Chapter 1
General Considerations

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Lymphedema is a progressive, usually unrelenting, and variably painful swelling of the limbs and/or genitalia resulting from lymphatic system insufficiency and deranged lymphatic transport. At the physical level, lymphedema is characterized by swelling of the tissues and eventual thickening and hardening of the skin and soft tissue. At the microvascular level, inadequate clearance of lymph causes the abnormal accumulation of interstitial fluid, which incites cellular proliferation and inflammation.[1] Chronic inflammation of lymphatic structures and surrounding tissue results in subcutaneous and lymph vessel fibrosis with irreversible structural damage.[2,3] As a result of underlying lymphatic damage, normal immune defenses are diminished. Therefore, lymphedema can best be described as a condition of impaired immunity, and a process of degeneration and chronic inflammation of the lymphatic structures and surrounding tissue.

Understanding of lymphatic system insufficiency depends on an understanding of normal lymphatic anatomy and physiology. The lymphatic system is a specialized network of vessels that regulates fluid homeostasis and immune defense. The prime function of the lymphatic system is to maintain fluid balance by clearing the interstitial spaces of excess water, large molecules, lipids, antigens, immune cells, and particulate matter. A large proportion of plasma proteins pass through the capillary wall daily, and not all of these return directly to the circulation. These are returned to the intravascular circulation by way of the lymphatic system.[4]

The lymphatic system is not a true circulatory system, but instead is a transport system for interstitial fluid. In contrast to the cardiovascular system, the lymphatic system is a low-pressure system that lacks a central pump and is not closed. Uptake of interstitial fluid begins in initial lymphatic vessels. The lymphatic capillaries are similar to blood capillaries, but there are gaps between the endothelial cells that allow the molecules that are too large for venous uptake to be reabsorbed.

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In collecting lymphatic vessels, valves facilitate the unidirectional movement of lymph by propulsion from external forces. A series of lymph nodes periodically interrupts the transporting vessels, which filter lymph as well as provide an immunological function.

Failure of any part of the lymphatic system causes the lymphatic load to exceed its transport capacity and causes fluid to accumulate in the interstitium. Inadequate clearance of lymph can occur in three distinct states; *dynamic insufficiency* (lymphatic system overload), *mechanical insufficiency* (intrinsic abnormality), or a combination of both mechanical and dynamic insufficiency, termed *safety valve insufficiency*.

Dynamic insufficiency of the lymphatic system, or high lymph flow failure, occurs when the normal functioning lymphatic structures are burdened with an increased load of microvascular filtrate, which reduces lymphatic transport capacity. Mechanical insufficiency, or low-output failure, refers to decreased lymphatic transport due to an intrinsic defect. Safety valve insufficiency occurs from the combined effect of increased lymph flow and a defective lymphatic system. The lymphatic defect may be due to an inherited abnormality, termed primary lymphedema, or an acquired cause, referred to as secondary lymphedema.

Classification of Lymphedema

Primary Lymphedema

Primary lymphedema encompasses a group of lymphatic disorders caused by inborn abnormalities of the lymphatic system, combined with abnormal structural development caused by mutant genes. Developmental lymphedema disorders may be caused by a single gene defect, chromosomal abnormality, or multifactorial inheritance.[5] Several genes have been identified as playing a role in embryonic and postnatal lymphatic development, including FOXC2, EphrinB2, VEGFR-3, VEGF-C, angiopoietin-2, Prox-1, and podoplanin.[6]

Most primary lymphedemas are actually truncular lymphatic malformations, arising during the later stages of lymphangiogenesis.[7,8] Many primary lymphedemas are congenital in nature. Lymphatic developmental disorders can be associated with combined malformations, arteriovenous malformations, and/or capillary malformations.[9]

Classification of primary lymphedema is based on several parameters, such as age at onset, anatomical variations, or pathophysiological phenomena. The most familiar system of classification used to describe primary lymphedema, however, is based on age at presentation; *congenital lymphedema*, also known as Milroy's disease if it is familial in an apparently autosomal dominant pattern of transmission, presents at birth or prior to age 2; *lymphedema praecox*, termed Meige disease, presents between ages 2 and 35; and *lymphedema tarda* presents after age 35.

Patients with known genetic mutations may develop lymphedema at puberty or at later stages of life. Therefore, classifying lymphedema into praecox or tarda is potentially misleading in understanding the etiology of these particular lymphedemas; the terms themselves may soon prove redundant. The future of the diagnosis and classification of primary lymphedema is likely to be determined by further insight into the genetic basis of this condition.

Secondary Lymphedema

Secondary lymphedema refers to an acquired cause of lymphedema, which may arise from the surgical removal of the lymph nodes or damage to lymphatic vessels by surgery, radiation, parasitic infiltration, malignancy, infection, inflammation, or filiariasis, the most common cause of secondary lymphedema worldwide. Filiariasis refers to infection by the parasitic nematode *Wuchereria Bancrofti.* Following transmission by a mosquito vector, the adult filarial worms lodge in the lymphatic vessels and initiate an immune response and subsequent activation of vascular endothelial growth factors (VEGF), thus promoting lymph vessel hyperplasia and inflammation as a result of the immune response.[10,11] Filariasis can be associated with lymphedema in the upper or lower extremities, breasts or male genitalia.

In developed countries, malignant neoplasms and their therapies are the most common cause of lymphedema. In the United States, breast cancer-related lymphedema of the arm is the most prevalent form. Nodal dissections and/or radiation therapy for gynecological, genitourinary, and head/neck malignancies have been implicated in the development of lymphedema. Nodal infiltration or metastasis to lymph nodes can occur from primary malignancies, such as lymphoma, melanoma, and a variety of gynecological and urological malignancies.

Interruption of the lymphatic vasculature during vein stripping surgery, vein harvesting procedures, recurrent cellulitis infections, and trauma are other mechanisms by which damage to lymphatic structures may occur.[12] Lastly, just as obstruction may occur in limb lymphatics, defects in central, abdominal or thoracic collecting trunks may cause either lymphedema in the limbs or chylous reflux in the body cavities. The latter phenomenon is described as chylous ascites when it affects the peritoneum, chylothorax when it affects pleura, chyluria when it affects renal lymphatics, and chylous metrorrhagia when it affects the uterus.

Clinical Presentation

The presentation of lymphedema may be at birth or in middle age; it may be sudden, or slow to develop. Edema is often painless at first, beginning on the dorsum of the foot or in the hand or forearm, and progressing proximally. Early in the presentation,

it subsides during recumbency and worsens towards the end of the waking day. The swelling becomes permanent with the passage of time, accompanied by architectural changes in the tissues. Early in the presentation, as the edema attacks the dorsum of the feet, the toes may become swollen also. The forefoot comes to resemble a buffalo hump and the skin on the dorsum of the toes thickens. The resulting inability to pinch the skin fold of the second toe is referred to as Stemmer's sign.[13]

As fibrosis ensues and the skin and subcutaneous tissues become thick and firm, edema no longer pits and the skin develops a *peau d'orange* (orange peel) appearance. The skin may become darkened and develop multiple warty projections. This is referred to as lymphostatic verrucosis. Elephantiasis nostras verrucosa (ENV) can be a late sequela of non-filarial lymphedema, although it is uncommon. A "pebbly" or cobblestone appearance, papules, verrucous lesions, enlargement, and woody fibrosis of the affected area characterize this condition.[14] Papillomas may result from local dermal lymphostasis and can be seen in other conditions associated with chronic limb edema.[15,16]

Lymphedema Staging

Lymphedema staging is based on the physical condition of the affected limb. Although there is some debate about staging, The International Society of Lymphology categorizes three stages of lymphedema.[17] The first stage is characterized by non-fibrotic edema that puts pressure on the affected limb and can be reduced by leg elevation. The second stage is characterized by lymphedema in which some degree of fibrosis is present. As a result, the edema does not put on pressure or reduce with leg elevation. Lymphedema in the third stage is associated skin and subcutaneous fibrosis and is irreversible (lymphostatic elephantiasis).

An additional stage of lymphedema (stage 0) has been introduced to represent the sub-clinical condition where swelling is not evident, although impaired lymph transport is present. Therefore, stage 0 may exist for months to years before overt lymphedema is present. For example, symptoms of lymphedema, such as limb heaviness, in breast cancer patients have been observed to occur long before gross edema.[18] None of the available systems includes tissue tenderness, limb shape, disability, or complications arising from lymphedema, such as skin breakdown and malignancy in lymphedema staging.

Diagnosis

Diagnosis of lymphedema can be determined by the clinical history and physical examination. History should include age at onset, travel to tropical countries, and a complete history inquiring into all possible causes of secondary lymphedema.

History of temporary edema of the affected area must be noted, and a detailed family history of limb swelling should be recorded. The examination should assess the distribution of edema, the condition of the skin, varicose veins, signs of lymphangitis or other skin lesions, past or present. The characteristic signs of lymphedema as described earlier in this chapter should be documented. Lymph vesicles, drainage of fluid, clear or milky, and yellow discoloration or other abnormalities of the nails must be noted. Finally, any complications, such as cellulitis, lymphangitis, malnutrition, immunodeficiency, or, rarely, suspected malignancy, must be documented.

Lymphedema in its early stages may be difficult to distinguish from other causes of non-pitting limb edema. Peripheral edema is most commonly caused by cardiac, hepatic or renal disease, or it can be induced by medication. Venous edema is more common than lymphedema. Lipedema can be confused with lymphedema, but can be clinically distinguished by its symmetrical distribution and characteristic sparing of the feet.

Confirmatory Testing

When the diagnosis is uncertain, the appropriate combination of non-to-minimally invasive tests should be able to provide all of the information necessary to ensure adequate diagnosis and lead to correct multi-disciplinary targeted treatment strategies.

X-rays of bones will identify limb length discrepancies, bony abnormalities, or phleboliths in patients with combined lymphatic and vascular malformations. Venous duplex studies will confirm any associated venous anomalies such as valvular incompetence, obstruction, ectasia, or localized dilations, and aneurysms. These studies should exclude venous obstruction as a cause or a contributing factor to the lymphedema.

Radionuclide lymphoscintigraphy (LSG) has largely replaced conventional oil contrast lymphography for visualizing the lymphatic network. LSG, performed with injection of 99mTc-labeled human serum albumin or 99MTc-labeled sulfur colloid subcutaneously into the first and second web-space of the toes and fingers is the test of choice to confirm or exclude lymphedema as the cause of the chronic limb swelling. Appearance time of the activity at the knee, groin, or axilla, as well as the absence or presence of major lymphatic collectors, numbers and size of vessels and nodes, and the presence or absence of dermal back flow should be looked for and carefully noted.[19] The presence of collaterals and reflux, as well as symmetrical activity in the opposite limb, must be recorded and used for interpretation. It can be easily repeated with minimal risk.[20,21]

Magnetic resonance imaging (MRI)/computed tomography (CT), typically of the pelvis and abdomen, can be useful to exclude underlying malignancy and for the differential diagnosis, and can differentiate amongst lymphedema and lipedema, chronic venous changes, vascular anomalies, and soft tissue hypertrophy. MR/CT

angiography is useful to exclude vascular anomalies, proximal obstruction, extrinsic iliac or vena caval compression.

Some invasive tests may be required to provide more information for an accurate differential diagnosis. Biopsy of an enlarged regional lymph node in the setting of chronic lymphedema is seldom needed to confirm the diagnosis, but is occasionally required for a differential diagnosis. Fine needle aspiration with cytological recommendations is strongly recommended as a substitute for excisional biopsy to minimize aggravation of the edema.

Finally, genetic testing may play a greater role in the future diagnosis of lymphedema to identify specific hereditary syndromes with genetic mutations.

Therapy

Physical and Non-Operative Therapy

The ultimate goal of treatment is to achieve better social, functional, and psychological adaptation in lymphedema patients. Therefore, therapy should improve the physical characteristics of the limb, alleviate symptoms, and reduce disease progression and secondary complications. The initial treatment for lymphedema is combined physical therapy (CPT) or complete/complex decongestive therapy (CDT), a two-stage treatment program. The first stage consists of manual lymphatic drainage (MLD), decongestive exercises and multilayer bandaging for compression. MLD is a specialized massage technique using specific pressures to stimulate lymphatic flow, redistribute fluid, which ultimately reduces limb volume.[22] As an adjunct to MLD, special short-stretch bandages, pneumatic sequential pumps, and other devices may be used for compression to promote venous and lymphatic flow.

The second phase is self-treatment with the above techniques for maintenance and prevention of re-accumulation of lymph. Prevention of infection can be accomplished with self-surveillance of the skin for early signs of infection, good hygiene, and skin care. Immediate antiseptic care of minor wounds and antibiotic treatment for early signs of infection is warranted. Antibiotic prophylaxis should be considered in patients who have had two or more attacks of cellulitis per year. The role of pharmacotherapy in treating symptoms of lymphedema has not been established.

Operative Therapy

Surgical treatment may benefit patients who remain refractory to all other treatment. There are three general surgical approaches to primary lymphedema: (1) Reconstructive surgery with microsurgical interventions (2) Debulking, ablative,

or excisional surgery, and (3) Liposuction. Indications for reconstructive surgery include failure to respond to therapy in the early stages of lymphedema, progression of the disease to the advanced stages, presence of chylous reflux or recurrent infections. The objective of debulking, ablative, or excisional surgery is to reduce the subcutaneous fat and fibrous overgrowth. Liposuction is designed to obliterate the epifacscial compartment by removal of excessive adipose tissue. Candidates for palliative excisional surgery should be in the late stages of lymphedema with grotesquely disfigured limbs and/or have failed conservative therapy.

Complications of Lymphedema

Patients with lymphedema are prone to repeated episodes of infection and inflammation of the skin, soft tissue, and lymphatic vessels. Gram-positive bacteria are the usual pathogen in attacks of cellulitis, lymphangitis, and erysipelas. Recurrent skin infections may be an early presentation of lymphedema before overt signs are present.[23] Dermatolymphangioadenitis (DLA) can occur as a complication of obstructive peripheral lymphedema. The clinical characteristics of acute DLA are local tenderness and erythema of the skin, red streaks that follow the distribution of the superficial lymphatics, enlarged inguinal lymph nodes, and systemic symptoms such as fever and chills.

A rare, but potentially lethal complication of chronic lymphedema is the development of a cutaneous malignancy, referred to as Stewart–Treves syndrome. Stewart–Treves syndrome is an aggressive lymphangiosarcoma that was originally described in women who had chronic lymphedema of the upper limb following mastectomy and axillary lymph node dissection for breast cancer.[24,25] Other neoplasms associated with chronic lymphedema are Kaposi sarcoma, B-cell lymphoma, squamous cell carcinoma, and malignant fibrous histiocytoma.

Conclusions

Lymphedema is fundamentally a failure of fluid transport and is usually diagnosed by its physical features. The hallmark of lymphedema is fibrosis of the skin and subcutaneous tissues, and progression to non-pitting edema. History and physical findings dictate its classification and grading. Specific testing is used only in difficult cases in which imaging studies clarify the diagnosis, although genetic testing will likely play a role in the future diagnosis of primary lymhedema. Treatment is primarily non-surgical. Surgical intervention may be of benefit to a few, well-selected individuals. Future therapy for primary lymphedema will likely involve molecular interventions and increased efforts to prevent secondary lymphedema.

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