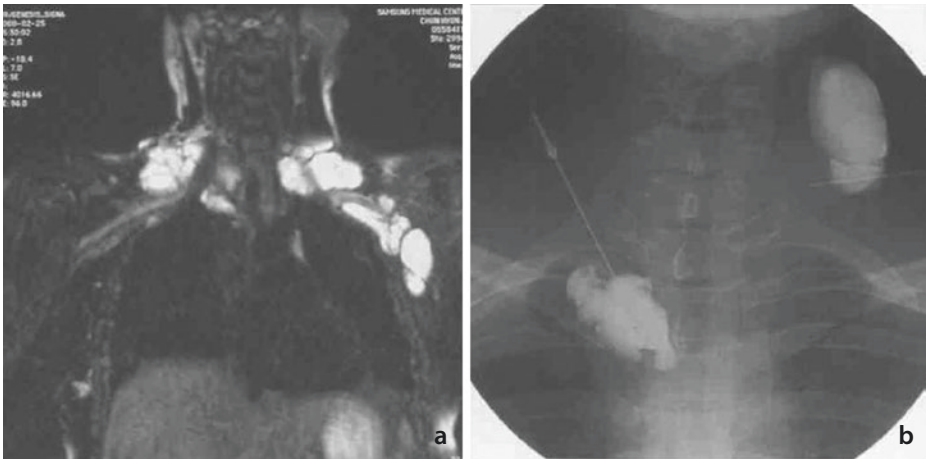

Fig. 58.4 **a** represents extensive «extratruncular» lymphatic malformation (LM) lesions affecting cervicothoracic region on both sides. They are consisted of microcystic and macrocystic lesions of de novo as well as recurrent natures following the surgical attempt to remove them. **b** shows one of the macrocystic LM lesions delineated by transcutaneous direct puncture approach for subsequent ethanol sclerotherapy. In view of its recurrent nature following other weaker form of sclerotherapy (e.g., bleomycin), it was treated with the ethanol

effective treatments in the management of both lymphedema and swelling due to chronic venous insufficiency [20, 30].

Some of the more novel concepts for treatment of CVMs are exogenous growth factor administration. Though not currently available for treatment, new studies have shown that anti-VEGFR-3 neutralizing antibody specifically inhibits lymphovascular regeneration [29–32] (Fig. 58.4a, b).

58.11 Endovascular Therapy

Endovascular therapy is preferred over traditional surgical excision alone in the treatment of HLMs [4, 30]. Sclerotherapy involves the injection of a sclerosant into the lumen of a vascular malformation. This chemical causes destruction of endothelium resulting in inflammation with thrombosis and fibrosis within the vascular lesion [34–36]. Sclerotherapy with absolute alcohol, sodium tetradecyl sulfate, polidocanol, and OK-432 have been used alone or in combination for the treatment of VM and LM lesions [33, 34].

Combining conventional sclerotherapy with coil and/or chemical embolization therapy may improve the efficacy of HLM treatment. Sclerotherapy and embolization are often performed as an adjunct to surgical excision of large venous malformations

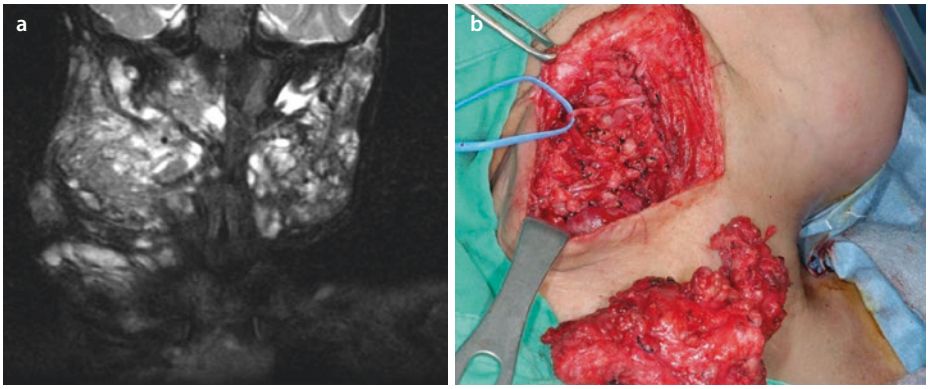

Fig. 58.5 **a** depicts MRI findings of extensive «extratruncular» lymphatic malformation (LM) lesions infiltrating along the entire upper neck soft tissue. Due to its proximity to the upper airway threatening the respiration during the acute swelling episode (e.g., *upper airway infection*), the lesion on the right neck was surgically excised first as shown in **b**

[34–36]. N-butyl cyanoacrylate and onyx are the two most commonly used liquid embolization agents [36].

In addition, endovenous thermal ablation utilizing radiofrequency or laser energy in the treatment of venous insufficiency in KTS patients has been reported [35–38]. Endovenous thermal ablation has been used in the treatment of symptomatic venous insufficiency in KTS patients [2, 37–39]. Frasier et al. reported their treatment results of radiofrequency ablation of the great saphenous vein performed in three female KTS patients with symptomatic lower extremity varicose veins and venous insufficiency [37]. There were no complications, and all three patients experienced improvement in their varicose veins and improvement in pain and leg edema (Fig. 58.5a, b).

58.12 Surgical Therapy

Surgical resection of HLM is usually the last line of treatment modality [30]. Because these malformations are not malignant, a complete excision is not necessary, and instead the care should be taken to preserve the vital structures and no inadvertent injuries are done. However it is important to note that reoperations will be difficult. It is important to discuss with the patient that he or she may need multiple operations to achieve the desired contouring of the tissue [5]. Drains should be left behind to account for lymphatic leak [39] Fig. 58.6a. In select patients, open surgical treatment can be a safe and durable option with comparable outcomes compared to endovascular therapy [5].

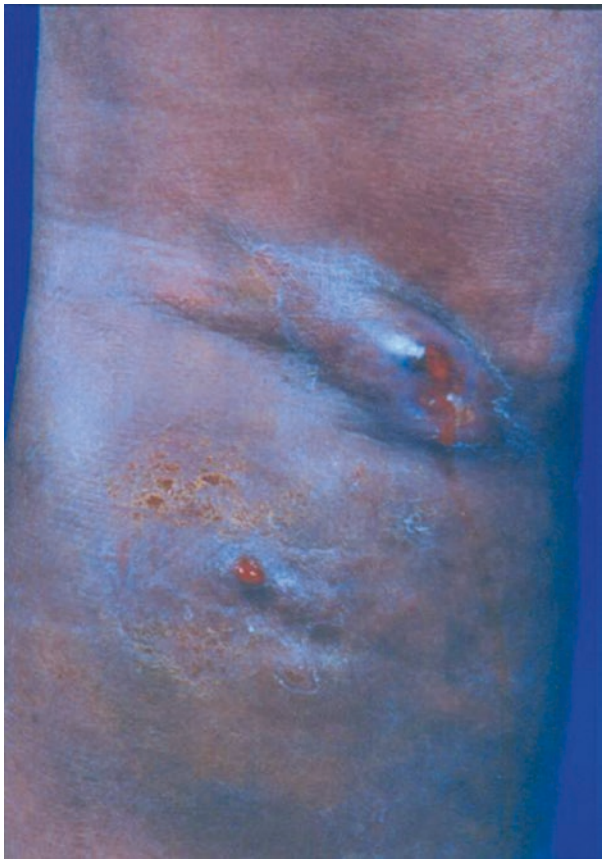

Fig. 58.6 **a** shows intermittent lymphatic leakage from the extratruncular LM lesions combined with the extratruncular VM lesion affecting left lower extremity, which is infrequently complicated by the subsequent infection

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Primary Lymphedema and Lymphatic Malformation

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Summary of Basic Concepts

Lymphatic malformations in primary lymphedema may involve lymphatic and/or lymph node. Primary lymphedema should not be managed as a chronic lymphedema without consideration of its background as a congenital vascular malformation.

Primary lymphedema is defined as edema caused by lymphatic dysplasia and/or dysfunction due to congenital [6, 7] or unknown factors. Primary lymphedema occurs in 1 of every 10,000 people in the general population [8]. A recent study in author's clinic showed that primary lymphedema accounted ~27% of the 3252 lymphedema cases in the last 2 years in author's lymphology clinic of Shanghai Ninth People's Hospital (unpublished data).

59.1 Classification

1. According to the Onset Time, Primary Lymphedema is Classified as:
   1. Congenital: Lymphedema occurs at birth or a few months after birth, which accounts for 10% of total incidence.
   2. Praecox: The onset of the disease during early childhood and adolescence before the age of 35, which accounts for 71% of total incidence.
   3. Tarda: Lymphedema occurs after age 35, which accounts for 19% of total incidence.
2. According to the Clinical Manifestations:

The clinical manifestations of primary lymphedema are variable. It most commonly occurs in one lower extremity, but may affect both lower limbs. The relatively rare types of primary lymphedema are edema in unilateral upper extremity, semi-face, and external genitals alone. In general, external genital lymphedema is mostly associated with edema of lower limb(s). In very rare case, lymphedema occurs in multisites as ipsilateral face, upper and lower limbs, or contralateral upper and lower extremities. However, even in the familial hereditary lymphatic edema with known genetic mutations, lymphedema only appears in some parts of the body and does not affect the whole body. The pathological mechanisms underlining the «selective location» in primary lymphedema are unclear.

In the lower limb, edema usually starts at the distal part of the limb, dorsum of the foot, and round the ankle. But edema can start from the thigh when the inguinal lymph node anomalies are the etiology. At the early stage, edema may disappear spontaneously in the morning and become evident during the night. The insidious onset and slow progression of symptoms usually result in delayed diagnosis. Along with the progress of the disease, the volume of the affected limb becomes evident like elephantiasis.

3. According to the Family History:

There are two types of inherited lymphedema:

1. The hereditary lymphedema type I. Milroy reported in 1892. Milroy disease (MD; MIM# 153100) is a rare autosomal, dominantly inherited primary lymphedema. Patients with MD generally present bilateral lower leg lymphedema at birth or shortly after birth [6–8]. The FLT4 gene (also known as

VEGFR-3), which encodes vascular endothelial growth factor receptor 3, was identified as being responsible for the majority of MD cases [9]. Clinical studies have found that not all members of the same family with VEGFR-3 gene variants have clinical symptoms. So far, 60 mutations in FLT4 have been reported [9–11]. with most reported as missense mutations. All the mutations are located in exons 17–20 and 22–26 of FLT4, within the tyrosine kinase domain of the receptor. A study found that mutations within the tyrosine kinase domains of FLT4 are sufficient to reduce tyrosine kinase activity [12]. thereby affecting lymphatic development. Typical lymphoscintigraphy image of MD is absence of observable lymphatic collector and inguinal lymph node in the affected limb. Some studies believe that MD is a disease caused by lymphatic dysfunction because (a) there are primary lymphatic vessels in the skin of the affected feet by immunohistochemical staining and (b) the main functional lymphatic tract is displayed on lymphoscintigrams in a few MD patients [1]. If so, a more complicated mechanism may underlie the pathology of MD, and more genes, other than VEGFR-3, may be involved in MD as modifier genes.

2. The hereditary lymphedema type II, also known as Meige's syndrome (MIM153200). Meige first reported in 1898. Meige's lymphedema accounts for about 65–80% of hereditary diseases. It is a chromosome dominant inheritance, begins sometime during puberty. Some may occur after 35 years old. Lymphedema is often accompanied by infection and mostly located in the lower extremity, but also occurs in the upper limbs and face. Other abnormalities are cardiovascular system abnormality, cleft palate, deafness, pleural lymphatic leakage, varicose veins, double row eyelash, and spinal deformities.

More than 90% of primary lymphedema cases do not have a family history.

4. According to the Lymphatic System Malformation Based on MR Lymphangiography:

The lymphatic system malformations in primary lymphedema have not been intensively studied until recent improvements of imaging technique with the use of MR lymphangiography [13, 14]. Dynamic and real-time observation of contrast enhancement of lymphatic vessels and drainage nodes with high-resolution images provide comprehensive information concerning both the structural and functional abnormalities of the lymphatic system in primary lymphedema [2]. The changes of lymphatic system in primary lymphedema may occur either in the lymph vessels or in the nodes or in both. On the MRL images, lymphatic abnormalities fell into two major categories, aplasia/hypoplasia or hyperplasia ◘ Fig. 59.1. Lymph node abnormalities fell into three major categories, aplasia/hypoplasia, hyperplasia, or structural abnormalities ◘ Fig. 59.2. The MRL findings of lymphatic system anomalies in primary lymphedema could be divided into three major patterns ◘ Fig. 59.3. Evident defects of the inguinal lymph node with moderate dilatation of afferent lymph vessels were found in 17% of patients. Lymphatic anomalies, including lymphatic aplasia, hypoplasia, or hyperplasia with no obvious defect of the drainage lymph nodes, were observed in 28% of patients. The abnormali-

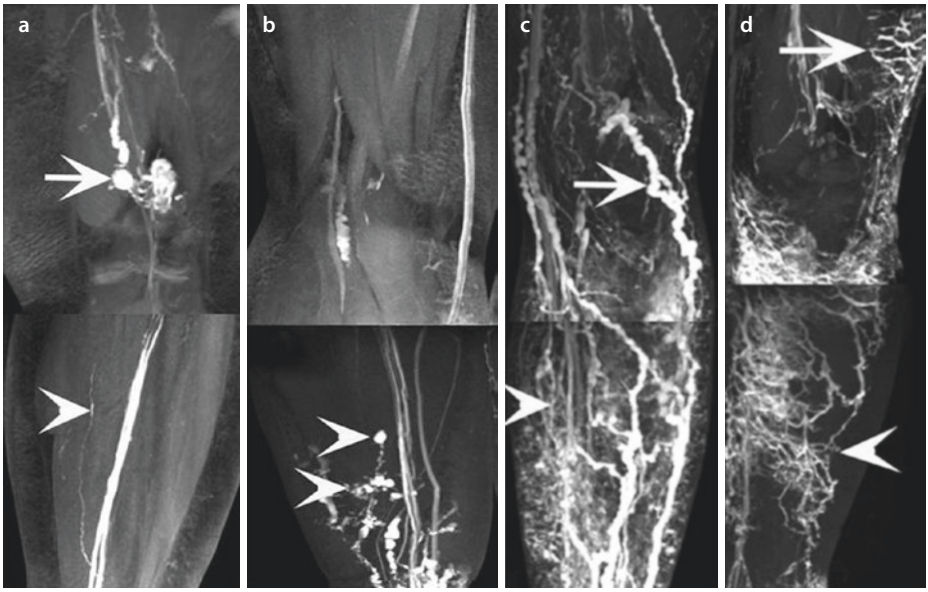

Fig. 59.1 Composition images of MR lymphangiogram show various lymphatic drainage pathways in primary lymphedematous limbs. **a** Single deep lymph vessel (*arrowhead*) and popliteal nodes (*arrow*) were enhanced with absence of superficial lymph vessel. **b** Enhanced lymph vessels with cystic dilatation (*arrowhead*) in the distal part of the leg. **c** Both superficial lymphatics (*arrowhead*) and deep lymph vessels and popliteal nodes (*arrow*) were involved. **d** A crisscross network of hyperplastic vessels in the thigh (*arrow*) and the calf (*arrowhead*)

ties of both lymph vessels and lymph nodes in the affected limb were exhibited in 55% of cases [3]. Thus, a classification of lymphatic system in primary lymphedema based on MRL imaging is proposed as follows:

1. Lymph nodes affected only with nodal structural abnormalities.
2. Lymph vessel affected only with:
    1. Lymphatic aplasia/hypoplasia.
    2. Lymphatic hyperplasia.
3. Lymph vessel and lymph node affected with subgroups:
    1. Lymphatic and nodal aplasia/hypoplasia.
    2. Lymphatic aplasia/hypoplasia + nodal hyperplasia.
    3. Lymphatic aplasia/hypoplasia + nodal structural abnormalities.
    4. Lymphatic and nodal hyperplasia.
    5. Lymphatic hyperplasia + nodal aplasia/hypoplasia.
    6. Lymphatic hyperplasia + nodal structural abnormalities.
4. Lymphatic dysfunction.
   Lymphatic slightly dilated with delayed enhancement.

There was no significant difference concerning the severity of the disease between lymphatic hypoplasia and hyperplasia groups. In general, edema was more

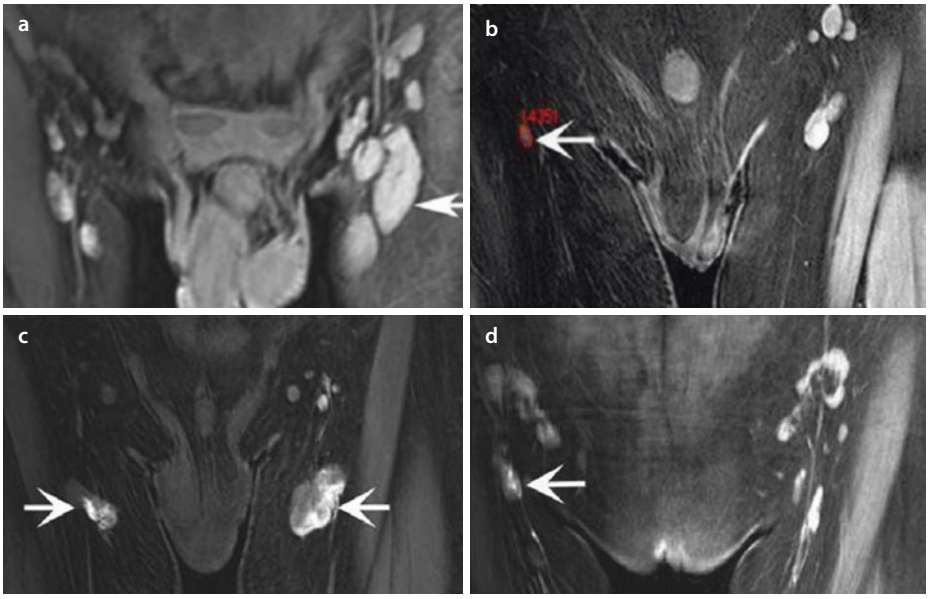

Fig. 59.2 Diverse inguinal node abnormalities of primary lymphedematous displayed on MR lymphangiograms. **a** Enlarged inguinal lymph nodes (*arrow*) with homogeneous texture in the left side in contrast with lymph nodes of normal size in the right side. **b** Single small node in a limb (*arrow*) with lymphatic hypoplasia and lymphedema is compared with lymph nodes in a limb without lymphedema. **c** Partially contrast-enhanced inferior inguinal nodes (*arrow*) in bilateral lymphedema with secondary lymphatic dilatation. **d** Small nodes that are irregular shaped (*small arrow*) in a limb with lymphangiectasia (*large arrow*)

extensive, and tissue fibrosis progressed as the course of the disease progressed in all groups. Edema in the ankle and foot was most common in lymphatic hypoplasia-only group. Edema in the thigh and/or extragenital and/or buttocks and lower abdomen wall was more common in inguinal lymph node aplasia/hypoplasia and nodal affected-only types. The malformations of lymph vessels were not always concordant with those of the lymph nodes in primary lymphedema. The lymph vessel and node may be involved together or affected alone and may express different types of anatomical anomalies. This updated classification clearly defines the location and pathological characteristics of the disease to provide a clear and more useful definition.

The imaging of lymphatic system with MR lymphangiography revealed the importance of the lymph nodes, as opposed to the peripheral vessels, in primary lymphedema. Nodal defects alone might be the cause of the disease or involved in both the lymphatic hypoplasia and hyperplasia groups. Similar to lymph vessels, diseased lymph nodes may be expressed as the aplasia, hypoplasia, and hyperplasia types; the most common form of lymph node pathology was nodal structural anomalies.

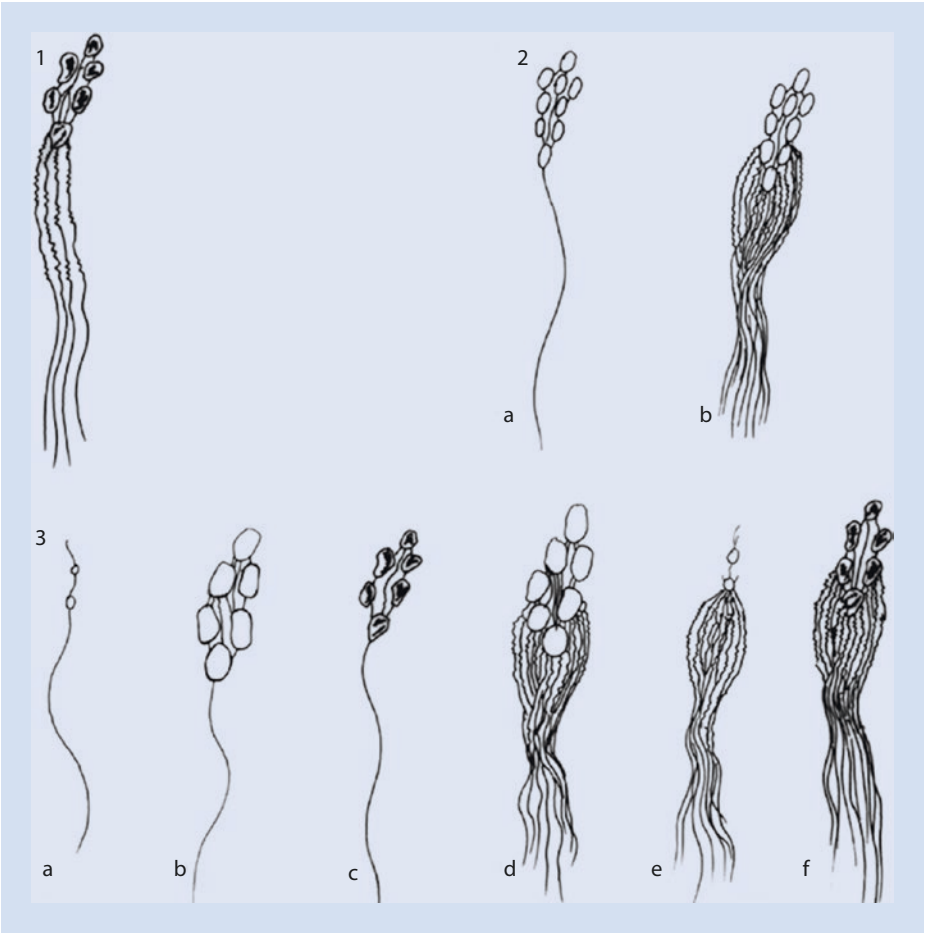

Fig. 59.3 Schematic drawing of the updated classification of primary lymphedema. **1** Lymph node affected only. **2** Lymphatic affected only: *a* lymphatic aplasia/hypoplasia and *b* lymphatic hyperplasia. **3** Both lymphatic and lymph node affected: *a* lymphatic and nodal aplasia/hypoplasia, *b* lymphatic aplasia/hypoplasia + nodal hyperplasia, *c* lymphatic aplasia/hypoplasia + nodal structural abnormalities, *d* lymphatic and nodal hyperplasia, *e* lymphatic hyperplasia + nodal aplasia/hypoplasia, and *f* lymphatic hyperplasia + nodal structural abnormalities

59.2 Lymphedema in Syndromes

The primary lymphedema is one of the symptoms of various syndromes, such as Klippel-Trenaunay syndromes, lymphedema-distichiasis syndromes, yellow nail syndromes, Turner's syndromes, Hennekam's syndromes, and hypotrichosis-lymphedema-telangiectasia syndrome. Among them, Klippel-Trenaunay syndrome is the most common one in the clinic. Edema and repeated erysipelas are frequently accompanied with the progress of the disease. However, the role of lymphatic system dysplasia in the

initiation and progression of Klippel-Trenaunay syndromes has long been overlooked. Recent study with the use of MR lymphangiography demonstrated that lymphatic system malformation is a common component of Klippel-Trenaunay syndromes [4]. as about 97% of the patients have lymphatic malformations and lymphedema. The lymphatic system dysplasia observed in Klippel-Trenaunay syndromes was similar to that seen in congenital primary lymphedema, such as lymphatic hyperplasia (34%), hypoplasia or aplasia (63%) of lymph vessels and/or lymph node hyperplasia (34%), or hypoplasia (9%). The coexistence of venous and lymphatic malformations in the extremities affected by Klippel-Trenaunay syndromes that are found in the majority of the patients implies again a close embryonic structure or developmental relationship between the two circulation systems. It is, therefore, essential to consider lymphatic system dysplasia in the diagnosis of Klippel-Trenaunay syndromes besides vascular system anomalies ◘ Fig. 59.4.

Lymphedema-distichiasis syndromes are relatively rare disease. The clinical manifestations of the patients with lymphedema-distichiasis syndromes are similar to hereditary lymphatic edema type II – Meige's syndrome. Foxc2 is one of the pathogenic genes [5]. The variation of FOXC2 gene can be different. The most prominent symptoms are double eyelashes, but usually not easy to find. Edema may affect single or bilateral lower limbs. The imaging of MR lymphangiography revealed a significant dilatation of superficial lymph collectors with valvular insufficiency. Lymph reflux in the collectors of the affected parts can be visualized with the use of indocyanine green (ICG) lymphography. Some patients show varicose veins; color Doppler ultrasound examination showed a deep venous reflux.

Yellow nail syndrome is a very rare disease and can be hereditary or not. FOXC2 mutation is identified in patients with yellow nail syndromes [15]. The three main symptoms of the disease were yellow nail of the hand and foot (89%), lymph edema (80%), and pulmonary lesions (63%). The cause of the formation of the lymphatic edema is the aplasia or hypoplasia development of the lymphatic vessels.

59.3 Special Type of Primary Lymphedema

1. Chylous reflux lymphedema is caused by malformation of the thoracic duct, chylocyst, lymphatic system in the intestine, and extremity. Lymph stasis in chylocyst can spread to the entire intestinal branch drainage area. Mesenteric lymph duct with chylous fluid may result in chylous lymphoma, rupture, and chylous ascites. Chylous reflux can also spread to the joint, often leading to joint pain and/or fever. There are complex connections of lymphatic and lymph nodes in between the thoracic and abdominal cavity; the stasis of chylous fluid can therefore spread to the axillary, subclavicular, posterior sternum, and inguinal lymph nodes.

The common clinical symptoms of chylous reflux are the vesicles on the surface of the skin of white chyle due to stagnant chylous in the dermal lymphatic, skin chylous leakage, ulceration formed after skin chylous leakage, and edema in the inguinal region and extragenital and/or lower limb. Primary chylous reflux may occur in children of less

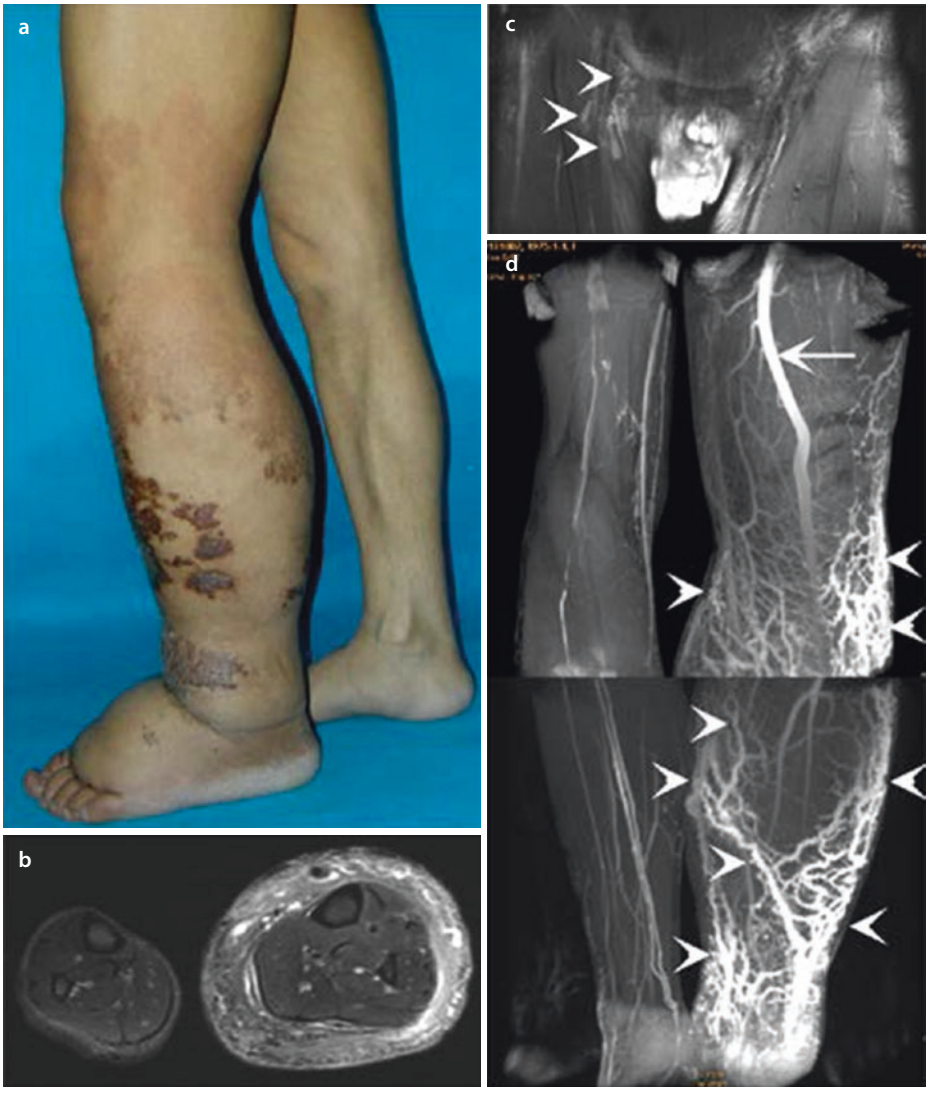

Fig. 59.4 **a** A man aged 34 with chief clinical features of KTS as skin port-wine stain and hypertrophy of the left lower limb. **b** Transverse section of T2-weighted MR image shows hypertrophy of subcutaneous tissue and edema fluid (*high signal intensity*) dispersing in the subcutaneous layer. **c** No inguinal lymph nodes were clearly visualized on the left side in contrast with lymph nodes (*arrowhead*) visualized on the contralateral side on coronal T2-weighted image. **d** Composition image of MR lymphangiogram shows numerous dilated lymphatic vessels (*arrowheads*) and enlarged deep vein (*arrow*)

than 1 year old. Most of the patients with chylous reflux were in the late stage when diagnosed and had been associated with frequent lymph leakage and/or infection of the affected region and limb for a long time. MR image is the best protocol for the diagnosis of chylous reflux lymphedema as to localize the lymphatic malformations in both the superficial and deep system Fig. 59.5.

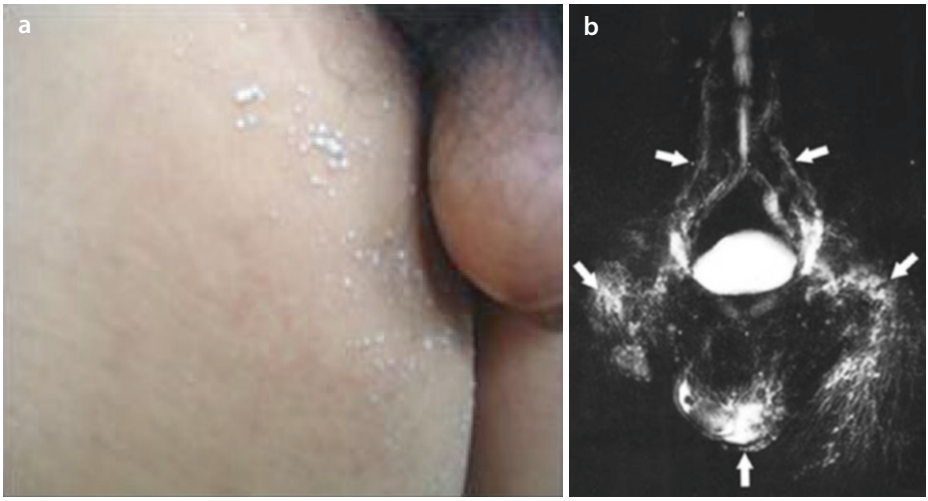

Fig. 59.5 **a** 45-year-old man with perineal skin chylous leakage for 30 years. **b** 3D MRI clearly shows dense mesh of the dilated lymphatic vessels in the groin, the scrotum, the left thigh, and the dilated bilateral lumbar trunk

2. Protein-losing enteropathy: Protein-losing enteropathy characterized by edema, abdominal pain, diarrhea, hypoproteinemia, and anemia associated with plasma protein leakage from the intestinal lymphatic duct to the intestinal lumen. The symptoms become more evident after high-fat meal. It is common in children. Majority of the primary protein-losing enteropathy is due to intestinal wall lymphedema resulting from intestinal lymphatic mechanical dysfunction and often associated with lymphangiectasia [16]. The thoracic duct and chylocyst dysplasia may be the pathogenesis of some cases. The lymph backflow of extremity may also be impaired, and patient may be associated with a primary lower limb lymphedema. The diagnosis is based on the clinical signs of edema and blood test of protein, globulin, calcium, vitamin D, and iron deficiency. Image tests with lymphoscintigraphy may detect the leakage of isotopic tracer into the lumen of the intestine in ~30% of cases. Capsule endoscopy may also help in observation of lesions in the intestinal wall. MR imaging is capable of demonstration of malformations (dilatation) of thoracic duct and enlarged mesenteric lymphatics [17].
3. Lymphangiomatosis: It is a syndrome of the lymphatic system malformation, that is, lymphangioma or cystic lesions of the lymphatic vessels [18]. There is no standard definition of the disease. The cause of lymphangiomatosis is a congenital malformation that arises from abnormal lymphatic system embryologic formation. The lymphangioma is isolated and localized, while lymphangiomatosis is located in multiple parts. The lymphangiomatosis originates in the lymphatic system and is benign in nature, but it can invade multiple parts and multiple organs of the body, showing progressive development. It commonly occurs in the lung, bone, kidney, chest, connective tissue, and spleen. The tumor tissue will cause osteolysis when violating the bone, most commonly in long bones, vertebrae, and ribs. It is also called «Gorham» syndrome when massive and vanishing bone occurs. The disease

can occur at any age, but most often in infants and young children, especially before the age of 20, no family heredity. The incidence is unclear. The diagnosis of the disease is based on the clinical, imaging, and histological analysis.

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Molecular Genetics of Lymphatic and Complex Vascular Malformations

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Summary of Basic Concepts

Lymphatic malformation (LM):

- Is usually a single lesion.
- Is usually a localized lesion.
- Can be isolated or part of a syndrome.
- Can be pure or combined lesion.
- When multifocal, commonly affects bones.
- The latter include Gorham-Stout syndrome and generalized lymphatic anomaly (GLA).
- Often causes pain, disfigurement, and dysfunction.
- Can be caused by a somatic mutation in PIK3CA.
- Mutations activate the PI3K-AKT-mTOR pathway.
- PI3K-AKT-mTOR inhibitors may be useful as treatment.

60.1 Lymphatic Malformation

Most lymphatic malformations – if not all – occur sporadically, i.e., there is no family history of the disease. The majority are present at birth and continue to grow with the growth of the child. The lesions can be a small area covered by lymphatic vesicles filled with clear fluid (microcystic LM) or large voluminous lesions formed by big lymph-filled vesicles (macrocystic LM). They can be superficial and/or deep invasive lesions. The neck area is a predilection site for LMs, yet they can be seen in any part of the body (head, thorax, abdomen, limbs, arms, hands, etc).

LMs most commonly cause pain, disfigurement, and dysfunction of the affected body part. Large lesions can, for example, hinder movement of the neck or an extremity. LMs in the oral cavity and/or tongue can hamper eating, speaking, and breathing, necessitating intubation or tracheostomy. Facial lesions are often unilateral and can cause important disfigurement. Some are associated with oozing. Usually these lesions are treated by sclerotherapy and surgery. Infections are common, and they can lead to spontaneous sclerosis of the LM.

60.2 Clinical Heterogeneity

There is an important heterogeneity in the clinical appearance of lymphatic malformations. They can present as a pure lymphatic lesion (a lymphatic malformation, LM) or as a combined lesion, e.g., a capillary-lymphatic malformation (CLM) or lymphaticovenous malformation (LVM). Moreover, they can occur as an isolated lesion or be part of a syndrome, such as Proteus syndrome, CLOVES syndrome (congenital lipomatous overgrowth with vascular anomalies, epidermal nevi, and scoliosis), or PTEN hamartoma tumor syndrome (PHTS).

This clinical heterogeneity reflects most likely differences in etiology, i.e., differences in cell types and time points of development in which causative defects have occurred. Accordingly, when only lymphatic (endothelial) cells are affected, an isolated, pure LM

is formed, whereas if both lymphatic and venous endothelial cells (due to a somatic change in a cell with potential to differentiate into both) are affected, combined lesions are formed. An earlier developmental event (in a multipotent progenitor cell) would lead to a more widespread defect affecting additional cell types, resulting in a syndromic presentation. For example, in CLOVES and Klippel-Trenaunay syndrome (capillary-lymphaticovenous malformation with overgrowth), the combined lymphatic malformations are associated with bony and soft tissue overgrowth.

60.3 Etiopathogenesis

The etiopathogenesis of LMs has remained unknown until recently. Hypotheses included environmental factors and stochastic cellular events. Genetic predisposition was not amenable to study because familial forms are nonexistent or extremely rare. An important step toward understanding the basis of localized lymphatic and vascular lesions was the identification of a somatic genetic origin for venous malformations (VMs) in 2009 [16]. These are also localized non-hereditary lesions, like LMs, but affect veins. A careful study of resected VM tissues demonstrated that tissular (somatic) genetic TIE2 mutations were present in a large number of samples. Currently, 80% of VMs can be explained by somatic mutations in two genes, TIE2 and PIK3CA [2, 16]. This groundbreaking discovery urged to study tissues of other localized lymphatic and vascular lesions, including LMs, for somatic genetic changes.

The concurrent development of massively parallel sequencing (commonly named next-generation sequencing, NGS) gave sensitive tools to study heterogeneous samples, such as resected LMs, which contain several different cell types, all of which might not contain the causative somatic mutation. With high depth of coverage (vertical coverage), sequencing a particular position, for example, a thousand times, the detection of somatic mutations present in as low as 1% of alleles in a sample became possible.

60.4 Genetic Cause of Isolated, Combined, and Syndromic LM

60.4.1 Isolated LM

Somatic mutations in the *PIK3CA* gene have been identified in isolated lymphatic malformations (Table 60.1) [4, 7, 17, 20]. This gene encodes the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (p110α), an important part of the PI3K complex, and receptor tyrosine kinase-PI3K-AKT-mTOR signaling pathway. Mutations occur particularly in some hot spots, such as p.E542K and p.E545K, but rarer ones are spread along the functional domains, yet sparing the RAS- and p85-binding domains. The frequency of the mutant allele varies from 0.5% to 12% in the samples screened so far [20]. It is to note that below 1%, the mutations were only detectable by technologies even more sensitive than NGS, such as droplet digital PCR (ddPCR), with the limitations that these methods interrogate only one or a few specific changes at a time.

Table 60.1 Diseases and genes associated with lymphatic malformations

Disease	Acronym (details)[a]	OMIM	Gene	Effect[b]	Inheritance	Mutation %	Ref
Vascular malformation							
Lymphatic malformation	LM	–	*PIK3CA*	GOF	Somatic	0.28–12	c, d, e, f
Capillary-lymphatic malformation	CLM	–	*PIK3CA*	GOF	Somatic	6.7	f
Capillary-lymphaticovenous malformation	CLVM	–	*PIK3CA*	GOF	Somatic	28	e, f
Lymphaticovenous malformation	LVM	–	*PIK3CA*	GOF	Somatic	2	f
Generalized lymphatic anomaly	GLA	–	–	–	Unknown	–	f
Gorham-Stout disease	GSD	123880	–	–	Unknown	–	f
Kaposiform hemangioendothelioma with or without Kasabach-Merritt phenomenon	KHE	–	–	–	Unknown	–	–
Vascular malformation and overgrowth							
Klippel-Trenaunay syndrome	KTS (CLVM + OGR)	149000	*PIK3CA*	GOF	Somatic	3–16	d, f

Congenital lipomatous overgrowth with vascular anomalies, epidermal nevi, and scoliosis syndrome	CLOVES (CLVM ± AVM + LipOGR)	612918	*PIK3CA*	GOF	Somatic	1–50	g, f
Proteus syndrome	(CM, ± VM, ± LM, asymmetric OGR)	176920	*AKT1*	GOF	Somatic	5–50	h
PTEN hamartoma tumor syndrome	PHTS (includes Cowden and BRRS)	158350 153480	*PTEN*	LOF	Somatic	–	i

[a] *AVM* arteriovenous malformation, *CM* capillary malformation, *VM* venous malformation, *OGR* overgrowth, *LipOGR* lipomatous overgrowth
[b] *GOF* gain of function, *LOF* loss of function
[c] Boscolo et al. [7]
[d] Luks et al. [17]
[e] Osborn et al. [4]
[f] Schlögel et al in prep
[g] Keppler-Noreuill et al. [13]
[h] Lindhurst et al. [1]
[i] Hansen-Kiss et al. [22]

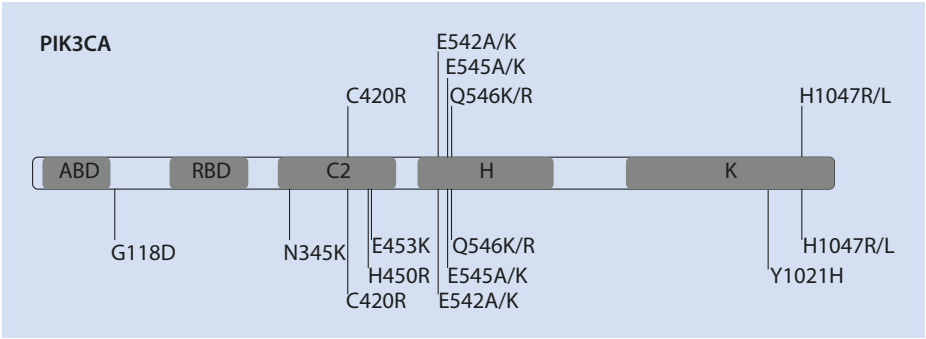

Fig. 60.1 PIK3CA protein and mutations. *ABD* p85alpha-binding domain, *RBD* Ras-binding domain, *C2 C2* domain, *H* helical domain, *K* kinase domain

60.4.2 Combined and Syndromic LMs

PIK3CA mutations have also been discovered in combined LMs and in tissues resected from patients with overgrowth syndromes, such as Klippel-Trenaunay (KTS) and CLOVES syndromes (Table 60.1 and Fig. 60.1) [7, 20]. Similar mutations have been identified in other overgrowth phenotypes without lymphatic or vascular malformations. The term PROS has therefore been coined to refer to PIK3CA-related overgrowth syndromes [13].

In CLOVES patients, the mutations are distributed over the entire protein (except the RasBD) (Fig. 60.1). In contrast, the mutations found in isolated LMs are concentrated in the helical domain. Interestingly, the frequency of the mutant allele seems to be higher in CLOVES tissues than in isolated malformations, reflecting a higher number of mutant cells. This fits with the wider distribution of the symptoms in CLOVES patients, with different types of cells being involved, due to a tissular mutation that likely appeared at an earlier developmental stage [18, 20].

Although some categories remain un-elucidated (such as kaposiform hemangioendothelioma with or without Kasabach-Merritt phenomenon, generalized lymphatic anomaly, and Gorham-Stout syndrome), the majority of lymphatic anomalies seem to be caused by activating somatic PIK3CA mutations (Table 60.1) [3]. It is at least the case for LM, LVM, CLM, CLOVES, CLVM, and CLVM with hypertrophy (KTS) [20]. The PIK3CA-negative patients represent only a small fraction and may simply represent technical challenges in mutation detection [20].

60.4.3 Other Genes

Two other syndromes, in which LM can be present, are caused by mutations in AKT1 (v-akt murine thymoma viral oncogene homolog 1) or PTEN (phosphatase and tensin homolog) (Table 60.1). Activating mutations in AKT1 cause Proteus syndrome, characterized by cutaneous overgrowth of cerebriform lesions and abnormal bone development, often accompanied by tumors. Inactivating mutations in PTEN have been shown

to cause Bannayan-Riley-Ruvalcaba syndrome (BRRS) and Cowden syndrome, now collectively called as PTEN hamartoma tumor syndrome (PHTS).

60.5 PIK3CA Function

PIK3CA encodes the catalytic subunit alpha (p110α) of the PI3-kinase (PI3K). PI3K is part of a major intracellular signaling pathway downstream of several tyrosine kinase receptors present on cell membranes, such as vascular endothelial growth factor receptor 2 (VEGFR2) and TEK (Fig. 60.2). The PI3-kinase activates AKT (among which AKT1), and thereby mTOR, and regulates, e.g., cell growth, proliferation, and migration. PTEN inhibits the PIK3CA activity by dephosphorylation. The mutations identified in LMs activate PIK3CA [4, 7, 20].

The same activating somatic changes have been identified in 20% of venous malformations [2] and in numerous cancers [19, 21]. However, venous and lymphatic malformations do not undergo transformation into a cancer. Therefore, to be able to induce oncogenic cell transformation, these PIK3CA mutations likely need (several) additional coexisting mutations. This is not the case in LMs and VMs.

When expressed in lymphatic endothelial cells (LECs), PIK3CA mutations induce cellular proliferation and sprouting in collagen compared to normal LECs [7]. The threonine 308 of AKT was also shown to be constitutively hyper-phosphorylated in mutant LECs isolated from a patient [7]. Treatment of cells with PI3-kinase inhibitors (wortmannin and LY294) inhibited proliferation and prevented the phosphorylation of AKT-Thr308 in both normal and mutant LECs [7]. Incubation with the mTOR inhibitor rapamycin (sirolimus) also diminished cellular proliferation, sprouting, and AKT phosphorylation, in mutant

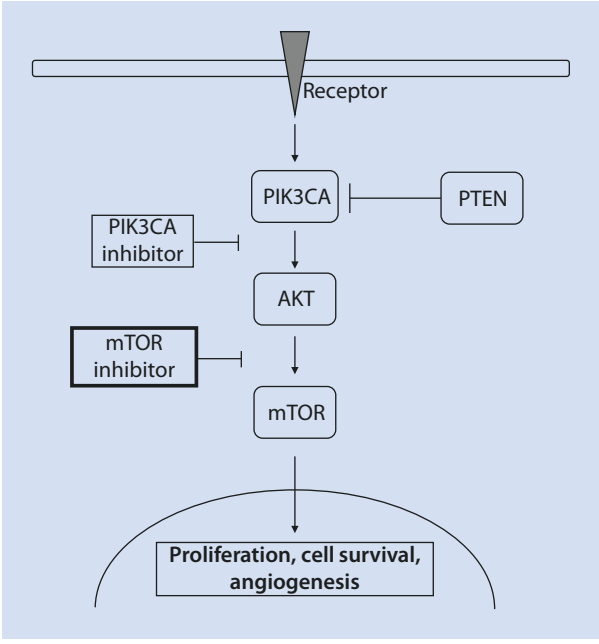

Fig. 60.2 PIK3CA/AKT signaling pathway and targets for inhibition

LECs [7]. When expressed in human umbilical vein endothelial cells (HUVECs), PIK3CA mutations also caused constitutive activation of AKT, dysregulation in expression of important angiogenic factors, and abnormal endothelial cell morphology. The p110α-specific inhibitor BYL719 restored all abnormal phenotypes [2].

Mutations in PIK3CA can affect its activity by, for example, enhancing its binding to the cell membrane and/or by activating its kinase. They may also inhibit the PIK3CA inhibitory tail at the C-terminus [8, 11]. In some cell types, such mutations induce multipotency of cells [14]. Moreover, in different cell types, effects may differ because of dissimilar intracellular context. For example, a cell expressing PTEN at a high level may be less sensitive to a PIK3CA-activating mutation. Thus, the phenotypic variability observed in patients likely depends on several factors, including cell type, cellular subpopulation, and time in development at which the somatic mutation occurred.

60.6 Disease Models

Endothelial cells that express activated signaling pathway components (TIE2 or PIK3CA mutants) are able to give rise to lesions in mice. Injection of mutant TIE2-expressing HUVECs under the skin of nude mice induced formation of lesions that mimic VMs [7]. Similarly, Cre-induced expression of Pik3ca-H1047R mutant induced cutaneous and spinal lesions that mimicked VMs [9, 10]. The lack of lymphatic malformations in the latter model is surprising and suggests that the developmental time of induced recombination may not have affected the lymphatic endothelial precursor cells. Lineage-tracing experiments could help understand this observation.

60.7 Diagnostic Screening

The identification of a genetic etiology for lymphatic and other vascular anomalies allows genetic screens to be used to help diagnosis. However, the number of patients reported so far is still limited. Thus, the frequency of PIK3CA mutations in larger cohorts, and whether all or just some subtypes of LMs are mutated, is unknown. As PIK3CA mutations can be identified in patients with LM, VM, and PROS, the clinical phenotyping remains important.

Most of the mutations are recurrent hot spot changes. Thus, they can be screened by sensitive cost-efficient tests, such as ddPCR, followed by targeted NGS if no hot spot change is found. Targeted NGS is efficient, as it allows to screen hot spots and the rest of the gene at once. It also allows simultaneous screening of several genes, which is particularly useful for disorders of varied genetic background (genetic heterogeneity). Such panel-based testing is now becoming commonplace. One limitation is that most of these mutations are somatic, requiring a tissular resection or a biopsy of the lesion to be performed.

For a patient, unraveling the genetic defect is most helpful. In addition to establishing or at least helping to confirm the clinical diagnosis, it pinpoints the target for future precision therapy. Stratification is also needed for evaluating current management

modalities. However, it is not always easy to distinct an amino acid-changing polymorphism from a disease-causing mutation. This is even more difficult for somatic mutations due to the low frequency of the mutant allele(s) in the background noise. Functional impacts are classically predicted using numerous bioinformatical tools that mostly base their analyses on evolutionary conservation, structural constraints, and chemical properties of the unchanged and changed proteins. Databases, such as dbSNP, 1000 Genomes, and ExAC, are used to identify frequent changes in the population. COSMIC regroups somatic or germinal variants found in cancer. Therefore, the evaluation of pathogenicity of a given variant requires an integrated method, using a software such as Highlander (▶ http://sites.uclouvain.be/highlander/) (Helaers et al., submitted). To ascertain the pathogenic impact of doubtful changes and to unravel downstream signaling pathway alterations, functional studies will be required.

60.8 Precision Therapy

Since LMs are due to somatic mutations causing activation of a signaling pathway (Fig. 60.2), molecular inhibition becomes a valid approach to develop future molecular (companion) therapies. Several inhibitors have been developed to target PI3K, AKT, and mTOR, in the quest to treat cancer. Rapamycin (also known as sirolimus), an inhibitor of mTOR, is known as an immunosuppressive agent, and it has been used for a long time for transplantation patients. Its toxicity and adverse effects are therefore well characterized.

Sirolimus has been used in preclinical and clinical studies to treat vascular anomalies. The first one was an off-label study, started prior to the discovery of the causative gene(s), and involved four LMs, one CLVM, and one KHE with Kasabach-Merritt phenomenon [12]. Boscolo and co-workers included five VM patients (three TIE2 and two PIK3CA mutated) and one PIK3CA-mutated CLVM with hypertrophy (KTS) [5]. Lackner and co-workers included two KHE, two LVMs, one pulmonary lymphangiectasia, and one LM (underlying molecular defects unknown) [15]. Finally, Adams and co-workers included a cohort of 60 patients (underlying molecular defects unknown) [6]. In all studies, most patients had beneficial effects of sirolimus, underscoring the interest of such a therapy for these malformations. The benefits also overcome the side effects. Indeed, some patients who stopped taking sirolimus due to undesirable effects restarted medication because of recurrence of the invalidating symptoms related to the malformation [5]. Thus, sirolimus proved to be an efficient drug to treat LMs and VMs, and the future seems bright for repurposing of cancer drugs to the field of lymphatic and vascular anomalies.

Conclusion

Lymphatic malformations can be isolated or part of a syndrome and often cause pain. Lymphatic malformations are caused by activation of the PI3K-AKT-mTOR pathway. This activation can be diminished by inhibitors. Sirolimus (mTOR inhibitor) has already demonstrated its efficacy.

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Syndromic Lymphedema and Complex Vascular Malformations with Lymphatic Involvement

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Summary of Basic Concepts

- Many syndromes have lymphedema as a predominant clinical feature.
- Somatic and genomic mutations have been identified in several of these syndromes, providing insight into the pathophysiology of these disorders.
- This chapter reviews the lymphedema syndromes and the involved genes and affected pathways.

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Lymphedema may be the predominant characteristic of a «lymphedema» syndrome, or a part of a multifaceted vascular malformation syndrome. This chapter will summarize these disorders. The term «lymphedema syndromes» is used loosely and includes conditions where isolated lymphedema is the only manifestation, since several genetic mutations have been elucidated for these heritable lymphedemas, providing insight into the pathogenesis of these disorders. The updated classification of vascular anomalies of the International Society for the Study of Vascular Anomalies (ISSVA) serves as a springboard for this review. The ISSVA classification can be accessed on the ISSVA website (▶ http://www.issva.org). A comprehensive description of this classification is provided in a manuscript by Wassef et al. [6]. There are several excellent reviews of lymphedema syndromes. Connell et al. present a diagnostic «classification pathway» algorithm, which incorporates phenotypic and genetic features [1]. Although the field is evolving as new genetic mutations are being discovered, this algorithm is very pragmatic.

There has been a great deal of research in the lymphatic system, and many genes which mediate lymphatic development have been identified. Mutations of VEGFR3 (Flt4) as well as downstream transcription factors and related modulatory genes have been identified as causal in lymphedema syndromes. One study identified mutations in ~40% of familial lymphedema and ~8% of sporadic cases. Most of the mutations were in VEGF-C/VEGFR-3 signaling pathway-related genes [2]. VEGFR-3 (Flt-4) mutations are responsible for Nonne-Milroy disease (hereditary lymphedema type IA; OMIM 153100), also known as congenital or early-onset lymphedema, which is the most common of the inherited lymphedemas.

Brouillard et al. provide a comprehensive review of the genetics of lymphedema and lymphedema syndromes, providing comprehensive tables and explanations [3]. Causal genes and the signaling pathways to which they belong are tabulated in ◘ Table 61.1. For those disorders for which genes have been identified, only a minority of patients have been identified to harbor mutations in those genes. The most common lymphedema syndrome with manifestations other than lymphedema is Noonan syndrome, an autosomal dominant disorder predominantly caused by mutations in genes in the RAS-mitogen-activating protein kinase (RAS-MAPK) pathway. The majority of cases are caused by mutations in the PTPN11 (protein-tyrosine phosphatase nonreceptor-type, 11) or *SOS1* (son of sevenless, drosophila, homolog 1; SOS1 guanine nucleotide exchange factor) genes. Approximately 25% of patients with Hennekam syndrome (characterized by widespread lymphatic dysplasia – lymphangiectasia, lymphedema, distinctive facial features, hearing loss, dental and skeletal abnormalities) have a mutation in the CCBE1 gene (collagen and calcium-binding EGF domain-containing protein 1), which is involved with extracellular matrix function [7].

Table 61.1 Summary of genes implicated in lymphedema and lymphedema-related syndromes

Affected pathway	Involved genes	
VEGF-C/VEGFR-3 axis	*VEGFR3 (FLT4)*	Vascular endothelial growth factor receptor
	CCBE1	Collagen- and calcium-binding EGF domain-containing protein 1
Transcription factors downstream from VEGF-C/VEGFR-3	*FOXC2*	Forkhead box protein C2
	SOX18	SRY-Box18 Sex-determining region Y-Box 18
	GATA2	GATA-binding protein 2
Nuclear and transcription factor regulators	*IKBKG*	Inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase gamma
	KIF11	Kinesin family member 11
Connexins (gap junction proteins)	CX47 – (GJC2)	Connexin 47 – gap junction protein 2
	C43 (*GJA1*)	Connexin 43 – gap junction protein 1
RASopathies	*PTPN11*	Protein-tyrosine phosphatase, nonreceptor-type, 11
	KRAS	Kirsten rat sarcoma viral oncogene homolog
	RAF1	Proto-oncogene serine/threonine-protein kinase
	HRAS	Harvey rat sarcoma viral oncogene homolog
	RASA1	RAS P21 protein activator 1
Other	*ITGA9* (*HGF/MET*)	Integrin α9 hepatocyte growth factor and c-MET receptor

Derived from Brouillard et al. [3]

Mutations of transcription factors downstream from VEGFR-3 include *FOXC2,* SOX18, and GATA2, corresponding to lymphedema-distichiasis syndrome (OMIM 153400), hypotrichosis-lymphedema-telangiectasia syndrome (OMIM 607823), and primary lymphedema with myelodysplasia (Emberger syndrome; OMIM 614038).

The majority of other syndromes are quite rare, yet causal genes have been identified in some patients, broadening the inventory of underlying constituents leading to these diseases. A complete list of lymphedema syndromes, including clinical features and reported genetic mutations, is listed in Table 61.2.

Germ line or somatic mutations in the Ras/MAPK signaling pathway have been identified in many disorders. Regarding lymphedema, Noonan, Costello, and cardio-facio-cutaneous syndromes, Ras–/MAPK-related genes include KRAS, NRAS, (Noonan), HRAS, and BRAF. Patients with these disorders harbor an increased inci-

Table 61.2 Syndromes associated with lymphedema

Syndrome/condition OMIM #	Clinical features	Genetic information
Turner syndrome	Short stature, broad chest, widely spaced nipples, skeletal, cardiac, renal and endocrine abnormalities, congenital lymphedema, infertility (ovarian failure), lymphedema	45,X (XO) or 46,X,del (Xp) or mosaic
Noonan syndrome 163950	Lymphedema Characteristic facies webbed neck, cardiac skeletal, ophthalmologic, hematologic, neurologic abnormalities	12q24.13 Autosomal dominant PTPN11 (protein-tyrosine phosphatase, nonreceptor type, 11) Sporadic or autosomal dominant Genetic heterogeneity Mutations of genes involved in RAS-mitogen-activated protein kinases (MAPK) signal transduction pathway SOS1, RAF1, KRAS, MEK1 (MAP2K1), NRAS, BRAF, SHOC2, CBL [16–19]
Klinefelter syndrome	Tall stature, sparse facial and body hair, taurodontism, lymphedema, gynecomastia, micro-orchidism, sterility, autoimmune disorders, emotional and learning disorders	XXY
Hereditary lymphedema type IA Nonne-Milroy lymphedema Milroy disease Primary congenital lymphedema; PCL 153100	Early-onset lymphedema	Autosomal dominant, autosomal recessive, or sporadic (de novo) Chr 5q35.3 Flt4 (VEGFR3 mutation) Heterozygous mutations in kinase domain of VEGFR3; rare sporadic cases with FOXC2 [20–23]
Lymphedema type IB (LMPH1B; «Milroy-like») 611944	Onset occurred in early childhood Maximum manifestations at puberty Lymphedema confined to the lower limbs	Autosomal dominant Chr 6q16.2-q22.1 VEGFC [24–26]

Hereditary lymphedema type IC	Early onset, between 0 and 20 years of age, of uncomplicated lymphedema of the lower limbs, and some later developed upper limb involvement	Autosomal dominant Chr 1q41-q42 GJC2 gene (Gap junction protein, gamma-2; connexin 47) [27, 28]
Lymphedema-distichiasis syndrome 153400	Lower limb lymphedema, often asymmetric, peripubertal onset Distichiasis (anomalous eyelashes growing from meibomian glands – double set or a single hair) Cardiac defects, cleft palate, extradural cysts, and photophobia Early-onset varicose veins	Autosomal dominant Chr 16q24.1 FOXC2 [29–34]
Hypotrichosis-lymphedema-telangiectasia – renal dysplasia (HLTS) 607823 Hypotrichosis-lymphedema-telangiectasia – renal dysplasia 137940	Leg lymphedema, telangiectasis; +/– renal failure (two patients)	Autosomal recessive or dominant Chr 20q13.33 SOX18 [35–37]
Microcephaly with or without chorioretinopathy, lymphedema, or mental retardation 152950	Microcephaly, small eyes, noninflammatory choroid (ocular vascular layer between retina and sclera) and retinal disease, pedal lymphedema, poor vision	Autosomal dominant Chr 10q23.33 KIF11 Kinesin family member 11 [38–40]
Emberger syndrome lymphedema, primary, with myelodysplasia 614038	Myelodysplasia (+/– monosomy 7) → acute myeloid leukemia (AML), primary lower extremity lymphedema, +/– warts, deafness, mild hypotelorism, webbed neck, thin fingers	Autosomal dominant Chr 3q21.3 GATA2 [41–43]

(continued)

Table 61.2 (continued)

Syndrome/condition OMIM #	Clinical features	Genetic information
WILD syndrome	Warts, cell-mediated immunodeficiency, lymphedema, anogenital dysplasia	Human papillomavirus associated [44]
Lymphedema-lymphangiectasia-mental retardation (Hennekam) syndrome 235510	Lymphedema Lymphangiectasia Developmental delay Flat face, flat, broad nasal bridge, hypertelorism Glaucoma, skeletal and dental anomalies, hearing loss, renal anomalies	Autosomal recessive Chr 18q21.32 CCBE1 gene (collagen- and calcium-binding EGF domain-containing protein 1) [7, 45–48]
Yellow nail syndrome 153300	Primary lymphedema Smooth over-curved, translucent yellow nails Chronic respiratory symptoms	Spectrum of lymphedema-distichiasis syndrome (nails thickened and opaque)
Lymphedema-cholestasis syndrome (Aagenaes syndrome) 214900	Severe neonatal cholestasis Chronic extremity lymphedema	Autosomal recessive Chr 15q [49, 50]
OLEDAID Osteopetrosis, lymphedema, octodermal dysplasia (anhidrotic), immunodeficiency 300301	Anhidrotic ectodermal dysplasia, severe immunodeficiency, osteopetrosis, lymphedema	Chr Xq28 NEMO gene (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase gamma; IKBKG, encoding NEMO – NF-B essential modulator) Mutation [51]

Oculodentodigital syndrome and primary lymphedema ODDD 164200	Oculodental dysplasia, finger 4,5 syndactyly, characteristic facies, microphthalmia, lower limb lymphedema	Autosomal dominant Chr 6q22.31 GJA1 gene (connexin 43, a gap junction protein) [52]
PTEN hamartoma tumor syndrome 158350 153480	Cowden syndrome Bannayan-Riley-Ruvalcaba syndrome (BRRS) Macrocephaly, vascular malformation, lipomas, thyroid disorders, penile lentigines (BRRS), trichilemmomas, papillomatous, high incidence of malignancy, especially the breast, thyroid, endometrium, gastrointestinal	Autosomal dominant Chr 10q23.31 Phosphatase and tensin homolog
Stewart-Treves syndrome	Lymphangiosarcoma in chronic lymphedema	[53, 54]
CM-AVM +/– lymphedema 608354	Multiple, small, round-oval, pink-red capillary malformations with pale halo, arteriovenous malformation or arteriovenous fistula, +/– lymphedema	*RASA1* Autosomal dominant 5q14.3 [9, 10]
Fetal chylothorax	Mutation present in fetal chylothorax with poor response to antenatal sclerotherapy	Integrin, alpha-9 ITGA9 [12]
Cardio-facio-cutaneous (CFC) syndrome with chylothorax	Facial dysmorphism, ectodermal and cardiac abnormalities, growth retardation, neurodevelopmental delay Single case report with chylothorax, lymphedema, sinus pericranii, craniosynostosis, seizures	12p12.1 BRAF KRAS K-RAS proto-oncogene, GTPase [55]
Costello syndrome 218040	Similar to cardio-facio-cutaneous syndrome, with bulbous nasal tip, full lips Case report of neonatal chylous ascites	11p15.5 HRAS (GTPaseHRas; transforming protein 21 [56]

dence of leukemias and solid tumors. In a study of German patients, the standardized incidence ratio (SIR) of malignancy in Noonan syndrome was 8.1 and 42.4 in Costello syndrome [8]. A minority of patients with the RASA1 mutation have, in addition to capillary malformations and arteriovenous malformations, lymphedema or other lymphatic abnormalities [9, 10].

61.1 Prenatal Diagnosis

Congenital lymphedema may present in the fetal period with polyhydramnios, edema, effusions (pleural, pericardial, peritoneal), and nonimmune hydrops [11]. One study identified a specific mutation in integrin alpha-9 gene in patients with prenatally diagnosed chylothorax and suggested this finding was a poor prognostic indicator [12].

In contrast to genomic mutations associated with the lymphedema syndromes mentioned above and in Table 61.2, a number of vascular malformation overgrowth syndromes have been found to be caused by somatic mutations, which present only in the affected tissues.

The phosphatidylinositol-3-kinase(PI3K)/AKT/mTOR pathway-related syndromes are collectively termed PIK3CA-related overgrowth spectrum (PROS) and include CLOVES syndrome (Congenital Lipomatous Overgrowth, Vascular Malformations, Epidermal Nevi, Scoliosis/Skeletal and Spinal) and Klippel-Trenaunay syndrome [4, 13]. AKT1 mutations have been identified in patients with Proteus syndrome [14]. Lymphedema may accompany these syndromes, from venous insufficiency and/or lymphatic dysplasia. Additionally, Maclellan et al. observed a cohort of patients with lower limb capillary malformations have associated ipsilateral lymphedema [15]. Heritable vascular anomaly syndromes which can be associated with lymphedema include the RASA1 capillary malformation-arteriovenous malformations discussed above and the PTEN (phosphatase and tensin homolog) hamartoma syndrome (Cowden syndrome and Bannayan-Riley-Ruvalcaba syndromes) [5].

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An Atlas of Neonatal and Infantile Lymphedema

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Summary of Basic Concepts

- Primary lymphedema (1°L) in the pediatric group has a special position among the congenital vascular malformations (CVM), because the majority represent a clinical manifestation of the «truncular» type of lymphatic malformation.
- There are 41 syndromes with peripheral primary lymphedema, added to 85 syndromes with primary generalized lymphedema.
- There are more than 15 extrinsic causes to the lymphatic system for the development of a secondary lymphedema, some of them are tumors, surgery, infections (filariasis, TBC), trauma, venous hypertension (troncular), radiation, podoconiosis, amniotic bands, hair tourniquet, compression, fractures, low-frequency respiratory assistance, malnutrition, chronic drugs (antibiotics, growth hormones), drug addiction, and burns.
- The genetic information would support the diagnosis; a certain condition of dysplasia and/or dysfunction would need a biopsy of a nodal or lymph vessel to establish an anatomo-pathological pattern.

62.1 Introduction

There are more than 250 million lymphedema patients throughout the world according to the WHO data, and a third are of the pediatric age group.

Primary lymphedema is the most frequent type among children, whereas secondary lymphedema is prevalent among adults as a consequence of specific treatment [1].

In pediatrics, diagnosis of lymphedema is usually delayed because the disease is little considered for differential diagnosis and for being a sign of orphan diseases.

The appearance of a lymphedema brings diagnosis closer and should be supported by medial, genetic, or imaging background (lymphoscintigraphy, MR lymphography, etc.).

Lymphedema is similar in terms of its semiological constant, and pediatrics must reveal its syndromic context.

In pediatrics, the treatment of secondary lymphedemas is based on the rehabilitation of the lymphatic system as per the specific diagnoses. In cases of primary lymphedema, the flow of lymph must be enabled because it has never flown adequately.

The impact of this lifelong condition on this pediatric group is much greater than that on the adult patient group; the psychological, physical, and also social impacts are much harder, not only for the affected child but also for the whole family.

However, the condition is manageable, with a remarkable response to multidisciplinary treatment, including specific conditions such as head, face, and neck lymphedema, genital lymphedema, lymph leakage, etc.

The scheduling and implementation of treatment and diagnosis of lymphedema in general are complicated, not only from the institutional perspective but also for family reasons.

Children can only receive assistance if their parents get involved, which is not always possible [2, 6, 7].

62.2 Primary Lymphedema

Primary lymphedema (1°L) in the pediatric group has a special position among the congenital vascular malformations (CVM), because the majority represent a clinical manifestation of the «truncular» type of lymphatic malformation [3, 4] (Figs. 62.1, 62.2, 62.3, and 62.4).

There is no pathognomic sign for primary lymphedema per se, but there are two findings/signs that are well accepted as clinical signs of the primary lymphedema among the pediatric group. However, the Stemmer sign is always positive, whereas pitting edema is not always positive in the fovea or Godet test (Figs. 62.5 and 62.6).

However, both signs are nonspecific and present in other edematous conditions. The Stemmer sign is also constant in segmentary corporeal hypertrophies, lipedemas, and lipodysplasias, and the pitting edema reflects an acute clinical appearance of a primary lymphedema or an inflammatory process [8, 9].

Primary lymphedema can be further classified into three groups [6, 10]:

1. Primary lymphedema due to the interstitial lymphatic endothelial dysplasia and dysfunction
2. Primary lymphedema due to lymphangiodysplasia and dysfunction
3. Primary lymphedema due to lymphadeno- or nodal dysplasia and dysfunction

It will result in various conditions of the defective lymphatic system from the initial lymphatics to the lymphatic vessel and/or lymph nodes resulting in lymphangiodysplasias (LAD I) and lymphadenodysplasias (LAD II).

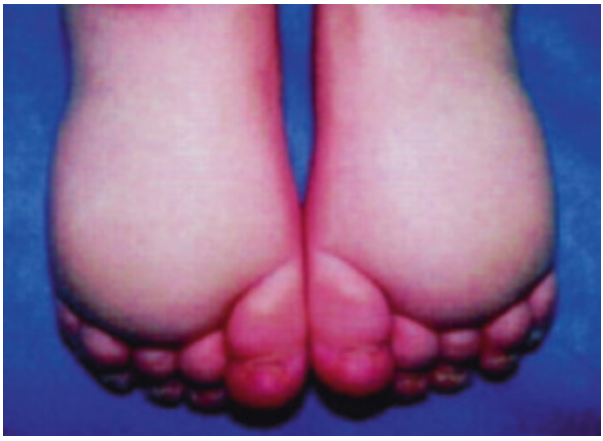


Fig. 62.1 Bilateral primary lymphedema

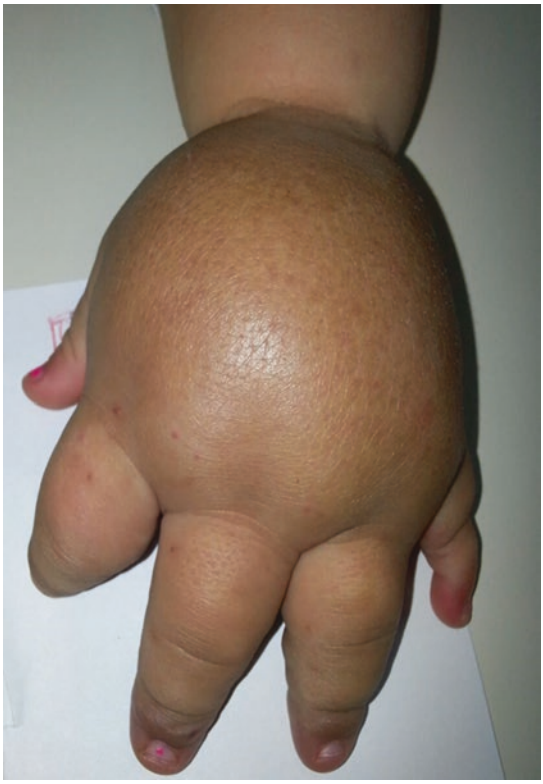


Fig. 62.2 Primary lymphedema of the hand and fingers in a child

LAD I: hypoplasia, hyperplasia/ectasia, lymphangiomatosis, lymphangioleiomyomatosis, dysvalvulosis, avalvulosis, lymphangio-neurosis cause organic or functional neurovegetative disturbance of the lymph vessels, and lymphangioma

LAD II: hypoplasia; global, central, and peripheral fibrosis; lymphangiomatosis; nodal angiomatosis; hemangiomatosis; follicular or medullary hyperplasia

LAAD: LAD I + LAD II, combined lymph system dysplasias

Primary lymphedema due to interstitial dysfunction or hypoplasia of the initial lymphatics or both are now named as three different syndromes with proper identification of specific gene mutations as the cause [11].

1. Milroy (Nonne–Milroy) disease: lymph capillary hypoplasia by defective VEGFR-3 [12]
2. Lymphedema–distichiasis syndrome: FOXC2 [13]
3. The lymphedema–hypotrichosis–telangiectasia syndrome: SOX18 [14]

There are 41 syndromes with peripheral primary lymphedema, added to 85 syndromes with primary generalized lymphedema [15]:

1. Noonan syndrome [16]
2. Turner syndrome [17]
3. Yellow nail syndrome [18]
4. Nevo syndrome [19]

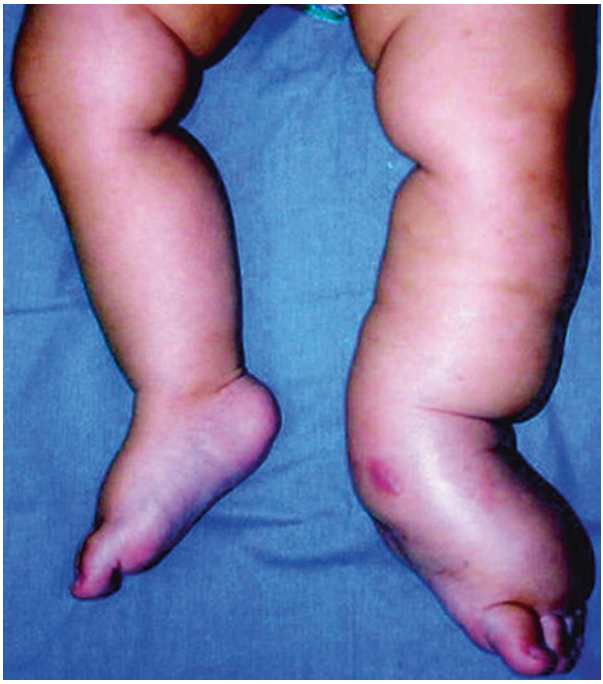


Fig. 62.3 Unilateral primary lymphedema with lymphangiomatosis

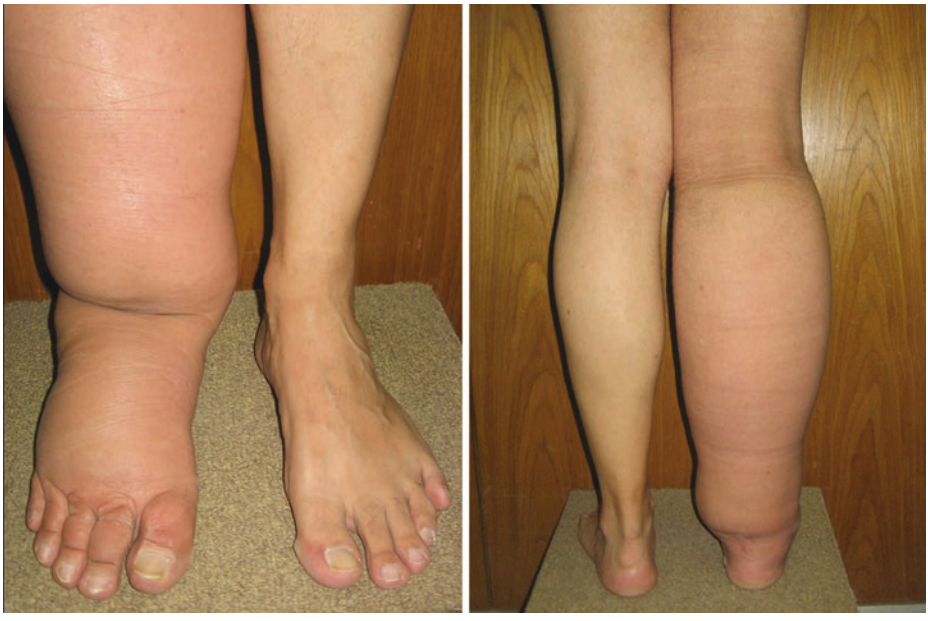


Fig. 62.4 Unilateral primary lymphedema of the right leg

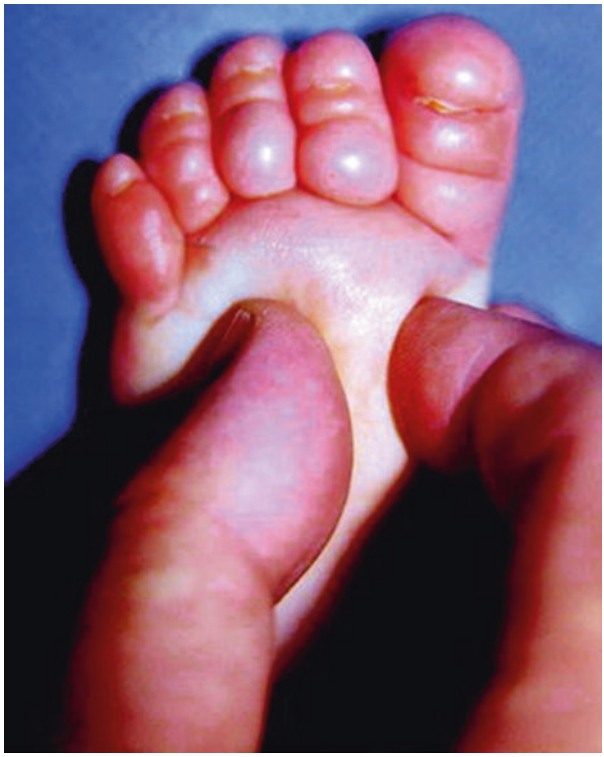


Fig. 62.5 Stemmer sign. Primary lymphedema

5. Aplasia cutis + 1°L (Bronspiegel syndrome) [20]
6. Cholestasis + 1°L (Aagenaes syndrome) [21]
7. Progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy (PEHO) syndrome [22]
8. Cerebral arteriovenous malformation + 1°L (Avasthey syndrome) [23]
9. Cleft palate + 1°L (Figueroa syndrome) [24]
10. Hypoparathyroidism + 1°L (Dahlberg syndrome) [25]
11. Distichiasis + 1°L syndrome [26]
12. Microcephaly + 1°L [27]

These 12 syndromes are most frequently mentioned among many others [10]. Such syndromes are often detected among the newborns and month-old pediatric patients, with primary lymphedema combined with various conditions: uni- or bilateral Wilms' tumor, unilateral suprarenal cysts, superficial and deep venous malformations, Klippel–Trénaunay syndrome [28], Parkes Weber syndrome, neurofibromatosis, and combined angiodysplastic syndromes.

Rarely, such a condition becomes more complicated with «the phantom bone disease»: Gorham–Stout syndrome [29], Haferkamp syndrome [30], Proteus syndrome [31], lipodysplasias, lipoblastomatosis [32], exudative enteropathies, and chylous reflux syndromes (Figs. 62.7, 62.8, 62.9, 62.10, 62.11, 62.12, 62.13, 62.14, 62.15, 62.16, 62.17, 62.18, 62.19, 62.20, and 62.21).

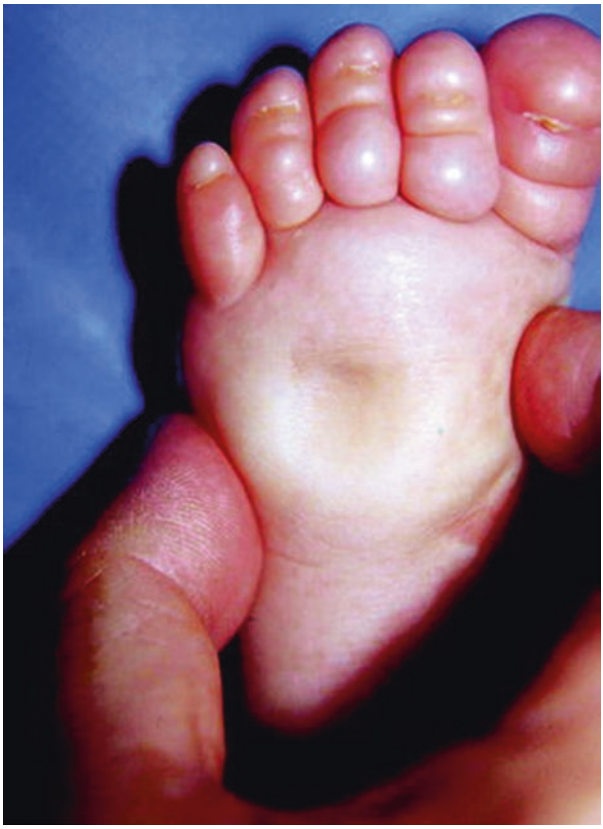


Fig. 62.6 Primary lymphedema with a positive pitting test (fovea)

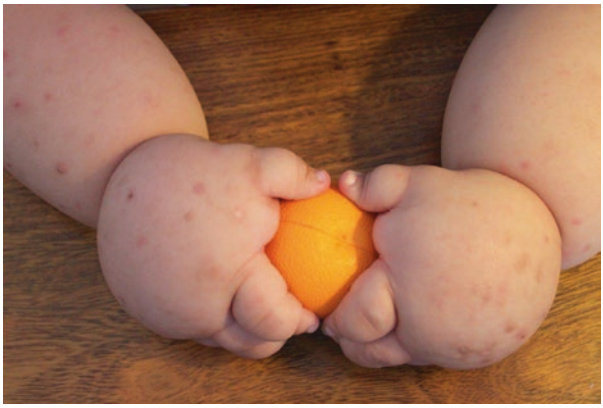


Fig. 62.7 Primary lymphedema of both hands and fingers

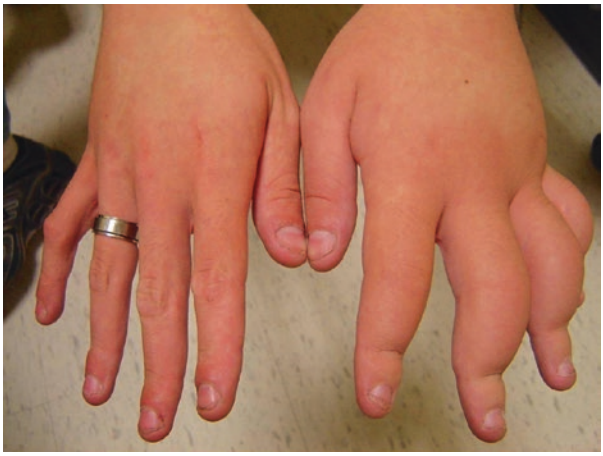


Fig. 62.8 Primary lymhedema in a hand and fingers

Fig. 62.9 Primary lymphedema with lymphangiomatosis in thumb

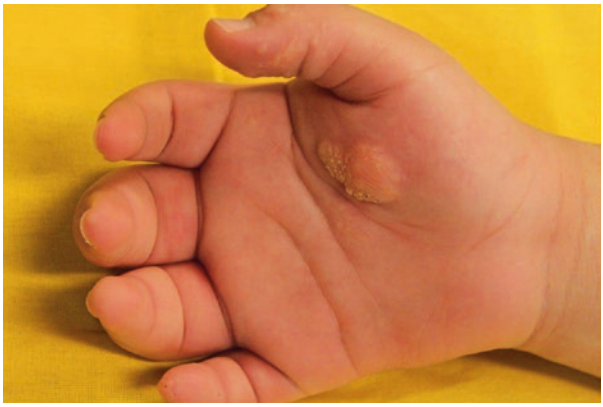


Fig. 62.10 Palmar verrucosis in a hand with primary lymph-edema

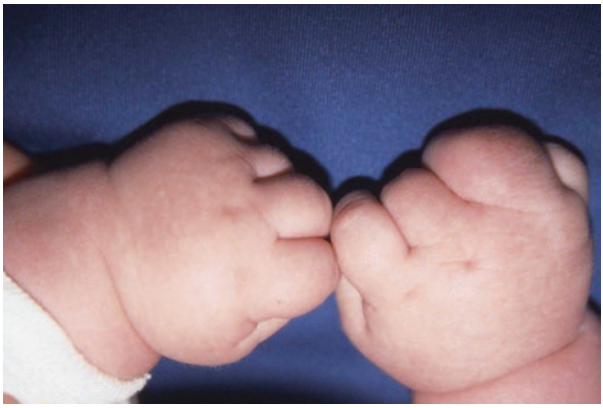


Fig. 62.11 Primary lymphedema of upper limbs

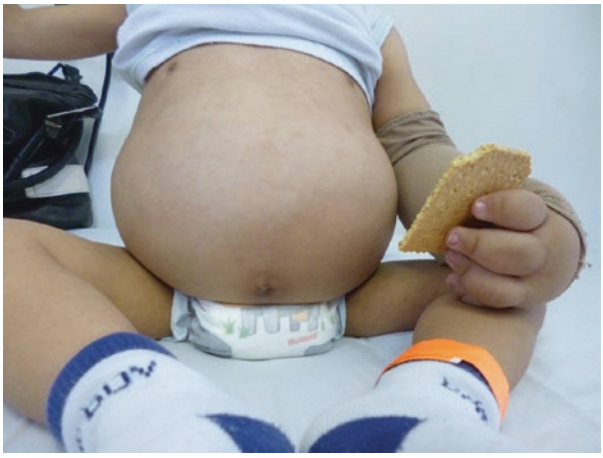


Fig. 62.12 Waldmann disease. Intestinal lymphangiectasia, quiloperitoneo, primary lymphdema in left upper limb and right lower limb

The classification of primary lymphedema into three groups of congenital, praecox, and tarda types is based on the age at first clinical manifestation [8], but they all have similar dysplastic and/or functional causes. Instead, primary lymphedema can be graded based on its expression in grades (0–3), as per the 0–III degree International Society of Lymphology (ISL) classification; 0–I are usually not diagnosed; degree II is postponed till better circumstances concur, as a result of the lack of therapeutic consensus in pediatrics, and degree III, severe, usually lacks adequate assistance resources for treatment, according to international consensus protocols not considered for pediatrics [11, 33].

In terms of incidence and prevalence statistics, degrees 0–I are not reported but are the most frequent ones. Thus, degree II is the most relevant and statistically significant degree, as degree III, elephantiasis, is the least frequent and considered to be rare.

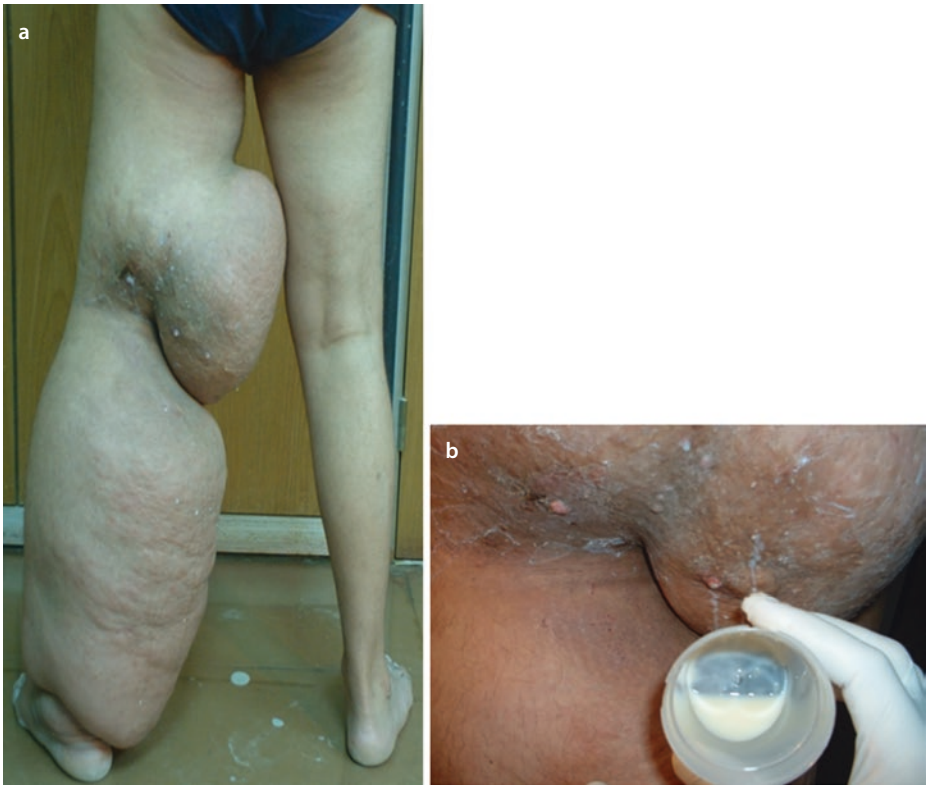


Fig. 62.13 **a**, **b** Primary lymphedema and chylous reflux. Chylo-cutanea fistula

62.3 Secondary Lymphedema

There are more than 15 extrinsic causes to the lymphatic system for the development of a secondary lymphedema, some of them are tumors, surgery, infections (filariasis, TBC), trauma, venous hypertension (troncular), radiation, podoconiosis, amniotic bands, hair tourniquet, compression, fractures, low-frequency respiratory assistance, malnutrition, chronic drugs (antibiotics, growth hormones), drug addiction, and burns [34–36] (Figs. 62.22, 62.23, and 62.24).

The most frequent being parasitism, e.g., filariasis, and venous hypertension, secondary to a troncular venous malformation. The latter is usually linked to an abnormality in the lymphatic system, resulting in a possible primary lymphedema, in addition to a lymphatic overload at the level of the interstice, resulting from a poor carrying capacity in the venous system. The latter is the cause of secondary lymphedema. Thus, lymphedema is both primary and secondary.

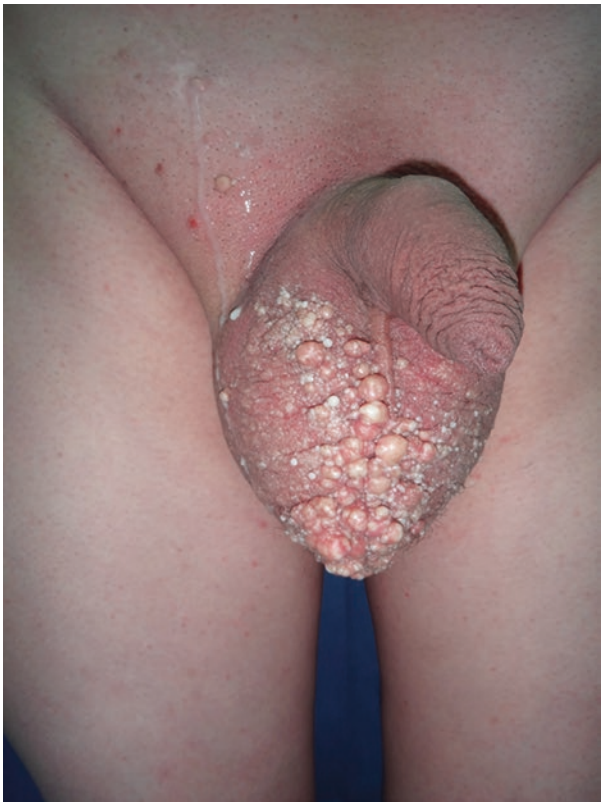


Fig. 62.14 Chylous leaks at scrotum and inguinal region. Chylous - cutanea fistula

62.4 Management

The treatment regimen with manual lymph drainage (MLD)-based complex decongestive physical therapy (CDP) is all indicated for pediatric lymphedema, and the LF (lymphedema framework) and ISL consensus documents remain a useful guideline [11, 33] (Figs. 62.25 and 62.26).

Although the genetic information would support the diagnosis, a certain condition of dysplasia and/or dysfunction would need a biopsy of a nodal or lymph vessel to establish an anatomo-pathological pattern as well as a thorough phlebography, lymphochromy, and Doppler ultrasound to explore the possibility of a lymphovenous anastomosis.

Phlebotropic agents are beneficial when primary lymphedema is associated with venous anomalies.

Various surgical options are possible, but are not easy in pediatric patients [5, 37, 38, 39].

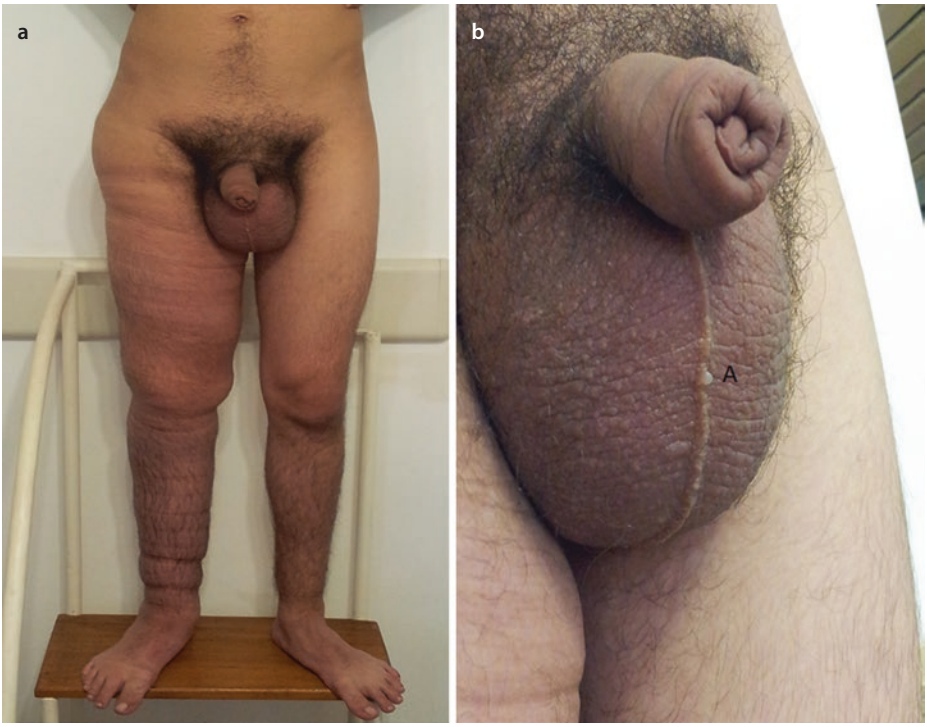


Fig. 62.15 **a** Primary lymphedema of the right leg, **b** Genital lmphedema (A chylous cutanea fistula)

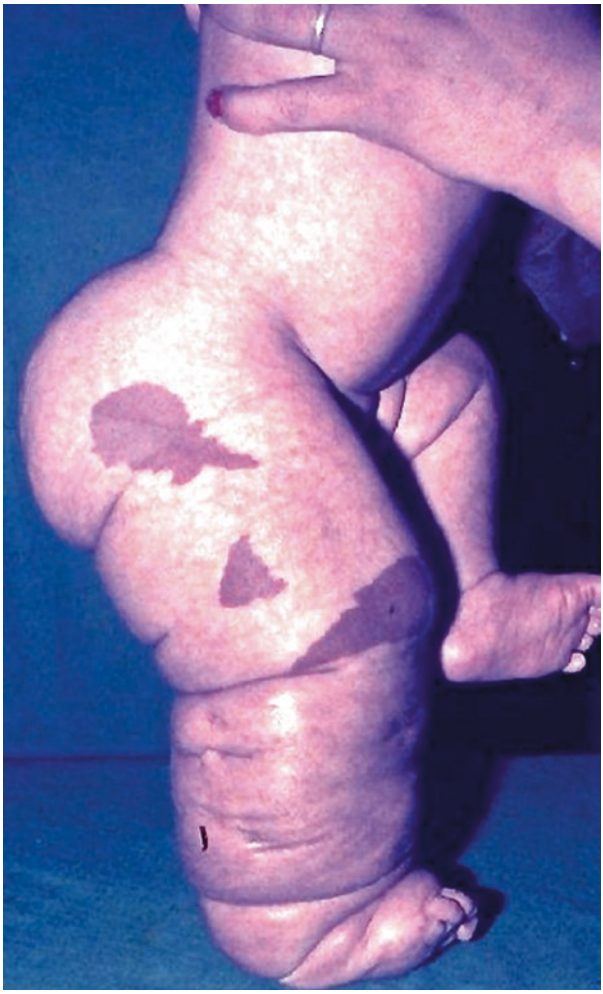


Fig. 62.16 Figure 62.2 Klippel Trenaunay in a lower limb and pelvis of a child

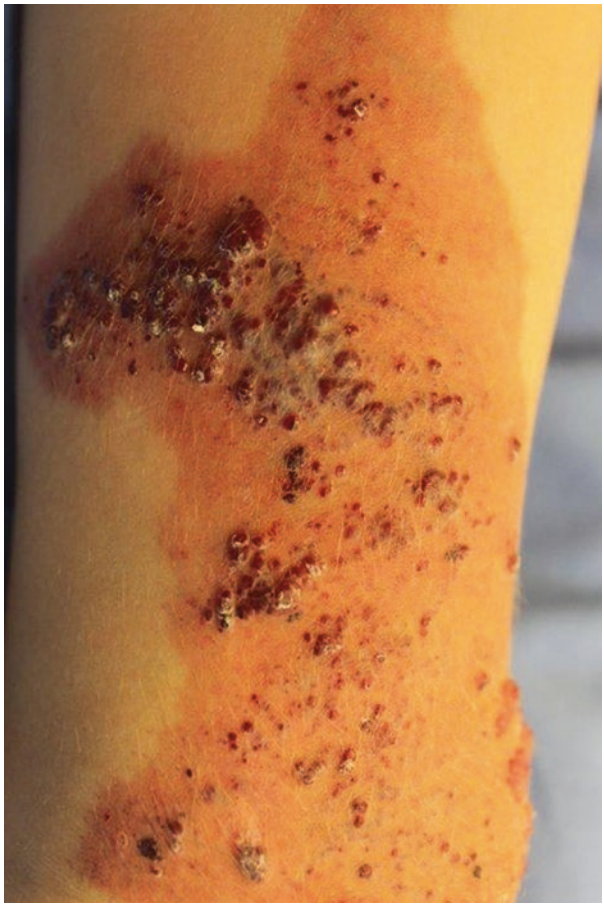


Fig. 62.17 Hemorrhagic lymphangiectasia KTS

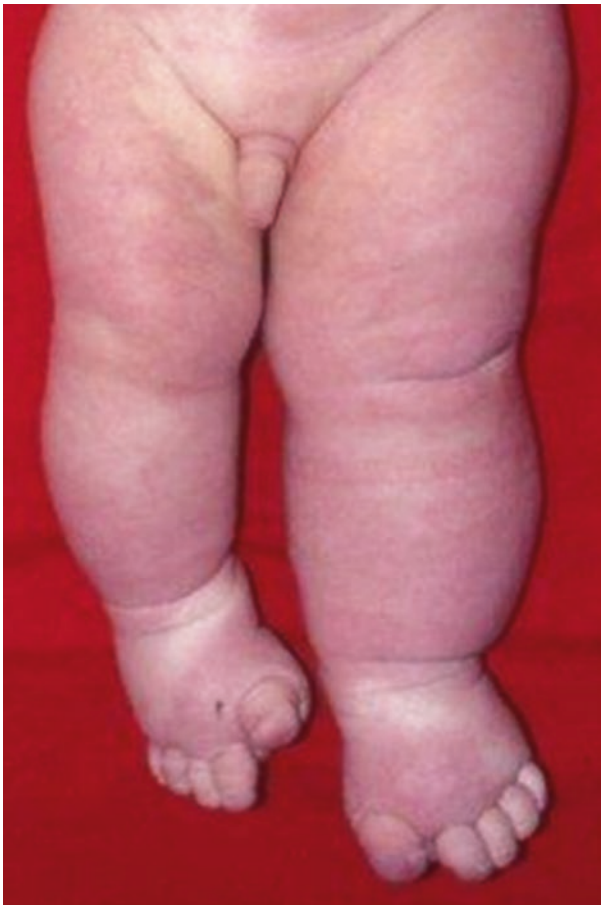


Fig. 62.18 Parks Weber sydrome. Lower limbs. Lymphangio adeno dysplasia with primary Lymphedema and lipomatous overgrowth

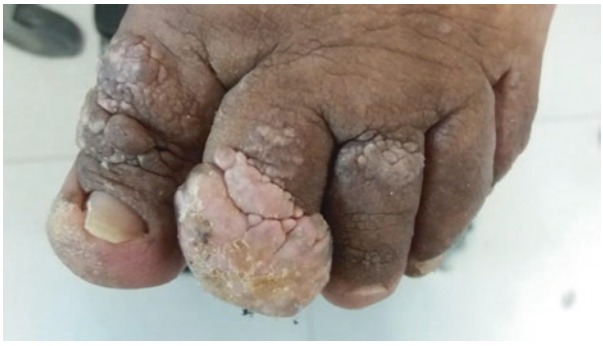


Fig. 62.19 Lymphostatic verrucosis in a foot with primary lymphedema.

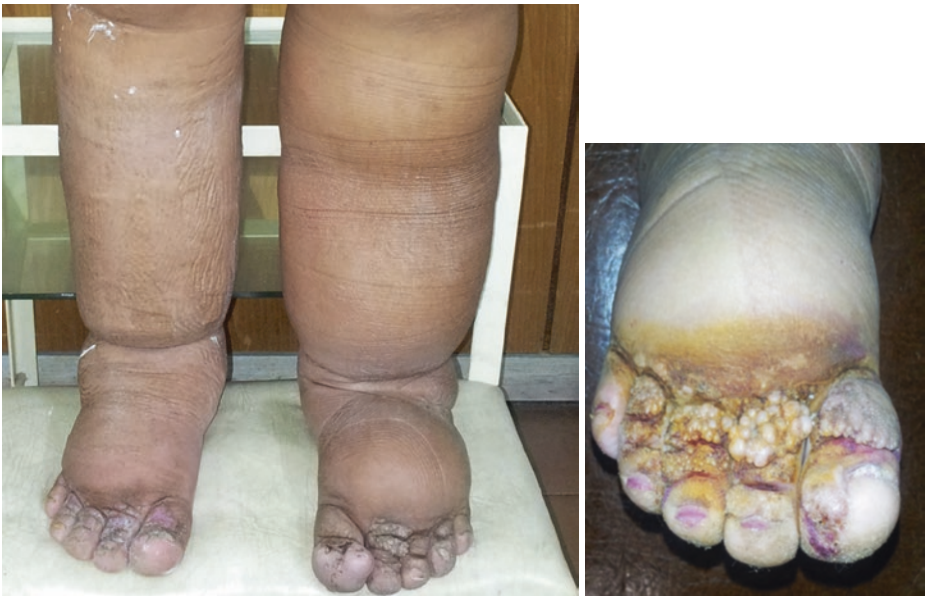
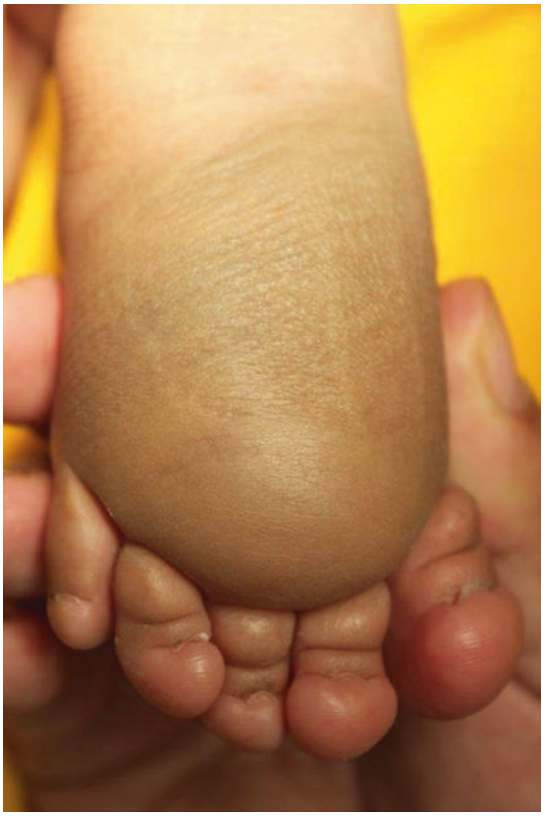


Fig. 62.20 Primary lyphedema of the legs with verrucosis of the fingers

Fig. 62.21 Primary lymphedema in a foot with melanic nevus



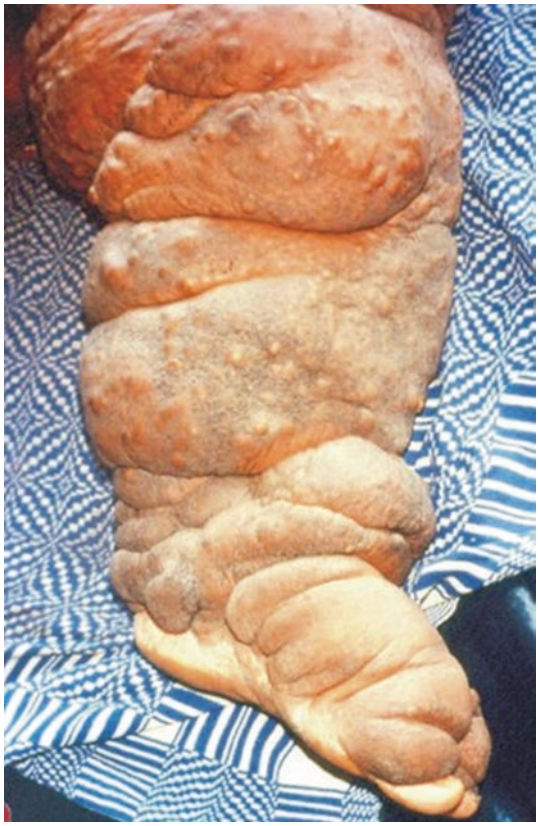


Fig. 62.22 Parasitic elephantiasis by Wuchereria Bancrofti. Filariasis in lower limb of a child. Dermoepidermitis with secondary lymphedema

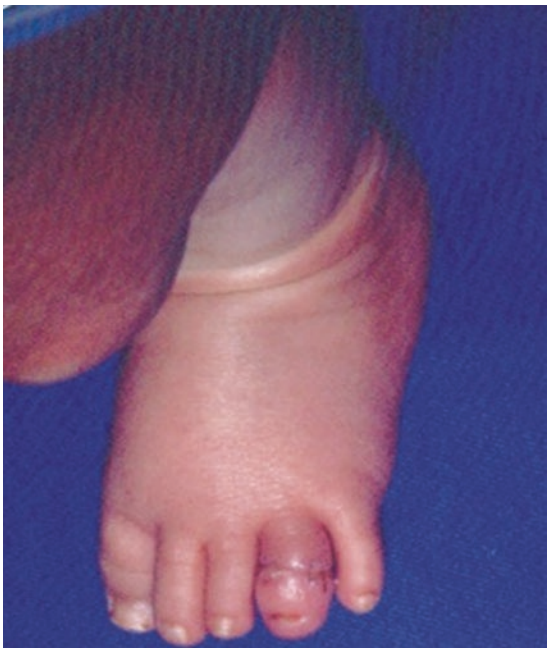


Fig. 62.23 Hair tourniquet syndrome in a newborn

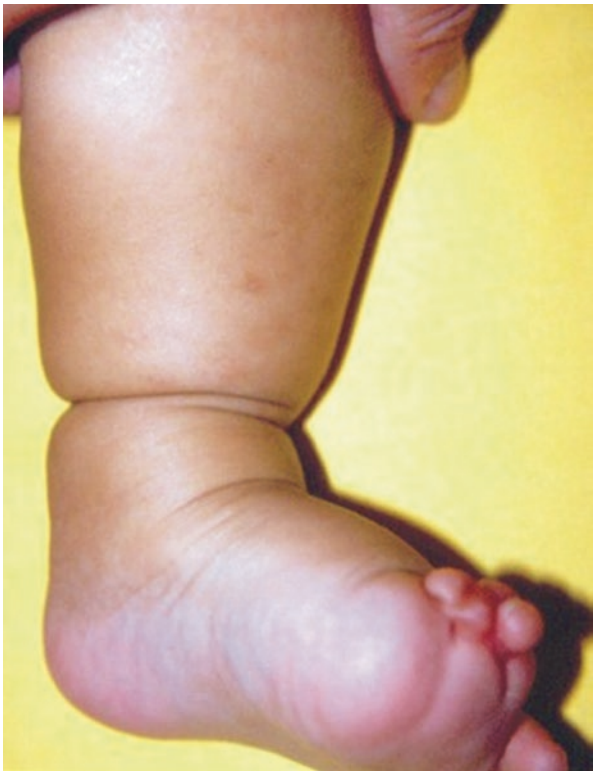


Fig. 62.24 Secondary lymphedema for amniotic bands

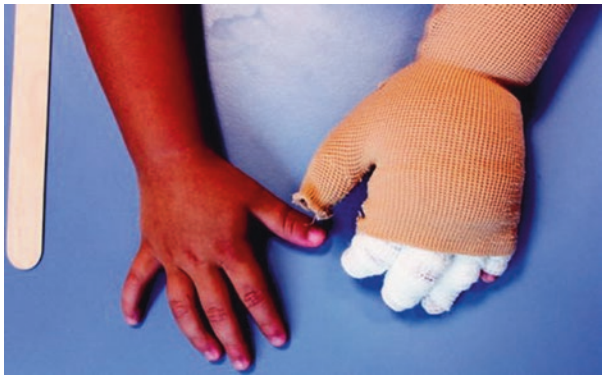


Fig. 62.25 Congenital syndromatic asymmetric 1° Lymphedema on upper limbs after and during physical treatment

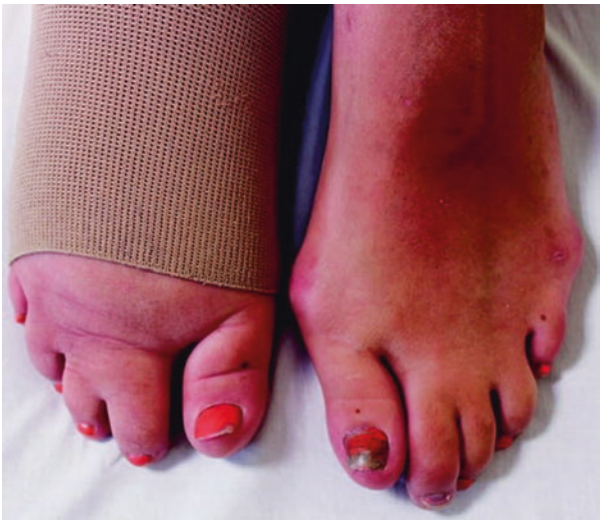


Fig. 62.26 Congenital bilateral asymmetric 1° Lymphedema in a young girl on the feet with elastic support, with bilateral syndactilia

Conclusion

The great difference from the adult patients with mostly secondary lymphedema is that this condition among the children is a condition for lifelong; when the child grows, it grows with this condition as well. Therefore, all therapy regimens must be adjusted constantly, although new measurements incur much higher costs (e.g., babies with bandages and elastic supports). Also, the increased risk of cancer development cannot be ignored through this lifetime chronic illness.

Lack of knowledge/interest in this disease often gives the wrong belief/prejudice that it is a contagious if not hereditary condition, which should be eradicated to provide reasonable quality of life to the children through full integration into school. This condition must be recognized as a part of mandatory social welfare [1, 2, 10].

Whenever possible, children should be treated through a separate health center and not mix with the adult patients. The suffering of the adult patients often gives severe psychological trauma to adolescent patients who are at a critical moment in their life and psychologically most sensitive. Proper recognition of all these issues makes it easier to assist pediatric patients in specialized centers.

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Management of Chyle Reflux and Effusions

Contents

Pathophysiology and Medical Management of Chylous Disorders

Francine Blei

B.-B. Lee et al. (eds.), *Lymphedema*, https://doi.org/10.1007/978-3-319-52423-8_63

Summary of Basic Concepts

- Chyle Leakage can occur in the chest, abdomen, pericardium, or other organs, and can result in chylous effusions, chyluria, chyloptysis and other symptoms.
- It is important to identify the etiology of the chyle leak, to formulate the most appropriate treatment
- Chyle leakage can result in hematologic, biochemical, and/or immune dysfunction.
- This chapter reviews the causes and consequences of chyle leakage, and reviews therapeutic options.

63

Chyle is a creamy white fluid formed in intestinal lacteals during digestion, which is normally transported through the lymphatics entering the venous circulation via the thoracic duct. Properties of chyle are listed in ◘ Table 63.1. Chyle is rich in triglycerides, protein, and white blood cells, especially T lymphocytes. Subsequently, patients with chylorrhea have low serum levels of protein, lymphocytes, and fat-soluble vitamins and develop a metabolic acidosis due to electrolyte imbalances. Immune dysfunction can arise due to loss of immunoglobulins and lymphocytes [6] (◘ Table 63.2).

Lymphatic drainage from multiple sites returns to the venous system to the thoracic duct, via the cisterna chyli. The relevant anatomy of lymphatic drainage is illustrated

◘ **Table 63.1** Properties of chyle

High protein (albumin)
High triglyceride level (>110 mg/dL)
WBCs – especially T cells

◘ **Table 63.2** Consequences of chyle leak

Hypoproteinemia (e.g., loss of albumin)
Lymphopenia
Hypocalcemia
Hyponatremia
Metabolic acidosis
Deficiencies of fat-soluble vitamins (ADEK)
Immunocompromise/susceptibility to infection (loss of immunoglobulins, T lymphocytes)

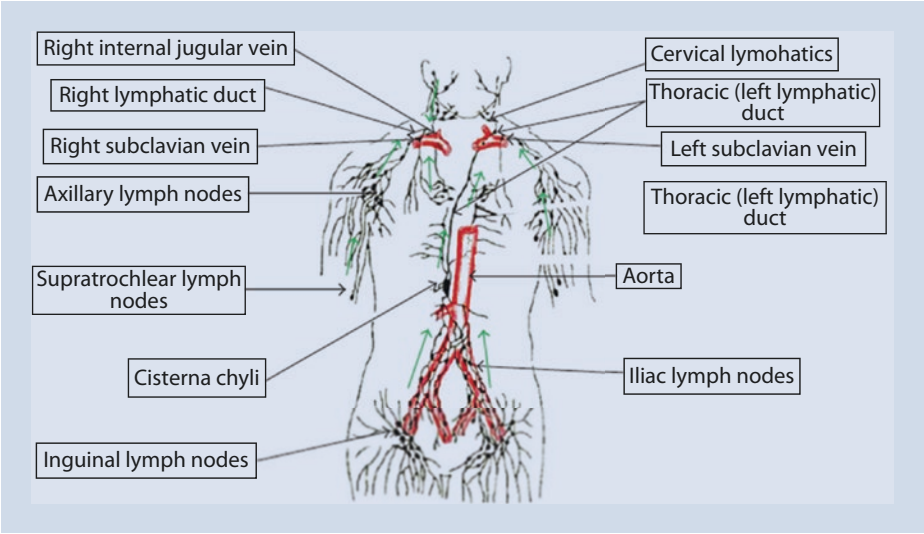

Fig. 63.1 Routes for drainage of lymph from lymph trunks into the thoracic and right lymphatic ducts. The *green arrows* indicate the direction of lymph flow (Said A. Al-Busafi et al. [7])

in Fig. 63.1. During normal digestion, chylomicrons are absorbed by the small intestines and then traverse omental lymphatics to the cisterna chili, anterior to the lumbar vertebrae. This connects to the lumbar, thoracic, and hepatic lymphatics, ultimately forming the thoracic duct which drains (all but the right chest, arm, neck, and head) into the venous system. When normal lymphatic vessels are obstructed (e.g., hypoplasia, extrinsic compression, fibrosis), or damaged (e.g., trauma), chylous leaks (also called chylous effusions) can occur. Obstruction or direct trauma to the lymphatics may lead to leakage of chyle into the pleural cavity (cisterna chyli damage causing pleural effusions) or peritoneal cavity (lymphatic damage in the gastrointestinal tract causing chylous ascites) [7].

Chyle leaks can occur in the prenatal, pediatric, and adult populations, with age-related etiologic correlation. In adults, chyle leaks are more commonly malignancy related. Symptoms of chyle leak can be acute or insidious, ranging from nonspecific discomfort to respiratory distress and abdominal distension.

Chyle leaks can be due to traumatic or atraumatic etiologies, as listed in Table 63.3. Chylothorax can result from trauma (post-cardiac, pulmonary, esophagus, head, and neck surgery, thoracic duct trauma, CPR, central venous catheter placement, diaphragmatic hernia repair), malignancy, congenital anomalies, or infections (TB). Trauma-related chyle leaks can be due to blunt damage to the thoracic duct or incomplete ligation of lymphatic vessels. Chylothorax may also result from lymphatic malformations, lymphangiectasis, lymphangioleiomyomatosis, generalized lymphatic anomaly (GLA), Gorham's disease, and lymphatic obstruction (e.g., due to congenital anomalies or hypoplasia, or malignancy) [1–3, 8–13]. Tutor provides a comprehensive review of etiologies of chylothorax in children [2]. Chylothorax has a high morbidity and often

Table 63.3 Etiological classification of chylous ascites

Astraumatic [7]		Traumatic
(I) Neoplastic	*Cardiac*	*(I) Iatrogenic*
Solid organ cancers	Constrictive pericarditis	*(A) Surgical*
Lymphoma	Congestive heart failure	Abdominal aneurysm repair
Sarcoma	*Gastrointestinal*	Retroperitoneal lymphadenectomy
Carcinoid tumors	Celtac sprue	Placement of peritoneal dialysis catheter
Lymphangioleiomyomatosis	Whipple's disease	Inferior vena cava resection
Chronic lymphatic leukemia	Intestinal malrotation	Pancreaticoduodenectomy
(II) Diseases	Small bowel volvulus	Vagotomy
(A) Congenital	Ménétrier disease	Radical and laparoscopic nephrectomy
Primary lymphatic hypoplasia	*Inflammatory*	Nissen fundoplication
Klippel-Trenaunay syndrome	Pancreatitis	Distal splenorenal shunts
Yellow nail syndrome	Fibrosing mesenteritis	Laparoscopic adrenalectomy
Primary lymphatic hyperplasia	Retroperitoneal fibrosis	Gynecological surgery
Lymphangioma	Sarcoidosis	*(B) Nonsurgical*
Familial visceral myopathy	Systemic lupus erythematosus	Radiotherapy
(B) Acquired	Behçet's disease	*(II) Noniatrogenic*
Cirrhosis	Peritoneal dialysis	Blunt abdominal trauma
Infectious	Hyperthyroidism	Battered child syndrome
Tuberculosis	Nephrotic syndrome	Penetrating abdominal trauma
Filariasis	*Drugs*	Shear forces to the root of the mesentery
Mycobacterium avium in AIDS	Calcium channel blockers	*(III) Idiopathic*
Ascariasis	Strolimus	Rule out lymphoma

Said A. Al-Busafi et al. [7]

presents as a pleural effusion, and diagnosis can be made by analysis of fluid from pleurocentesis. Chylothorax may be associated with chyloptysis, chyle-containing sputum [14].

Lymphoscintigraphy or lymphangiogram may be useful to define anatomy [15, 16]. Shibasaki et al. describe the use of bedside indocyanine green (ICG) lymphography for evaluation of lymphatic dysfunction in neonates with congenital chylothorax and chylous ascites. Dermal backflow of dye in the extremities was assessed with an infrared camera system. The degree of backflow in the limbs correlated with severity of the effusions [4, 17]. Shackcloth recommends preoperative administration of oral cream to patients prior to esophageal surgery, as this intervention helps identify the thoracic duct and surrounding lymphatic channels, decreasing the chance of trauma and postoperative chylothorax [18].

Chylothorax can be identified (and treated) prenatally [5, 19, 20]. Caserio reported 29 cases of congenital chylothorax, 94% diagnosed in utero, 66.7% of which had fetal hydrops, with an overall survival rate of 56% at 3 years of age [21]. Ergaz reported 11 neonates with congenital chylothorax, nine of whom were diagnosed prenatally, five of which underwent intrauterine pleurocentesis [22]. Most of the patients [12] had chromosomal abnormalities. Lee et al. reported 29 infants with prenatally diagnosed chylothorax, the majority presenting with hydrops. In this series, most cases were bilateral, and those infants diagnosed prior to 34 weeks of gestational age who received antenatal therapy had an improved outcome [5].

Chylous ascites, due to disruption of the abdominal lymphatics, can manifest as abdominal distention or dyspnea. In adults, this is most commonly due to malignant obstruction. Other etiologies include lymphangiectasis, cirrhosis, trauma, and lymphangioleiomyomatosis [2, 7, 13, 23]. Trauma-induced chylous ascites may be due to secondary portal hypertension, which can disrupt the integrity of lymphatics. Retroperitoneal lymph node dissection, abdominal aortic aneurysm, and renal surgeries are most commonly associated with chylous ascites [24].

There are several nonsurgical treatments of chyle leaks, summarized in Table 63.4. Treatment of chylorrhea often begins with dietary modification – enteral nutrition with

Table 63.4 Nonsurgical treatments for chylorrhea

Octreotide
OK432
Etilefrine
Sirolimus
Factor XIII
Sclerotherapy
Radiation

no-/low-fat diet and medium-chain triglycerides (MCT) oil. MCT are directly absorbed into the portal system, bypassing the lymphatics. Total parenteral nutrition (TPN) with bowel rest may also ameliorate chyle leaks [7, 25]. If nutritional measures are inadequate, medical or surgical interventions may be effective.

Pleurodesis, various shunting techniques, and/or thoracic duct embolization may be effective for chylothorax or chylous ascites [26–28].

63.1 Medical Therapies for Chylorrhea

Octreotide [Sandostatin, Novartis Pharmaceuticals] is a long-acting somatostatin analogue, which inhibits many hormones (including growth hormone glucagon, insulin), diminishes secretions from the intestine and pancreas, and decreases intestinal motility. This drug is FDA approved for the treatment of acromegaly and carcinoid syndrome; however there are many published reports documenting efficacy in managing primary or secondary chylothorax and chylous ascites [11, 24, 29–39] including newborns [40]. Octreotide may indirectly decrease chyle secretion via binding to lymphatic somatostatin receptors and reducing bile acid secretion into the intestine and has also been effective in traumatic thoracic duct trauma-related chyle leak [41].

There are several reports of successful antenatal (in utero) treatment with intrapleural OK-432 (Picibanil) for fetal chylothorax [42–44]. Matsukum showed successful results with postnatal treatment with OK-432 for unrelenting octreotide-resistant congenital chylothorax in newborns [45].

Intravenous etilefrine hydrochloride was shown to decrease chyle leaks in eight of ten patients. The authors conclude: «by inducing contraction of the smooth muscle fibres present in the wall of the main thoracic chyle ducts, etilefrine can be considered as a useful adjunct in the management of post-operative chyle leak» [46]. Sirolimus (Rapamycin, Wyeth Pharmaceuticals) has been shown to be effective for the treatment of lymphangioleiomyomatosis (LAM), including chylous effusions [47–51]. There is one report of factor XIII infusion for recalcitrant post-lung transplantation chylothorax in a patient with underlying lymphangioleiomyomatosis [52]. What is evident is that there is no consensus for the management of chylorrhea and nor have there been randomized case control studies [36, 53].

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Surgical Management of Chylous Reflux and Effusions

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Summary of Basic Concepts

- Chylous disorders are rare.
- Conservative therapy is usually the first-line treatment option, but endovascular and surgical treatments are available as are peritoneovenous shunts (PVSs) to direct chyle into the central venous system.
- The outcomes depend on etiology, the site of lymph leaks, the amount of drainage volume, and the extent of chylous disease. Also, the increasingly performed endovascular treatment such as percutaneous embolization has challenged the use of traditional open surgeries.
- Principles, indications, results, and problems of surgical techniques are reviewed in this chapter.

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Chylous reflux is the term used to describe retrograde flow in the incompetent lymphatic system secondary to lymphangiectasia and loss of lymphatic valve function. Chylous effusion results when dilated lymph vessels rupture and chyle accumulates in body cavities or in joints. Rupture of skin lymphatics results in chylous leak. Chylous effusions are uncommon but serious and frequently life-threatening conditions. The etiology of chylous effusions includes primary developmental abnormalities of the lymph vessels, such as lymphangiectasia, atresia, or hypoplasia [1], or secondary causes due to trauma, surgery, or tumor [6, 7]. Disruption of the lymphatics can cause chylous effusions such as chylothorax, chylous ascites, chyloperitoneum, or chylopericardium. Management of chylous reflux alone is usually conservative. Treatment of chylous effusions largely depends on the underlying cause and the amount of drainage volume. Conservative therapy including nutritional and medical management is the mainstay of treatment, and it is effective in many patients, especially in those with postoperative chylous effusions [2, 3, 7]. Therapeutic paracentesis or thoracentesis is indicated in patients with severe dyspnea and/or abdominal discomfort, to drain the accumulated chyle [8].

Although percutaneous endovascular therapy has been increasingly used recently [9–15], open surgical ligation of the lymphatic leaks or the thoracic duct (TD), with pleurodesis for chylothorax [7, 16], is still frequently performed in patients who fail to conservative management but not eligible for endovascular treatment or in those who fail to endovascular management. In some patients, lympho-venous reconstruction (LVR) with lympho-venous anastomosis (LVA) or grafting can be performed using microsurgical techniques, while, in others, a peritoneovenous shunt (PVS) can be placed to shunt the chyle from the abdominal cavity into the central veins [3, 4, 7]. Surgical management of chylous effusions is challenging due to the diversity of the disorders in terms of etiology, site of lymph leaks and extent, and the frequently high surgical risk; in addition, some procedures are technically demanding, requiring microsurgical techniques.

Conservative management of chylous disorders is discussed in ▶ Chap. 63. In this chapter, we review principles, indications, results, and problems of the surgical interventions. Since chylous effusions occur rarely, the literature is sparse and consists of case reports and observational series with evidence of low or very low quality.

64.1 Principles

Management of a chylous effusion depends on the underlying cause; conservative therapy should be the first-line treatment option unless there is a life-threatening condition caused by high volume of chyle leak. In some instances, treatment of the underlying causes can also improve chylous effusions.

Medical treatment as discussed in ► Chap. 63 should be initiated when diet or nutritional measures prove ineffective or served as an adjunctive method to nutritional management. Therapeutic paracentesis or thoracentesis is indicated in patients with severe dyspnea and/or abdominal discomfort. If the chyle flow rate is <500 ml for chylothorax, conservative measures can be applied, and spontaneous closure of the leak may occur in 28–90% of the patients. Conservative management is effective particularly for postoperative chylous ascites, with success rates ranging from 67% to 100% [2, 3, 17].

Open surgical treatment of chylous effusion today is reserved for those who are refractory to conservative management and who are not candidates or fail to endovascular treatment. Open surgical treatment includes ligation of the lymph leaks or vessels, excision of the incompetent lymphatics, LVRs, or placement of a PVS, with simultaneous pleurodesis or sclerotherapy, based on the site and extent of chylous effusion. Ligation of TD under video-assisted thoracoscopy (VATS) or LVR using microsurgical techniques is usually performed to facilitate the procedure.

The goal of surgical treatment of chylous effusion is to obliterate persistent lymph leak which may cause malnutrition, immunocompromised state, and severe electrolyte abnormalities, by ligation or excision of the lymph leaks or vessels or incompetent lymphatics, or promote chylous fluid drainage by LVR or PVS.

64.2 Indications

Surgical treatment is indicated for all patients who have high-output lymph leaks that result in refractory chylous effusions or in patients who do not benefit from conservative treatment or who fail to minimally invasive management. Surgical treatment options are varied and individualized based on the etiology, site, extent, and severity of chylous disorders.

Surgical indications for chylothorax have been well described in several studies. Cerfolio et al. [18] recommended early reoperation and ligation of the TD when drainage was more than 1000 mL/day based on their experience on 47 chylothoraces developed after thoracic operations. Browse et al. suggested surgery if the fluid loss exceeded 1.5 L per day for more than 5–7 days in an adult or more than 100 mL per day in a child with chylothorax [6]. Schild et al. [12] reviewed literature on chylothorax published between 1995 and 2013 and recommended surgical treatment if: ① More than 1000–1500 mL chyle is drained every day (>100 mL/kg body weight in children); ② Drain output is up to 1000 mL/day for five treatment days (100 mL/year of age in children); ③ A chyle leak (100 mL/day) persists for more than 2 weeks; ④ Drain output remains unchanged over 1–2 weeks; and ⑤ Clinical deterioration such as malnutrition or metabolic problems occur. Early surgical treatment is recommended in young patients with high-volume chyle leaks and in children with body weight below 4 kg. In patients with chylothorax

after esophagectomy, a delay of 2–4 weeks is recommended to avoid to put the anastomoses at risk [12]. Takuwa and colleagues [19] suggested surgical treatment for chylothorax that developed after mediastinal lymph node dissection and resection of primary lung cancer, if the drainage exceeds 500 ml during the first 24 h after initiation of a low-fat diet.

Early intervention with VATS is recommended for most patients with a high-output fistula (>1000 mL/24 h), although some authors recommend at least a 1-week trial of conservative therapy. If the chylous output remains greater than 200 mL/24 h after 1 week, VATS intervention is considered [7, 20].

In patients with postoperative chylous ascites, surgical treatment is considered only in those refractory to conservative treatment. In a grading system for chylous ascites after pancreaticoduodenectomy proposed by van der Gaag et al., Grade C patient may require surgical intervention; in this category, the duration of chylous ascites is usually longer than 14 days despite of the treatment [21].

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64.3 Open Surgical Treatments

Currently, there are no strong recommendations regarding management of chylous effusions. In patients with primary chylous disorders who fail conservative or endovascular management, the selective use of ligation of lymphatic fistulas, excision of dilated lymphatics, sclerotherapy, lymphatic reconstruction, and placement of a PVS are considered [3].

64.3.1 Ligation of the Thoracic Duct and Sclerotherapy for Chylothorax

Traditionally, TD ligation was performed via open thoracotomy. Since VATS has been introduced in the early 1990s, TD ligation with VATS is increasingly used due to its advantage of minimally invasive technique, magnification of the thoracic structures which can facilitate the ligation, efficacy, low expense, and low morbidity. This minimally invasive procedure can also avoid a lengthy conservative course with concomitant loss of chyle and a long hospital stay.

Technique

Preoperative lymphangiography may localize the site of the chylous fistula or document occlusion of the TD. Although percutaneous or tube pleurodesis may be effective in other forms of nonmalignant chylothorax, it is less effective for primary chylothorax. Surgical pleurodesis, either with open thoracotomy [22, 23] or with VATS [7, 24–29], with excision of the parietal pleura is the optimal treatment. After a fatty meal, thoracotomy or VATS is performed and the lymphatics are oversewn or clipped. In most cases, this is followed by talc or mechanical pleurodesis.

Ligation of the TD far above the diaphragm may be more successful than clipping of the TD near the diaphragm when VATS is performed. Additionally, if extensive fibrosis is present and the TD is not easily identified, VATS may be used to ligate the mass of tissue between the azygos vein and the aorta with good success [7, 20].

Results

Cerfolio et al. [18] from Mayo Clinic reported 47 patients in whom chylothorax developed after thoracic operations. Nonoperative therapy was successful in one third of the patients, but 32 patients required ligation of the TD, and 2 were treated with mechanical pleurodesis and fibrin glue. Surgery was successful in 31 of the 34 patients (91%). In a series of Browse et al. [6], a total of 20 patients were treated for primary or secondary chylothorax; pleurectomy was performed in 7 patients with primary and in 4 patients with secondary chylothorax, with good outcomes. The authors concluded that open pleurectomy was the most successful treatment to prevent recurrence of the effusion when no distinct chylous leak can be identified. Our earlier experience in 8 procedures for chylothorax included thoracotomy with decortication and pleurodesis ($n = 4$), ligation of TD ($n = 3$), and resection of a TD cyst (patient = 1), showing excellent early results in all patients [4]. Bender et al. summarized literature on the surgical management of chylothoraces published between 1981 and 2009; surgical ligation of the TD was successful in 67–100% of the cases, with the best results after treatment for traumatic chylothorax [17].

For postoperative chylothorax following esophagectomy and supradiaphragmatic ligation of the TD for esophageal cancer, Brinkmann and colleagues reported an incidence of 1.9%. In patients with high-output chylous fistula, an early rethoracotomy with repeat ligation of the TD was safe and effective [30].

A summary paper from Kumar and Pawar in 2004 reported a total of 21 VATS cases for the treatment of chylothorax ($n = 16$), chylopericardium ($n = 4$), and cervical chylous leak ($n = 1$), without postoperative complications [20]. Other case reports have demonstrated that VATS is an accepted technique for the management of chylothorax when the occlusion of TD is located between the azygos vein and the descending thoracic aorta [24–28].

Slater et al. [29] reported on the largest case series of TD ligation using VATS, applying a combination of tissue sealer (5 mm LigaSure®, Covidien Energy, Boulder, CO; 3 mm, Justright Surgical, Boulder, CO) and/or sutures, along with mechanical pleurodesis and administration of fibrin glue for the management of chylothorax. Twenty-one patients were treated, all through the right chest with 3 ports. Technical success was 90%; two patients who failed to respond had successful thoracoscopic pleurectomy and chemical pleurodesis.

64.3.2 Ligation, Excision, and Sclerotherapy of the Incompetent Lymph Vessels for Chylous Ascites and Chylous Reflux

In patients with chylous ascites or reflux of chyle to the genitalia or the limbs, ligation, oversewing, excision, and sclerotherapy of the incompetent or ruptured lymph vessels or lymphatics can be performed, with or without LVR or lymphatic bypass grafting [31].

Technique

Patients are fed with 60 g of butter or 16 oz. of whipping cream 4 h before the procedure. For lower extremity lymphedema due to chylous reflux, the lymphatics are approached retroperitoneally through a flank incision. The fatty meal allows ready visualization of

the retroperitoneal lymphatics during exploration. Dilated and ruptured lymphatics can be oversewn, ligated, or clipped. Careful ligation of the lymph vessels should be done in order to avoid further lymphatic avulsion and leak (Fig. 64.1a–d).

For chylous ascites caused by ruptured abdominal or pelvic lymphatics, a midline transabdominal approach is used. Chylous cysts, when found, are excised. The most involved segments of the small bowel can be resected in those patients who have severe protein-losing enteropathy due to primary lymphangiectasia. Success of the exploration is improved if a well-defined abdominal fistula because of a ruptured lymphatic vessel or cyst is identified. Sclerotherapy, as an adjunctive procedure, is performed by injecting tetracycline or doxycycline solution, 500–1000 mg diluted in 20 mL of normal saline, directly into the dilated retroperitoneal and pelvic lymph vessels to provoke obstructive lymphangitis.

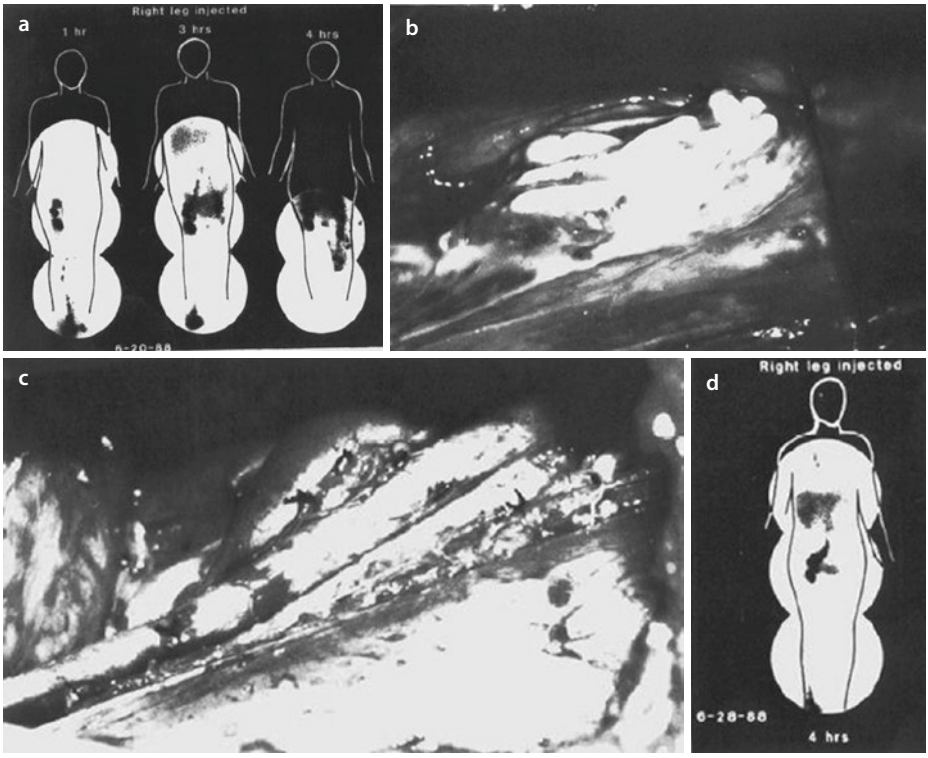

Fig. 64.1 **a** *Right* lower extremity lymphoscintigraphy in a 16-year-old girl with lymphangiectasia and severe reflux into the genitalia and *left* lower extremity. Injection of the isotope into the *right* foot reveals reflux into the pelvis at 3 h and into the *left* lower extremity at 4 h. **b** Intraoperative photograph reveals dilated incompetent retroperitoneal lymphatics in the *left* iliac fossa containing chyle. **c** Radical excision and ligation of the lymph vessels were performed. In addition, two lympho-venous anastomoses were also performed between two dilated lymphatics and two lumbar veins. **d** Postoperative lymphoscintigram performed in a similar fashion reveals no evidence of reflux at 4 h. The patient has no significant reflux 4 years after surgery (From Gloviczki et al. [33])

Results

Servelle published excellent and durable results from ligation and excision of the dilated refluxing lymphatics in 55 patients [32]. In a series of 19 patients who underwent ligation of the retroperitoneal lymphatics for chylous reflux to the limbs and genitalia (antireflux procedure) by Kinmonth [1], permanent cure was achieved in five patients and alleviation of symptoms, frequently after several operations, in 12 patients. No improvement or failure was noted in two cases.

Browse et al. [22] reported on a series of 45 patients with chylous ascites. The age at presentation ranged from 1 to 80 (median 12) years; 23 patients were aged 15 years or younger. The chylous ascites was primary in 35 patients and secondary in 10 patients including non-Hodgkin's lymphoma in six. Other associated lymphatic abnormalities were present in 36 patients, lymphedema of the leg being the most common (26 patients). All patients were initially treated conservatively with dietary manipulation with best results in patients with leaking small bowel lymphatics. Closure of a retroperitoneal or mesenteric fistula, when present, was the most successful operation, curing 7 of the 12 patients. If chylous ascites reaccumulates, reoperation with ligation of the fistula was the most effective treatment. Mean follow-up was 50 months (range 1 month–17 years), 10 patients were cured, and 11 were improved [22].

In 35 patients with primary chylous disorders we treated over a 24-year period [33], 10 patients underwent resection of retroperitoneal lymphatics with or without sclerotherapy of lymphatics, 4 had LVA or grafts, 4 had PVSs, and 1 patient had a hysterectomy for periuterine lymphangiectasia. All patients improved initially, but five had recurrence of some symptoms at a mean of 25 months (range 1–43 months). In three patients with leg swelling, postoperative lymphoscintigraphy confirmed improved lymphatic transport and diminished reflux.

In a retrospective single-center study, Campisi et al. [5] reported on the surgical results of primary chylous ascites in 12 patients with a mean follow-up of 5 years (range 3–7 years). They found laparoscopy was advantageous for confirming the diagnosis, draining the ascites, and evaluating the extension of dysplasia. Carbon dioxide laser was also used as an adjunct for "welding" lymphatic vessels with a low degree of dilatation in 75% of the patients. Eight patients had no relapse of ascites, three had mild recurrence, one of which was treated effectively with a PVS, and one patient died 1 year after surgery from an unrelated cause.

In a recent systemic review of treatment options for postoperative chylous ascites following major abdominal surgery [2], of 36 papers analyzed, surgical treatment was described in case series in nine papers [34–42]. In the study by Pabst et al., 5 patients underwent surgical lymphatic fistula closure, all had chylous ascites resolved although one patient required reintervention for a second fistula closure [34]. In another study, the attempt to surgical identification and ligation of the cisterna chyli was failed in all three patients refractory to conservative management; of these patients, lymph leak was not identified on preoperative lymphangiogram or lymphoscintigraphy [39].

64.3.3 Lympho-Venous Reconstruction

LVR is performed either with a direct anastomosis between a large lymph vessel or the TD and a vein or using a vein interposition graft between the lymphatic and the venous system. LVR works well if a patent TD or large lymphatic vessel is available for a microsurgical anastomosis with the venous system.

Technique

This procedure is technically demanding and requires microscope enhancement to complete the anastomosis. If the upper TD is occluded on lymphangiography, resulting in reflux of chyle into the pleural, pericardial, or peritoneal cavity, LVR with TD–azygos vein anastomosis can be attempted to reconstruct the TD and improve lymphatic transport. Through a right posterolateral thoracotomy, an anastomosis between the lower TD and the azygos vein is performed in an end-to-end fashion, with 8–0 or 10–0 nonabsorbable interrupted sutures and magnification using loupes or the operating microscope (Fig. 64.2a–c). Kinmonth [1], who performed this operation in several patients, suggested that the anastomosis alone is not effective for decompressing the TD; ligation of the abnormal mediastinal lymphatics and oversewing of the sites of the lymphatic leak are also necessary. For terminal TD occlusion, LVR with TD–internal jugular vein (IJV) anastomosis can be considered [43–45].

In patients with chylous reflux, LVA can also be performed, although reflux of blood into the incompetent lymphatics may be a problem; a competent valve on the venous side using a saphenous vein graft will avoid reflux and increase the chance of successful lymphatic drainage [4].

Results

Varying results after LVR have been obtained from case reports. Browse et al. reported on three patients who underwent TD–azygos vein anastomosis for primary (n = 2) or secondary (n = 1) chylothorax, but all anastomoses occluded at 1 year [6]. Our previous study reported on primary chylous disorders that included LVAs (n = 2) or saphenous vein interposition grafting (n = 2) (Fig. 64.3) in addition to retroperitoneal lymphatic ligation. During a median follow-up of 40 months, three of the four LVR patients (75%) were symptomatically improved; additionally, in three patients, improved lymphatic transport and diminished reflux was confirmed on postoperative lymphoscintigraphy [4].

LVR can be applied to the treatment of a TD cyst. In a patient with persistent cervical swelling with spontaneous chylothorax and chyloperitoneum caused by a TD cyst with a terminal obstruction of the TD, which was confirmed on lymphangiography, LVA with a side-to-side anastomosis between the cyst and the IJV was performed. Postoperative course was unremarkable, there was no recurrence or vein thrombosis on cervical ultrasound at 3 months, the patient remained symptom-free at 3 years [45].

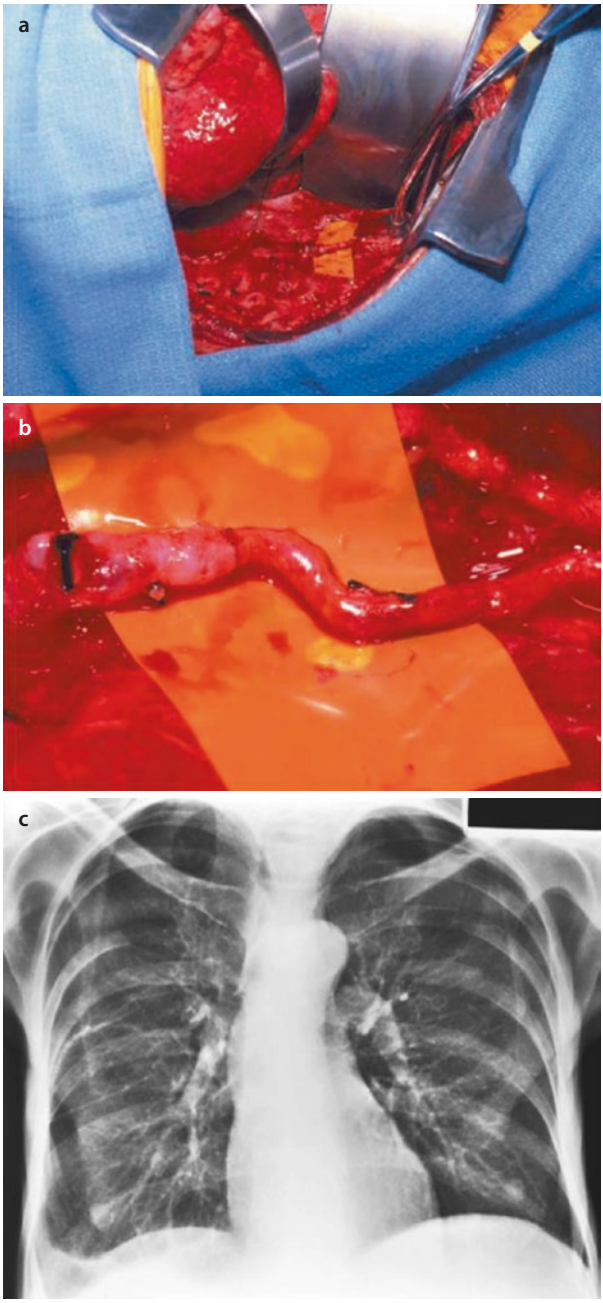

Fig. 64.2 **a**, **b** Thoracic duct–azygos vein anastomosis performed through a *right* posterolateral thoracotomy in an end-to-end fashion with interrupted 8–0 Prolene sutures. **c** Chest radiograph 2 years later confirms the absence of chylothorax (From Gloviczki et al. [31].)

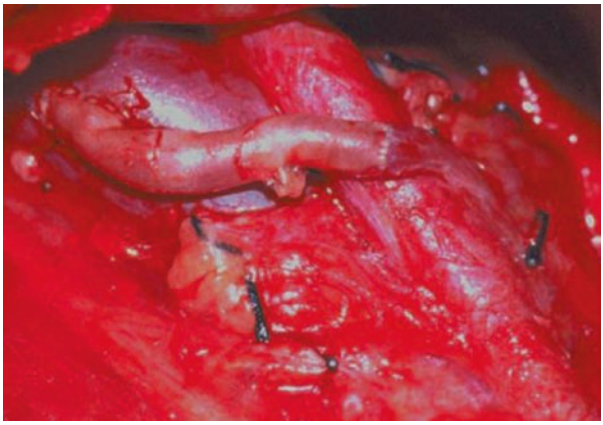

Fig. 64.3 Lympho-venous anastomosis using a saphenous vein graft between a large retroperitoneal lymph vessel (end-to-end) and the *right* common iliac vein (end-to-side). The competent valve in the vein prevents reflux of blood into the dilated and incompetent lymph vessel (From Huang et al. [3])

LVR was reported successful in treating a young lady with persistent chylous vaginal discharge, which was considered secondary. LVA to the right external iliac vein along with meticulous ligation of all visible megalymphatics in the pelvis, parametrium, and iliac region was performed, and the patient remained asymptomatic at 4-year follow-up [46].

LVR was also reported to treat idiopathic lymphatic effusions in neonates. Mihara et al. reported five cases treated with LVA at the extremities in neonates aged 0.5–7 months, based on indocyanine green lymphography. Postoperatively, chylous effusion ended in two of the five cases and decreased in one case [47].

64.3.4 Peritoneovenous Shunt

PVS is performed for chylous ascites using LeVeen shunt (Becton Dickinson, Franklin Lakes, NJ) or Denver shunt (CareFusion, San Diego, CA). This technique is also considered in patients with fibrosed, aplastic, or hypoplastic mesenteric lymphatic trunks, when diffuse exudation of the chyle is the main source of the ascites [3]. LeVeen shunt was introduced in 1974 [48], but it was withdrawn from the market in the late 1990s and it is no longer available. Denver shunt (CareFusion, San Diego, CA) was introduced in 1970, for the treatment of hydrocephalus [49], and received interest in the management of ascites thereafter. The Denver shunt is offered in two French sizes (11.5 and 15.5 Fr), with either a single or a double valve. The one-way valve prevents the reflux of blood into the venous limb of the shunt, and the second valve acts as a check valve to prevent reflux of ascites or blood from the venous limb of the shunt into the valve chamber while it is refilling after compression pumping.

Technique

The right IJV is accessed, with the help of a 16-Fr peel-away sheath that is placed into the superior vena cava (SVC) and through the right atrium into the inferior vena cava (IVC). The tip of the catheter is positioned between the SVC and the right atrium. The container of the shunt is placed over the edge of the eighth and ninth ribs. In cases of IJV or SVC occlusion, catheter-based shunt placement can be performed from the peritoneal cavity through the great saphenous vein (GSV) and common femoral vein (CFV) into the IVC. Before shunt placement, the ascites should be drained, leaving only a small amount of ascites with which to prime the shunt. In some patients, resection or ligation of pleural, retroperitoneal, and mesenteric lymphatics with or without sclerotherapy of lymphatics or sclerotherapy of lymphatics alone can be performed simultaneously [3].

Results

Results with PVS have been mixed; patency is usually judged by recurrence of ascites. In the study by Browse et al. [6], the nine PVSs were all occluded within 3–6 months after placement. We reported previously on using the LeVeen shunt in three patients with good results, although one patient developed symptomatic superior vena cava syndrome due to thrombosis around the shunt [4].

In the systemic review of postoperative chylous ascites following major abdominal surgery [2], case reports of PVS were described only in five papers [34, 35, 37–39]. Pabst et al. reported a mortality rate of 20% and chylous ascites resolution rate of 80% in five patients with PVS; cause of death of the patient was shunt infection [34]. In the study by Kaas et al., three patients underwent PVS, at 1 month, one patient developed sepsis, and the shunt was found nonfunctional [35]. Evan and colleagues reported a shunt replacement rate of 80% in five patients requiring PVS [37].

There were few scattered case reports on Denver shunt in the management of chylous ascites; the results have been varied, showing efficacy [50–56] or adverse events including loss of the shunt patency [35, 57–59], gastrointestinal bleed [52], and sepsis [34, 35]. The most recent publication on 28 patients with PVS is by far the largest series of using Denver shunt in the management of chylous ascites. Causes of chylous ascites in these patients were postoperative chylous ascites following retroperitoneal lymph node dissection (RLND) for cancer in 17 patients and cancer related in 11 patients. Ascites were resolved in 92% (26/28) of patients. Complications included shunt malfunction or occlusion ($n = 6$), SVC thrombosis ($n = 2$), subclinical disseminated intravascular coagulopathy (DIC, $n = 2$), and systemic infection ($n = 1$), resulting in a complication rate of 37% [60]. Due to the etiology of chylous ascites, the effectiveness of Denver shunt in the management of chylous ascites continues to be controversial.

64.4 Problems with Surgical Treatments

Currently, there is no evidence-based guideline regarding optimal management of chylous effusions, and management is recommended by the American Venous Forum based on expert consensus opinion as best practice (Table 64.1). Although the increasingly

Table 64.1 Guidelines 6.5.0 of the American Venous Forum on the management of chylous disorders

No. of guideline	Guideline	Grade of recommendation 1. Strong 2. Weak	Grade of evidence A: High quality B: Moderate quality C: Low or very low quality
6.5.1	For primary treatment of chylous effusions and fistulas due to reflux, we recommend first a low-fat or medium-chain triglyceride diet, followed by drug therapy that may include somatostatin and its analogs, diuretics, and sympathomimetic drugs to enhance thoracic duct contractions. This is followed by percutaneous aspirations of chylous fluid by thoracentesis or paracentesis	1	B
6.5.2	In patients with chylous effusions, we suggest percutaneous embolization using coils or glue as the first line of treatment, once conservative management fails	2	B
6.5.3	If endovascular treatment is not possible or fails, we suggest open surgery for treatment of chylous effusions and symptomatic lymphangiectasia. These procedures include ligation of lymphatic fistulas, excision of dilated lymphatics, sclerotherapy, video-assisted thoracoscopy with pleurodesis and ligation of the thoracic duct, lymphatic reconstruction, or, as a last resort, placement of a peritoneovenous shunt	2	C

performed endovascular treatment such as percutaneous embolization of TD has challenged the use of traditional open surgery [9–15], surgical therapy remains the treatment of choice in patients who fail or who are not eligible for endovascular treatment. Outcomes after surgical management of chylous effusions largely depend on the underlying cause, the site of lymph leaks, the amount of drainage volume, and the extent of chylous disease. Therefore, individualized treatment is mandatory.

Ligation and/or excision of the incompetent and leaking lymph vessels frequently has good results for patients with lymphangiectasia and lymphatic reflux [1, 32] or for postoperative chylous effusions [6, 17, 18, 34]. However, the procedure may fail when the site of the leak is not seen on preoperative imaging [39]. For patients with chylotho-

rax, TD ligation via VATS is recommended by most authors if the site of the chylous effusion is not well visualized [17]. LVR is technically demanding and can be performed only in microsurgical centers of excellence. Besides, the success of LVR depends on the caliber and patency of the lymph vessel and the vein and the etiology of chylous disease as well. LVR is suggested in selected patients with obstructive, secondary chylous effusion, early in the course of the disease. Simultaneous excision of the incompetent or ruptured lymphatics is needed to achieve better results.

Finally, results after PVS are inconsistent; the efficacy of PVSs in the treatment of chylous ascites still remains controversial. In addition, Denver shunt is currently the only available shunt to be used in PVS, and in our experience, durability of these shunts is strictly limited. Improvements in technology to design new shunts or invent other drainage techniques to treat chylous effusions are needed.

Conclusions

Chylous disorders are fortunately rare. Conservative therapy is the first line of treatment unless there is a life-threatening condition caused by loss of high volume of chyle. Surgical treatment is indicated in patients refractory to conservative therapy or who fail to endovascular management. For chylothorax, ligation of the leaking lymphatics and the TD along with pleurodesis via thoracotomy or VATS is frequently effective. In selected patients with chylothorax, LVR with a TD–azygos vein or TD–IJV anastomosis may be considered. Ligation of the incompetent retroperitoneal lymphatics and oversewing ruptured lymphatics can produce long-term improvement in lymphangiectasia and lymphatic reflux. Chylous ascites can be treated with ligation of the mesenteric or retroperitoneal lymphatic fistulae or with LVR or bypass grafting in cases with larger lymph vessel and patent adjacent venous system. The role of PVSs in the treatment of chylous ascites remains controversial because the Denver shunt in most reports has limited durability of patency in patients with chylous ascites. Individualized treatment based on the etiology, site of lymph leaks, the amount of drainage volume, and the extent of chylous reflux and effusions is mandatory to achieve treatment success.

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Endovascular Catheter-Based Management of Chylous Effusions

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Summary of Basic Concepts

- Diagnosis of chylous effusions is often uncertain, especially in not traumatic cases. For patients on a normal diet, the concentration of triglycerides has to be within hundreds of mg/dl, typically higher than 300 mg/dl, and percentage of lymphocytes in the lymph is usually higher than 70%. When the diagnosis is in question, food challenge is recommended.
- Intranodal lymphangiogram replaced traditional pedal lymphangiogram as a less technically challenging alternative.
- Thoracic duct embolization (TDE) technique consists of two parts: diagnostic lymphangiogram and percutaneous embolization of the thoracic duct.
- Thoracic duct embolization is an effective treatment for chylothorax.
- Dynamic contrast MR lymphangiogram provides an excellent imaging of central lymphatic system.
- Abnormal pulmonary lymphatic flow from thoracic duct toward mediastinum, termed pulmonary lymphatic perfusion syndrome (PLPS), is a pathophysiological mechanism of condition such as plastic bronchitis, neonatal chylothorax, and nontraumatic chylothorax.
- The causes of idiopathic chylothorax are chylous ascites, PLPS, and leakage of the chyle from the lymphatic mases.
- Thoracic duct embolization is an effective treatment of plastic bronchitis and chyloptysis.

65.1 Etiology of the Chylous Effusions

Chylous effusions are accumulation of chyle in the body cavities, which present as a milky exudate high in lymphocytes and triglyceride content. The characteristics of the chylous effusion can vary depending on nutritional status, enteral intake, and comorbidities. For patients on a normal diet, the concentration of triglycerides in chylous effusions has to be within hundreds of mg/dl, typically higher than 300 mg/dl. Chyle is the lymphatic fluid and for that reason it is rich in lymphocytes. The ratio of lymphocytes in the lymph is usually higher than 70%. Differentiation of chyle effusion from non-chylous is critically important before initiation of the treatment. If the diagnosis is in doubt, food challenge with high-fat-content food can be attempted, and as a result, the concentration of the triglycerides will increase significantly if the fluid is chylous.

There are multiple classifications of chylous effusions, but for practical purposes, we divide chylous effusion into two types, traumatic and nontraumatic. Traumatic chylous effusion occurs in close proximity to iatrogenic (most common) and accidental trauma. Surgeries in the areas that are reach of lymphatic channels, such as retroperitoneum, neck, and posterior mediastinum, are usually most commonly associated with chylous leaks. The source of the leak in traumatic chylous effusions can be easy visualized with lymphangiogram, and for that reason the outcome of percutaneous treatment is excellent. Nontraumatic chylous effusions are those not associated with a recent history of trauma. The most common causes of nontraumatic chylous effusions are idiopathic and blood malignancies.

65.2 Lymphatic Imaging

Traditional pedal lymphangiography is both time-consuming and technically challenging, as well as requiring specialized equipment, which may not be readily available in the average radiology department. Intranodal lymphangiography has been described for the use in TDE and is a less technically challenging alternative to conventional pedal lymphangiography [6]. Based on a simple ultrasound (US)-guided puncture of the inguinal lymph nodes, this technique is within the basic skill set of any interventionalist practicing US-guided procedures [7].

In this technique, an inguinal lymph node is directly accessed under ultrasound guidance with a 25-gauge spinal needle (BD Medical, Franklin Lakes, NJ) with the needle tip positioned in the hilum of the node. Subsequently, an oil-based contrast agent (Lipiodol; Guerbert, Villepinte, France) is injected by hand at a rate of about 1–2 mL per 5 min. If successful, immediate opacification of the lymphatic vessels is observed under fluoroscopy (Fig. 65.1). A total volume of approximately 6 mL of contrast is injected into a lymph node in each groin to opacify the abdominal and pelvic lymphatics in an adult patient. In order to further propel the contrast in the lymphatic system, the injection of Lipiodol is followed by injection of saline («saline flash»). The injection of the saline into the lymph nodes can be mildly painful for the patient. Thus, adequate intravenous sedation is necessary before intranodal injection of saline.

The feasibility of using intranodal lymphangiography for TDE was demonstrated in a recent study [6]. Using intranodal lymphangiogram, the abdominopelvic lymphatics, cisterna chyli, and TD were visualized successfully in all patients. Subsequently, the TD was successfully catheterized and embolized in all patients. This technique also reduced the embolization time, mainly due to faster transit

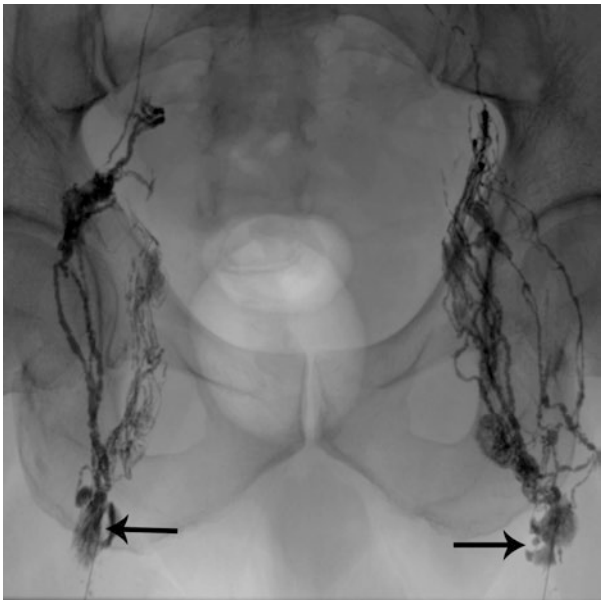

Fig. 65.1 Fluoroscopic image of the intranodal lymphangiogram, demonstrating the 25 G needles located in the bilateral lymph nodes (*arrow*). Contrast material propagates from the lymph nodes into pelvic lymphatic vessels

between the site of the initial Lipiodol injection and the TD. Overall, intranodal lymphangiography for TDE appears to be easier, safer, and faster than the older method of pedal lymphangiography.

65.3 MR Lymphangiogram: T2 Imaging and Dynamic Contrast Enhanced MR Lymphangiography (DCRML)

Heavy T2-weighted MR lymphangiography has been reported to image the central lymphatic system by several authors [8–14]. This imaging utilizes the differences in T2-weighted signal intensity between soft tissue and lymphatic structures with high water content that produces high T2 signal. It allows visualization of lymphatic masses, as well as segments of the central lymphatic anatomy including the anatomy of the thoracic duct in disease states such as liver cirrhosis as well as in patients with single ventricle physiology [12, 15–18]. We utilize this imaging as a part of the MR lymphangiography study, to delineate better the lymphatic anatomy, including the abnormal lymphatic masses and the location and the extent of the lymphatic effusions (Fig. 65.2).

The T2 imaging, however, doesn't provide information about flow in the lymphatic system and lacks specificity to the lymphatic tissue. This, however, can be resolved by introducing contrast into the lymphatic vessels.

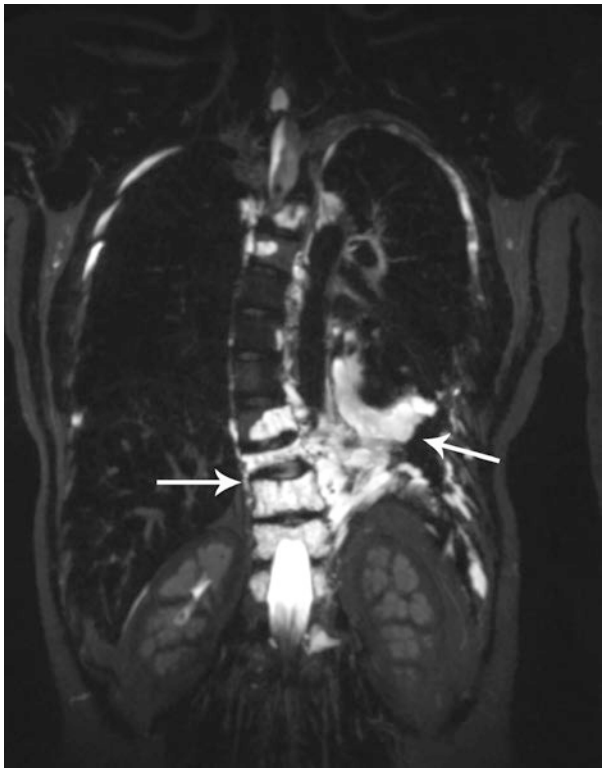

Fig. 65.2 Heavy T2 imaging of the spine, chest, and abdomen of the patient with generalized lymphatic anomaly. It demonstrates high signal from the lymphatic masses involving spinal vertebrae and left pleural space (*arrows*)

Dynamic contrast MR lymphangiography (DCMRL) utilizes inguinal intranodal injection of the MR contrast, similar to intranodal lymphangiogram, and shows both anatomy of the lymphatic system and dynamic flow with excellent temporal and spatial resolution [1, 19, 20]. DCRML became the modality of choice for identification of the etiology of the lymphatic flow disorders and interventional planning. Current indications for DCMRL include nontraumatic chylous leaks, complicated traumatic lymphatic leaks where the source of the leak cannot be visualized with conventional lymphangiography, cardiac and lymphatic plastic bronchitis, neonatal lymphatic flow disorders such as neonatal chylothorax, and neonatal chylous ascites and congenital lymphatic dysplasia.

65.4 DCMRL Technique

The ideal systems for performing DCRML utilize a setup that couples an MR machine and catheterization suite which share the same procedural table, for example, XMR lab (Siemens, Erlangen, Germany). This setup allows a smooth transition of the patient between the units and minimizes the dislodgement of the injection needles. DCMRL procedures are started in a fluoroscopy suite or in a suite with available ultrasound and c-ARM where access to the lymph nodes is performed. After positioning the patient on the table, the inguinal lymph nodes are directly accessed under ultrasound guidance with a 25 gauge spinal needle connected to a 3 cc syringe via a short connector tubing as described by Nadolski et al. [6]. Once confirmed, the needle is fixed with adhesive tape, and the patient is transferred to the MRI scanner using a Miyabi sliding table that connects the MR and catheterization labs for imaging.

65.5 DCMRL Protocol

Any modern 1.5 T or 3 T MRI scanner is suitable for DCMRL imaging. A volume of 0.1 mmol/Kg of undiluted contrast or gadolinium-based contrast (Gadavist, Bayer Healthcare Pharmaceuticals Inc., Wayne, NJ) is injected by hand into each lymph node at a rate of 0.5–1 mL/min. One minute after the initiation of the injection, scanning is started. For dynamic imaging a contrast-enhanced time-resolved MRA sequence is used. Typical scanning parameters are matrix 320 × 240, field of view 300 to 450, repetition time 3, time to echo 1, flip angle 25, slice thickness 1.2, isotropic voxel size 1.2 × 1.2 × 1.2, and scan time per 3D volume of 3–6 s with a total scan time ≈15 min. At the end of the dynamic phase, static high-resolution MRA scans can be obtained after the dynamic imaging. A navigated 3D spoiled gradient echo sequence with inversion recovery works well with typical scanning parameters as follows: matrix 320 × 240, field of view 300 to 450, repetition time 300, time to echo 1.5, flip angle 20, slice thickness 1.2, and isotropic voxel size 1.2 × 1.2 × 1.2. Scan time for this sequence varies between 1 and 2 min (Fig. 65.3).

We utilize DCMRL for assessment of central lymphatic system anatomy to determine the location of lymphatic leaks and to determine the pattern of lymphatic flow. All this information allows us to plan interventional lymphatic procedures.

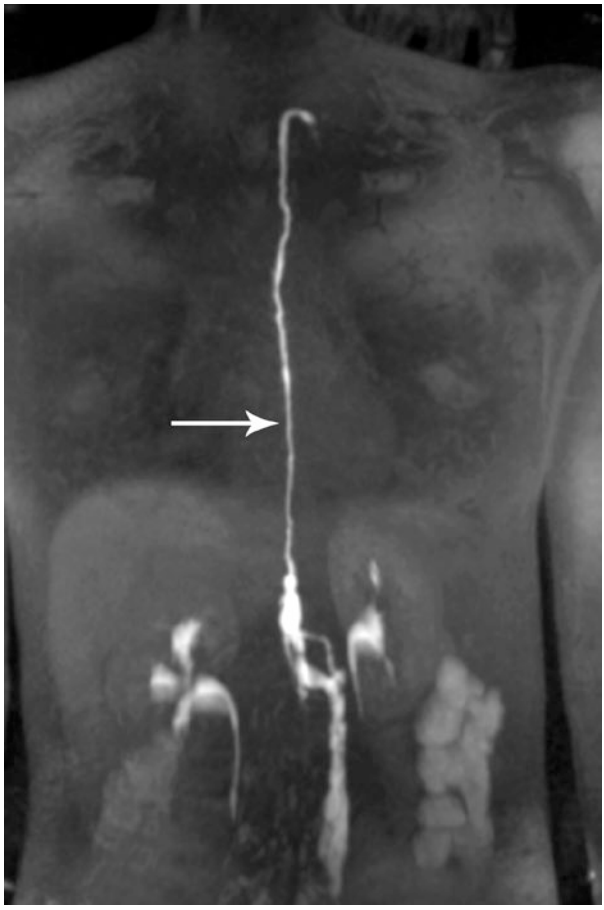

Fig. 65.3 DCRML image demonstrating normal appearing thoracic duct (*arrow*)

65.6 Technique of Thoracic Duct Embolization (TDE)

As with any image-guided procedure, TDE consists of two parts, lymphatic imaging and lymphatic intervention. Intranodal lymphangiogram is initially performed to identify the access point to the lymphatic system, which in most cases is cisterna chyli and its contributories. After the cisterna chyli and its contributing lymphatics are visualized, they are accessed transabdominally using a 21–22G needle. To prevent leakage of chyle from the cisterna chyli, access to the lymphatic system is performed through its contributing lymphatic feeders just below the cisterna chyli. Using this access, stiff 0.018″ wire (V-18, Boston Scientific, Natick, MA) is then advanced into the TD, followed by a 3F microcatheter (Rapidtransit, Cordis Hialeah, FL). Contrast is then injected through the catheter into the thoracic duct to demonstrate the cause of the chylous effusion. In traumatic chylothoraces, the cause of the leak is most often a tear of the TD or leakage from a TD branch/collateral (Fig. 65.4). In nontraumatic chylothoraces, frequently the cause of the chylothorax is occlusion of the upper part of the thoracic duct.

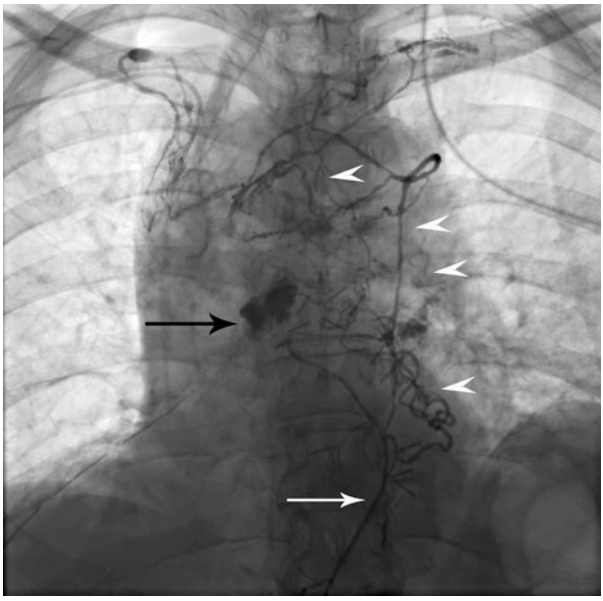

Fig. 65.4 Patient with iatrogenic postsurgical chylothorax. Contrast material is injected into the thoracic duct through the catheter (*white arrow*) leaks in the right chest (*black arrow*). The main thoracic duct is absent in the middle and upper chest, with multiple collateral vessels in the mediastinum *(white arrowheads)*

After the cause of the chylothorax is identified, embolization of the TD is performed below the leak point or lymphatic abnormality. If the leak is identified from the branch of the TD, selective catheterization of the branch can be attempted. The embolization is performed using a combination of platinum embolization coils and N-butyl cyanoacrylate glue (Truefill, Codeman Neuro, MA). If the leak is suspected to be from multiple small collaterals, embolization with glue only can be performed.

In cases where TD catheterization is technically unsuccessful, TD needle disruption can be performed using «twiddling motion with the needle» as previously described [2, 21–23]. Traumatic disruption of the lymphatic vessels most probably results in controlled venous bleeding into the lymphatic vessels with subsequent formation of blood clots and/or local inflammation, which close the leak.

65.7 Thoracic Duct Embolization of Traumatic Chylothorax

Percutaneous treatment of traumatic chylous leaks has become the main treatment choice for these patients, with a very high cure rate, especially when imaging is able to demonstrate the leak source [2, 24, 25]. In patients with traumatic chylothorax, DCMRL can help in identifying the source of the leak and assist in planning interventions by identifying the underlying lymphatic anatomy and potential therapeutic targets.

Iatrogenic injury of the TD or its branches during thoracic, cardiac, or cervical neck surgery is the main cause of traumatic chylothorax; less frequent is blunt or penetrating trauma to the chest. Rarely traumatic chylous ascites can present as chylothorax due to

negative pressure in the chest during the breathing cycle, causing chyle to migrate from the abdomen into the pleural space through diaphragmatic openings [26, 27].

Postoperative chylothorax most often presents within the first 2 weeks following a surgery [28]. The incidence of chylothorax complicating pulmonary resections can be as high as 4%, and a recent report suggests the incidence may be rising given the increased frequency of extensive resections and lymph node dissections during thoracic surgery [28]. The morbidity and mortality of a chylothorax are significant. A recent study of post-esophagectomy chylothoraces found a statistically significant increase of 30-day major complications (85% vs 46%; $p < 0.001$) and death (17.7% vs 3.9%, $p < 0.001$) compared to patients without chylothorax [29].

Initially, chylothorax is treated conservatively with drainage of the chylous effusion and diet modification. Reduction of food intake, especially fat, reduces chyle flow from the intestine, thus facilitating spontaneous closure of the TD leak [30, 31]. Surgical alternatives include drainage and pleurodesis or surgical ligation of the thoracic duct. In a recent report, the success of TD ligation to treat post-esophagectomy chylothorax was as high as 67% [29]. Although these results are promising, the operative risk, morbidity, and poorer outcomes of surgical ligation compared to TDE make TDE the preferred alternative to surgical ligation to treat chylothoraces [2, 6, 21, 32, 33]. The growing experience with TDE supports its use as the first-line treatment for traumatic chylothorax [34].

The largest series of TDE in treating traumatic chylous effusions included 109 patients [2]. In 73 of 109 cases (67%), the TD was successfully catheterized. Subsequently, TDE with endovascular coils and/or glue was performed in 71 of 73 patients. The leak resolved in 90% of these patients ($N = 64$). In 18 of the 33 cases in which TD catheterization was unsuccessful, needle interruption of the TD below the diaphragm was attempted and resulted in resolution of the chylothorax in 72% of patients ($N = 13$). Overall success of an intent-to-treat basis of the entire series of patients was 71% ($N = 77$). In the 20 patients in the study who had failed previous surgical ligation, embolization or interruption was attempted in 17 and successful in 15 (88%) demonstrating the utility of TDE after failed surgical intervention. There were three (3%) minor complications in this study.

In the pediatric patient population, chylothorax most commonly occurs after cardiac surgery and has been reported to occur at an incidence between 2 and 5% [35]. TDE in pediatric patients is more challenging due to the small size of the lymphatic vessels. Recently, two cases of TDE to treat postoperative chylothorax in infants have been reported [3]. In both cases, the chylothorax was resistant to conventional conservative and surgical treatment including TD ligation. In both patients, the effusions resolved following TDE [3]. These initial results show the promise for TDE to manage chylous effusions in the pediatric population. The development of the less technically challenging intranodal lymphangiogram may further facilitate the adoption of TDE to pediatric patients [6, 36].

65.8 Thoracic Duct Embolization of Nontraumatic Chylothorax

Nontraumatic lymphatic leaks are a heterogeneous group of diseases in which the leak is developed without a major precipitating traumatic event. The etiologies include idiopathic chylothorax, chylous leaks due to primary lymphatic disorders such as Gorham's

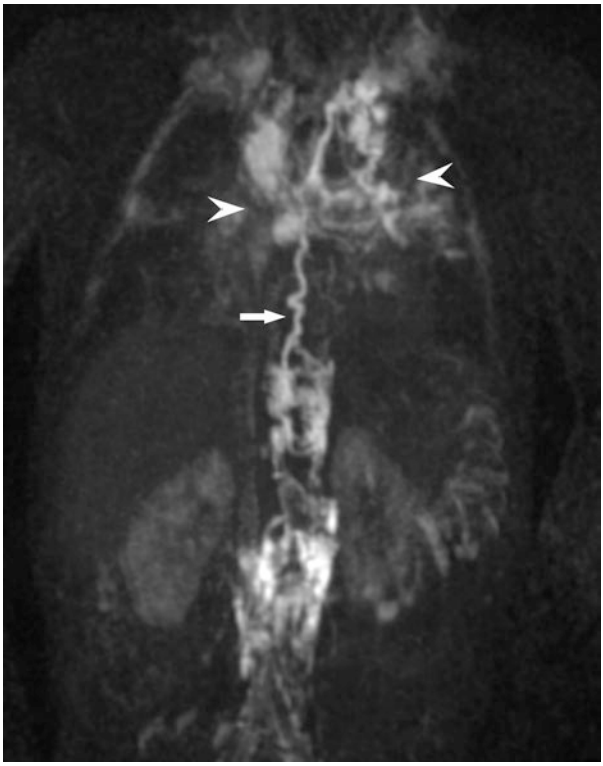

Fig. 65.5 DCRML image of the patient with PLPS, demonstrating single thoracic duct (*arrow*) and abnormal lymphatic flow from the thoracic duct toward lung parenchyma (*arrowheads*)

disease (GSD), generalized lymphatic anomaly (GLA), Kaposiform lymphangiomatosis (KLA), lymphangioleiomyomatosis (LAM), malignancies, systemic diseases (e.g., SLE, Behcet's disease), and infection (e.g., tuberculosis) [4, 37, 38]. The cause of chylous leaks in oncological processes and primary lymphatic disorders can be obstruction/erosion of the lymphatic channels leading to the leak. In idiopathic chylothorax, leaks can originate from lymphatic masses/malformations that can produce large amount of lymph. Variability of the causes of the lymphatic leaks provides a significant diagnostic and treatment challenge. Thorough understanding of the underlying lymphatic anatomy and flow patterns and identification of a possible leak source with imaging is essential for planning an intervention and for interventional success [38].

There are three types of underlying anatomical abnormality that result in nontraumatic chylothorax: (1) chylous ascites that presents as chylothorax, (2) abnormal pulmonary lymphatic flow (pulmonary lymphatic perfusion syndrome) (Fig. 65.5), and (3) chylothorax associated with lymphatic malformation.

Over the years, we have developed an algorithm to evaluate and treat patients with nontraumatic chylothoraces (Fig. 65.6). Initially, we perform heavily weighted T2 MR imaging of the chest and abdomen to exclude lymphatic malformation and to define the anatomy of the thoracic duct [17]. During the same session, we would perform DCRML to further understand the lymphatic anatomy and demonstrate the cause of the leak. If free fluid in the abdomen is identified, chylous ascites and

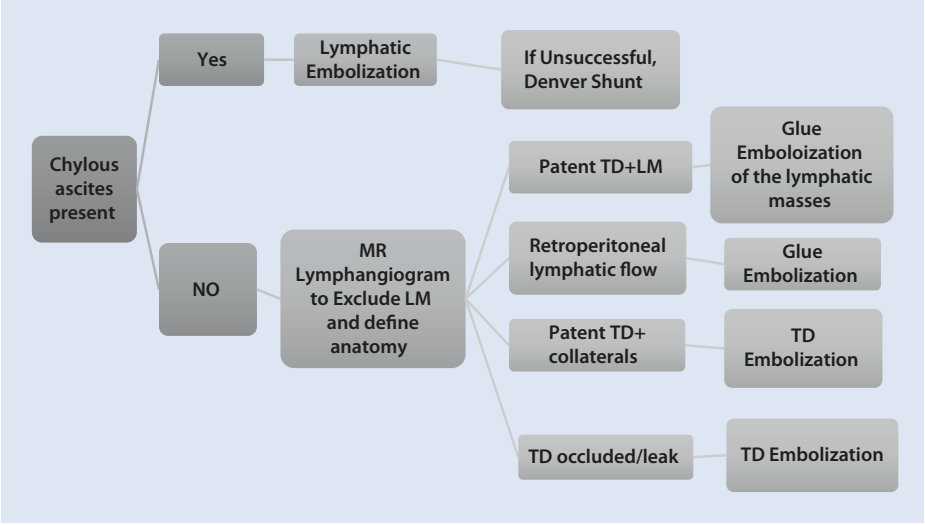

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Fig. 65.6 Nontraumatic chylothorax imaging algorithm

migration of the chyle from the abdomen into the chest through diaphragmatic holes are suspected. In these cases, sampling of the abdominal fluid and testing it for chyle is recommended. DCRML provides excellent imaging of the anatomy and pathology of the thoracic duct. In cases where there is abnormal pulmonary lymphatic flow, TDE is performed. If lymphatic malformations/masses are identified on the MRI or lymphangiogram, direct injection of the lymphatic masses with N-BCA glue is performed.

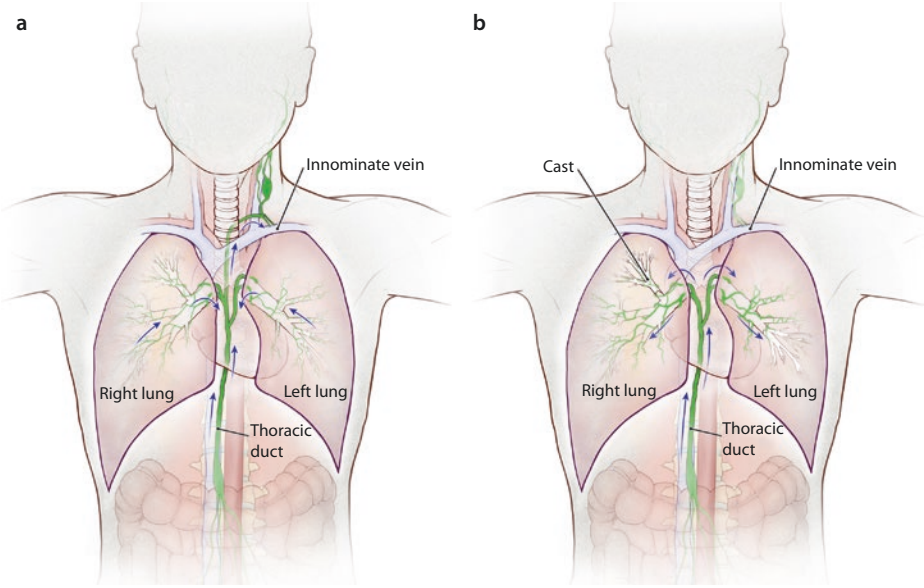
The only published study of utilization of TDE in patients with nontraumatic chylothorax was before the introduction of the abovementioned algorithm and before introduction of the MR lymphangiogram [4]. In this study, TDE was performed in 34 patients presenting with nontraumatic chylous effusions. TD catheterization and embolization was technically successful in 24 of 34 patients (70.6%). Overall, the intent-to-treat clinical success rate was 53% ($N = 18$ of 34). In the group in which the TDE was technically successful ($N = 24$), the clinical success rate was 67.7% ($N = 16$). The clinical success rate was observed to vary based on the lymphangiographic pattern. The greatest clinical success (88%) occurred in patients who were found to have an occlusion of the TD with multiple mediastinal collaterals and no passage of contrast from the TD into the subclavian vein. The lowest success rate (16%) was observed in patients with a normal TD on lymphangiography. The overall intent-to-treat clinical success rate (53%) for TDE in nontraumatic chylous effusions was compared favorably with the previously reported 27% success rate using a combined approach of conservative and surgical management for nontraumatic chylothorax reported by Maldonado et al. [39]. Over the last few years in our institution, we have been utilizing MR lymphangiogram and the abovementioned treatment algorithm to treat all patients with nontraumatic chylothorax. Using this methodology, we have been able to control the chylothorax in the majority of our patients (unpublished data).

65.9 Pulmonary Lymphatic Perfusion Syndrome

Pulmonary lymphatic diseases have been recognized for many years and have been referred to as pulmonary lymphangiectasia, pulmonary lymphangiomatosis, plastic bronchitis, and idiopathic chylothorax/chylopericardium [40].

Recent development of the DCMRL allowed better visualization of the thoracic lymphatic anatomy and the extent of abnormal pulmonary lymphatic flow [19]. This improved visualization of the anatomical distribution of pulmonary lymphatic flow allowed the identification of lymphatic enhancement of the mediastinal and lung tissues that we termed «pulmonary lymphatic perfusion syndrome (PLPS)» (■ Fig. 65.7) [5].

Ninety to eighty percent of the lymph in the body is generated below the diaphragm in the abdomen, primarily in liver and intestine [41]. The lymphatics from the liver, intestine, and soft tissue then converge together in the cisterna chyli that conducts lymph further into thoracic duct that in turn discharges the lymph into the venous system in the area of the junction of left jugular and subclavian veins. Traversing through the mediastinum, the thoracic duct accepts lymphatic contributories from the mediastinal organs, such as the heart, esophagus, and lungs. In patients with PLPS, part of the lymph flows retrograde from the thoracic duct toward lung parenchyma and mediastinum through the aberrant lymphatic vessels. We hypothesize that these vessels are collaterals and developed as a decompression mechanism to in utero occlusion/stenosis/compression of the downstream parts of the thoracic lymphatic system. We also assume that these lymphatic collaterals are often not clinically significant if their course is deep in the soft tissue; however they can become



■ **Fig. 65.7** **a** Schematic representation of the normal pulmonary lymphatic flow from pulmonary parenchyma toward thoracic duct (*green color*). Thoracic duct empties in the left subclavian vein. **b** Schematic representation of the abnormal pulmonary lymphatic flow in plastic bronchitis from the thoracic duct toward lung parenchyma (*green color*). There is occlusion of the upper part of the thoracic duct (Reprinted by permission from the Children's Hospital of Philadelphia)

symptomatic if they abut serous and mucosal surfaces such as pleura, pericardia, and bronchi where under certain circumstances they can start to leak in these compartments [42]. The commencement of the symptoms can be provoked by (1) silent trauma that would result in rupture of these lymphatic vessels causing chylothorax or chylopericardium; (2) severe upper respiratory infection, which can cause injury of the bronchial lining causing lymphatic plastic bronchitis in adult patients [43]; and (3) overdistention of the lymphatic vessels due to increase of lymphatic production in patients with congenital cardiac diseases causing plastic bronchitis or chylothorax [5]. Clinically PLPS can present at any age starting from newborns (neonatal chylothorax) to older adults as chylothorax or plastic bronchitis.

Neonatal chylothorax is a condition that is often diagnosed on prenatal US as a pleural effusion. Ninety percent of all pleural effusions in utero are chylothorax [44]. To prevent the underdevelopment of the lung parenchyma due to its compression by pleural effusion, drainage of the pleural space is performed by placing a thoracoamniotic shunt [45]. In our practice all newborns with neonatal chylothorax undergo DCRML. Typical findings on DCRML are complete occlusion of the midthoracic duct and development of abnormal pulmonary lymphatic flow (Fig. 65.8a). It is very important to differentiate isolated chylothorax from chylothorax that presents with chylous ascites and tissue edema. The latter condition is called congenital lymphatic dysplasia and is caused by general dysplasia of the lymphatic system and is one of the most difficult neonatal conditions to treat [46].

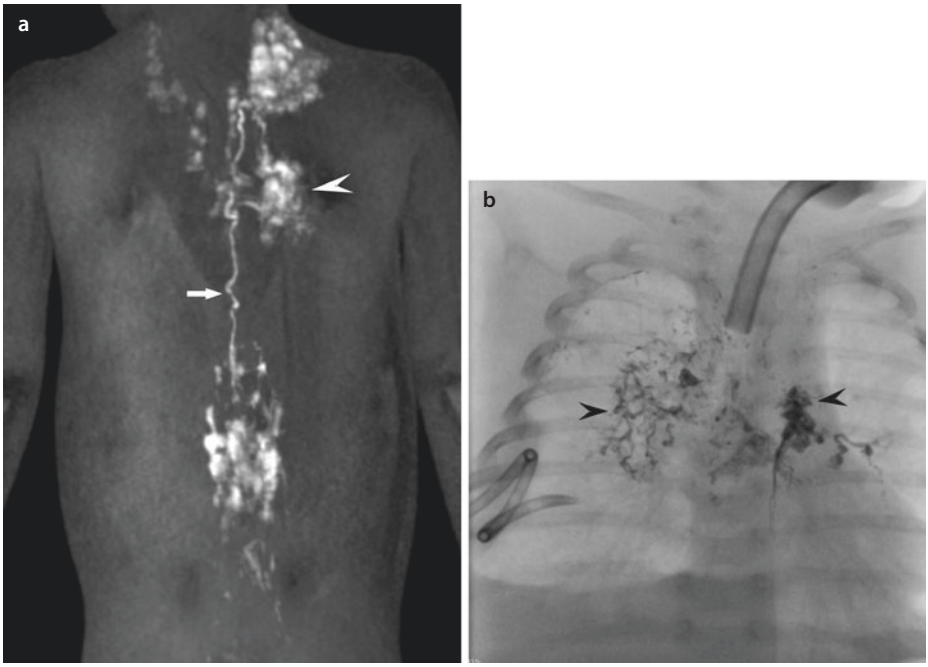


Fig. 65.8 Patient with neonatal chylothorax. **a** DCRML demonstrating abnormal pulmonary lymphatic perfusion (*arrowheads*). There is a single thoracic duct (*arrow*). **b** Fluoroscopic image of the Lipiodol in the abnormal pulmonary lymphatic vessels (*arrowheads*) that was injected into inguinal lymph nodes. In addition to imaging, Lipiodol provide the embolization effect and thus is therapeutic in this patient population

Immediately following the DCRML, we perform intranodal lymphangiography. The findings on intranodal lymphangiography correlate well with the findings on DCRML and include complete occlusion of the thoracic duct in middle mediastinum and retrograde flow of the contrast in the lung parenchyma (Fig. 65.8b).

The rate of the chylothorax leak in these patients is often very slow, in the range of tens of milliliters a day, and for that reason lymphangiography that utilizes a small amount of the oil-based contrast Lipiodol is often curative due to its well-known embolization effect [47, 48]. The amount of Lipiodol that is used during lymphangiography however has to be less than 0.25 ml/kg [49] because larger doses can embolize nontarget lymphatic vessels resulting in generalized edema.

Plastic bronchitis is a condition in which children or adults expectorate casts of their bronchial tree. It is most commonly associated with congenital heart diseases such as in children with a single ventricle who underwent Fontan palliative procedure. In these children the blood from SVC and IVC flows passively into the pulmonary veins, causing significant elevation of the central vein pressure and as a result increased lymph production [5]. Plastic bronchitis can also present as a lymphatic plastic bronchitis in adult patients [43].

In all patients with plastic bronchitis regardless of cause, the underlying pathology is PLPS and is very similar to the lymphagiographic picture of patients with idiopathic chylothorax [5, 43]. The main difference however is that the abnormal lymphatic perfusion occurs in the bronchial mucosa, where the lymph «seeps» into the lumen of the bronchi and then dries up to form the cast of the lung. When injecting a color indicator (methylene blue or Lymphazurin 1%) through the catheter positioned in the thoracic duct while performing the bronchoscopy, we can visualize these submucosal vessels.

Percutaneous embolization of these abnormal pulmonary lymphatic vessels results in alleviation of the symptoms of plastic bronchitis in adults and children close to 100% of the patients with minimal complications [5, 43].

Conclusion

Development of minimally invasive image-guided methods of embolization of the lymphatic system, such as TDE, provided an effective solution for patients with lymphatic flow disorders and became the treatment of choice for patients with traumatic chylothorax. The recent introduction of the technically simple intranodal lymphangiogram eliminated the challenges of pedal lymphangiogram and allowed wide dissemination of lymphatic embolization techniques. The latest addition of MR lymphangiographic techniques, such as heavy T2 imaging and DCRML, allowed better understanding of the underlying pathology of nontraumatic chylothorax and several pulmonary conditions by demonstrating abnormal pulmonary lymphatic flow from the thoracic duct toward pulmonary parenchyma (PLPS). Percutaneous embolization of these abnormal pulmonary lymphatic vessels has been proven to be a successful treatment of these conditions with minimal complication rate. We believe that PLPS is a congenital anatomical lymphatic variant that can present clinically under certain conditions. It is possible that other poorly understood lung conditions and even pulmonary symptoms in some patients with heart failure could be explained by PLPS. Wider acceptance and utilization of DCRML and percutaneous embolization techniques can further expand our knowledge and treatment options for these pulmonary conditions.

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Lymphatic Filariasis

Contents

Epidemiology

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Summary of Basic Concepts

Lymphatic filariasis is a mosquito-borne disease that, in its advanced forms, can manifest as severe lymphedema, hydrocele, and elephantiasis. It is estimated that there are 1.3 billion people living in endemic areas in 81 countries and that 120 million people are infected. More than 90% of these infections are caused by *W. bancrofti*, for which humans are the only natural host. There can be potential acute manifestations of infection, particularly acute filarial lymphangitis and acute dermatolymphangioadenitis. The clinical manifestations of chronic lymphatic filariasis include lymphedema, elephantiasis, and hydrocele. Lymphedema management involves leg hygiene, early treatment of bacterial and fungal infections, elevation, and exercises. The chronic clinical manifestations of lymphatic filariasis lead to adverse psychological and economic consequences, making lymphatic filariasis one of the leading causes of disability and an impediment to economic and social development:

- Lymphatic filariasis is a mosquito-borne, neglected tropical disease that can cause lymphedema, hydrocele, and elephantiasis.
- The disease is second only to malaria for disability-adjusted life years.
- Lymphatic filariasis is endemic in Africa, Asia, the Indian subcontinent, the western Pacific Islands, focal areas of Latin America, and the Caribbean, particularly Haiti and the Dominican Republic.
- The distribution of lymphatic filariasis is highly focal within an endemic area.
- During a blood meal by the mosquito vector, larvae penetrate the skin and home to lymphatic vessels and nodes. Adult worms can live in the lymphatic vessels and produce microfilaria for 5–10 years.
- Acute manifestations of infection can include acute filarial lymphangitis and acute dermatolymphangioadenitis.
- The clinical manifestations of chronic lymphatic filariasis include lymphedema, elephantiasis, and hydrocele. These generally increase in frequency with age.
- Factors that favor the progression of filarial lymphedema to elephantiasis include repeated attacks of acute dermatolymphangioadenitis, the intensity of filarial transmission within a population, and the presence of the bacterial endosymbiont, *Wolbachia*. Lymphedema management involves leg hygiene, early treatment of bacterial and fungal infections, elevation, and exercises.

Lymphatic filariasis, a mosquito-borne disease that, in its advanced forms, can manifest as severe lymphedema, hydrocele, and elephantiasis [6], is one of the neglected tropical diseases targeted for global elimination by 2020 [7]. Among tropical diseases, lymphatic filariasis is second only to malaria in terms of disability-adjusted life years [8].

Lymphatic filariasis can be the result of infection with any of three species of parasite: *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*. Estimates of prevalence vary, based upon available epidemiological data; at present, it is estimated that there are 1.3 billion people living in endemic areas in 81 countries and that 120 million people are infected. More than 90% of these infections are caused by *W. bancrofti*, for which humans are the only natural host.

Table 66.1 Characteristics of filarial parasites of humans

Most common tissue location						
Species	**Adult**	**Microfilaria**	**Geographic distribution**	**Estimated no. infected**	**Vector**	**Periodicity**
Wuchereria bancrofti	Lymphatics	Blood	Tropics worldwide	115 million	Mosquitoes	Nocturnal or subperiodic
Brugia malayi	Lymphatics	Blood	Southeast Asia	13 million	Mosquitoes	Nocturnal or subperiodic
Brugia timori	Lymphatics	Blood	Indonesia	Thousands	Mosquitoes	Nocturnal

Lymphatic filariasis is endemic in Africa, Asia, the Indian subcontinent, the western Pacific Islands, focal areas of Latin America, and the Caribbean, particularly Haiti and the Dominican Republic (see Table 66.1) [9]. Of these, the greatest numbers of infected persons live in sub-Saharan Africa, south Asia, and the western Pacific. Although both China and the Republic of Korea were previously considered endemic, these countries have declared elimination of lymphatic filariasis as a public health problem in 2007 and 2008, respectively (Global Programme to Eliminate Lymphatic Filariasis (GPELF) Progress Report 2000–2009 and Strategic Plan 2010–2020). Infection with *B. malayi* is limited to Asia (India, Malaysia, and formerly China) and several Pacific island groups (Indonesia and the Philippines); there are fewer than 10–20 million persons in these areas who are infected with *B. malayi*. Unlike *W. bancrofti*, *B. malayi* has feline and primate reservoirs. *B. timori* is only found on the Timor island of Indonesia.

The distribution of lymphatic filariasis is highly focal within an endemic area, as a result of the varying feeding behaviors of the mosquito vectors for lymphatic filariasis transmission, as well as to the local ecological factors that favor the breeding of these mosquito vectors. *W. bancrofti* is transmitted in much of rural Africa by *Anopheles* species [10], while in many urban areas of the world, including India and the Western Hemisphere, the same nematode is transmitted by *Culex* mosquitoes [11]. *Culex quinquefasciatus* thrives and proliferates excessively in crowded city areas with poor sanitary, sewerage, and drainage facilities [12]. For this reason, urban LF also often shows a marked focality in distribution, with most cases clustered in areas inhabited by the less privileged city populations [12]. Other vectors include *Aedes* species and *Mansonia* [13]. Lymphatic filariasis is less commonly transmitted than other vector-borne parasitic infections and, therefore, uncommonly infects travelers to endemic areas with short-term exposure [14]. The microfilariae of *W. bancrofti* and *B. malayi* have a nocturnal periodicity: large numbers of the organisms are present in the peripheral circulation between 9 p.m. and 2 a.m., coinciding with the time period when most mosquito vectors take their blood meal [15]. In contrast, there is no clear-cut periodic cycle for *Aedes*-transmitted microfilariae in the South Pacific.

At the time of feeding, infective L3 larvae escape from the proboscis of the mosquito, penetrate the skin, and home to lymph nodes and lymphatic vessels. It then takes between 6 and 12 months for the L3 larvae to become sexually mature adult female worms (L5 stage) capable of producing first-stage L1 larvae called microfilariae that circulate in the blood. The adult worms can live in the lymphatic vessels and produce microfilaria for 5–10 years. Microfilariae are taken up in the blood meal of mosquitoes and develop into infective L3 larvae in the thorax of the mosquito over a period of 7–21 days and are then ready to infect another host.

Infection with lymphatic filariasis is most often clinically inapparent, although it has been demonstrated that even asymptomatic infected individuals have underlying lymphatic damage in the form of lymphatic dilatation and dysfunction [16, 17]. Initial infection, detected as the presence of circulating filarial antigen, commonly occurs between the ages of 2 and 4 years in highly endemic areas [1, 2]. In these areas of intense transmission, the prevalence of microfilaremia in the population increases rapidly between the ages of 5 and 10 years and continues to increase until the third and fourth decades of life.

More recently, it has been discovered that several human filarial parasites, including *W. bancrofti* and *Brugia* species, possess a bacterial endosymbiont, *Wolbachia* [18]. These are rickettsia-like endosymbiotic bacteria that are involved in the normal development, viability, and fertility of the adult worm [19]. *Wolbachia* has been investigated as a potentially important chemotherapeutic target as well as for its potential to act as a disease-causing organism for lymphatic filariasis [3, 20, 21].

There can be potential acute manifestations of infection, particularly acute filarial lymphangitis and acute dermatolymphangioadenitis. Acute filarial lymphangitis produces acute inflammation of a lymphatic vessel that progresses distally along the vessel and is thought to be caused by the death of the adult worm [22]. Acute dermatolymphangioadenitis is a clinically distinct presentation that is precipitated by bacterial infection of the small collecting lymphatic vessels in areas of lymphatic dysfunction [22, 23]. Unlike filarial lymphangitis, the cutaneous changes develop in a reticular, rather than a linear, pattern, and the episodes are more commonly associated with severe pain, fever, and chills.

The clinical manifestations of chronic lymphatic filariasis, including lymphedema, elephantiasis, and hydrocele, occur infrequently in persons younger than 10 years of age and generally increase in frequency with age [2]. It is estimated that of the 120 million persons infected worldwide, approximately one third, or 40 million, have some form of clinically overt disease: 25 million with hydrocele and 15 million with lymphedema or elephantiasis [9]. In a rural setting, when infected individuals are detected by antigenemia, whose prevalence is age dependent, lymphedema and hydrocele attributable to *W. bancrofti* were observed in 4.05% of subjects examined. Generally, hydrocele was observed in 1.69% of males, whereas lymphedema was present in 2.36% (1.35% females, 1.01% males) of the studied population. None of the male subjects had both the two clinical features [8]. Furthermore, lymphatic filariasis is not the sole cause of these pathologies in endemic areas: in one series of 511 patients, lymphedema resulted from trauma (40.7%), chronic venous insufficiency (12.5%), deep mycoses (10.8%), lymphatic filariasis (9.2%), elephantiasis nostras verrucosa (7.0%), tropical ulcer (6.3%), leprosy (4.9%), recurrent

infections (3.1%), podoconiosis (1.8%), tuberculosis (1.0%), malignancy (1.3%), Kaposi's sarcoma (1.0%), leishmaniasis (0.2%), and neurofibromatosis (0.2%) [24].

Factors hypothesized to favor the progression of filarial lymphedema to elephantiasis include repeated attacks of acute dermatolymphangioadenitis [4], the intensity of filarial transmission within a population [25], and the presence of *Wolbachia* [26]. Lymphedema management involves leg hygiene, early treatment of bacterial and fungal infections, elevation, and exercises [27].The chronic clinical manifestations of lymphatic filariasis lead to adverse psychological and economic consequences, making lymphatic filariasis one of the leading causes of disability [28] and an impediment to economic and social development [29].

Recognition that lymphatic filariasis can be eradicated using currently available chemotherapies has led to the 1997 World Health Assembly (WHA) resolution to eliminate lymphatic filariasis as a public health problem (WHA 50.29, 13 May 1997) [5]. After this resolution in 2000, the Global Programme to Eliminate Lymphatic Filariasis (GPELF) was launched with the dual goals of interrupting transmission by annual mass drug administration of diethylcarbamazine or ivermectin plus albendazole to the entire population in endemic areas [6] and alleviating the suffering of people affected by chronic disease through morbidity management [7]. Drug donations of ivermectin by Merck & Co. and albendazole by GlaxoSmithKline have been critical to making the global elimination program a reality. Since the inception of the GPELF, there has been a steady increase in the number of countries implementing MDA from 12 in 2000 to 52 out of 81 lymphatic filariasis endemic countries in 2009 [30]. In the first 8 years of the global elimination program, more than 1.9 billion treatments have been provided through yearly mass drug administration to at least 570 million individuals, thereby protecting more than 16 million people from filarial infection or progression of clinical disease and averting 32 million disability-adjusted life years [5]. In Africa, the number of people requiring treatment for lymphatic filariasis in the 35 endemic countries decreased from 472.1 million in 2013 to 409.7 million in 2014 [31] . However, the presence of high microfilarial rates, vector infectivity rates, and clinical cases in the study population after mass drug administration warrants continued concerted efforts for effective implementation and monitoring of the lymphatic filariasis elimination program [24].

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Etiology and Pathophysiology

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Summary of Basic Concepts

- Lymphatic dilatation in filarial infection is initiated by the parasite and/or parasite products.
- Lymphatic obstruction, the hallmark of disease associated with lymphatic filariasis, is characterized by lymphangiectasia and inflammatory reactions around the adult worms.
- Disease associated with lymphatic filarial infection occurs as a consequence of a failure to modulate the host's parasite-specific T-cell response.

67.1 Introduction

Human lymphatic filariasis (LF) is among the neglected tropical diseases. Caused by infection with three closely related filarial parasites—*Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*—there are an estimated 120–129 million infected individuals in 73 endemic countries ([6], refer to Leanne Fox, Epidemiology chapter [7] in this edition).

These parasitic nematodes with similar life cycles (Fig. 67.1) are transmitted by mosquito vector(s), and infection occurs when the infective larvae (L3) deposited on the skin migrate through the puncture wound of the mosquito bite. Though the exact mechanisms are not known, the infective L3 larvae home to the lymphatics and develop into adult worms following a series of developmental molts (L4 and L5). Mating of the adult female and male worms results in the production and release of microfilariae (L1) that enter the blood circulation and can be taken up by a mosquito during a blood meal. The ingested microfilariae undergo two developmental molts in the mosquito as they develop into L2 and then into the infective L3 larvae.

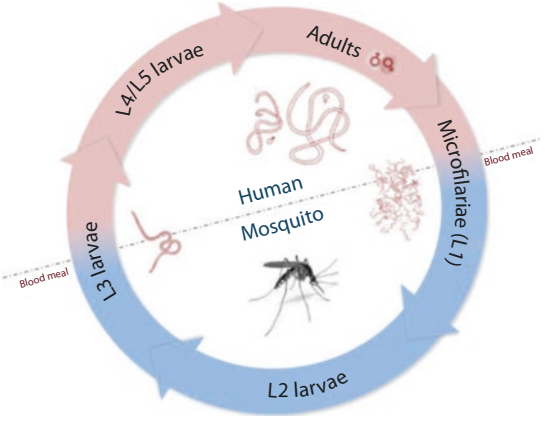

Fig. 67.1 The life cycle of Brugia and Wuchereria parasites. The microfilariae (L1 larvae) are taken up by a mosquito during a blood meal and develop into L2 and L3 larvae. The infective L3 larvae enter the human host during another blood meal and develop into L4, then into L5 larvae, and finally into adult males and females that reside in the afferent lymphatics

67.2 Clinical Manifestations

The most common clinical manifestations of LF are (1) asymptomatic (or subclinical) infection, (2) acute adenolymphangitis (ADL), (3) hydrocele, and (4) lymphedema.

67.2.1 Asymptomatic (Subclinical) Infection

In areas where *W. bancrofti* or *B. malayi* is endemic, the overwhelming majority of infected individuals have few overt clinical manifestations of filarial infection often with circulating microfilariae in the peripheral blood. Although they may be clinically asymptomatic, virtually all persons with patent infection with *W. bancrofti* or *Brugia spp.* have some degree of subclinical disease that includes microscopic hematuria and/or proteinuria [8], dilated (and tortuous) lymphatics visualized by imaging [9, 10] (Fig. 67.2), and—in men with *W. bancrofti* infection—scrotal lymphangiectasia [11, 12] detectable by ultrasound (Fig. 67.3).

Fig. 67.2 Lymphoscintigram of patient with unilateral (*right leg*) lymphedema with evidence of blockage of the central deep lymphatic channel and dermal backflow

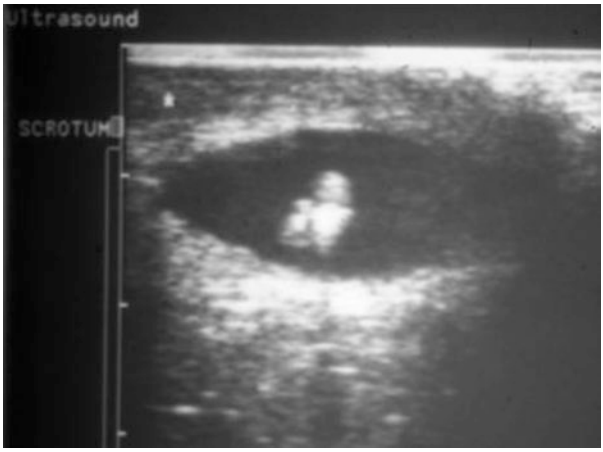

Fig. 67.3 Ultrasound image of a dilated scrotal lymphatic with an echodense adult worm centrally located within the dilated lymphatic

67.2.2 Adenolymphangitis (ADL)

Adenolymphangitis (ADL) is characterized by high fever, lymphatic inflammation (lymphangitis and lymphadenitis), and transient local edema. The lymphangitis is retrograde, extending peripherally from the lymph node draining the area where the adult parasites reside. Regional lymph nodes are often enlarged, and the entire lymphatic channel can become indurated and inflamed. Concomitant local thrombophlebitis can occur as well. In brugian filariasis, a single local abscess may form along the involved lymphatic tract and subsequently rupture at the surface (Fig. 67.4). The lymphadenitis and lymphangitis can involve both the upper and lower extremities in both bancroftian and brugian filariasis, but involvement of the genital lymphatics occurs almost exclusively with *W. bancrofti* infection. This genital involvement can be manifested by funiculitis, epididymitis, scrotal pain, and tenderness [13–15].

In endemic areas, another type of acute disease—dermatolymphangioadenitis (DLA, Fig. 67.5) [16]—is recognized as a syndrome that includes high fever, chills, myalgia, and headache. Edematous inflammatory plaques clearly demarcated from

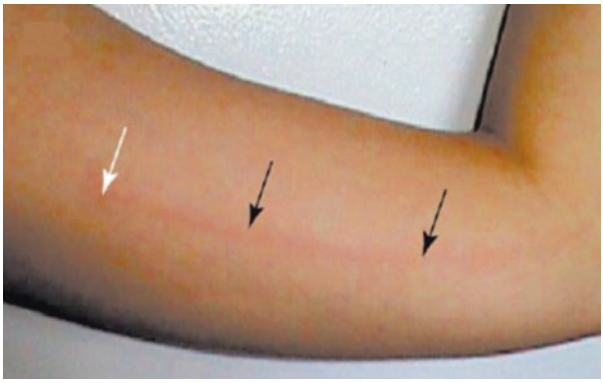

Fig. 67.4 Adenolymphangitis in the arm of infected patient

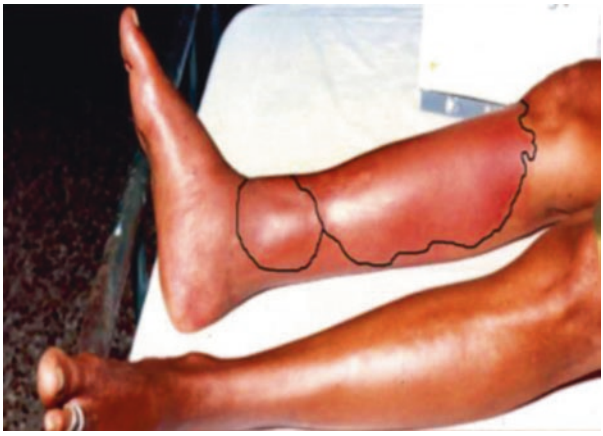

Fig. 67.5 Dermatolymphangioadenitis (DLA) characterized by tenderness and erythema of the skin

normal skin are seen. Vesicles, ulcers, and hyperpigmentation may also be noted. There is often a history of trauma, burns, radiation, insect bites, punctiform lesions, or chemical injury. Entry lesions, especially in the interdigital area, are common. DLA is often diagnosed as cellulitis.

67.2.3 Lymphedema of the Arms, Legs, and Breasts

Swelling of the upper or lower extremities is the most common chronic manifestation of lymphatic filarial infection (Fig. 67.6). Disease of the lower extremities is more prevalent. Leg involvement in bancroftian filariasis may include the entire limb, whereas only the area below the knee is usually involved in brugian filariasis. In some persons with filarial-associated edema, the overlying skin may exude serous fluid suggestive of lymph. Although it is possible that this sign occurs as a result of increased hydrostatic pressure in the lymphatics draining the skin, skin turgor alone cannot reliably be used to distinguish between edema due to lymphatic disease and that from other causes, such as cardiac failure and liver disease. Unilateral or bilateral involvement of the female breast occurs in adult residents of filarial endemic areas. This should be distinguished from chronic mastitis and other causes of chronic breast inflammation.

67.2.4 Disease Involving the Genitourinary System

Along with lymphatic disease of the lower extremities, disease of the male genitalia is the most common manifestation of bancroftian filariasis. Indeed, in many endemic areas, its prevalence is greater than that of lymphedema. Genital involvement is uncommon in *Brugia* infection. The prevalence of disease of the female genitalia is not known since systematic surveys have not included examination of this anatomical area. Anecdotal evidence suggests that the frequency of vulvar disfigurement is low. Acute painful episodes of epididymitis or funiculitis last several days and are accompanied by fever and malaise. Involvement is commonly unilateral.

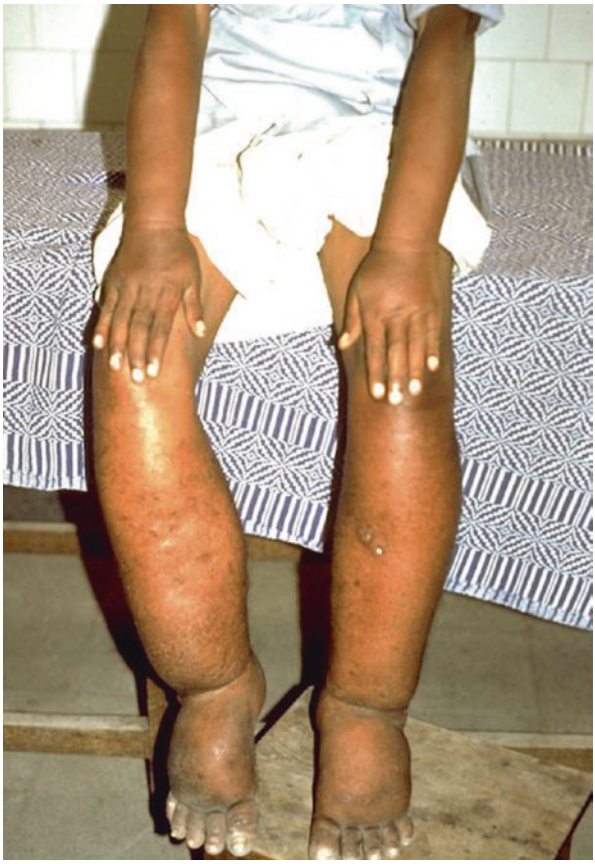

Fig. 67.6 Bilateral lymphedema of both arms and legs of patient infected with *W. bancrofti*

Hydroceles

Chronic disease of the male genitals mostly produces hydroceles (Fig. 67.7), which vary in diameter from less than 5 to over 30 cm. As is the case with other causes of hydrocele, the scrotal contents appear translucent when transilluminated. Hydroceles are usually not painful unless they are complicated by acute epididymitis or funiculitis. Thickening of the spermatic cord commonly accompanies hydroceles. The skin of the scrotum may also be thickened and have a "brawny" character on palpation. If hydrocele fluid is drained, it is clear and straw colored. Parasites are usually not found in this fluid. Inguinal lymph nodes and other nearby lymph nodes may also be enlarged.

Lymphedema of the Genitalia

Swelling of the scrotum when accompanied by thickened scrotal or penile skin may have a characteristic "peau d'orange" appearance [1]. In long-standing cases, verrucous lesions and lymphorrhea are common [17], the latter being a condition in which lymph oozes out to the exterior directly from dilated ruptured lymphatic vessels in the scrotal wall.

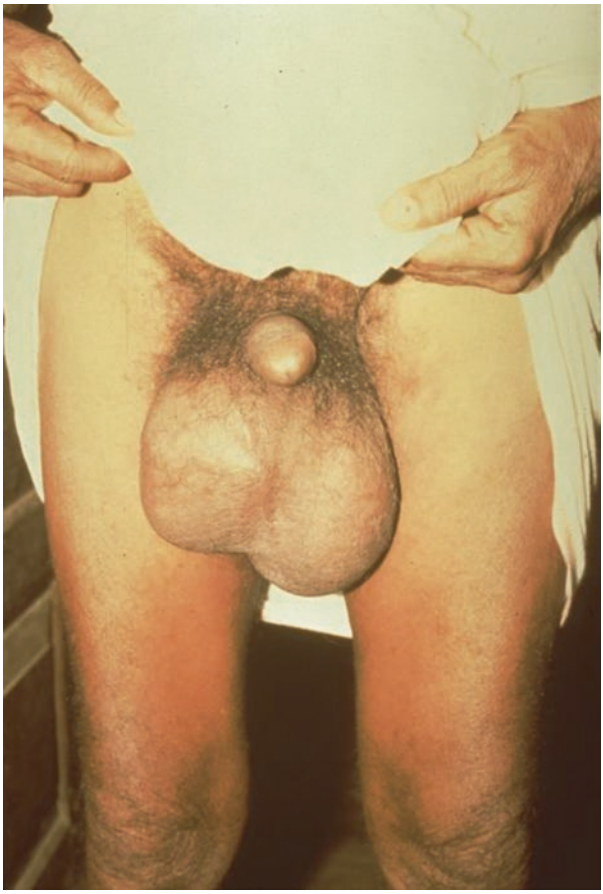

Fig. 67.7 Hydrocele in a patient with *W. bancrofti* infection

Chyluria

Chyluria, resulting from obstruction or physiologic impairment of the renal lymphatics with passage of lymph from the lacteals draining the genitourinary tract, is a rare but serious manifestation of lymphatic filariasis. Chyluria may have serious nutritional consequences in that large amounts of fat and protein are lost in the urine. Its precise frequency in filarial endemic areas has not been established, but is exceedingly low compared to lymphedema of the extremities and hydroceles [18].

67.3 Infection to Disease

The relationship between infection and disease has largely been deduced from cross-sectional data of individuals living in endemic areas (for lack of comparable clinical features in experimental animal models), experimental infections of human [19, 20], or instances where individuals have moved from a non-endemic to endemic areas.

Broadly, two models (not mutually exclusive) exist: (1) a "static" model where the nature of the host immunological response to the parasite leads either toward a patent (subclinical) infection or to one prone toward immune-mediated pathology or (2) a "dynamic" model that relies on a sequential progression from infection, microfilaremia to chronic obstructive disease without microfilaremia [21, 22]. Longitudinal studies, however, indicate that microfilaremia often does not precede chronic disease and conversely that chronic disease is not an inevitable consequence of the microfilaremic state [22–24].

Experimental infections in humans [19] that have served as a model of the early phase of infection indicated that lymphadenitis and transient edema within 4–6 weeks following infection were associated with enlargement of draining lymph nodes.

Based on animal models, the infective larvae are in the afferent lymphatics within 24 h of infection and migrate to the periphery of the draining lymph node. The lymphatics harboring the growing larvae dilate and become tortuous and dysfunctional [25, 26]. The endothelial cells' hypertrophy and lymphatic valves are thickened and distorted, with occasional occlusion of the lumen with lymph thrombi [26]. Exposure to secondary infections exacerbates the inflammation, blockage, fibrotic vessel walls, and collateralization of vessels that bypass the dysfunctional nodes and vessels [27–30].

67.4 Pathology

The development of the pathological manifestations is usually minimal as long as the adult worm is alive; upon death of the worm, a granulomatous reaction ensues [1, 31]. This inflammatory response is a reaction to the dead worm and not the cause of death of the adult worm as other adult worms can remain viable for an extended period of time after the death of other worms in the same or distal locations [32, 33]. The proliferation of endothelial and connective tissue, tortuosity of the lymphatics, and damaged or incompetent valves result in lymphatic dilatation and dysfunction felt to lead to lymphedema.

Lymph nodes from infected individuals are characterized by distended sinuses containing histiocytes and eosinophils, septal fibrosis, thickened capsules, and hyperplasia of follicles in the absence of worm(s) [34, 35] that have parallels in observations in cats infected with *Brugia pahangi* [36].

67.5 Pathogenesis of Disease in Lymphatic Filariasis

The two primary components of lymphatic filarial disease are lymphangiectasia and inflammatory reactions around the adult worms. Lymphangiectasia is commonly found in all infected individuals and develops in the vicinity of adult worm nests with patent infections [1], but is not restricted to the exact segment of lymphatics harboring the adult worms [37, 38]. Subclinical lymphangiectasia of the lymphatics containing live adult worms has been shown to occur with no apparent or only a fleeting inflammatory response to the live adult worms [2, 37, 39, 40]. Collectively, these indicate a role for the soluble products excreted or secreted by the parasites that act on the lymphatic endothe-

lial cells in mediating the lymphatic dysfunction. It is clear that with the host inflammatory responses toward the dead or dying worms, a stage of irreversible lymphatic dysfunction is established [31, 34, 41].

Lymphatic dysfunction predisposes infected individuals to secondary bacterial and fungal infections and triggers inflammatory reactions in the skin and subcutaneous tissues that accelerates the progression of lymphedema and development of elephantiasis [42, 43]. This biphasic mode of pathogenesis (parasite-induced lymphatic dysfunction and host-induced lymphatic obstruction) can be seen in immunodeficient animals that, with chronic infection, develop reversible lymphatic dilation. Immune reconstitution of these immunodeficient animals results in cellular hyperplasia and fibrosis and irreversible lymphatic obstruction [44–47].

The lymphatic endothelium is in constant contact with the adult worm and its soluble factors and closely associated with the pathogenesis of the lymphatic disease in the form of lymphangiectasia (that can also be observed distal from the worm nest) or development of collaterals. The endothelial cells lining the affected vessels have bulging nuclei, many pinocytic vesicles, and abundant multi-oriented collagen bundles [2, 40]. The proximity of the adult worm to the lymph node increases the level of lymphoid hyperplasia, hypercellularity of paracortical areas, and sinus histiocytosis [31]. These dynamic anatomical changes in the lymphatic architecture suggest active remodeling of the lymphatics involving endothelial cell growth, migration, and proliferation as an important feature of the disease [48, 49].

Soluble products of the filarial worms induce activation, proliferation, and tube formation of the endothelial cells of lymphatic origin [3, 50]. Changes in the global gene expression of monolayers of lymphatic endothelial cells revealed alteration in genes involved in junction adherence pathways that decreased trans-endothelial transport, implicating parasite-induced alterations in normal physiology of the lymphatic endothelium [3]. Moreover, soluble factors present in the serum of patently infected or diseased individuals induced significant proliferation of the lymphatic endothelial cells that was associated with increased levels of matrix metalloproteinases (MMPs) and inhibition of their endogenous inhibitors—tissue inhibitors of MMPs (TIMPS) [3].

Progression from asymptomatic infection to lymphedema and elephantiasis is accompanied by progressive fibrosis and extracellular matrix remodeling. The interstitial fibrosis is thought to be due to long-standing lymph stasis and/or immunological responses to products released from live or dead worms. Recent data highlight a possible role of the elevated levels of MMPs and TIMPs as underlying factors in the pathogenesis of tissue fibrosis in filarial lymphatic disease [51]. Lymphangiogenesis in lymphatic filarial disease has been associated with increases in vascular endothelial growth factors (VEGF) [52–54] and other angiogenic and/or lymphangiogenic factors (VEGF-receptors, PDGF, and angiopoietins) [55].

Immunologically, the conditions of microfilaremia, amicrofilaremia, and obstructive disease relate to low, medium, and high levels of immune responsiveness [21, 56] in the sequential progression from infection to disease in most, if not all, individuals. It is unlikely that the contrasting systemic immune responses in the amicrofilaremic (Th1) and microfilaremic (Th2) groups influence the pathogenesis as both groups exhibit similar clinical features of lymphangiectasia and absence of inflammation around the living worm [57].

Though beyond the scope of this chapter, a large number of studies have implicated a role for the adaptive immune systems in mediating the pathology seen in LF [10, 58–67]. This immune-mediated pathology appears to be mediated by a failure to modulate (through IL-10, regulatory T cells) the antigen-specific pro-inflammatory responses that mediates pathology in LF [4, 62, 68]. The mechanisms of how these pro-inflammatory mediators, Th1, Th9, and Th17 cells, interact with innate cells and endothelial cells (directly or indirectly) in the development of lymphatic damage and fibrosis remains to be elucidated. However, this interaction is thought to reflect the elevated levels of C-reactive proteins, pro-inflammatory cytokines, and other mediators such as TNF-α, soluble TNF receptor, endothelin-1, IL-2, IL-6, IL-8, MIP-1α, MIP-1β, MCP-1, TARC, and IP-10 (reviewed in [4]).

67.5.1 Bacterial Infections (Including Wolbachia)

Each of the lymphatic dwelling filarial parasites harbor *Wolbachia* endosymbiotic bacteria [69]. The endosymbiont may also be a factor involved in the initiation of pro-inflammatory responses through its interaction with the pattern recognition receptor TLR4 [70]. However, although filarial antigens can interact with TLRs [62, 71], not all studies favor a role for *Wolbachia* in inducing lymphatic pathology [55, 72]. Nevertheless, treatment of infected individuals with doxycycline (a regimen that eliminates *Wolbachia*) showed significant reduction of the elevated levels of VEGF-C and sVEGF-R3 and improvement of lymphedema [54].

Translocation of microbial molecules contributes to the induction of inflammation by stimulating immune effector cells directly through their pattern recognition receptors [73]. Intra- and perilymphatic damage—underlying features of filarial disease—might also contribute toward the presence of microbial translocation products in the bloodstream. This is reflected in the increased levels of circulating LPS (marker of microbial translocation) and decreased levels of LPS-binding protein (LBP) in individuals with filarial disease and serve as markers of pathogenesis [5]. Though high-protein lymphedema can lead to progressive sclerosis of the skin and pachyderma elephantiasis [74], the presence of secondary bacterial and fungal infections in infected individuals [16, 42], in close association with leaky and damaged lymphatics, may serve as a potential nidus for bacterial translocation that triggers the immune activation and inflammatory reactions and precipitation of elephantiasis.

67.5.2 Host Genetics

The susceptibility to infection and disease in a variety of infectious diseases is known to be associated with host genetics. Though major histocompatibility complex (MHC) was implicated previously [75, 76], subsequent analysis of HLA class II loci (DQA, DQB, and DRB) failed to identify an association with filarial infection or outcomes with the infected group [77]. More recent findings suggest a genetic basis for developing pathology [78] that have included (1) VEGF polymorphisms in hydrocele development [53], (2) host responses [79, 80], and (3) FOXC2 and FLT4 polymorphisms in lymphedema

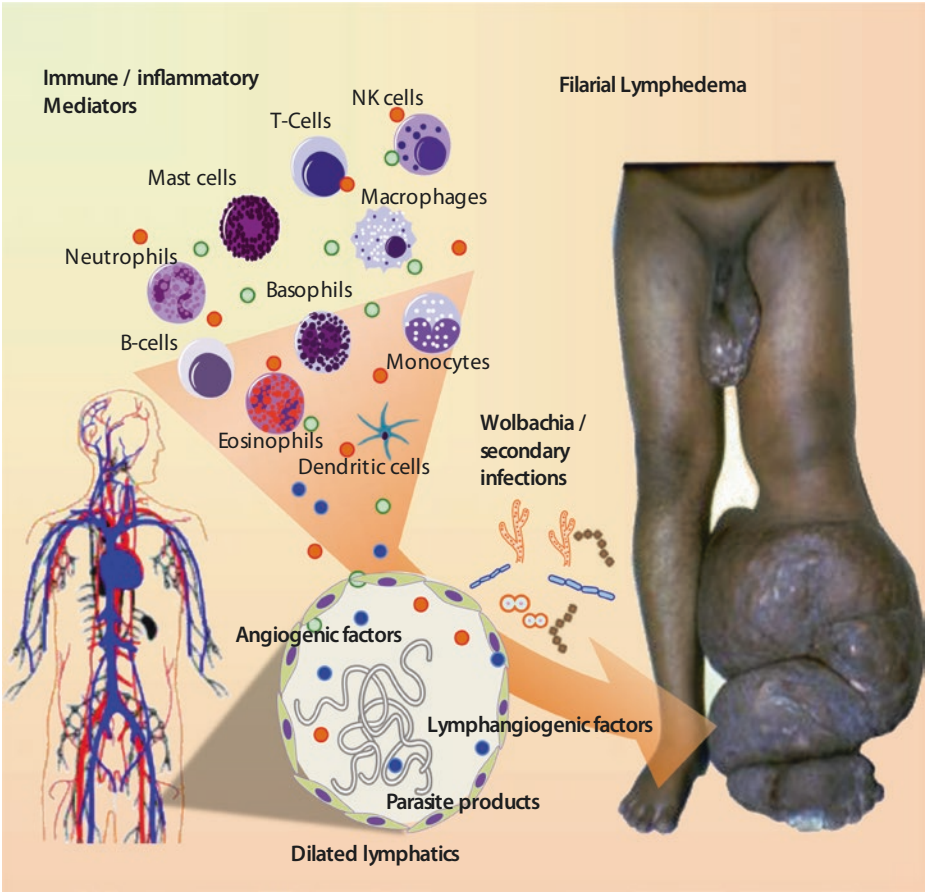

Fig. 67.8 Pathogenesis of filarial disease. Live filarial parasites and/or their products drive lymphatic dilatation leading to dysfunctional vessels. The interplay between the host inflammatory and immune mediators, attrition of parasites, *Wolbachia*, and other factors contributes to pathogenesis and development of filarial disease. Secondary microbial infections further aggravate this pathology

progression [81]. Although the causes of differential susceptibility to clinical manifestations of filarial infections due to genetic factors have been shown to be important, the pathogenesis of lymphedema and hydrocele might be influenced by host genetics in association with environmental cues [82, 83].

Conclusion

Filarial pathology clearly arises through a complex interplay between the parasite and the host immune response (Fig. 67.8) that very likely reflects both the host's genetic predisposition, the quality of the host immune response, and many undetermined factors that shape tissue remodeling in and around the lymphatic system.

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Clinical Overview: Diagnosis and Management

Gurusamy Manokaran

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Summary of Basic Concepts

- LSA and ICG Lymphangiography is the gold standard at present.
- MR lymphangiogram, though good, is not available in many centers, is expensive, and is time-consuming.
- Multimodal approach only can give a good outcome.
- Avoid pneumatic compression devices.
- MLD or CDT is the most effective treatment.
- Multiple-stage surgery is also indicated.
- Post-op follow-up is very important.
- Prevention and elimination of the disease is the focus of the future.

There are about 120 million people at risk for and 70 million people who have established lymphatic filariasis, of which 40 million are suffering from lymphedema; thus, it is very important for medical, paramedic, and health planners to understand this disease and to provide morbidity control including surgery for these unfortunate patients. The World Health Organization is working towards elimination of lymphatic filariasis by 2020 [1–17].

Lymphatic filariasis is a chronic debilitating parasitic disease caused by *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*. This is transmitted by the female *Culex* mosquito to humans. Prevention and elimination of this disease is vital, but it will take a long time because the third-world countries are struggling to cope up with the basic needs of drinking water, food, and shelter (Figs. 68.1 and 68.2).

We have presented the most common manifestation of lymphatic filariasis, namely, lymphedema and its present management strategies.

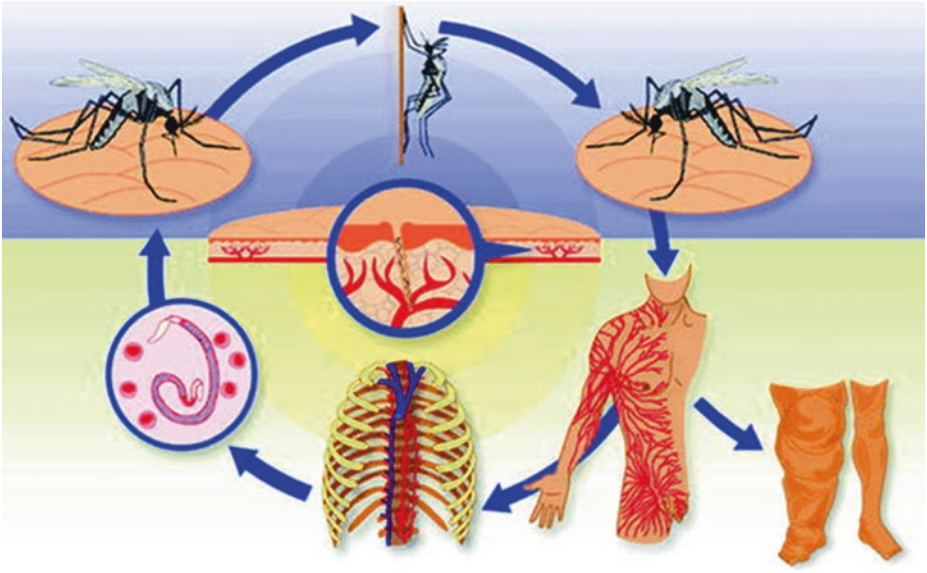

Fig. 68.1 Life cycle of *Wuchereria bancrofti*

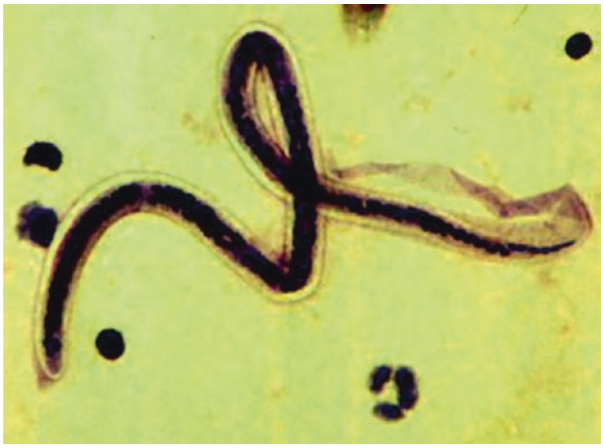

Fig. 68.2 *Wuchereria bancrofti*

68.1 Manifestations

Lymphatic filariasis can manifest as (a) hydrocele, (b) lymphedema of both upper and lower limbs, (c) chylothorax, (d) chyluria, (e) chylascitis, (f) genital manifestations (filarial scrotum, Ramp horn penis genital vesicles, and edema), and (g) *atypical lymphatic filariasis* in the form of fleeting joint pains and lymphangitis (string sign). It can affect the breast, gluteal region, abdomen, and suprapubic region in the form of isolated lesions. The lower limb is the commonest manifestation, and women are more frequently affected than men (Figs. 68.3 and 68.4) [16, 18–22].

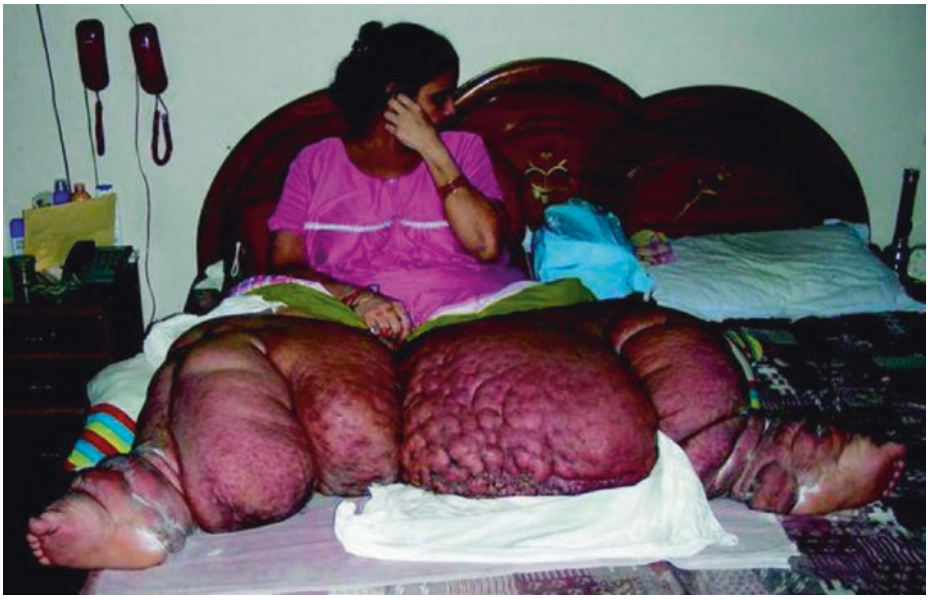

Fig. 68.3 A female patient with bilateral lymphedema due to lymphatic filariasis (elephantiasis)

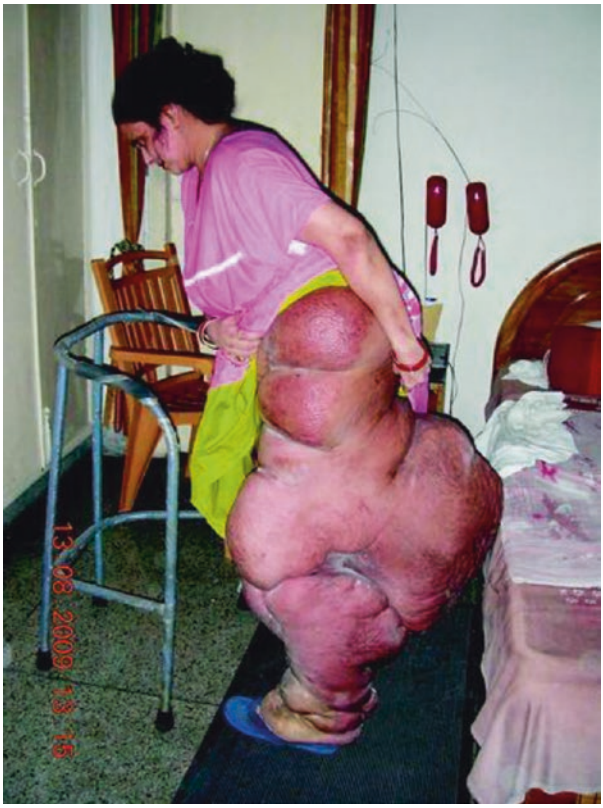

Fig. 68.4 The same patient – lateral view

The chemotherapeutic management [23] of these problems is either diethylcarbamazine [DEC] alone or in the following combinations – DEC + albendazole, DEC + ivermectin – along with periodic antibiotics like penicillin, doxycycline, and sulfonamides. Doxycycline is very useful in symbiotic bacterial infections called *Wolbachia* [24–28] (Figs. 68.5 and 68.6) which reside inside the parasite and cause resistance to antifilarial drugs. The entire topic of lymphatic filariasis is beyond the scope of this chapter, which will be restricted to the management of filarial lymphedema.

68.2 Diagnosis

When diagnosing a case of filarial lymphedema, history is very important because it provides an indication regarding the cause of lymphedema. Careful clinical examination involving color of the skin, the texture of the skin, and skin changes is very important in staging the disease. Circumferential measurements at fixed points of both upper and lower limbs are documented. Height and weight of the patient also are recorded.

The immunochromatographic test (ICT) [29, 30] card test gives a bedside test for lymphatic filariasis, which is highly sensitive for *W. bancrofti* 90–95%.

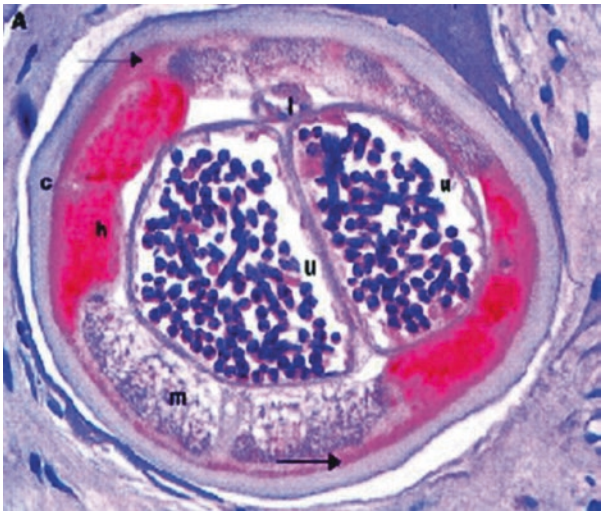

Fig. 68.5 Symbiotic infection with *Wolbachia*

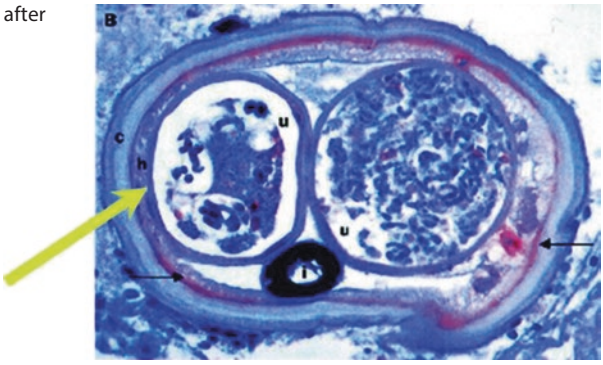

Fig. 68.6 Wolbachia eliminated after chemotherapy

Ultrasound [31–34] in lymphatic filariasis is used in endemic areas as a screening test that can sometimes show *dancing adult worms* in the scrotum in men and in the breast in women. Patients positive for adult worms on ultrasound may not have had any clinical signs and symptoms; thus, removing the adult worms surgically from these patients will prevent the occurrence of lymphatic filariasis (Fig. 68.7).

Lymphoscintigraphy [19, 35–38] is the single most useful investigation in establishing diagnosis grading and etiology. This investigation can tell us about the outcome of this treatment both after chemotherapy and postsurgical results (Fig. 68.8).

Magnetic resonance imaging [39] will be useful when there are associated problems.

For practical purposes we divide filarial lymphedema into four clinical grades:

- Grade 1: edema appears and disappears spontaneously, pitting in nature, uniform in size.
- Grade 2: edema persisting, pitting, and uniform.
- Grade 3: edema persisting, non-pitting, and uniform.
- Grade 4: giant lymphedema with complications like ulcers, warty growth, and loss of limb shape (elephantiasis).

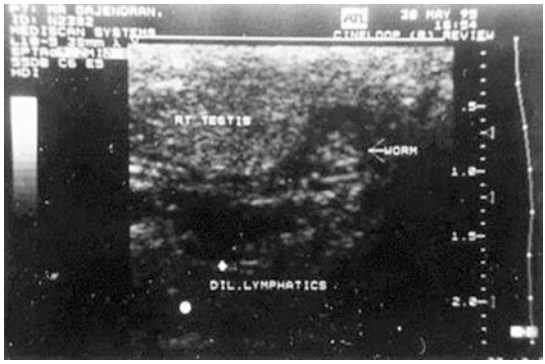

Fig. 68.7 Ultrasound showing the worm in the scrotum

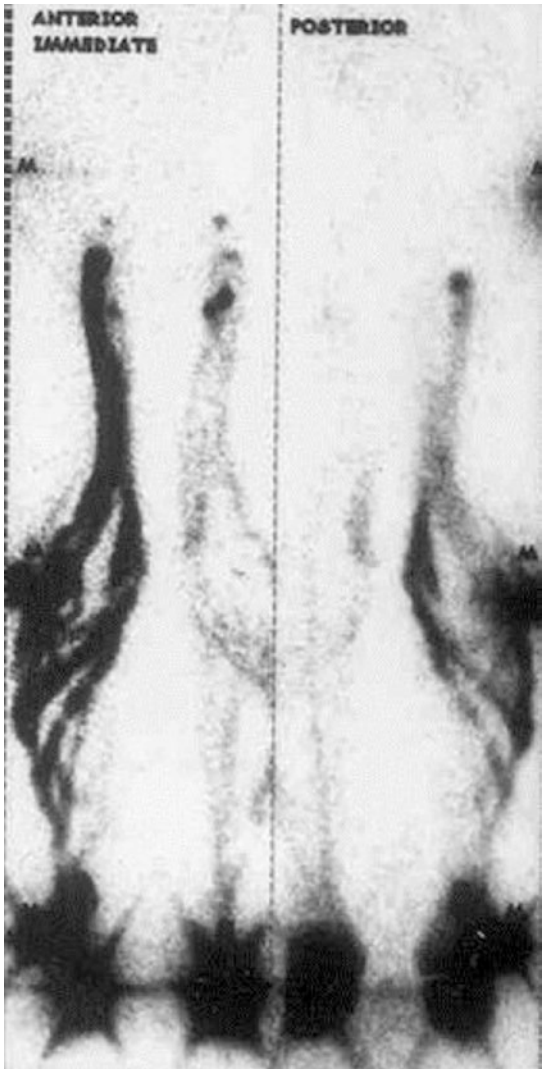

Fig. 68.8 Lymphoscintigraphy of lower limb grade III lymphedema. Showing multiple, dilated, lymphatic channels with dermal back flow

68.3 Management

68.3.1 Basic Management

For all four grades of lymphedema, the recommendations below should be followed.

Grades 1 and 2 of lymphatic filariasis lymphedema are the only forms of lymphedema that are reversible after this protocol of treatment, which has been demonstrated by lymphoscintigraphy before and after treatment (Fig. 68.9).

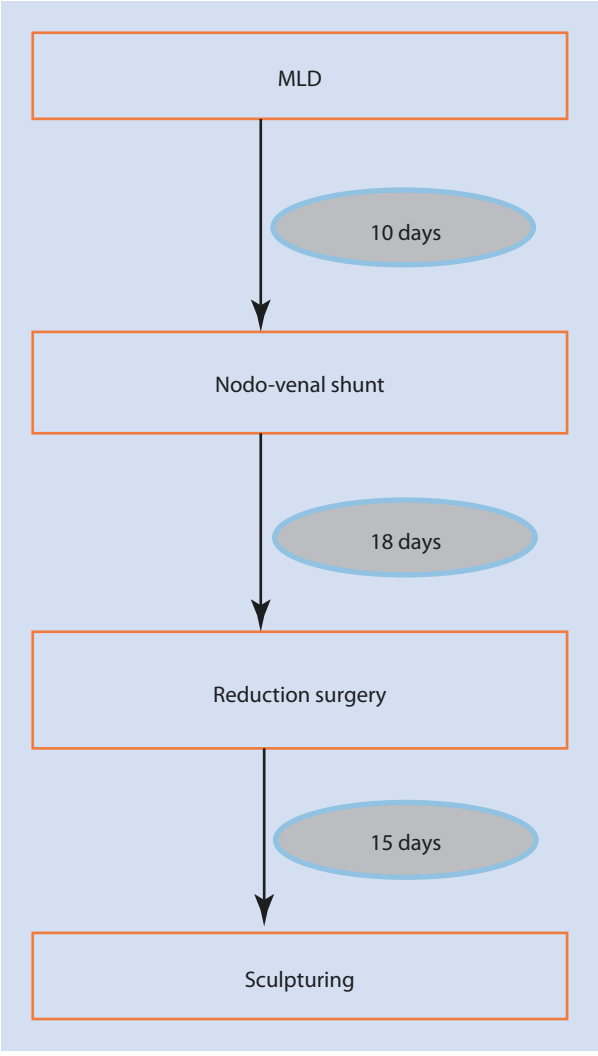

Fig. 68.9 Dr. G. Manokaran's protocol of management

Recommendations for Grades I and II

- Foot care
- Avoiding injury and injections to the affected limb
- Elimination of the focus of sepsis like caries teeth and intertrigo – fungal infection
- Complete decongestive therapy (CDT) followed by
- Pressure garments
- Elevation of the affected part
- Cyclical chemotherapy (antibiotic and antifilarial) to prevent secondary infections

Secondary infections from injury or focus of sepsis like intertrigo and caries teeth are responsible for the progress of lymphedema and not lymphatic filariasis. Avoid injection, blood sampling, and tight garments in the affected limb. Thus, prevention of secondary infection in the initial stages of lymphatic filariasis can completely reverse the damage done by the parasite (Dr. G. Manokaran's observation).

Management of Grades III and IV

Apart from the basic recommendations listed earlier, surgical correction has to be undertaken. Our policy is to combine physiological surgery like a nodovenous shunt or a lymphovenous shunt immediately followed by a reduction or debulking procedure without skin grafting. In our experience of 25 years, we have evolved the technique where the functional and aesthetic aspect of the limb is preserved. Although microvascular surgery like free lymphatic channel transfer, lymph node transfer, omental transfer, and supra-microvascular surgery like lymphatico-lymphatic anastomosis is useful in congenital and postsurgical lymphedemas, this did not play much of a role in filarial lymphedemas.

68.4 Nodovenous Shunt

In ▶ Chap. 43 all the detailed information about lymph nodovenous anastomosis, including the crucial technical aspect, was thoroughly reviewed.

68.5 Reduction Surgery (Dr. G. Manokaran's Technique)

Under tourniquet control we usually use incision only on the medical side of the limb. We use an elliptical incision for excising the redundant skin and subcutaneous tissue followed by a nodovenous shunt; we do not go below the fascial level. We try to use the same skin as far as possible, unless there is an ulcer or warty growth, which will be either included in the ellipse, or a tangential excision is made (sculpturing). In the case shown in the photograph, we have used multiple circular incisions up to the subdermal level and retained the subcutaneous fat of reasonable thickness; no undermining of the skin was made, which gives a functional and cosmetically acceptable outcome. As far as the thigh is concerned, we make a vertical medial incision and reduce the size of the thigh (◘ Figs. 68.10, 68.11, 68.12 and 68.13) (Dr. G. Manokaran's technique).

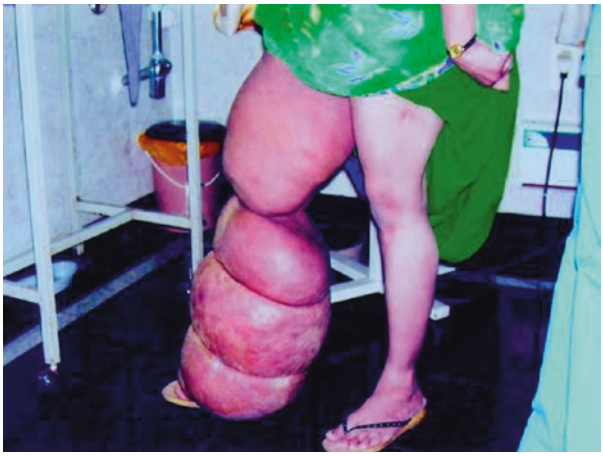

Fig. 68.10 Picture showing a 27-year-old female patient with filarial lymphedema of 20-year duration

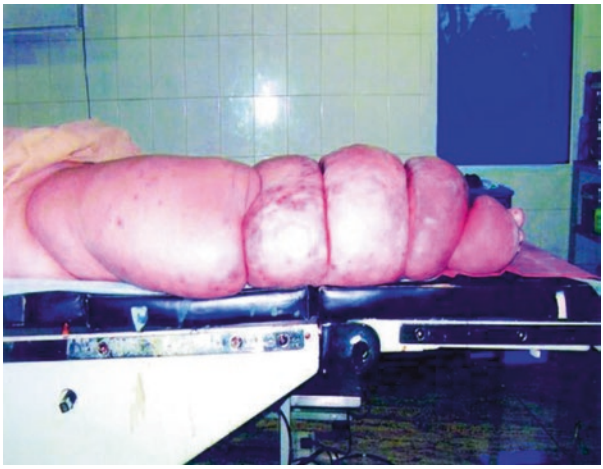

Fig. 68.11 Patient just before nodovenous shunt

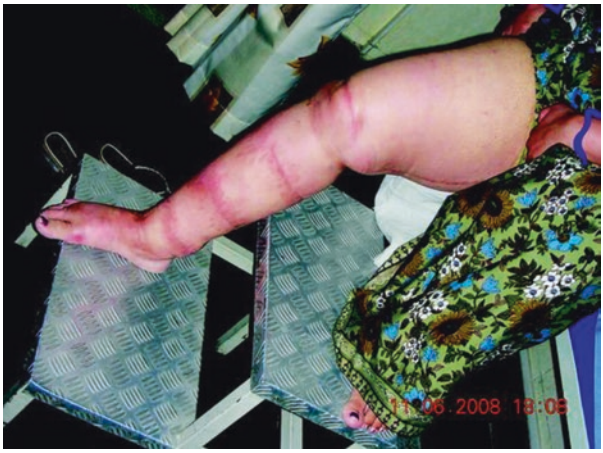

Fig. 68.12 Patient after the author's technique of reduction

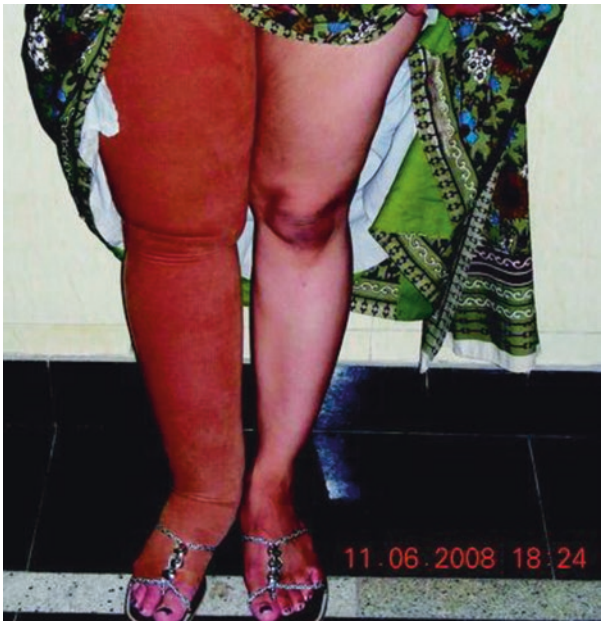

Fig. 68.13 At 3-year follow-up, with stockings (note that the patient is using footwear of the same size on both feet)

Although this is the most useful protocol that gives the best acceptable results in lymphedema due to lymphatic filariasis, we have to modify our technique or time duration depending upon individual patients. All patients are advised to follow foot hygiene, eliminate the focus of the sepsis, avoid injury to the affected limb, and retain the shape of the limb with the help of pressure garments postoperatively.

Stage III and IV lymphedema cannot be cured, it can only be controlled.

The older debulking procedures like the Charles, Kondoleon, and Thompson procedures are no longer performed because the long-term results are not good and they produce a bottleneck deformity and cobblestone appearance; this is due to the excision of the skin and subcutaneous tissue up to the fascia, which eliminates all the lymphatics in the subdermal layers.

Further detailed discussion was provided in ► Chap. 55: «Principle of Debulking Procedures.»

68.6 Complications

- Lymphorrhea
- Lymphocele
- Wound dehiscence and flap necrosis
- Hemorrhage

These are the possible complications in this kind of surgery. Although there were a few morbidities, there was no mortality resulting from these surgical procedures. A good preoperative assessment and preparation avoid all unwanted complications postopera-

tively. As we routinely do MLD and bandaging or CDT preoperatively, we don't need to give blood transfusion in any of our surgical cases, so that we can avoid transfusion-related complications.

Acknowledgement I acknowledge Dr. Leela Praveen Kumar for helping me in bringing out the chapter succesfully.

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Oncology and Lymphedema

Contents

Breast Cancer

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Summary of Basic Concepts

- Breast cancer treatment is a common cause of lymphedema of the arm, hand, and trunk/chest regions.
- The majority of women who develop lymphedema will have only mild physical changes.
- Detection of early signs of swelling is assisted by having presurgical measurements of the limbs or through the use of evidence-based diagnostic thresholds.
- Ongoing surveillance of woman at high risk of developing lymphedema is required.

69.1 Breast Cancer and Lymphedema

As a consequence of treatment for breast cancer, lymphedema can occur in the extremity, as well as in the trunk region (i.e., breast and anterior and posterior chest) ipsilateral to the side of surgery. A cross-sectional study examining the prevalence of lymphedema based on the region affected found that 77%, 37%, and 35% of participants reported arm, hand, and trunk/chest region affected with lymphedema, respectively [1]. Oliveri et al. [6] similarly found that of the women who presented with lymphedema, one-third experienced it in the hand. Notably, lymphedema-related symptoms were more severe with trunk/chest lymphedema compared to that experienced for arm lymphedema [1].

For many women treated for breast cancer, the swelling that develops on the side ipsilateral to surgery, particularly in the first year, is transient [2, 3, 7, 8]. Swelling experienced in the first year may be a result of surgery or due to other treatment-related factors such as taxane-based chemotherapy [9, 10]. However, at this point, it is unclear who will progress to intransient lymphedema.

Women with mild intransient lymphedema (e.g., swelling obvious to the patient only) experience symptoms and increased levels of distress compared with women without lymphedema [2, 6, 11]. Symptoms experienced prior to any visible changes include sensations of heaviness, swelling, tightness, and discomfort/pain [2]. These symptoms reflect underlying changes in fluid levels which commonly occur in localized regions [12]. Detection may require tools that measure a section within the arm rather than the whole limb, per se, e.g., circumference of the limb or segmental bioimpedance spectroscopy [4, 13].

For women in whom the lymphedema becomes intractable, progression of lymphedema can affect both limb volume as well as composition. Subcutaneous and subfascial adipose deposition commences early [14] and continues to progress so that, by the advanced non-pitting stage, much of the excess volume in the lymphedematous limb is adipose tissue [15, 16]. Other changes to the affected limb include cutaneous thickening and hypercellularity and progressive fibrosis [17]. However, we know little about progression in severity of the condition beyond the fact that it cannot be explained simply by duration of disease [1, 14]. More than half do not progress beyond a mild stage [1, 2, 18].

69.2 Prevention and Early Identification of Lymphedema

At the time of surgery, women treated for breast cancer are advised about prevention strategies. These strategies include avoidance of medical procedures to the 'at-risk' arm, airplane travel, and overuse of the 'at-risk' limb. Regardless of whether surgery includes axillary lymph node dissection (ALND) or sentinel lymph node biopsy (SLNB), there is no evidence that avoidance of these activities prevent development of lymphedema [3, 19–21]. In contrast, preliminary data suggests that resistance training with the 'at-risk' arm prevents development of lymphedema [22, 23].

For women treated for breast cancer, ongoing surveillance is important but lacking. This gap was identified in a round-table discussion hosted by the American Cancer Society (February 2011) from which a surveillance model was generated to identify and manage the secondary physical impairments arising from treatment [24]. However, monitoring beyond the immediate postsurgical period is still uncommon [25].

Surveillance should commence with measurements of the upper limbs prior to surgery [26–28]. A range of tools are available to monitor the upper limb in particular. Regardless of what tool is used, such as bioimpedance spectroscopy or tape measures, the inter-limb difference can be large [29, 30]. Without presurgery measurements, normative inter-limb differences may obscure early changes.

Cost of ongoing surveillance of all women treated for breast cancer may be a barrier to implementation. Findings from studies investigating risk factors for lymphedema can be used to identify to whom the resources should be allocated. In addition, interventions can be trialed in women at high risk of lymphedema to prevent its development. To date, effective conservative interventions to prevent lymphedema, beyond exercise, are yet to be identified [31]. For those at high risk, surgical options such as reverse mapping [32] or prophylactic surgery [33] may be an option in the future.

69.3 Identification of Women at High Risk for Lymphedema

To date, data arising from risk factor research has not been used to stratify the degree of surveillance offered to women treated for breast cancer. This may be, in part, due to issues which have confounded identification of risk factors for lymphedema. One major issue is related to its diagnosis. As illustrated in recent systematic reviews [5, 34], a range of tools and thresholds are used for diagnosis of lymphedema. Up to now, there has been no evidence to determine whether one approach was better than the other, particularly when no presurgical measurements are available. This gap has now been addressed: a range of thresholds from various tools, including tape measure, perometry, and bioimpedance spectroscopy, were compared to the presence of dermal backflow, a feature unique to lymphedema [4]. For detection of mild lymphedema, only normatively determined thresholds, which accounted for limb dominance, using circumferences [29] and whole arm bioimpedance spectroscopy [30], had high sensitivity and specificity and a clinically useful positive and negative likelihood ratio. Commonly used thresholds including

2 cm inter-limb difference, 5 cm sum of arm circumference (SOAC) inter-limb difference, 10% inter-limb volume difference, and 200 ml inter-limb volume difference all had low sensitivity.

A second issue is related to axillary surgery and how it is defined. Typically, axillary surgery is dichotomized in incidence and risk factor research as ALND or SLNB, irrespective of the number of nodes removed. However, the number of nodes removed during SLNB can vary widely [3, 35–37]. This broad range may contribute to the wide-ranging incidence of lymphedema for those who have undergone SLNB [34]. The number of nodes removed, rather than the label ALND vs SLNB, improves identification of risk in the presence of lymph node surgery as well as provides greater insight into what is the risk of lymphedema attributed to axillary surgery. The importance of defining the number of nodes removed was highlighted by investigations on risk of taxane chemotherapy on lymphedema. For women with ≥5 nodes removed, taxane was identified as a risk factor [3, 10, 38]. In contrast, when the sample under investigation comprised predominantly no surgery or SLNB [39] or <5 nodes removed [3], taxane-based chemotherapy was not a risk for lymphedema.

A third factor affecting the determination of risk factors for lymphedema is the timing of when women are diagnosed. During the first year, many women experience transient swelling [2, 3, 7, 8]. Inclusion of cases of transient swelling in studies on those with intractable swelling will confound identification of risk factors.

Although these issues have complicated determination of the risk factors for the development of lymphedema, certain factors are emerging as important. First and foremost, having ALND increases risk of lymphedema [5, 40]. In the presence of ALND or at least five or more nodes removed, other factors that contribute to risk of lymphedema include taxane-based chemotherapy [3, 38], being overweight or obese at time of surgery [5], radiotherapy to the axilla [37], and other factors associated with advanced disease [3, 5]. While these factors heighten the risk for lymphedema, the presence of arm swelling in the first year is a much higher risk for lymphedema beyond the first year [3], strongly supporting the need for ongoing surveillance.

For women with only a few nodes removed, i.e., <5 nodes removed, the risk of lymphedema is 3–8% beyond the first year following surgery [5, 34]. Many factors identified for women who had many nodes removed do not necessarily apply to this group (e.g., 6, 39) although many women in this group do experience arm swelling in the first year [34]. One factor which may increase risk of lymphedema in this group is obesity at time of surgery [41].

Consideration of risk data suggests that it is women who undergo ALND, or have at least five nodes removed, who require ongoing surveillance beyond the immediate post-surgical period. In contrast, women with no or only a few nodes removed require education about lymphedema but may not need the same level of surveillance as those with more nodes removed. Stratification of risk may be further improved with improved understanding of the underlying physiology [42] and genetic predisposition of lymphedema [43–46].

Once identified, interventions for lymphedema can be instigated. Preliminary evidence suggests, for example, compression garments applied when a 3% increase in limb volume is detected effectively resolve early mild swelling [28]. Early intervention appears to be critical as women living with chronic lymphedema reported limited satisfaction with treatments currently available [1].

Conclusion

For women treated for breast cancer, lymphedema can develop in the upper limb as well as in the trunk/breast region. For the majority of women in whom lymphedema develops, the condition is mild. The challenge for clinicians is to prevent it from becoming established and progressing to a more advanced stage where significant tissue changes occur and treatment options are limited.

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Lower Extremity Cancers

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Summary of Basic Concepts

Secondary lower limb lymphedema (LLL) is commonly associated with surgical excision of inguinofemoral lymph nodes and/or radiation of the respective node-bearing areas. The condition of LLL presents as progressive swelling of one leg or both, most typically within the first 12 months after the treatment for cancer. Once it develops, it is typically unremitting and often progressive. The incidence of, and risk factors for, LLL will vary depending on cancer type and treatment regimen. LLL is one of the important survivorship issues reported after cancer treatment, aggravating financial difficulties and impacting on quality of life.

- Secondary lower limb lymphedema (LLL) is commonly associated with surgical excision of inguinofemoral lymph nodes and/or radiation of the respective node-bearing areas.
- The incidence of, and risk factors for, LLL vary depending on cancer type and treatment regimen.
- The most common timing of the onset of LLL is within the first year following treatment.
- LLL is the most frequent problem impacting quality of life after cancer treatment of the relevant neoplasms.

Secondary lower limb lymphedema (LLL) is commonly associated with surgical excision of inguinofemoral lymph nodes and/or radiation of the respective node-bearing areas. The condition of LLL presents as progressive swelling of one leg or both, most typically within the first 12 months after the treatment for cancer. Once it develops, it is typically unremitting and often progressive.

The occurrence of LLL after treatment of reproductive, gastrointestinal, and urinary malignancies and of melanoma is reportedly quite common, although reliable incidence estimates vary substantially. In recent years, postoperative LLL has been recognized as the most frequent complication after pelvic lymphadenectomy [6–8].

The incidence estimates of secondary LLL after cancer treatment apparently are influenced by the type of cancer (Table 70.1). The incidence varies from 0.6% to 73%, depending on the type of cancer, stage, treatment, and sensitivity of the measurement tool (Table 70.1). The highest relative incidence has been reported after vulvar cancer treatment and the lowest after prostate cancer [9–11]. The reported incidence of secondary LLL has declined in publications that have appeared since 2000, presumably as a reflection of the adoption of less invasive surgical (sentinel lymph node biopsy vs. full inguinofemoral lymphadenectomy) and radiotherapeutic treatment regimens. However, the improved survival rates for all gynecological cancers are likely to have an augmenting effect upon the number of patients with LLL.

Postoperative LLL is associated with several risk factors. A higher incidence of LLL is reported after the administration of adjuvant radiotherapy (37.1–67.9%) [1, 12, 13]. Other commonly identified risk factors are the removal of circumflex iliac nodes [2], cellulitis [2], the number of lymph nodes removed [11, 14], infection [14], and the presence of postoperative lymph cysts [14].

Table 70.1 Incidence/prevalence of lower limb lymphedema as a consequence of cancer treatment

Primary cancer	Method of diagnosis	*N*	Incidence/prevalence	Year	Reference
Ovarian cancer	Medical records and subjective symptoms	135	21.1%	2009	[1]
	Clinical diagnosis and subjective symptoms	234	Total: 20.5% Symptomatic: 15.8% Diagnosed: 4.7%	2007	[9]
	Retrospective survey	141	7.1%	2003	[31]
	Retrospective study using ISL criteria	137	21.9% without adjuvant radiotherapy	2015	[2]
	Cross-sectional survey	23	30.4%	2015	[5]
Cervical cancer	Physical examination	228	Stage I–IIA: 31%	2002	[32]
	Clinical diagnosis and subjective symptoms	197	Total: 26.4% Symptomatic: 14.2% Diagnosed: 12.2%	2007	[9]
	Retrospective survey	120	17.5%	2003	[31]
	Clinically detectable finding by patient or physician	192	23.4%	2008	[33]
	Medical records and subjective symptoms	252	29.8%	2009	[1]
	Retrospective chart review with the ISL criteria	398	Total: 20.1% Removal of CINDEIN: 17.1% No removal of CINDEIN: 3%	2015	[8]
	Physical examination by gynecologic oncologist with presence of symptoms, grading by circumference at ankle, midcalf, and midthigh	596	Total: 12.6% Mild: 3.5% Moderate: 7.6% Severe: 1.5%	2012	[22]
	Retrospective study following ISL criteria	100	21% without adjuvant radiotherapy 3 months postsurgery: 55.9%	2015	[2]

(continued)

Table 70.1 (continued)

Primary cancer	Method of diagnosis	*N*	Incidence/prevalence	Year	Reference
	Cross-sectional survey	34	50%	2015	[5]
Endometrial cancer	Limb volume, MFBIA, and self-report	60	40% by volume, 67% by MFBIA, 22% by self-report	2010	[34]
	Limb volume, clinical history, and physical examination	286	37.8%	2010	[13]
	Retrospective chart review excluding chronic lower limb lymphedema related to other medical conditions	670	Uterine corpus cancer follow-up of 3 years: 2.4%	2006	[35]
	Retrospective survey	141	17.7%	2003	[31]
	Retrospective study using ISL criteria	121	22.3% without adjuvant radiotherapy	2015	[2]
	Cross-sectional survey	95	3 months after surgery: 34.7%, At the time of survey: 32.9%	2015	[5]
	Circumference measured in 3 locations	39	12.8% with 20% increase postoperatively	2015	[36]
Vulvar cancer	Clinical diagnosis and subjective symptoms	53	Total: 50.9% Symptomatic: 15.1% Diagnosed: 35.8%	2007	[9]
	Medical records and subjective symptoms	295	27.8%	2009	[1]
	Retrospective survey	68	47.1%	2003	[31]
	Persistent swelling >2 months	61	26%	2004	[37]
	Clinically obvious or elastic bandages requirement beyond 3 months postoperatively	172	28%	2003	[38]
	Quality-of-life questionnaire	60	Symptomatic leg swelling in 73% and in 80% of radiotherapy recipients	2014	[39]

Table 70.1 (continued)

Primary cancer	Method of diagnosis	*N*	Incidence/prevalence	Year	Reference
	Retrospective chart review	99	10.1%	2015	[40]
	Retrospective observational study	116	16%	2016	[41]
Prostate cancer	Subjective symptoms	16	13%	1990	[42]
	Subjective symptoms	289	Stage A2–C: 3.1%	1991	[43]
	Subjective symptoms	372	1.3%	1993	[44]
	Unknown	123	4.1%	2003	[45]
	Leg volume difference calculated from circumference measures, tissue dielectric constant, palpation, and subjective symptoms	22	Grade I, 27% Grade II, 9%	2013	[46]
	Unknown, prospective monocentric study	303	Extended lymphadenectomy: 15.7% Limited lymphadenectomy: 0.6%	2014	[11]
Penile cancer	Subjective symptoms, retrospective analysis	53	Scrotal and leg edema: 23%	2002	[47]
	Circumference measure	10	23%	2003	[48]
	Unknown, retrospective analysis	234	Inguinal lymph: 25% Ilioinguinal lymph: 29%	1993	[49]
	Leg volume difference	66	Inguinal SNB: 6% Inguinal SNB and groin dissection: 64%	2006	[50]
	Retrospective audit	40	37.5%	2004	[51]
	Clinical assessment with a checklist	170	4.1%	2013	[52]
	Unknown, retrospective analysis	20	Salvage ILND for recurrent cancer: 20%	2014	[53]
Melanoma with inguinal node involvement	Self-report, clinical assessment	28	29%	2003	[54]

(continued)

Table 70.1 (continued)

Primary cancer	Method of diagnosis	*N*	Incidence/prevalence	Year	Reference
	Late radiation morbidity scoring system	33	4 weeks of radiation in the groin area: 66%	2002	[55]
	Limb volume change >10% at 6 months	154	25%	2013	[56]
	Limb volume change >10% at 12 months	117	27.1%	2013	[56]
	Clinical assessment	605	Moderate/severe: 19%	2016	[57]

CINDEIN circumflex iliac nodes distal to the external iliac nodes, *MFBIA* multifrequency bioelectrical impedance analysis, *SNB* sentinel node biopsy, *ISL* International Society of Lymphology, *ILND* inguinal lymph node dissection

The reported timing of the onset of LLL after the diagnosis of cancer varies considerably [3]. A study by Beesley and colleagues reflects that 75% of affected individuals were diagnosed with lymphedema within the first year, 19% in the following year, and 6% between 2 years and 5 years after diagnosis [9]. Another recent study reports the cumulative incidence of LLL at 1, 3, 5, and 10 years after cancer surgeries as 12.9%, 17.3%, 20.3%, and 25.4%, respectively [2]. By general consensus, the most common timing of the onset of LLL is within 1 year of the index surgery. The initial symptom is usually painless swelling. The patient may also complain of a feeling of heaviness in the limb, especially at the end of the day and in hot weather. Symptoms can vary throughout the menstrual cycle [15].

In the earliest stages of the lymphedema, the swelling presents as pitting edema, but, with time, classical non-pitting edema will appear [16]. The distribution of the lymphedema is asymmetrical. A positive Stemmer sign (inability to tent the skin at the base of the second toe) is a useful clinical sign [17]. LLL can spread proximally (or distally) in the early stages, but this is uncommon after the first year. Nevertheless, the condition can be progressive if treatment is not administered [18]. With the passage of time, the affected swollen limb increasingly manifests chronic cutaneous changes, with enhanced skin creases, hyperkeratosis, increased skin turgor, and papillomatosis [16, 19]. Symptomatology may include mild pain or a sense of heaviness or fullness. In severe cases, the skin can break down; lymphorrhea (lymph exuding through any break in the skin) is associated with an increased risk of soft-tissue infection. Indeed, recurrent infections, cellulitis, and lymphangitis are common. Repeated infection can lead to further deterioration in lymphatic function, ending in a vicious cycle of infection and repetitive worsening of the condition. Associated clinical features of LLL include tightness of the shoes or inability to wear them; itching of the legs, feet, or toes; burning sensations in the legs; sleep disturbances; and loss of hair on the affected limb. One

published study suggests that patients with LLL are more likely to present with swelling, heaviness, tightness, and skin problems than their counterparts with upper limb lymphedema [20].

LLL is one of the central survivorship issues reported by women after gynecologic cancer treatment. Yost et al. [21] have shown that lymphedema was the problem with the most frequent impact on quality of life in 15 women after vulvar cancer treatment. Similarly, in another published study, 82 women with LLL after gynecological cancer treatment reported that the lymphedema had a significant impact on their quality of life, financial state, physical and social activities, the clothes that could be worn, and, overall, on their emotional well-being [10]. A more recent study by Kim and colleagues reported that LLL-related symptoms resulted in decreased quality of life and aggravated financial difficulty in 33 Korean women [22]. While symptoms experienced by individuals with LLL are similar to those of individuals with upper limb lymphedema, a higher intensity and level of distress is reported in individuals with LLL, as well as a high prevalence of fatigue (≥75%) [4].

One of the major problems associated with LLL after cancer treatment seems to be the limited awareness of the public and among healthcare professionals. Women with LLL after gynecological cancer treatment experienced barriers in access to treatment, delays in lymphedema diagnosis, and conflicting information on the management of the lymphedema [10]. A recent UK study also suggested that a greater proportion of patients with LLL than those with arm lymphedema may have progressed to a chronic stage before consulting a health professional; in the population studied, only 24.2% of patients with LLL sought treatment within 3 months of symptom onset compared with 56.1% of patients with arm lymphedema reporting such patterns [23]. The diagnosis and treatment of LLL may have a lower level of recognition within public consciousness when compared with that of ULL after breast cancer treatment [20]. Many cancer treatment centers now have trained breast cancer nurses who provide advice and services to breast cancer survivors regarding lymphedema prevention and early detection, whereas comparable services for LLL patients are generally much less readily available.

In clinical practice, the diagnosis of LLL is based upon measures of limb circumference and/or volume. In unilateral presentations, concurrent measurement of the contralateral leg can be used to assess whether the affected leg is actually swollen. However, the disease often affects both lower limbs, or, alternatively, premorbid asymmetry in the two lower limbs may hamper the ability to accurately compare the limbs in the assessment of edema presence and magnitude. A cloth tape measure can be used to measure circumferential asymmetries between the two limbs, but this technique is unreliable. Water displacement volumetry, although not commonly used, directly measures limb volume [24] and can be more accurate than calculating the leg volume with a tape measure [25]. In lymphedema, the tissue tonicity (degree of tissue resistance to mechanical compression) is either higher or lower than that of the unaffected leg [26]. Measurement of tissue tonometry is more useful for the assessment of the response to treatment than in the initial assessment of disease. Bioimpedance spectroscopy has been used successfully for the evaluation of swelling in patients with breast cancer-related lymphedema, but has not yet been validated for the assessment of leg edema [27]. In addition, there is no normative data set available for LLL.

The chief treatment goals for patients with LLL are to prevent the progression of disease, to achieve mechanical reduction and maintenance of limb size, to ease the symptoms arising from lymphedema, and to prevent skin infection. Treatment depends on the symptoms and the severity of the condition and can be divided into conservative, pharmacological, and surgical approaches. As in breast cancer-related lymphedema, conservative treatments include manual lymphatic massage, multilayer bandaging and complex decongestive physiotherapy, compression garments, limb exercises and limb elevation, pneumatic bio-compression, and low-level laser therapy [28]. There is scanty published support for the specific efficacy of complex decongestive physical therapy to reduce LLL volume in patients who have undergone groin dissection [29]. There is no conclusive published evidence that pharmacological intervention, with agents such as benzopyrones and selenium compounds, adds benefit in the management of secondary LLL [30]. Surgical intervention is generally recommended for only a small subset of such patients [30].

Both cancer incidence and survival rates continue to increase; thus, the incidence and the public health burden of secondary LLL can be expected to increase in parallel. There is an obvious imperative to provide appropriate guidelines, not only for patients but also for healthcare professionals. The lack of methodologically sound research on secondary LLL imposes barriers to the development of evidence-based guidelines regarding incidence, risk factors, diagnosis, and treatment. Undoubtedly, there is still much to be learned and studied. However, there is enough knowledge to raise awareness of a condition whose prevalence and population disease burden are likely to be underestimated. During and following cancer treatment, patients can be educated regarding the potential triggers for the onset of overt lymphedema and, thus, the potential strategies for effective prevention. Patients can be informed to facilitate appropriate decisions regarding treatments and elective lifestyle behaviors. For those who experience the onset of overt problems, measures should be undertaken to help them appreciate that treatment for secondary LLL can be expected to ameliorate function and that omission of treatment can promote progression and increase the likelihood of complications.

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Radiation Considerations

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Summary of Basic Concepts

- The risk and etiology of lymphedema in oncology patients is multifactorial, with tumor and treatment characteristics impacting clinical outcomes. Treatment decisions must achieve a balance between tumor eradication and possible treatment-related complications and morbidity.
- Lymphedema is most common in breast cancer patients but may also occur in patients with malignant melanoma, gynecological malignancies, genitourinary malignancies, extremity sarcoma, and head and neck cancer.
- Radiotherapy contributes to an increased risk of lymphedema through disruption or dysfunction of cutaneous lymphatics and by promoting tissue fibrosis via transforming growth factor (TGF) β1-dependent mechanisms.
- Radiation treatment techniques, such as three-dimensional treatment planning and intensity-modulated radiotherapy, may play a role in decreasing normal tissue toxicity and subsequent risk of lymphedema.

71.1 Pathophysiology of Radiation-Associated Lymphedema

Clinical studies have demonstrated that radiotherapy is an independent risk factor for the development of lymphedema, with postoperative radiotherapy increasing the risk three- to fourfold compared with surgery alone [6, 7]. The exact mechanisms by which radiation contributes to this risk, however, are still being elucidated. Investigators have shown that radiation is associated with cutaneous lymphatic dysfunction [8] as well as a decrease in the overall number of cutaneous lymphatics [1, 9], resulting in disequilibrium between the microvascular filtration rates of the capillaries, venules, and lymphatic drainage system. Microscopic and functional studies of lymphatics suggest that this damage originates in the smooth muscle cells of the lymphatic vessel walls. Interrupted drainage from superficial lymphatic vessels leads to dermal backflow and retained lymphatic fluid [1]. Although disruption of the deep lymphatics may contribute, the development of lymphedema after radiotherapy appears to be influenced mostly by the depletion or dysfunction of cutaneous lymphatic channels [10].

Another mechanism by which radiation is thought to increase the risk of lymphedema, particularly after surgery, is by promoting tissue fibrosis via transforming growth factor (TGF) β1-dependent mechanisms [11, 12]. TGF-β1 and its co-receptor endoglin have been shown to be negative regulators of lymphatic regeneration during wound repair [13], as well as direct inhibitors of lymphatic endothelial cell (LEC) proliferation and function [14].

Using irradiated mouse tail models, investigators have demonstrated a dose-dependent, long-term decrease in lymphatic function associated with LEC apoptosis, a long-term decrease in the number of cutaneous lymphatic vessels, and the development of soft tissue fibrosis [10]. In patients irradiated for breast cancer, investigators have demonstrated a correlation between changes in TGF-β and endoglin levels, the density and caliber of lymphatic vessels, and macrophage infiltration. Increased endoglin levels may stimulate cytokine production in macrophages and amplify irradiation-induced vascular damage [2].

Even at low doses, radiation causes a significant and dose-dependent increase in LEC senescence compared with controls. The decrease in LEC proliferation and function may be attenuated with short-term inhibition of TGF-β1 [10]. Prevention of radiation tissue fibrosis may be an avenue of investigation for protection against lymphedema.

71.2 Radiotherapy and Disease-Specific Risk of Lymphedema

71.2.1 Breast Cancer

Lymphedema is most common in breast cancer patients, with an estimated 5-year cumulative incidence of 42% [15]. The risk of lymphedema after the treatment of breast cancer can vary according to the type of breast and lymph node surgery performed, as well as the radiotherapy treatment fields delivered. Patients diagnosed with early-stage invasive breast cancer may be candidates for breast conservation therapy, which includes a lumpectomy followed often by postoperative whole-breast radiotherapy to reduce the risk of an in-breast tumor recurrence. Whole-breast radiotherapy consists of tangential radiotherapy fields that target the breast tissue, including the axillary tail of the breast. In patients who have evidence of nodal involvement after a standard lymph node dissection (which includes axillary levels I and II), particularly in those with four or more nodes involved, an additional treatment field is added to target the level III axillary nodes and the supraclavicular lymph nodes.

The incidence of lymphedema after lumpectomy plus axillary lymph node dissection (ALND) ranges from 1.8% to 10–16% [16–18]. While postoperative radiotherapy to the breast alone does not appear to contribute significantly to lymphedema risk [17], this risk increases to 18–31.5% in those receiving whole-breast radiotherapy plus supraclavicular/axillary apical radiotherapy treatment after ALND [16, 17]. With the addition of a posterior axillary boost field, an additional field that is designed to increase the dose to the axilla in patients with high-risk features, the risk of lymphedema is further increased to approximately 30–40% [19]. Thus, compared with treatment to the breast alone, the addition of a supraclavicular field or a posterior axillary boost field increases the risk of lymphedema approximately two- and threefold, respectively [19].

Patients with more advanced disease are often treated with mastectomy and level I/II axillary dissection. Postoperative radiotherapy is often incorporated if the tumor is ≥5 cm with any lymph node involvement or if four or more lymph nodes are involved, as these patients have been shown to have a high rate of locoregional recurrence without the use of radiotherapy. Treatment fields in the postmastectomy setting target the mastectomy scar and chest wall, the axillary apex (level III) and supraclavicular nodes, and occasionally the internal mammary lymph nodes.

Data from the National Surgical Adjuvant Breast and Bowel Project B-04 study reported the long-term incidence of lymphedema to be 31% in women treated with radical mastectomy (removal of the breast plus axillary level I/II and III dissection), 15.5% in women treated with total mastectomy (removal of the breast tissue without intended nodal dissection or sampling), and 14.8% in those treated with total mastectomy plus radiotherapy to the chest wall and nodal regions [20]. Interestingly,

these findings suggest that mastectomy alone may cause significant disruption of the lymphatics, and that the extent of lymph node resection is additionally associated with the risk of lymphedema.

With the introduction of sentinel lymph node biopsy in patients who are clinically node negative, the removal of one or two lymph nodes rather than a complete axillary dissection for staging has led to a reduction in the risk of lymphedema, with women having a 3-year risk of lymphedema of 14–15% after a complete ALND compared with 5–8% in those who only had a sentinel lymph node biopsy [21]. As a result of these data and other studies confirming that axillary dissection is significantly associated with lymphedema [22], more recent trials have investigated axillary radiation instead of ALND in node-positive patients and have demonstrated a lower rate of lymphedema with axillary radiation (10%) compared to ALND (21%) at 5 years [3].

It is important for the radiation oncologist to spare skin and uninvolved tissues when possible to allow for collateral lymphatic drainage [23, 24]. Other radiotherapy treatment-related factors, including total dose and extent of the treatment field [25, 26], need to be taken into consideration in order to minimize the risk of lymphedema. Interestingly, fraction size (1.8 Gy vs 2.0 Gy per day), beam energy (6 MV vs 10 MV), and type of breast tangent (simple vs multifield) are not significantly associated with lymphedema [27, 28]. Three-dimensional treatment planning is now routinely used to allow for more homogenous dose distribution and to minimize normal tissue toxicity.

Early studies on lymphedema urged patients with breast cancer to avoid injections, blood draws, and blood pressure monitoring in the affected arm, with the thought that patients with surgically removed lymph nodes may have compromised lymphatic channels with decreased fluid-clearing abilities [4, 29]. However, a recent large, prospective study provided clear evidence that there is no significant association between blood draws, injections, and blood pressure readings on the risk of lymphedema [4]. The factors that were associated with an increase in lymphedema were axillary lymph node dissection, regional lymph node radiation, body mass index (BMI) $\geq$25, and cellulitis.

71.2.2 Malignant Melanoma

Postoperative radiotherapy is often recommended after resection of the primary melanoma lesion if there are pathological features to suggest a high rate of local recurrence [30, 31]. Radiotherapy is also utilized after regional lymphadenectomy when there are $\geq$4 lymph nodes involved, bulky adenopathy, or extracapsular extension [32]. The risk of lymphedema after radiotherapy for melanoma depends on the size of the treatment field and the number of lymph nodes resected, with the risk of lymphedema increasing by about 5% for each additional lymph node removed [33]. Lymph node dissection confers more than a threefold risk of mild to moderate lymphedema compared to sentinel lymph node biopsy alone [1].

The risk of lymphedema also varies according to the anatomical site. Although the overall incidence of lymphedema after treatment for melanoma has been reported to be approximately 16%, the incidence is much higher after treatment involving the lower extremity (28%) compared with the upper extremity (5–13%) [5, 33]. This is partly due to the fact that lymphadenectomy of the inguinal region portends a higher risk than

lymphadenectomy of the axillary or cervical region [34]. The rate of lymphedema after surgery alone for inguinal or pelvic nodal metastases from melanoma ranges from 7% to 28% [35]. With the addition of postoperative radiotherapy, the 3-year actuarial rate of lymphedema can be as high as 39–48% [35, 36]. Furthermore, the risk of edema has been associated with body mass index (BMI), with a 24% incidence of lymphedema reported in patients with a BMI < 30 kg/m^2 and a 55% incidence in patients with a BMI ≥ 30 kg/m^2 [35].

Based on early in vitro data suggesting that melanoma was radioresistant [37, 38] and that there may be a higher likelihood of clinical benefit with larger fraction sizes [39, 40], the dose per fraction and total dose delivered for malignant melanoma are often higher than those used for breast cancer, which can potentially further increase the risk of edema. In a series of patients treated with postoperative radiotherapy using a high dose per fraction after axillary lymph node dissection, the incidence of arm edema was reported to be 21%, with patients treated with more extended fields to include the axilla as well as the uninvolved supraclavicular fossa having a higher incidence than those receiving axillary radiotherapy alone [41]. Because local control did not seem to differ, it is important to consider the risk of lymphedema versus risk of disease recurrence when considering including uninvolved nodal regions in the treatment field.

Similar to breast cancer patients, the risk for lymphedema seems to increase over time, with 3-year, 5-year, and 10-year rates of lymphedema reported to be 17%, 19%, and 23%, respectively, after lymphadenectomy and postoperative radiotherapy.

When considering radiotherapy treatment fields for high-risk melanoma, it is important to balance the treatment complications with the risk of disease recurrence. The extent of treatment (involved field versus extended field), the treatment site (inguinal versus axillary), the dose per fraction, and the total dose can contribute to radiation-associated lymphedema risk. When designing fields, the radiation oncologist should minimize the dose to normal uninvolved tissues in order to spare lymphatic vessels.

71.2.3 Gynecological Malignancies

The risk of lower extremity lymphedema after treatment for gynecological malignancies varies according to the disease site, extent of surgical resection and lymphadenectomy, and the radiotherapy treatment fields. Overall, the risk has been reported to be approximately 20% [5]. Patients with cervical and vulvar cancers experience higher rates of lymphedema at 27% and 30%, respectively, compared to those with endometrial cancers (1%) [5].

Radiotherapy can be used as definitive treatment with chemotherapy in locally advanced cervical cancer or medically inoperable patients. It is also often used postoperatively after resection and lymphadenectomy for cervical, endometrial, and vulvar cancers. Treatment fields and dose differ depending on the disease site. For resected cervical cancer with high-risk pathological features, radiotherapy fields typically cover the pelvic lymph node regions, including the external and internal iliac nodes and the presacral nodes, and occasionally the para-aortic nodal regions. Pelvic radiotherapy is also often used postoperatively after resection of endometrial cancer with adverse pathological features. Occasionally, radiotherapy is delivered to the vaginal cuff using an intracavitary cylinder placed into the vagina. This type of radiotherapy treatment gives

local treatment and therefore does not appear to increase the risk of lower extremity lymphedema. After surgical resection of vulvar cancer, however, radiotherapy is often targeting not only the pelvic nodes but also the inguinal nodal regions, which increases the risk of lower extremity edema compared with pelvic radiotherapy alone.

For patients with endometrial cancer, lymphadenectomy and lymph node positivity are associated with an increased risk of lymphedema [42]. The additional impact of postoperative radiotherapy appears to depend on the extent of nodal resection. In a series of patients with endometrial cancer treated with lymphadenectomy and a median of 40 lymph nodes removed, the incidence of lower extremity lymphedema was 34.5% in patients who did not receive radiotherapy and 67.9% in those patients treated with adjuvant pelvic radiotherapy [43]. However, other series with a lower median of 10–13 lymph nodes removed have not found an increased risk of lymphedema with adjuvant radiotherapy using either physician-reported or patient-reported outcome data [42].

Patients with vulvar cancer often undergo surgical resection of the primary as well as inguinofemoral lymphadenectomy. Bilateral lymphadenectomy may be performed in women with higher stage disease or central lesions, which can increase the risk of bilateral lymphedema. Postoperative pelvic and inguinal radiotherapy is recommended in patients with multiple lymph nodes involved [44]. In patients treated with lymph node dissection and postoperative radiotherapy for vulvar cancer, the prevalence of lower extremity lymphedema may be as high as 47% within a 5-year follow-up period [45]. Similar to breast cancer, the sentinel lymph node biopsy is being incorporated into the staging of vulvar cancer with the goal of reducing the risk of lymphedema.

As with other disease sites, it is important to minimize dose to normal lymphatics when designing radiotherapy treatment fields in order to minimize the risk of lymphedema in these patients. Techniques such as intensity-modulated radiotherapy (IMRT) are often used to achieve such goals [46].

71.2.4 Genitourinary Malignancies

The overall incidence of lymphedema among patients with genitourinary malignancies is approximately 10%. Among those with penile cancer, bladder cancer, and prostate cancer, the incidence of lymphedema has been reported to be 21%, 16%, and 4%, respectively [5]. Similar to patients with gynecological malignancies, those with genitourinary malignancies may undergo pelvic lymph node dissections followed by radiotherapy. The reported pooled incidence of lymphedema in genitourinary patients who undergo radiation treatment is 16% [5]. There is sparse literature on the specific impact of radiotherapy on lymphedema for genitourinary patients, which presents an opportunity for further research.

71.2.5 Extremity Sarcoma

The risk of lymphedema after treatment for sarcoma depends on the treatment site (upper versus lower extremity), the timing of radiotherapy in relation to surgery (preoperative versus postoperative treatment), the size of the radiotherapy treatment field, and whether the normal compartments of the extremity can be spared. The overall inci-

dence of lymphedema in patients with sarcoma is reported to be approximately 30% [5], with a higher incidence in lower extremities compared to upper extremities [47].

Surgical resection is an essential component of the treatment of sarcomas; however, the risk of local recurrence after excision alone is high, particularly in those with large tumors or tumors with high-grade features. Although more radical surgery can reduce the risk of recurrence, postoperative radiotherapy can maximize the functional outcome without the morbidity and cosmetic deformity that radical surgery creates. Except in select histologies, most adult soft tissue sarcomas carry a low risk of nodal metastasis and therefore do not require lymph node dissections in patients without clinical or radiographic evidence of nodal involvement. Patients who undergo resection of a major vein are more prone to lymphedema following surgery [48].

Postoperative radiotherapy increases the risk of extremity edema [49]. Higher doses of radiation, long radiation treatment fields, and irradiation of more than 75% of the extremity diameter have been associated with higher lymphedema rates [50, 51]. The timing of radiotherapy is also important. Although there was no difference noted in local control or survival in a randomized trial investigating preoperative versus postoperative radiotherapy in the treatment of sarcomas [52], the risk of lymphedema was more common in the postoperative arm (23.2% versus 15.5%) [53]. This is likely due to the larger field sizes required in the postoperative setting as well as the higher doses used in those patients given a boost to the surgical bed. As a result, preoperative radiotherapy is often the preferred approach since the treatment field sizes are smaller and there is a lower rate of late complications.

When designing radiotherapy treatment fields, three-dimensional treatment planning is important to allow smaller and more accurate treatment volumes. The use of magnetic resonance imaging (MRI) in the preoperative approach can help define the target volume with more precision than with other imaging modalities to help minimize unnecessary treatment of normal tissues. It is important to irradiate only a portion of the cross section of the extremity to spare normal lymphatic channels. IMRT may be used to improve dose conformity within the tumor and reduce the dose to normal structures; however, care must be taken to limit larger areas of tissue receiving lower-dose treatment [47, 54].

71.2.6 Head and Neck Cancer

Lymphedema in patients with head and neck cancer has historically been considered relatively rare, with an estimated overall incidence of approximately 4–8% [5, 55]. However, a recent prospective study reported that 75.3% of patients experienced some degree of visible swelling in the skin, soft tissues, or mucosa on posttreatment physical examination [56].

Knowledge of the cutaneous lymphatics of the head and neck is critical to the clinical evaluation and appropriate management of lymphedema, and oncologists should take the complexity of the head and neck lymphatics into consideration during treatment planning [57]. IMRT is now commonly used for treating patients with head and neck cancer as it can deliver high doses while optimally sparing normal tissues. Proper immobilization of the head and neck region may also contribute to increased accuracy of radiation doses to the tumor and decreased radiation to normal tissues and lymphatic vessels [58].

Conclusions

The impact of radiotherapy on the development of lymphedema is most striking when used in combination with surgery. The proposed mechanisms involve radiation-induced dysfunction of cutaneous lymphatic vessels via a decreased number of lymphatic channels as well as increased TGF-β1 activity that promotes tissue fibrosis and inhibits lymphatic endothelial cell proliferation and function. The risk of lymphedema can vary according to the disease site and type of surgery performed, as well as the size of the radiotherapy treatment fields, the dose to normal tissues, the total dose, and the technical quality of the radiotherapy treatment plan.

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Phlebolymphedema

Contents

Diagnosis and Management of Primary Phlebolymphedema

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Summary of Basic Concepts

Phlebolymphedema (PLE) is the condition of combined insufficiency of both the venous and lymphatic systems of various etiologies, often the result of a hemolymphatic malformation. Basic compression therapy to control both the venous and lymphatic insufficiency in addition to resection of certain anatomic variants is beneficial.

72.1 Definition and Classification

Phlebolymphedema (PLE) is a unique condition of combined insufficiency of both the venous and lymphatic systems of various etiologies [6–8]. Primary PLE is caused by a congenital defect of the venous and lymphatic systems. Its occurrence is rare with the most common manifestation occurring as part of Klippel–Trenaunay syndrome (KTS) [9, 10]. While the clinical spectrum is broad, KTS by definition manifests both venous malformation (VM) and lymphatic malformation (LM) [11, 12].

In contrast, secondary PLE is an acquired condition that begins with chronic venous insufficiency (CVI) of various causes. CVI causes lymphatic dysfunction leading to chronic lymphatic insufficiency (CLI) as a complication [13–15]. In patients with advanced CVI, 20–30% have associated lymphatic dysfunction; however, this association is commonly under recognized and underdiagnosed [1]. Generally, the CLI of secondary phlebolymphedema is limited as a regional/local condition (e.g., indolent venous stasis ulcer) [16, 17]. This is in contrast to CLI of PLE where the lymphedema is often diffused as a result of a truncular LM [2, 18]. In addition, the CVI generally exists concurrently with CLI in primary PLE given that the etiology of the CVI is a VM [19, 20].

Proper understanding of the relationship between venodynamics and lymphodynamics is required for correct interpretation of the «dual» outflow system failure that leads to CVI and CLI. When functioning normally, both systems are «mutually complementary» and functionally inseparable [3, 21]. The insufficiency or overload of one or both systems, however, allows the other to play an auxiliary role in compensating fluid return through micro- and macro-anastomoses. Thus when one of the two systems loses its normal function (e.g., chronic venous hypertension, lymphedema), such mutual interdependence can generate additional burden/load to the other systems. Long-term single system failure results in total failure of this «inseparable» dual system, resulting in the unique clinical condition of phlebolymphedema.

In secondary lymphedema, CVI results in an excessive fluid load at the tissue level, disrupting the check and balance function of the capillary system creating additional load to the lymphatic system. When this overload exceeds the maximum capacity of normal lymphatic compensation, CLI results and can become very prominent, especially in a compromised lymphatic drainage system because of lymphatic dysfunction due to various etiologies (e.g., surgery and radiotherapy associated with cancer treatment). Secondary phlebolymphedema also occurs during the advanced stages of CVI of nonhealing venous stasis ulcer.

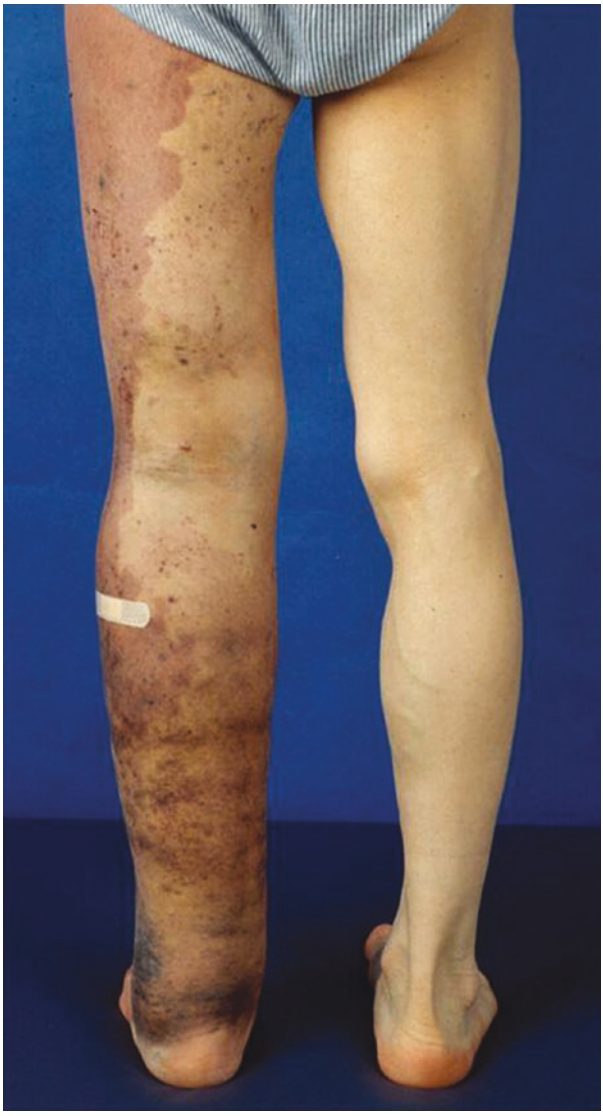

Fig. 72.1 Primary phlebolymphedema as a clinical manifestation of Klippel–Trenaunay syndrome by its vascular malformation component: VM + LM

In contrast, «primary» phlebolymphedema appears to be a concomitant disruption of both the venous and lymphatic systems. The underlying mechanisms are still not well understood though clearly the pathology is a result of a «hemolymphatic» malformation (HLM). The HLM consists of a VM and LM, most commonly in KTS as previously mentioned (Fig. 72.1). Of note, when an arteriovenous malformation (AVM) [22, 23] is present in a patient with KTS, this condition is also known as Parkes–Weber syndrome [24, 25]. The presence of an AVM makes the overall condition of primary phlebolymphedema much more difficult to manage and often resistant to traditional therapies (Fig. 72.2).

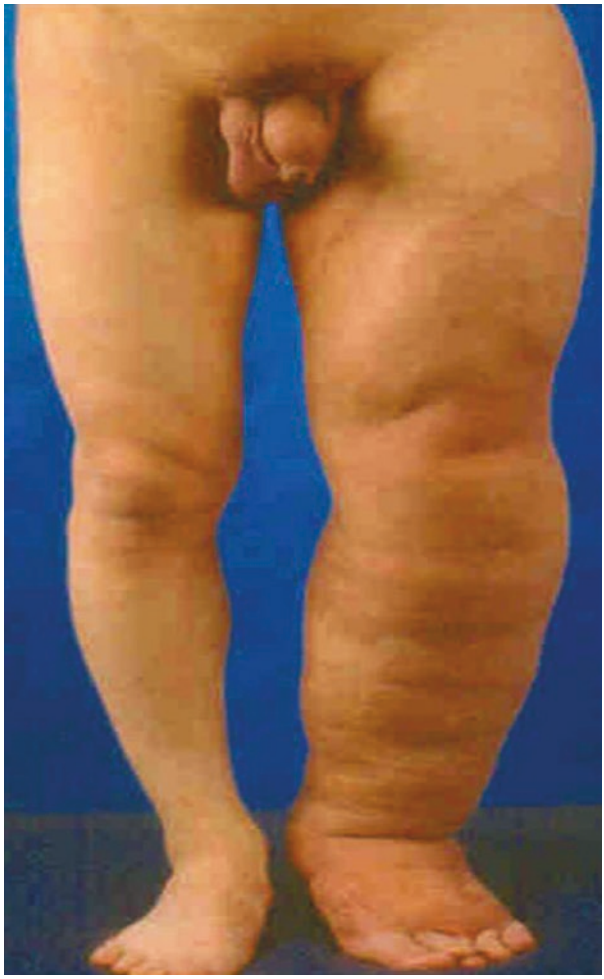

Fig. 72.2 Primary phlebolymphedema as a clinical manifestation of Parkes–Weber syndrome by its vascular malformation component: VM + LM + AVM

72.2 Diagnosis and Clinical Evaluation

The clinical manifestation of phlebolymphedema (PLE) is quite variable depending on the etiology (primary and secondary) and the degree and extent of both the CVI and CLI. In general, phlebolymphedema is clinically more distinct in the lower extremities [16, 26] requiring simultaneous evaluation of both the venous and lymphatic system. There are various laboratory tests available for venous and lymphatic system assessment. The appropriate combination of diagnostic tests is dependent on the individual case of PLE [27–33].

The assessment of the extent and severity of the CVI should begin with duplex ultrasound and may include various plethysmographic studies in addition to ascending/descending phlebography to identify the etiology (Fig. 72.3) [34, 35]. Intravascular

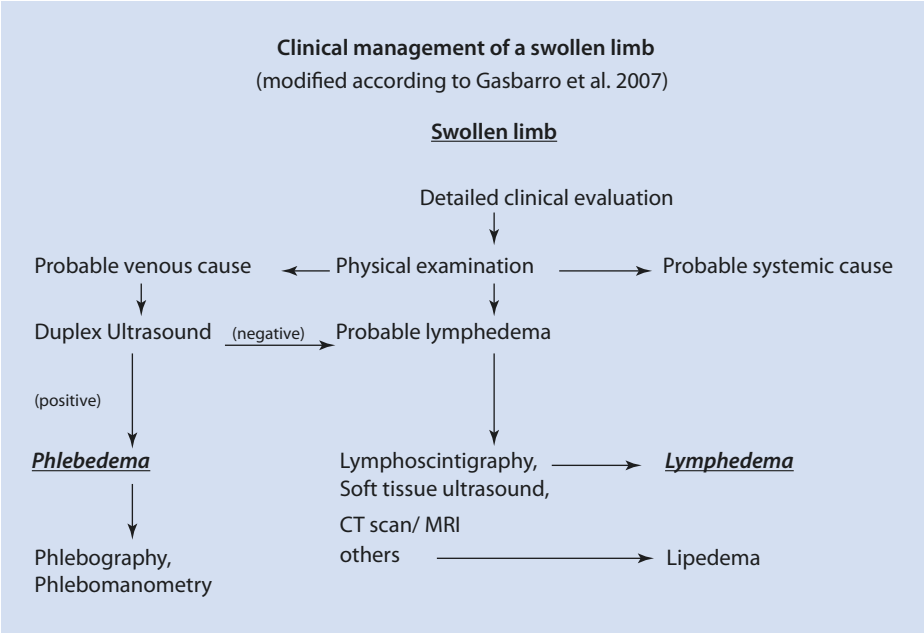

Fig. 72.3 Clinical management of a swollen limb

ultrasound (IVUS) has also been recently explored as a more sensitive and definitive diagnostic tool, particularly with iliac lesions which are frequently missed with duplex evaluation [1].

The most common VM that causes CVI in patients with primary PLE is the «lateral embryological or marginal vein» [4–6] causing venous reflux and venous hypertension. The second most common VM is deep vein dysplasia (e.g., iliac vein agenesis, hypoplastic femoral vein) or defective vein (e.g., web, stenosis, vein valve agenesia, aneurysm, ectasia) with venous outflow obstruction and venous hypertension. If the extratruncular VM lesion is thought to be involved in the development of CVI and to contribute to PLE, investigation to exclude other VM components of KTS should be considered. Detailed information on truncular and extratruncular VMs in primary PLE is available elsewhere [15, 19, 34].

In the evaluation of CLI, the functional status of the lymphatic system should be determined first with radionuclide lymphoscintigraphy as the initial baseline investigation to delineate excessive fluid accumulation in the tissues of the limb or affected lymphatic territories. Additional tests are also required when the extratruncular LM is involved in KTS. Of note, CLI as a result of primary PLE is most commonly due to «primary lymphedema by truncular LM lesions (e.g., lymphatic dysplasia, aplasia, hypoplasia, or hyperplasia). Extratruncular LM lesions (e.g., lymphangioma) are only rarely involved in CLI. When present, extratruncular LM should be evaluated with MRI and/or whole-body blood pool scintigraphy [16, 26]. Other optional tests may be included depending upon the overall CVM components (Table 72.1).

Table 72.1 Laboratory evaluation for the phlebolymphedema

Venous system
Venous duplex ultrasound – test of choice
Air plethysmography: functional assessment
CT with/without contrast
MRI study; standard and MR venography (MRV)
Radioisotope venography
Ascending and descending venography
Percutaneous direct puncture phlebography
Volumetry
Whole-body blood pool scintigraphy (WBBPS)[a]
Transarterial lung perfusion scintigraphy (TLPS)[a]
Lymphatic system
Lymphoscintigraphy – test of choice
CT – exclude underlying malignancy
Standard MRI – potentially most useful
Lymphangiography (oil contrast): optional for the candidate for venolymphatic reconstructive surgery
Volumetry
MR lymphangiography: optional
Ultrasound lymphangiography: optional
Miscellaneous – dermascan, tonometry, fluorescence microlymphography, ultrasound measurement of subcutaneous edema: optional

[a]For the congenital vascular malformation assessment

72.3 Clinical Management

The management of PLE involves an in-depth appreciation for the delicate mutual interrelationship between VMs and LMs. In general, the management of the CVI should have priority over that of the CLI unless there is a serious complication of the LM component (e.g., leakage with or without sepsis). In our experience, this management focus is due to the greater degree and extent of negative impact of the CVI on the CLI than CLI on the CVI. As such, effective control of the CVI often results in a much improved CLI condition. Baseline therapy for the CLI component of primary PLE is compression therapy because the absolute majority of the CLI is limited to lymphedema. Reinforced

gradient compression therapy based on complex decongestive therapy (CDT) controls the CVI and CLI together.

Low- versus high-grade compression remains a subject of controversy. While some espouse that the external pressure exerted on the surface of a limb to reduce CVL and CVI should be several times greater than the pressure inside the vessels acting directly on the outflow [36–39], others argue that higher pressures can damage the lymphatic vessels resulting in adverse consequences such as pain and damage to skin vessels [40, 41]. A recent pilot study from Taradaj et al. specifically comparing 120 mmHg versus 60 mmHg of pressure found that patients with phlebolymphedema-treated high pressure significantly helped to reduce edema compared with low pressures which were ineffective [39]. Further studies are needed to fully understand the optimal pressure level for compressive therapy in PLE patients.

Potential surgical management of the CVI in primary PLE is dependent on its etiology as defined by radiographic imaging. When the reflux of the marginal vein (MV) is the source of the CVI, the MV should be treated either with open surgical resection or endovascular obliteration. Treatment of the MV requires a normal deep venous system that can tolerate the sudden influx of diverted blood volume from obliteration of the MV system [4, 5, 34, 35, 42]. When the CVI of primary PLE is due to deep vein dysplasia, conservative management is usually adopted unless there is clear evidence for significant hemodynamic gain by bypass surgery of the hypoplastic, aplastic iliac, and femoral veins to relieve venous hypertension in patients with chronic venous ulcers with indolent ulcers [13].

Treatment of lymphedema caused by CLI in primary PLE is more challenging to treat than CLI due to independent primary lymphedema with no CVI component. The CLI and CVI are often resistant to conventional treatment based on CDT, and the disease has a distinct tendency to progress. Aggressive care with a strict prevention regimen (e.g., infection) is warranted and emphasized even more so that for maintenance compared with the solitary condition of primary lymphedema.

The benefit of surgery over the basic conservative therapy of CVI in patients with primary PLE (e.g., MV resection) should be carefully weighed against the potential deleterious effects on the coexisting LM with a marginally compensated CLI which could worsen the clinical condition. Of note, when a truncular LM causing primary lymphedema is combined with the extratruncular LM (lymphangioma), additional treatment with sclerotherapy of the coexisting extratruncular LM is rarely required. When such a lesion is present, it has direct communication with the lymph transporting system which produces a significant burden to the truncular LM and is the underlying cause of the CLI. In addition, the management of primary PLE generated by a hemolymphatic malformation (HLM) as a manifestation of KTS should be treated by a multidisciplinary team as outlined within the KTS guidelines in ▶ Chap. 52.

72.4 Clinical Experience

72.4.1 Group A (*n* = 9)

Group A is defined by chronic venous insufficiency by the marginal/lateral embryonic vein. (MV) Six patients have only MV, while three have another truncular VM, hypoplasia of the deep vein system, and MV.

Chronic lymphatic insufficiency in Group A is defined by lymphatic malformation (LM). Six patients have primary lymphedema by truncular LM lesion alone, and three have both truncular and extratruncular LM.

All patients fall under clinical Stage II of chronic lymphedema. Five have healed (2) or active (3) ulcers.

72.4.2 Group B (*n* = 4)

Group B is defined by chronic venous insufficiency by deep vein hypoplasia/aplasia alone. CLI is solely due to primary lymphedema (truncular LM). No ulcers exist in this group. Three patients belong to clinical Stage II and one patient to Stage I of chronic lymphedema.

Groups A and B underwent diagnostic and therapeutic assessment of the VM and LM with the standard protocol of MRI/MRV, duplex ultrasound, and/or CT angiography in addition to ascending phlebography and air plethysmography of the venous system. Radionuclide lymphoscintigraphy with and without percutaneous lymphangiography was performed for the lymphatic system.

72.4.3 Methods

Groups A and B received identical treatment of the CVI with the compression therapy in addition to leg ulcer care with daily wound dressing. All groups received reinforced compression therapy for the lymphedema based on CDT and followed a standard protocol for chronic lymphedema. Six patients in Group A received additional treatment with surgical excision of the MV. Two patients in Group A with extratruncular LM received OK 432 sclerotherapy for multiple macrocystic lymphangioma lesions in addition to the CDT for CLI.

Treatment outcome assessment was made based on the objective evaluation and findings of the ulcer as well as measurement of limb swelling using a sliding scale. Its score was combined with those of subjective improvement of the symptoms. Average follow-up assessment at 6-month intervals was a minimum of 4 years (range 4.1–6.2 years).

72.4.4 Results

Group A

The best outcome of the care was obtained in 5 out of 6 patients with MV resection. These patients had MV identified as the cause of CVI and primary lymphedema for CLI with an average scale of 8/10 with two healed ulcers. The worst outcome with no improvement was observed in one patient who underwent MV resection and sclerotherapy for the combined extratruncular lymphangioma (LM) lesion with no ulcer healing and further increase in symptoms, showing the scale of 2/10.

Group A patients in general had satisfactory improvement of the CVI by aggressive control with MV resection, especially when primary lymphedema was the sole cause of CLI. Combined lesions of another VM, such as deep system dysplasia, do not seem to affect the outcome of the care of the CVI when MV is taken care of properly.

Group B

All four patients showed subjective (e.g., aches/pains) as well as objective (e.g., swelling, recurrence of ulcers) improvement within 6 months of proper treatment of CVI as well as CLI and remained throughout the follow-up period on the scale of 8/10. In Group B, CVI due to deep vein dysplasia alone seemed to be easy to control as well as CLI with conventional compression therapy alone, with good long-term results.

Conclusion

Phlebolymphedema can be managed more effectively when open and/or endovascular therapy is added to the basic compression therapy to control the CVI and CLI together. Primary PLE with CVI by the reflux of MV can be treated successfully with MV resection, while CVI by deep vein dysplasia can be treated with conventional compression therapy alone in the majority of cases.

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Diagnosis and Management of Secondary Phlebolymphoedema

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Summary of Basic Concepts

- PLE of the lower and (more rarely) upper limbs is due to a venous and lymphatic insufficiency, which may result from a series of vein diseases or conversely from LYM with concomitant or subsequent venous organic or functional disorders.
- Diagnostics are based on clinical exam, CDU and LSG
- Treatment of PLE includes physical rehabilitation means, drugs and selectively surgery or endovenous therapies

73.1 Premise

Phlebolymphoedema (PLE) is characterised by an accumulation of fluid in the interstitial tissues which is caused by a combination of venous (primarily) and of subsequent lymphatic diseases. More rarely also limb lymphedema (LYM) may be considered as a PLE, due to concomitant vein abnormalities (e.g. post-breast cancer surgery arm lymphedema). The chronic venous-lymphatic insufficiency is the common ground for the clinical manifestation of PLE, which is a result of an imbalanced tissue-microvascular homeostasis. Venous and lymphatic systems are somehow considered mutually complimentary [1], and chronic oedema derived from ambulatory venous hypertension is to be considered as PLE, regardless of its primary venous origin.

At a microcirculatory level the physiological homeostasis has been studied and detailed long time ago by Starling, Landis and Pappenheimer [2]. In the last years a significant revision of this proposed balance has been provided by a few authors, and especially Levick and Michel [3], through in vivo and in vitro experimental studies, have «overshadowed» the traditional view of filtration-reabsorption balance, at least in most tissues, while a major emphasis has been finally put on lymphatic function for fluid balance.

Whichever venous impaired drainage (due to obstruction and/or reflux and/or functional impairment without any organic vein lesion) may lead to an increase of the lymph load which overcomes the lymphatic transport capacity; similarly in the advanced stages venous stasis may lead to organic changes in the previously healthy (though overloaded) lymphatic vessels and nodes, which may result in a further derangement of the fluid drainage and ultimately of the tissue-microcirculation pathologic conditions [6].

It has been somehow demonstrated that there is often a mutual involvement of both venous and lymphatic systems in the aetiopathogenesis of many primary or secondary vascular oedemas and the word PLE has become more familiar in the last 30 years [1, 2, 4, 7–13]. Still PLE is somehow neglected and/or underestimated among vascular specialists [1, 12], and its role also in the late stages of chronic venous insufficiency is to be emphasised accordingly [14]. Typically post-thrombotic syndrome (PTS), which occurs in 20–50% of the patients after deep vein thrombosis (DVT), has been studied in details by Partsch [15] and other subsequent authors [6, 11, 16] by means of lymphoscintigra-

phy (LSG); a constant progressive degeneration of the lymphatic collectors/nodes has been highlighted especially in later stages and mainly in the sub-fascial layers, all of which result in a secondary PLE of the lower limb (analogue changes may occur in the upper limb after DVT).

Similarly in later stages of varicosis of the lower limbs, clinical and ultrasound investigations may elicit the presence of some distal PLE, which may be attributed to a decompensation of the lymphatic system [4, 6, 16], to outbalanced microcirculatory flow and tissular mechanisms. Later stages of saphenous incompetence with PLE proved to be associated with lipid accumulation in the vein wall and especially with lymphatic vessel alterations [17], which may interact each other to favour vein degeneration and lymph drainage derangement.

More generally speaking, in many cases of secondary chronic venous insufficiency in the lower limbs, the lymphatic system is involved in any tissue changes, starting from oedema to venous ulcer. The lymphatic component makes PLE richer in protein content than cardiac-renal, liver oedema or than pure venous oedema [2, 10], which may result in a cascade of detrimental events towards tissue trophism deterioration.

Primary PLE is linked to vascular (namely, venous and lymphatic) malformations, which take place on a congenital basis, and the related clinical and instrumental patterns reflect an organic alteration of the venous and lymphatic component (sometimes combined with an arterial congenital malformation as well) in the limb or in other body areas.

Diagnostic and therapeutic management of primary PLE are elucidated in the specific related chapter of this book; hence a focus on management of secondary PLE is detailed in this chapter accordingly.

Secondary PLE is related to a few pathologic clinical conditions where an altogether of negative effects on the interstice and thus on lymphatic flow is highlighted: PTS, post-traumatic oedema (with or without deep vein thrombosis), post-varicose vein (VV) treatment (saphenous stripping, namely) oedema, cancer-/surgery-/radiotherapy-related fibrosis and/or compression on the venous and lymphatic axes (mainly in the abdominal and pelvic regions), other compressions caused by cysts or arterial/venous aneurysms (mainly at popliteal level), the underestimated [18] abdomino-pelvic veins compression/obstruction (such as May-Thurner syndrome), all those musculoskeletal-neurologic-joint-ligament diseases which lead to a plantar-calf pump dysfunction and morbid obesity which may be correlated to several vein and lymphatic dysfunctions. Finally the so-called revascularisation oedema of the lower limb, which is a result of the veno-lymphatic contingent thrombosis/disruption [19], but also of the overloaded and disregulated microcirculation, is to be considered a secondary PLE [2, 19].

In case of a primarily arisen LYM, the venous comparticipation has been elucidated in a few clinical conditions, such as the breast cancer-related LYM of the upper extremity, where several authors [20–22] have highlighted haemodynamics impairment in the subclavian-axillary venous axis, through colour duplex ultrasound or venography in up to 31% of the breast cancer-operated patients. In limb LYM, the copresence of venous insufficiency, if not addressed, may result in poorer outcomes of the typical complex decongestive treatment [23]. More recently Selvaraj and colleagues showed 51% preva-

lence of venous abnormalities on CDU in patients with LSG-based diagnosis of LYM in the lower limbs [24].

73.2 Diagnosis and Treatment of Secondary Phlebolymphoedema

A few basic common steps are undertaken when facing a swollen limb, more specifically when a secondary PLE is suspected. Anamnesis or history taking is of paramount importance, due to the extreme relevance of an antecedent event which may have caused the veno-lymphatic impairment. Hence any data on known DVT or suspicious «phlebitis» episode, or on any acute/subacute swelling of the limb, should be properly addressed. Many other specific disorders or conditions should be known in details, including active/antecedent cancer, surgical operations (with relative intra- to post-operative details), traumas, concomitant relevant cardiac-renal-liver-gut diseases, intake of oedema-favouring drugs such as calcium blockers, alpha-lytics, nitro-derivatives and corticoids. Concerning oedema itself, the patients should report about time of onset and oedema reversibility after night rest, due to the remarkable prognostic value of these data.

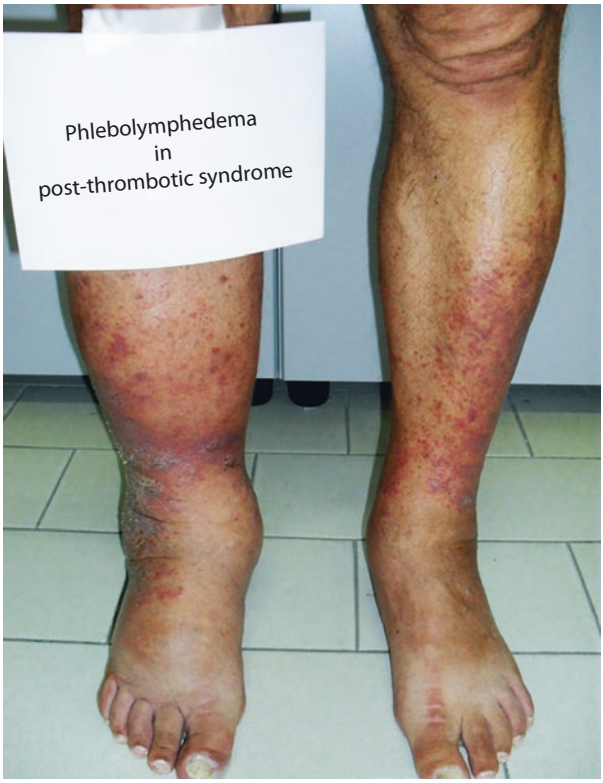

Fig. 73.1 Post-thrombotic syndrome of the right lower limb, with PLE and dystrophic skin in the distal lower leg

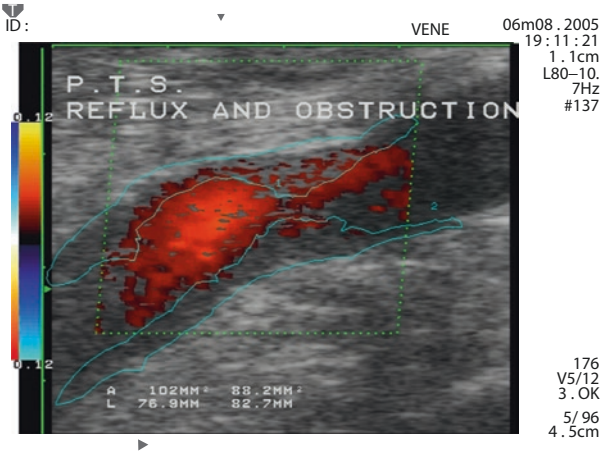

Fig. 73.2 Colour-duplex ultrasound imaging of the popliteal vein in a post-thrombotic limb: residual obstruction and reflux (*red colour* flow)

The physical examination of a phlebolymphedematous limb (Fig. 73.1) may comprehend inspection of any vein disease signs such as varices, skin discolouration and dystrophic changes, uni (more specific)- or bilateral oedema, localisation of the oedematous areas; in case of an oedema which is visible only at the root of the limb, the diagnostic pathways must be promptly addressed towards a research of any proximally located vein/lymphatic obstruction, which sometimes turns to be an unknown cancer. Other useful signs to be collected are degree of oedema pitting, skin temperature, palpable dilated lymph node collections more commonly at the groin/axilla/popliteal areas, evoked pain, Stemmer's sign, main arterial pulses palpation and last, but not least, the signs of a dysfunction of the plantar-calf muscle-vascular pump.

From the instrumental diagnostic point of view, colour duplex ultrasound (CDU) represents the gold standard investigation, and it may address the vast majority of the necessary diagnostic issues and provide the information needed for a tailored and proper treatment of PLE.

In fact CDU may highlight with great accuracy several findings in cases of PTS, where a combination of refluxing and obstructed/occluded veins is usually imaged (Fig. 73.2), together with ectatic collateral vein pathways [25]; similarly CDU may reliably provide information about the morpho-haemodynamic changes which characterise varicose vein disease [25–27] and about the associated lymph stasis (see Chap. 19 in this book) (Fig. 73.3).

When an antecedent trauma, surgery and radiotherapy may have caused PLE, CDU may address any venous flow alterations with good reliability in the veins of the lower and upper limbs, whereas a lower accuracy in abdominal-pelvic area has been acknowledged. Pathological lymphatic findings (lymph collections, lymphocele, lymphatic collectors dilation, hyperechogenic tissues) in the conditions mentioned above are also elicited through ultrasound investigation.

Any cava-iliac vein abnormality is more properly investigated through venous magnetic resonance (MR), venous computed tomography (CT), intravascular ultrasound (IVUS) or through venography [5, 18, 29], due to the complexity of the abdominal region and the decreased diagnostic power of CDU. In the latest years, Raju and Neglen [18]

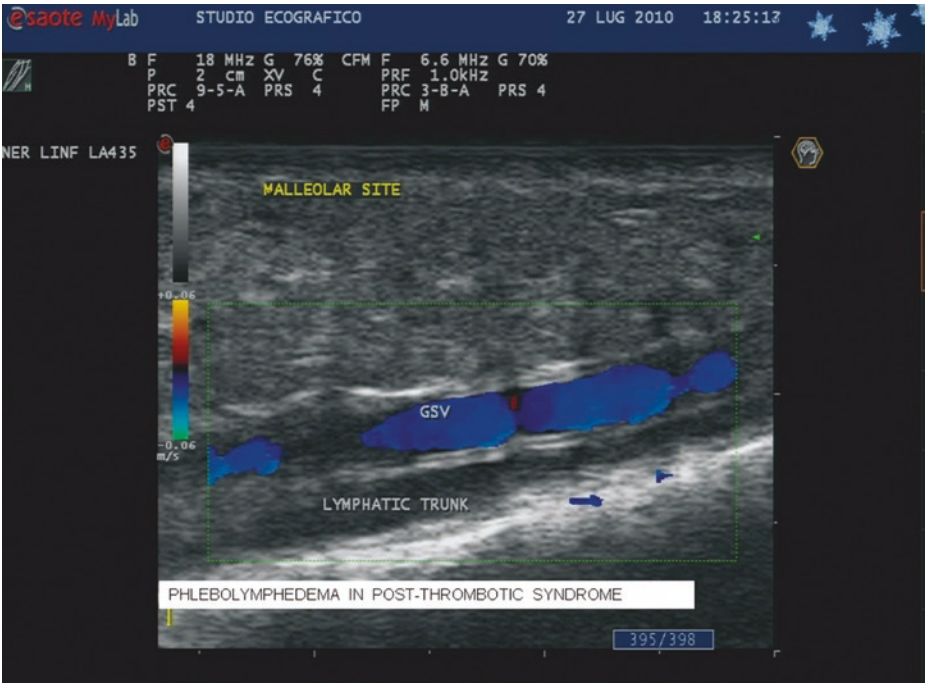

Fig. 73.3 Colour-duplex ultrasound imaging of ectatic lymphatic trunks in the peri-saphenous (GSV) area of the distal lower leg in a post-thrombotic limb

have focused on the obstruction-related diseases of the pelvic-abdominal veins, thus highlighting a much higher degree of underestimated cava-iliac pathology in cases of DVT and of primary/secondary PLE.

Plethysmographic methods are currently used to assess venous function and, more specifically, the plantar-calf muscular-vascular pump dysfunction [28].

The diagnostic approach to PLE may include in most cases the usage of LSG to detail the functional pathologic conditions of the lymph vessels/nodes; several quail-quantitative findings have been described and proposed in LSG investigation. This diagnostic method has undergone several reappraisals in the last 30 years to refine modalities, standardisation and possibly to strengthen its accuracy, reproducibility and finally to get more qualitative and quantitative data.

The swollen limb, both in cases of vascular oedema and in cases of non-vascular origin oedema, is currently investigated by means of CDU with the usual implementation of LSG in case of any relevant lymphatic flow impairment. Although a major lack of morphological information subsides for this method, therapies for PLE (especially manual lymphatic drainage and compression) may be targeted according to the LSG findings.

Several other methods have been proposed to complement the diagnostic approach to PLE (see Table 73.1), but most of them have a pure scientific, experimental value, being of little usage in common clinical practice. CT and MR technologies have been employed in LYM [5, 29] and proposed as essential investigations when any neoplasm/

Table 73.1 List of the possible diagnostic investigations in PLE

Colour duplex ultrasound
Lymphoscintigraphy
Computed tomography
Magnetic resonance
Venography
IVUS
Air/strain gauge/reflection light plethysmography
Fluorescence microlymphography
Laser-Doppler flowmetry
Tonometry
Intra-lymphatic pressure measurement
Patent Blue (dye)
Indocyanine green imaging
(Direct lymphography)
Water volumetry
Tape measurement
Multi-frequency bioimpedance spectroscopy
Laser volumetry
Optoelectronic volumetry

neoformation is involved in PLE but also in any case of suspected abdominal-pelvic abnormality in venous/lymphatic outflow, to overcome the objective limitations of CDU and to complement LSG data. MR/CT images in PLE are characterised in most cases by the «honeycomb» appearance of the lymphoedema component [29], and these two methods may help in differential diagnosis of pure venous oedema, lipoedema and others.

With reference to IVUS and venography, again the abdominal-pelvic vein diseases may benefit of these technologies to achieve a more reliable diagnosis, but their costs and invasiveness address towards a selective use of these investigations. When an endovenous treatment is required in PTS, in any abdominal-pelvic vein segments, these two investigations become fundamental to depict the pre-, intra- and post-operative morpho-functional state [18, 25, 28].

Fluorescence microlymphography has been used in a few centres to study lymphatic microcirculation before and after LYM treatment [30], and a possible diagnostic role in

oedematous conditions has been postulated [31], but its complexity and costs limit this method to scientific applications mainly.

Tonometry [5, 32] data seem to correlate with the degree of fibrosis of the skin/subcutaneous tissues, hence with the higher or lower lymphatic component of PLE.

The proper measurement of fluid accumulation in a phlebolymphedematous limb is crucial to have an accurate idea of the severity of the disease and especially to monitor treatment over time. Among the possible tools which have been validated to measure oedema in the lower and upper limb, the following ones have each specific possibilities and limitations [33]: water volumetry, tape measurement, multi-frequency bioimpedance spectroscopy (BIS), laser volumetry and optoelectronic volumetry. The relatively new technology of BIS has got a scientific validation in segmental unilateral oedema assessment and especially in early (preclinical) detection of fluid retention. The objective BIS limitations linked to bilateral oedema and to the presence of fibrosis in the oedematous tissues may be addressed through the analysis of raw data related to each limb; this innovative approach led to interesting developments of BIS usage in PLE and in LYM patients [34].

Differential diagnosis of primary or secondary PLE may include DVT (in case of acute onset), acute dermatolymphangioadenitis, lipoedema (abnormal fat deposition and fluid retention in both limbs), myxoedema (bilateral distal lower limb oedema characterised by «viscous» interstitial tissue with fluid retention, due to thyroid disease), popliteal cyst rupture/limb haematoma, any oedema of the lower limbs generated by severe cardiac/renal/liver disease or by hypo-dysprotidemia or finally by oedema-favouring drugs.

Classification and/or staging of PLE has never been finalised, though a mediation between CEAP [35], lymphologic CEAP [36] and «old» proposals [2] is in the auspices of the scientific community.

Therapy of PLE may be basically addressed at the possible causal disease(s) and at the fluid stagnation, within the context of a holistic, integrated therapeutic protocol.

The basic treatment strategy of secondary PLE includes a few common therapies, which are currently employed under the form of an integrated holistic decongestive therapy for LYM patients [2, 37, 38], according to consensus documents [5] and current best clinical practice [39]. The therapies which are more commonly employed are (a) compression (bandages and/or garments), which represents the cornerstone treatment of any vascular oedema [40] and which must include medium/low-elasticity material as well as inelastic material in worse cases [41]; (b) drugs (anticoagulants, phlebo-lymphotropic drugs such as coumarin, diosmin, rutin, antibiotics and NSAIDs or corticoids when needed); (c) manual lymphatic drainage (MLD); (d) electro-medical devices such as sequential intermittent pneumatic compression, electro-(ultra)sound wave devices [42]; calf-pump stimulators and laser-based treatments; (e) topical treatments; (f) rehabilitation exercises and veno-lymphatic hygiene rules (limb elevation!); (g) possible psychological support; and (h) skin care to reduce and to prevent infections and to improve skin trophism. The altered immunity in the compromised area, related to lymph stagnation [43], may induce subclinical or overt episodes of dermatolymphangioadenitis (cel-

lulite, erysipelas, lymphangitis), which impose local antisepsis and systemic usage of antibiotics and anti-inflammatory drugs according to the clinical condition.

Most of the treatments listed above are detailed in literature and in this book elsewhere, with respect to their usage in LYM patients; some peculiarities may attain to «venous» drugs, which are used especially in PTS and more in general in chronic venous insufficiency [5, 44]. Life-lasting anticoagulation with dicumarols is provided to patients with relevant post-thrombotic residual vein occlusions and/or with recurrent venous thromboembolism and especially in patients with significant thrombophilia or active cancer. Fractionated or unfractionated heparins are currently used in clinically «decompensated» limbs with PLE and ulcer, to enhance microcirculation collateral flow and to provide some angiogenesis in the dystrophic skin areas.

Alternative, less frequently applied and less validated treatments in PLE may include mesotherapy, ablative or reconstructive surgery for lymphatics and/or for fat deposition, vibrational therapy, heat wave therapy, etc.

In cases of PLE related to PTS, a few reconstructive surgical treatments have been proposed in the last years [45], achieving interesting outcomes in properly selected patients, though better results are obtained in primary deep vein diseases and most data need to be validated through larger-scale protocols. Similarly endovenous (PTA +/− stent) treatments have gained a great popularity [18, 25, 45], with cumulative haemodynamics and clinical promising data at midterm for patients with cava-iliac vein obstruction/occlusion; some lymphoscintigraphic improvement has been documented after correction of the venous lesions as well [46]. Secondary VV in PTS may be treated with (ultrasound-guided) foam sclerotherapy (FS) [47–49], which has a very low impact on the fragile limb tissues, as well as endovenous treatments have been proposed in selective cases. Mini-invasive surgery still holds a place, and the proper indication to these treatments is still debated, though patency of the deep veins is recognised as the basic prerequisite before addressing post-thrombotic VV in PLE patients.

In presence of an active leg venous ulcer, therapy of PLE must comprehend the typical locoregional treatments devoted to debridement, granulation enhancement and second-intention healing of the ulcerated area.

As to primary VV associated with PLE, several treatment modalities have been proposed in the last 100 years, though the suboptimal knowledge of the morphology and haemodynamics mechanisms which subside in varicose degeneration make any treatment still palliative and the recurrence rate still quite high at long term. A tailored, mini-invasive surgical approach has been advocated in the last 20 years, on the basis of a detailed preoperative CDU and local anaesthesia usage [50, 51]. In the meantime a few endovenous treatments have been validated, questioning the role for surgery as the gold standard for these patients with PLE and primary VV: laser, radiofrequency, FS, glue and mechanochemical obliteration. Notwithstanding a lack of agreement on the indications for these therapies, when facing the late stages of VV disease which are more often combined to PLE, mini-invasive surgery, laser and radio frequency may be beneficial at midterm to long term. An overall 30% recurrence rate at 5 years has been showed in literature [52], and a tailored, mini-invasive and possi-

Conclusions

The diagnostic-therapeutic approach to secondary PLE is usually of multifaceted nature, in order to assess the related vascular (and non-vascular) diseases and the fluid accumulation with the possible tissue dystrophic changes; CDU represents the basic diagnostic method to highlight most vein and lymphatic abnormalities, especially if combined with LSG.

Physical rehabilitation approach is the cornerstone treatment for the oedema component, but several vein-directed therapies are necessary as well, in order to achieve a better and longer-lasting outcome. Patient's compliance is in fact the key factor to achieve more durable results, and as a matter of fact the LYM component, if relevant, may make any treatment of complex and often, but not always, palliative nature.

bly inexpensive approach has been advocated more recently. The combination of phlebectomy of varicose tributaries with catheter FS, combined with perivenous tumescence infiltration and saphenous irrigation [48], seems to produce interesting short- to midterm clinical and CDU outcomes, also in those cases of larger veins associated with PLE.

The presence of LYM component of PLE raises the issue of possible lymphatic complications after whichever treatment on VV [53–55]; hence mini-invasiveness and specific technical precautions have to be taken in consideration in case of surgery [56] and in case of endovenous treatments.

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Management of Phlebolymphedema Ulcer

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Summary of Basic Concepts

- Venous and lymphatic systems are two interconnected outflow networks.
- Impairment of one system can be initially compensated by the other, but whenever the overload overwhelms the system performance, phlebolymphedema occurs: an interstitial oedema of both venous and lymphatic oedema.
- Phlebolymphedema can severely impact ulcer pathophysiology and healing by acting on the interstitial pressure, on the metabolism by-product accumulation and on the predisposition to infection.
- Adequately chosen venous treatment is the priority in order to relieve the interstitial overload on the lymphatic system. Decongestive lymphatic therapy is in support of the lymphatic function restoration.
- Special care must be taken in the early identification of lymphatic involvement in the clinical evaluation of the ulcer.
- Patient's medical awareness and active participation in the treatment protocol are mandatory to obtain a successful and long-lasting outcome.

74.1 Phlebolymphedema Impact on the Ulcer Environment

Phlebolymphedema represents a specific pathological condition influencing lower limb chronic ulcer management in such a significant way as to require a dedicated description.

Venous and lymphatic systems constitute two interconnected outflow networks aimed to drain fluids and metabolites back to the heart [6, 7].

In particular, the lymphatic system reabsorbs the interstitial fluid and the plasma proteins that are left after the filtration into venous capillaries.

When the pressure of the interstitial fluid is greater than the pressure inside the lymphatic capillaries, a filtration inside the lymphatic network occurs.

Interstitial proteins are drained inside the lymphatics rather than the venous capillaries because of the larger intercellular lymphatic junctions.

Lymphatic capillaries allow the uptake of even larger particles, such as cell debris, pathogens and cancer cells.

All these components can travel inside the body through the lymphatics, also representing a potential risk, as in case of infectious pathogens.

Lymph nodes are the stations in which the immune system can control and eventually neutralize potential threats [8, 9].

As in the venous system, the lymphatic flow is propelled by the same conduit smooth muscle layer contraction, by muscle masses systole, by thoraco-abdominal pump and by nearby arterial pulsations.

Compromise of the lymphatic drainage system can lead to the fluid retention and tissue swelling (i.e. lymphoedema) [10, 11].

The close interconnection among venous and lymphatic systems makes them complementary, with mutual potential compensation or overload [12].

Venous insufficiency creates an intravenous hypertension that leads to an increased transcapillary filtration inside the interstitial space [13].

In an early stage, the lymphatic system compensates for this fluid overload by increasing its drainage, in doing so, avoiding oedema formation.

Whenever the filtration overwhelms the lymphatic transport capacity, an interstitial fluid accumulation occurs, thus generating the so-called phlebolymphedema: a combination of venous and lymphatic dysfunction [1, 14].

Initially, a low-protein phlebolymphedema is formed. But when the lymphatic system becomes severely deranged, the interstitial fluid is comprised also by a high-protein oedema.

Venous ulceration is the end-stage consequence of venous hypertension and of the associated inflammation, with consequent leucocyte activation and remodelling of the extracellular matrix.

Recent evidence demonstrates how the same inflammatory products have a main role in deteriorating venous system function, so triggering a vicious circle of impairment [15].

Considering the lymphatic system as a route for tissue inflammation detoxification, it becomes evident how the healing process of a venous ulcer can become seriously hindered by a phlebolymphedema condition.

74.2 Pathophysiological Considerations

The lymphatic systems carry out mainly four physiological roles: (1) maintenance of interstitial tissue fluid homeostasis, (2) absorption of metabolic by-products, (3) immune control by infectious agents and other pathogen eradications and (4) absorbance of long-chain fats from the intestinal tract.

Considering these functions, it becomes evident how an impairment of the lymphatic system can have a crucial influence on venous ulcer pathophysiology and consequent management [16].

Failure of appropriate lymphatic drainage leads to an interstitial fluid hypertension that enhances the pro-inflammatory state that was already triggered by the ulcer environment [12].

Initially, a dynamic insufficiency occurs because of the inability of the lymphatic system to drain the fluid overload [17].

A mechanical insufficiency can follow, or be contemporaneously present, by the time the lymphatics have been damaged by overuse or other physical/biochemical factors (inflammation, surgery, radiotherapy, trauma, infections).

A not to be forgotten condition of combined venous and lymphatic impairment is represented by the Klippel-Trenaunay syndrome and by all the conditions of primary venous (i.e. marginal vein and venous dysplasia) and/or lymphatic malfunction [2, 3, 18–20].

In phlebolymphedema fluids, macromolecules and proteins accumulate in the interstitium.

Mechanical damage of the lymphatics has been reported in the same ulcer environment, and lymph fluid has been identified inside the ulcer exudate [21, 22].

Reactive oxygen and nitrogen species are formed, extracellular matrix proteins deteriorate and infiltrating leucocytes and resident immune cells release hydrolytic enzymes.

Leucocyte diapedesis is associated with interendothelial junction widening. Consequently, red blood diapedesis follows, leading to the deposition of haemosiderin.

Moreover, the lack of absorption of metabolic by-products creates a further aggravation in the pathological process. Oxygen and other nutrient diffusions are impeded, while toxic by-products of cellular metabolism are accumulated and fibrosis is promoted.

The increase in interstitial fluid pressure can even physically compress the capillaries, thereby reducing nutritive tissue perfusion [23].

This tissue hypoxia is further aggravated by fibrin cuff formation that follows the increased inflammatory state, promoting fibrinogen leakage [24–26].

Interstitial proteins physiologically exert tensional forces to the attached lymphatic endothelial cells, so favouring fluid absorption.

Damage of these proteins represents a further impairment of the whole process of interstitial fluid homeostasis.

Breaks in the skin potentially lead to bacteria introduction.

Pathogen proliferation is enhanced in the protein-rich interstitium, also favoured by the diminished lymphatic drainage of the same bacteria and of their related by-products.

The same infection propagation into the lymphatic system can further aggravate the lymphatic damage, so establishing a self-propagating cycle of disease progression.

An intensification and expansion of the inflammatory and infectious ulcer state occur [27].

Interstitial fluid hypertension, metalloproteinase unbalance, fibrosis and infections are all identified risk factors for venous leg ulcer healing failure, and, at the same time, they are all affected by an impaired lymphatic drainage [28].

The lymphatic system can be easily damaged both by drainage overload and by the inflammatory environment created by the fluid stasis.

A vicious circle is created by the impairment of the venous and lymphatic system, so potentially seriously complicating the ulcer management (Fig. 74.1) [12, 29].

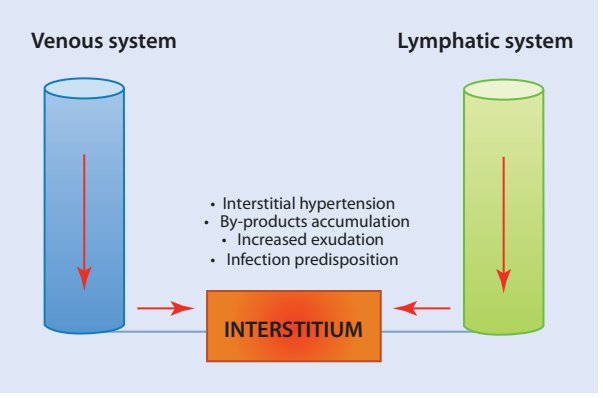

Fig. 74.1 Venous and lymphatic systems are one interconnected outflow network aimed to drain the interstitium. Impairment of both drainage routes increases the interstitial fluid hypertension, accumulates by-products, increases exudation and predisposes to infection. Phlebolymphedema ulcer management requires treatment protocols equally addressed to both the venous and lymphatic system restorations

74.3 Clinical Aspects

Despite the literature demonstrating the crucial role of the lymphatic system in drainage balance, lymphatic impairment is often underestimated and underdiagnosed in everyday clinical practice [30].

Also for this reason, up to now accurate epidemiological data are missing [31].

Indirect data can be found in investigations like the one performed by Franks et al., where leg ulceration was found in up to 30.4% of lymphoedema patients [32].

Other indirect evidences are reported by the Bonn Vein Study, where 11.1% of C5 patients presented with signs of lymphoedema [33].

A high index of clinical suspicion is fundamental in phlebolymphedema ulcer management.

The suspicion of lymphatic impairment overlapping venous derangement must guide the diagnostic and therapeutic approach [34].

Lymphoedema patients can easily complain for recurrent bacterial/fungal infections together with leg heaviness, pain, increased warmth and pruritus.

Limb discomfort and limited ankle range of motion can also occur.

Special care must be dedicated to obese patients.

Obesity represents a more common than typically thought risk factor, not only for venous hypertension but also for lymphatic impairment.

Prevalence of lymphoedema in morbidly obese patients has been reported in up to 74% of cases [35].

Abdominal pressure is directly related to abdominal girth.

Moreover, in obese patients, it must be remembered that a large pedunculated pannus may impair superficial lymph flow.

In the pathophysiological link among obesity and lymphoedema, other factors have been discussed and included, such as arteriovenous proliferation within oxygen demanding fat tissue, impaired diaphragmatic movement and structural lymphatic changes.

Appropriate management of these patients is mandatory, particularly considering the unique obesity-related problems and the risk of recurrence in case of failure to maintain weight loss [35–38].

In a swollen lower limb, the most immediate evidence of a lymphatic impairment is the involvement of the foot dorsum («buffalo hump») and/or toes (so-called sausage toes).

In distinction to phlebolymphedema, lipoedema is a disease of the adipose tissue characterized by abnormal depositions of subcutaneous fat with oedema, and the foot is usually spared (Fig. 74.2).

A typical finding of phlebolymphedema is the association among oedema with ankle hyperpigmentation: a consequence of the combined venous and lymphatic impairment [30].

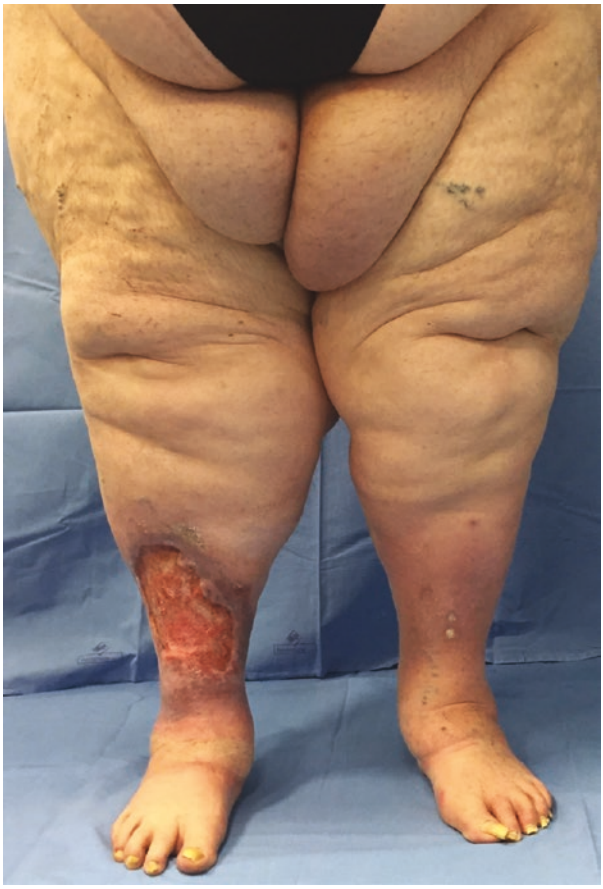

Fig. 74.2 Obesity represents a risk factor both for venous and lymphatic impairments. In the picture hyperpigmentation and fibrosis are evident, together with a tourniquet effect on the foot dorsum hump. Middle and lower thirds of the legs show the typical «inverted champagne bottle» shape associated with lipodermatosclerosis. Pedunculated adiposity contributes to direct mechanical lymphatic impairment, to reduced skin hygiene and to infections

Other classic clinical manifestations that suggest a lymphatic involvement are:

- Hyperkeratosis
- Lymph vesicles
- Lymphorrhea (lymph fluid leakage)
- Papillomatosis (papules and nodules)
- «Orange peel» skin
- Fibrotic skin
- Cellulitis
- Hypoplastic toenails (more often in primary cases)

Pitting oedema (so-called positive fovea sign) of the early phase can turn in a non-pitting oedema in middle to late stages because of fibrosis development.

Special attention must be paid in the detection of the so-called lymphoedema rubra.

The affected skin presents with a burn-like erythema that can be easily misinterpreted as cellulitis.

These patients usually have a history of previous antibiotic treatments for presumed cellulitis but have no history of fever. This is a misdiagnosis, as this condition is not initially associated with an infection, rather with the early lipodermatosclerotic inflammatory process and with skin warmth due to the reactive hyperaemia.

It is mandatory to properly identify a lymphoedema rubra in a phlebolymphedema ulcer presentation. Particular attention should be paid in order to avoid not only pointless but also potentially harmful antibiotic administration that could increase the antibiotic resistance in that patient to a drug that could eventually be necessary in case of wound infection.

On the other hand, cellulitis and erysipelas must be detected rapidly and considered as potential signs of clinical or subclinical lymphatic involvement.

In an interesting investigation by Damstra et al., an abnormal lymphoscintigraphy was identified in the contralateral leg of 79% patients affected by unilateral cellulitis, so demonstrating the role of the cutaneous infection as a sentinel for subclinical lymphatic impairment [39, 40].

Long-term and/or severe impairment of the lymphatic system can lead to elephantiasis nostra verrucosa.

In these patients, ulceration is accompanied by hyperkeratotic and papillomatous plaques and easily associated with lymphorrhea and skin fissuration.

Patients with phlebolymphedema ulcers are exposed to complications related to lymphatic failure: wound infections, contact allergic and irritant dermatitis, cellulitis, lymphangitis, osteomyelitis and ankle ankylosis.

Fundamental in the clinical evaluation of these wounds is the detection of those signs of inflammation that are clues for an impending infection: swelling, increased temperature, erythema and pain.

Moreover, extensive fibrosis and recurrent or chronic infections increase the risk of lymphangiosarcoma, a rare and aggressive cutaneous angiosarcoma of the lymphatic system endothelial cells, often associated with long-lasting lymphoedema. Blue-red or purple marks on the skin can represent initial signs of the disease.

Special attention must be paid in these patients presenting in this manner in order to facilitate early detection and prevention of such complications.

74.4 Diagnosis

The most important aspect to the diagnosis of phlebolymphedema is understanding the clinical signs and symptoms in order to have an appropriate clinical index of suspicion.

Despite its frequent involvement, the lymphatic system remains an underrecognized and underdiagnosed contributor in lower limb drainage.

An accurate history and thorough physical examination must be taken and performed in order to identify the potential causes of lymphatic involvement [41].

Primary and secondary causes of lymphoedema must be excluded (Table 74.1). Among these main conditions to be ruled out are patient's family genetic disease, renal insufficiency, congestive heart failure, hepatic insufficiency, malignancy and drug-related side-effects.

Table 74.1 Causes of lower limb swelling

Heart, kidney and liver failure
Drug induced edema (NSAIDs, hormones, calcium channel blockers, beta blockers, etc.)
Severe hypothyroidism
Trauma
Obersity
Recurrent cellulitis
Nutritional deficiency/disease (protein losing enteropathy)
Pulmonry hypertension
Muscle pump impairment

At the same time, knowledge of the possible primary and secondary causes of phlebolymphedema is fundamental to guide the assessment.

In particular, it is mandatory to look for possible venous malformations, like the presence of a marginal vein, deep vein dysplasia, Klippel-Trenaunay syndrome and more rare congenital defects, potentially leading to phlebolymphedema [42, 43].

An investigation should be performed on the lymphatic system, looking for potential primary causes of phlebolymphedema such as truncular (dysplasia/hypoplasia/aplasia) and extra-truncular (lymphangioma) lymphatic malformations.

During the physical examination of a patient with ulcers, the following signs and symptoms are to be identified and documented:

- Oedema of the affected limb (initially pitting, progressing to non-pitting)
- Stasis dermatitis (generally located around the gaiter area, usually dry, flaking skin with occasional weeping, associated with pruritus)
- Erythema
- Hyperkeratosis (dry, flaky skin built-up in multiple layers)
- Fibromas (benign skin lesions formed by fibrous connective tissue)
- Papillomas (benign skin growth of epithelial neoplasm, containing villous or fibrous vascular outgrowths)
- Folliculitis
- Intertrigo (mainly between the toes and in skinfolds)
- Haemosiderin staining
- Skin fissurations
- Lymphorrhea
- Lymphocyst (collection of impaired lymphatic fluid in the connective tissue, looking like a translucent bubble)
- Superinfections

- Nail abnormalities
- Squaring of the toes
- Puffiness of the forefoot (buffalo hump)
- Elephantiasis

In the suspicion of primary causes of lymphoedema, it is fundamental to detect capillary, venous and arteriovenous malformations together with any tissue overgrowth/asymmetry [44].

Kaposi-Stemmer sign represents a pathognomonic manoeuvre to identify a lower limb lymphatic impairment [45, 46].

It consists in the inability to pinch a fold of the skin of the foot between the fingers. The sign is considered negative when the skin easily tents. A positive sign occurs when the skin cannot be pinched.

While a positive Kaposi-Stemmer sign is considered diagnostic for lymphoedema, a negative sign cannot exclude lymphoedema, because of possible regional functional or diurnal variations of the lymphatics.

Whenever treating an ulcer that is suspected to be associated with a lymphoedema condition, it is important to define the underlying causes of lower extremity oedema, in order to rule out other causes.

Liver and renal blood tests, urine analysis and eventual neoplastic and/or thyroid markers are to be performed, especially whenever the aetiology is unclear. If an infection is to be excluded, a complete blood count with differential is to be considered.

Circumferential lower limb measurements, volumetry by water plethysmography and local area pitting tests can be used to evaluate and monitor the oedema presence.

Traditionally, venous and lymphatic impairment can be classified as primary or secondary. Nevertheless, this distinction has been considered quite too simplistic, considering that recent evidences are showing genetic mutations leading to both primary and secondary lymphoedemas. Further investigations on the topic are awaited both to clarify the pathophysiology and to identify patients with higher risk of lymphoedema at an early stage [4, 17, 47].

Imaging is not strictly necessary to make a diagnosis of lymphoedema. At the same time, different studies can confirm the diagnosis, assess the extent of the impairment and guide the therapeutic strategy.

A detailed description of the different diagnostic tools is reported in the dedicated chapter.

In the specific case of phlebolymphedema ulcers, the following imaging can provide a deeper diagnostic assessment:

- *Plain radiographs* are useful in excluding bone abnormalities.
- *Ultrasonography* has a fundamental role in the evaluation of both the venous and lymphatic systems. In particular volumetric and structural changes can be identified in the lymphatic system while determining the specific reflux pattern contributing to the lower limb oedema.
- Extreme caution must be paid in order not to neglect a lymphatic component just with the assumption that the eventually found venous abnormality is the only cause of oedema. Plethysmographic and phlebographic investigations can add valuable data regarding the haemodynamic impairment.

- *Radionuclide lymphoscintigraphy* remains the gold standard for clearly identifying a lymphatic impairment. It provides an accurate visualization of the lymphatic system, assessing both the flow dynamics and the eventual obstruction severity. Attention must be paid in the evaluation of phlebolymphedema patients: in case of dynamic lymphatic insufficiency caused by a venous-induced overload, lymph transit speed can remain normal or even faster than the normal, so potentially representing a cause of false negative [3, 17].
- *Magnetic resonance imaging* is useful to depict nodal architecture, lymph trunk anatomy and secondary lymphoedema causes.
- It is also useful to differentiate a lymphoedema from lipoedema (fat accumulation without fluid) and to add anatomical data to a lymphoscintigraphic evaluation [48].
- *Magnetic resonance lymphangiography* is capable of assessing the anatomical and functional status of the lymphatic systems and has recently proved to be more sensitive and accurate than lymphoscintigraphy itself [49].
- *Computed tomography* is less useful in lymphoedema. It localizes the oedema, the skin thickening and the subcutaneous tissue involvement. It can have a fundamental role in malignancy identification [3].
- *Fluorescent lymphography* using indocyanine green is becoming a non-invasive alternative to traditional lymphoscintigraphy in superficial lymphatic assessment [5].
- *Fluorescence microlymphography* visualizes lymphatic capillaries, with a high sensitivity and specificity for lymphoedema [50].
- *Bioimpedance spectroscopy* is an effective technique for the detection of subtle changes of interstitial fluid. This type of imaging has shown the ability to potentially antedate lymphatic failure [51–53].
- *Whole body blood pool scintigraphy* is a diagnostic modality for the evaluation of congenital vascular malformations, with high accuracy and the ability to evaluate the whole body [54].

Lymphangiography is an invasive technique that is now rarely used because of its potential adverse effects, among which includes an inflammatory reaction of the lymphatic endothelium.

Invasive tests like direct puncture lymphangiography and fine needle aspiration biopsy of lymph nodes are rarely used in the diagnostic process of a phlebolymphedema ulcer, with the exception of skin/ulcer biopsy in cases of a not clinically apparent diagnosis or of failure to progress in wound healing despite adequate treatment [55].

Considering the higher risk of infection associated with the lymphatic impairment, particular attention must be addressed to early infection detection [56].

Bacteriological wound cultures become mandatory in case of evidence of clinical infection (redness, cellulitis, pain, purulent exudate, pyrexia, odour) [57–59].

A careful examination of the ulcer is mandatory, particular in phlebolymphedema patients. Location, drainage quality and quantity, skin condition, pain, odour, wound perimeter, together with wound measurements (area and depth) and bed tissue characteristics (fibrosis, granulation, necrosis) are fundamental to guide a proper management.

In the end, particularly whenever dealing with phlebolymphedema ulcers, it is mandatory to assess also the impact on patient quality of life and his/her compliance with treatment: two crucial factors for a successful outcome.

74.5 Therapy

Venous ulcer is recognized as a condition severely affecting the quality of life [60].

In phlebolymphedema cases, this impact is to be added to the one associated with the lymphatic impairment [61].

Only a correct management of both systems' failure can avoid to create a negative synergistic effect among venous and lymphatic insufficiency [62].

A proper management of the various comorbidities potentially influencing the lower limb drainage and/or affecting the healing process is mandatory. In the same way, drugs like calcium-channel blocking agents and all the other medications affecting the venous or lymphatic drainage are to be avoided if possible.

The initial treatment is to be addressed towards correction of venous impairment [63, 64].

Effective control of the venous insufficiency is per se an improvement of the lymphatic insufficiency, thanks to the reduction in the filtration overload.

For this reason, in phlebolymphedema patients, management of the venous reflux/obstruction should have a priority, unless the lymphatics are not affected by severe complications.

Extreme caution must be adopted in adequately balancing the benefit of venous reflux suppression with the potential direct harm to the lymphatic system induced by the venous treatment itself.

Lymphatic collectors follow the main veins and can be found also along the same adventitia, so being potentially damaged by accidental surgical or thermal injury during the same venous procedure. The same sclerosant agents can enter the lymphatics, potentially affecting their functionality.

Protecting the lymphatic system from iatrogenic damage is mandatory. Procedural mini-invasiveness is not always associated with the smallest «lymphatic invasiveness».

Together with the technical choice of the less harmful device, in phlebolymphedema patients, it becomes fundamental to identify the most effective strategy to suppress the venous reflux.

In order to limit the lymphatic insult, a therapeutic plan aimed to restore the venous drainage ablating the smallest amount of vein conduit or, whenever possible, sparing the saphenous vein is to be preferred [65, 66].

Angioplasty and venous stenting are to be taken into consideration in case of significant venous outflow occlusive disease.

In the case of primary phlebolymphedema associated with a coexisting lymphatic extra-truncular malformation (i.e. lymphangioma), a sclerotherapy treatment also for the lymphatic side can be taken into consideration [64, 67].

Once the venous hypertension has been treated, the lymphatic component of the disorder can resolve or move from a long-standing high-output overload to a low-output insufficiency.

Early awareness of a potentially reduced lymphatic transport is fundamental in the management of these patients.

Decongestive lymphatic therapy remains the treatment of choice for the lymphatic component and includes limb compression, manual lymphatic drainage, multicompartmental sequential pneumatic compression and adequate lifestyle and conservative therapeutic measures [68].

The compression component in all its forms represents the cornerstone of this treatment: bandaging, elastic stockings and intermittent pneumatic compression.

Compression administration must be considered as a drug prescription: an extreme attention must be paid in order to maximize the positive impact, avoiding potential adverse effects.

Poor choice of therapeutic material, inadequate hyperpressure and contact dermatitis are to be avoided, in particular in phlebolymphedema patients [69].

Short-stretched multicomponent compression bandage is to be preferred to elastic ones, in order to maximize the muscle pump effect on the venous and lymphatic drainage.

As the patient walks against bandages, a high pressure is exerted, so promoting lymph flow through the dermis.

Bandaging of the toes can be considered in case of severe lymphatic involvement and in order to avoid retrograde accumulation of lymph fluid.

In the case of bony or tendinous prominences, during bandaging on limbs with phlebolymphedema limbs, it is fundamental to apply foam pads in order to avoid iatrogenic lesions on the particularly sensitive skin [29, 70].

Elastic stockings represent the mainstay of a phlebolymphedema correct management, significantly impacting both the outcome and its maintenance.

Particularly in case of lymphatic involvement, adequate stocking sizing becomes mandatory, eventually relying on customized fitting.

Graduated elastic stockings of the proper compression level and size are to be used also after the ulcer resolution in order to reduce its recurrence risk [70].

In case of significant lymphatic impairment, flat-knit stockings rather than circular knit hosiery are to be chosen. The first are usually custom-made and stretchless, so providing a more effective compression.

Innovative adjustable compression wraps offer an effective and comfortable solution in moderate to severe cases of lymphatic impairment.

Compared to inelastic multicomponent compression bandages, these garments have demonstrated to produce a more pronounced volume reduction in the first 24 h, allowing the patients to self-adjust the exerted compression, so overcoming the loss of effectiveness along time [71].

Even if fundamental, compression per se removes the interstitial fluid accumulated by venous and lymphatic insufficiency, so increasing the interstitial protein concentration. Consequently, an effective phlebolymphedema management regimen requires also manual lymphatic drainage in order to push the protein-rich fluid back into the lymphatics.

At the same time, literature lacks specific evidence regarding the direct effect of manual lymphatic drainage in ulcer healing [70, 72, 73].

Intermittent pneumatic compression increases healing rates of venous ulcers compared with hosiery alone [74, 75].

This kind of compression has recently demonstrated a specific potential in phlebolymphedema ulcer healing thanks to its action in promoting lymphatic flow and the drainage of the extravascular fluid.

Nevertheless, long-lasting active ulcers don't respond to a single session of intermittent pneumatic compression, and investigations on the effect of repeated sessions are still awaited [5, 75].

It must be remembered that an accurate evaluation must exclude congestive heart failure, deep vein thrombosis and active infection before prescribing an intermittent pneumatic compression.

Up to now intermittent pneumatic compression is recommended only for the treatment of refractory oedema and leg ulceration after 6 months with standard compression [76, 77].

Supervised active exercise is recommended in order to maximize the muscular pump activation and joint range of motion, so promoting both venous and lymphatic returns [70].

Particularly in phlebolymphedema patients, special attention must be paid in order to avoid skin and wound infections [55].

A careful clinical evaluation of phlebolymphedema ulcer is mandatory in order to avoid those complications that are favoured by the lymphatic component, with particular attention to exudation and infection.

Antimicrobial therapy must be administered in case of clinical evidence of infection, by systemic antibiotics in accordance with sensitivity tests performed on wound culture.

Topical antibiotics are to be avoided, favouring topical dressings (alginates, foam) able to manage the exudate without increasing the risk of local skin reactions.

Skin lubricants underneath compression are useful to reduce dermatitis that can easily affect phlebolymphedema patients.

In case of clinical skin infection around the leg ulcer, early treatment with systemic gram-positive antibiotics is indicated [78].

Hygiene and skin care are mandatory in order to avoid recurrent cellulitis or lymphangitis. Regular inspection is recommended.

Benzopyrones can be administered as stimulants of proteolysis that favours interstitial protein fragmentation, which in turn facilitates reabsorption and tissue drainage.

Retinoids can help in normalizing the keratinization and decrease the inflammatory and fibrotic reactions [79].

For long-standing or large ulcers with a predominant venous component, either pentoxifylline or micronized purified flavonoid fraction can be used in combination with compression [69].

Other fundamental conservative approaches include weight loss, leg elevation, appropriately fitting footwear and avoidance of even minor trauma and of constricting clothes that could exert a potential tourniquet effect [3, 80].

Active involvement of the patient represents the first step in a correct phlebolymphedema ulcer management.

Patient's awareness of his/her pathological condition is fundamental in order to obtain the best compliance to the treatment and to the self-maintenance of the achieved outcome.

The complexity of an ulcer in phlebolymphedema patient requires a multidisciplinary approach.

Aetiology identification, correct diagnostic testing, adequate therapeutic planning, appropriate wound care and competent supervision of the outcome maintenance are all aspects requiring a team of different experts.

Medical specialists in venous and lymphatic disease, wound care experts and nurses, certified lymphoedema therapists, psychologists and physical and occupational therapists are to be involved.

Caregivers dealing with phlebolymphedema ulcers must be instructed for an early detection of those conditions requiring referral to a dedicated treatment centre.

These specialized treatment centres must demonstrate perfect collaboration among vein and lymphatic specialists. Such professional collaboration must by the mainstay of a health-care network spread on all the assistant levels, aimed to properly treat and prevent the diffuse but still underestimated pathology of phlebolymphedema. Only the creation of a dedicated circle of collaborators can effectively manage the vicious cycle established by the contemporaneous venous and lymphatic impairment.

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Supplementary Information

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