Etiology and Classification of Lymphatic Disorders

Stanley G. Rockson

2.1 Development of the Lymphatic System – 10

2.2 Lymphatic Vascular Disease Classification – 11

2.2.1 Lymphedema – 11

2.3 Lymphatic Vascular Malformation – 24

2.4 Protein-Losing Enteropathy and Intestinal Lymphangiectasia – 24

2.4.1 Complex Vascular Malformations – 25

2.5 Infectious Diseases – 26

2.5.1 Lipedema – 26

2.5.2 Lymphangioleiomyomatosis – 26

Highlighted References – 27

B.-B. Lee et al. (eds.), *Lymphedema*, https://doi.org/10.1007/978-3-319-52423-8_2

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	

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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

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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	

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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)

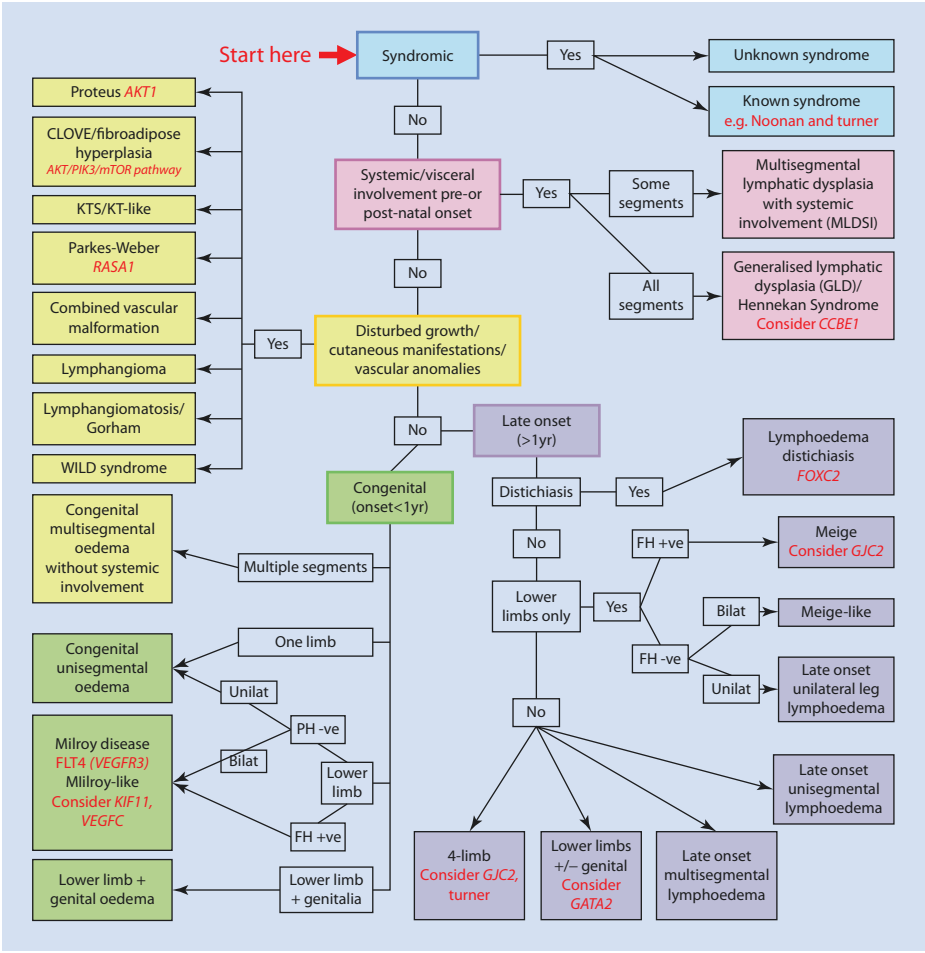
Table 2.1 (continued)

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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