Lymphedema

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Opinion statement

Aggressively applied decongestive measures (ie, manual lymphatic drainage, low-stretch bandaging, exercise, skin care, application of compressive elastic garments) are the mainstay of lymphatic therapy. Therapeutic regimens should differentiate between the sequential goals of acute volume reduction and maintenance of limb volume. Elastic garments should not be employed until maximal volume reduction has been attained through decongestive lymphatic techniques. It is my opinion that use of intermittent pneumatic compression devices can play an important adjunctive role to decongestive lymphatic therapy but should not be substituted for these techniques. At this time, I am not inclined to use pharmacologic therapy in these patients but anxiously await the results of studies that might demonstrate efficacy for molecular approaches. Surgical intervention is reserved for a small number of well-selected patients. Liposuction for volume reduction appears to be a very promising approach for specific patients.

Introduction

The diagnostic entity of lymphedema includes a group of pathologic states that are characterized by an abnormal accumulation of protein-rich fluid in the interstitial tissue compartment. This protein-rich edema accumulates when the lymphatic circulation is unable to accommodate the demand for lymphatic flow. The impairment in lymphatic flow can result from either primary or acquired (secondary) anomalies of lymphatic transport. It is likely that many of the conditions known as primary lymphedema are actually a variety of acquired secondary conditions in which the provoking insult to the lymphatic circulation defies identification. In addition to the manifestations of edema in the extremities, lymphedema can, less frequently, produce abnormalities of visceral function.

LYMPHATIC VASCULAR INSUFFICIENCY (LYMPHEDEMA)

In health, the lymphatic vasculature possesses the requisite transport capacity to accommodate the fluid load placed upon it. It is sustained accumulation of fluid within the interstitium that characterizes the presence of lymphedema (Fig. 1) [1]. Thus, lymphedema is the consequence of an imbalance between the rate of lymph production (lymphatic load) and its removal through lymphatic channels (lymphatic transport capacity). The production of lymph can be enhanced by increased capillary permeability, venous hypertension, or diminished capillary oncotic pressure. Thus, local inflammatory responses, venous thromboembolism, or hypoproteinemia can each, respectively, produce a clinical presentation of lymphedema, even in the absence of concomitant damage or dysfunction of the lymphatic vasculature. Conversely, when the lymphatic vasculature is disrupted, malformed, or displays inadequate functional responses, the same clinical picture will ensue, with the expansion of protein-laden interstitial fluid volume, despite a normal rate of interstitial fluid production. The initiating factors for the development of impaired lymphatic transport capacity include heritable disorders of lymphatic vascular development, infection, trauma (either spontaneous or iatrogenic), extrinsic compression, and intraluminal tumor invasion.

DISORDERS OF LYMPHATIC TRANSPORT CAPACITY

A natural classification schema for the diseases that impede lymphatic flow distinguishes the heritable disorders from those that are acquired in postnatal life. Primary lymphedema, subsequently, results from an inborn defect of lymphatic structure or function, whereas secondary lymphedema reflects an acquired loss of vascular function.

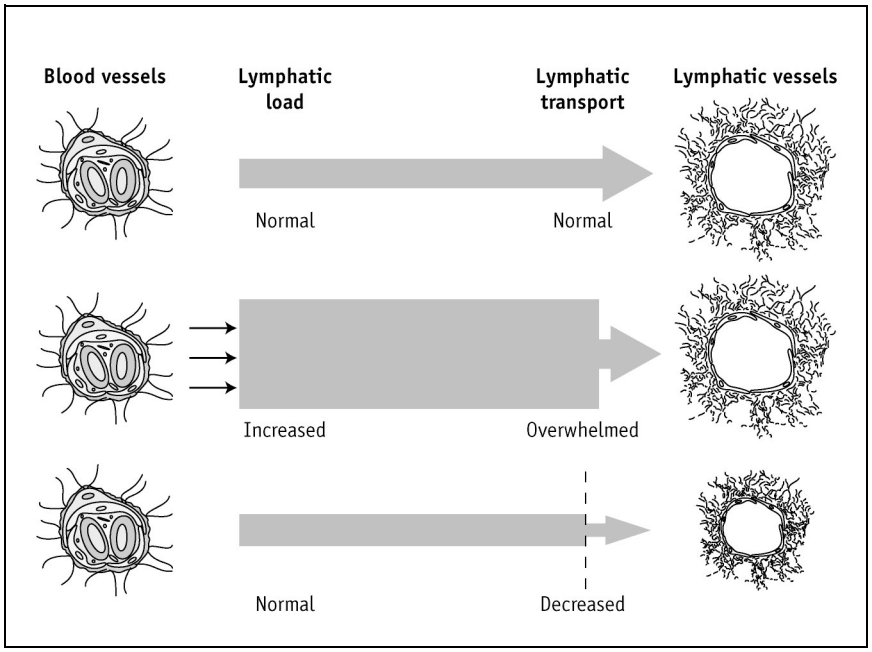

Figure 1. The pathogenesis of lymphedema. (*Adapted from* Rockson [1].)

Primary lymphedema Primary lymphedema is neither common nor rare [2]. Prevalence estimates suggest that congenital lymphedema occurs in 1 of every 6 to 10,000 live births. Despite the identified autosomal-dominant pattern of transmission identified in many of these conditions, there is a female predominance, with the female:male ratio estimated variously as between 2.5 and 10:1.

The presence of primary lymphedema generally reflects an aberration of vascular structural development. These patterns have been identified historically through contrast lymphography, an approach that has subsequently been largely abandoned. Primary lymphedema can be characterized by the presence, alternatively, of lymphatic vascular aplasia, hypoplasia, or hyperplasia, the latter often accompanied by vascular tortuosity and lymphatic valvular incompetence [3].

Primary lymphedema represents a heterogeneous group of disorders and, therefore, its classification schemata are numerous. Affected individuals can be classified by age of onset, by functional anatomic attributes, or by clinical setting. Failure of lymphatic development can affect either proximal or distal vasculature [4]. Proximal anatomic derangements tend to be severe and progressive over time; in contrast, disease that initially spares the proximal segments more typically carries a more benign prognosis, with a diminished tendency to progress in the involved limb or extend to the uninvolved extremities. Megalymphatics, characterized by hyperplasic or dilated lymphatic channels, represent the least common anatomic pattern, and are associated with a greater extent of involvement and a less favorable prognosis.

The earliest classification schemata for primary lymphedema have emphasized the distinctive age of the patient at the time of edema onset [5]. Congenital lymphedema is clinically apparent at the time of birth, or shortly thereafter; lymphedema praecox is an older term to describe the onset of edema before age 35 and, most typically, at the time of puberty; lymphedema tarda, by definition, appears after the age of 35. Many patients with primary lymphedema present with abnormal phenotypes [6]. The diseases that present with primary lymphedema have increasingly yielded to genetic linkage and molecular characterization.

Even in the absence of accompanying phenotypic abnormalities, the propensity for primary lymphedema to cluster in families has long been recognized. Originally described in 1892, the eponymously named Milroy disease is characterized by an autosomal-dominant form of familial primary lymphedema [7]. More recently, in several family cohorts of Milroy's disease, it has been determined that the presence of disease reflects the transmission of missense inactivating mutations of the tyrosine kinase domain of vascular endothelial growth factor receptor-3 (VEGFR-3) [8,9••]. Initially mapped to the telomeric part of chromosome 5q [8], the defect was ultimately linked to the FLT4 locus that encodes VEGFR-3 [9••]. All of the disease-associated alleles examined in the affected families encoded proteins with an inactive tyrosine kinase, preventing downstream gene activation [10]. Thus, some cohorts of patients with Milroy disease can now more properly be characterized as reflecting a defect in lymphatic vasculogenesis, with defective VEGFR-3 signaling leading to hypoplastic lymphatic vascular development.

The praecox form of primary lymphedema has often, historically, carried the eponym of Meige's disease [11]. It is likely that many, or most, of these patients would now be assigned the diagnosis of lymphedema-distichiasis. This autosomal-dominant dysmorphic syndrome is associated with pubertal or postpubertal onset of distal lymphedema, and presents in association with a supplementary row of eyelashes

(distichiasis) that arise from the meibomian glands. This condition has also yielded to chromosomal linkage analysis; in this case, the disorder is linked to truncating mutations in the forkhead-related transcription factor, FOXC2 [12]. More recently, haploinsufficiency of FOXC2 expression has similarly been associated with an array of primary lymphedema phenotypes [12]. Furthermore, recent mechanistic investigations suggest that an abnormal interaction between lymphatic endothelial cells and pericytes, as well as valve defects, underlie the pathogenesis of lymphedema-distichiasis [13•].

A more unusual form of congenital lymphedema, hypotrichosis-lymphedema-telangiectasia, has been linked to mutations in the transcription factor gene *SOX18* [14]. Autosomal-dominant and recessive patterns of transmission have both been described. This association suggests that, in addition to its previously described role in hair and blood vessel development, the SOX18 transcription factor has a role in the development and/or maintenance of lymphatic vessels; the nature of this role remains to be elucidated. Patients with cholestasis-lymphedema syndrome suffer severe neonatal cholestasis that usually lessens during early childhood and becomes episodic. They also develop chronic severe lymphedema. The disorder has been mapped to chromosome 15q [15].

In general, autosomal- or sex-linked recessive forms of primary lymphedema occur less commonly than the dominant forms of inheritance. Primary lymphedema has been described in association with various forms of chromosomal aneuploidy, such as Turner's and Klinefelter's syndromes, in several dysmorphogenic-genetic anomalies, such as Noonan's syndrome and neurofibromatosis, and with many seemingly unrelated disorders, such as yellow nail syndrome, intestinal lymphangiectasia, lymphangiomyomatosis, and arteriovenous malformation [16].

Distinguishing primary mechanisms of lymphedema pathogenesis has relevance to the natural history, prognosis, and genetic counseling of patients. At the current time, there are no treatment implications to these distinctions, inasmuch as the same therapeutic approaches are applied to individuals with primary and secondary forms of the disease. It is likely that future advances in the molecular delineation of pathogenesis will yield treatment approaches that may be specific to these individual disorders. Furthermore, it must be stressed that the majority of patients with so-called primary lymphedema reflect the manifestation of disorders whose pathogenesis remains unidentified.

Secondary lymphedema Obliteration of previously normal lymphatic channels is the hallmark of secondary, or acquired, lymphedema. A broad array of pathologic processes can contribute to these transformations.

Infection: Filariasis, a nematode infection endemic to regions of Asia and Africa, is the most common cause of secondary lymphedema in the world. It is estimated that, globally, 2.0% of the world population is affected, representing approximately 119 million cases [17]. The disease is transmitted by a mosquito vector. Recurrent lymphangitis leads to the eventual fibrosis of the diseased lymph nodes. Although it has been demonstrated that annual mass treatment with antibiotics such as diethylcarbamazine can virtually eliminate the reservoir of microfilariae and greatly reduce the new appearance of clinical lymphatic abnormalities [18], there is currently no treatment or cure for those who have sustained active infection with ensuing lymphatic damage. These cases, often called elephantiasis, represent among the most severe manifestations of lymphatic vascular insufficiency encountered by clinicians. Although filariasis occurs sporadically in North America, infectious causes of acquired lymphedema in the United States are predominated by recurrent episodes of bacterial lymphangitis that ultimately produce thrombosis and fibrosis of the lymphatic vasculature [19]. Although it is difficult to accurately identify the pathogen in many of these cases, the culprit is usually felt to represent a gram-positive organism, most often from the streptococcal group. Tuberculosis is another, less common, infectious cause of acquired lymphedema.

Lymphatic trauma: The most common cause of acquired lymphedema in developed countries, including the United States, is iatrogenic. This large patient group reflects the lymphatic trauma that ensues from surgical and radiotherapeutic interventions for cancer [20]. Within the category of cancer therapy–related disease, the problem of breast cancer–associated lymphedema is the one commonly encountered. Axillary lymph node dissection and adjuvant radiation therapy are both predisposing factors, particularly when the axilla is included in the radiation field [21]. Incidence estimates of this problem vary, but the most recent observations suggest that lymphedema ultimately occurs in approximately 20% of breast cancer survivors who have undergone axillary interventions [22,23]. The accrual of new cases is linear to exponential in the first 3 years following interventions; thereafter, new case appearance diminishes in number but persists throughout the natural history of the survival period. Even with recent improvements in surgical and radiotherapeutic techniques, lymphedematous complications cannot be obviated and are, in fact, not uncommon [24,25]. The reported frequency of leg edema after pelvic or genital cancer surgeries, particularly when there has been inguinal and pelvic lymph node dissection or irradiation, varies between 1% and 47% [26,27]. Pelvic irradiation increases the frequency of leg lymphedema after cancer surgery [28,29]. Lymphedema can be acquired from other forms of lymphatic vascular trauma. These include burns and large or circumferential wounds to the extremity, but relative prevalence estimates are not readily available.

Malignant diseases: Lymphedema acquired as an iatrogenic consequence of cancer treatment should be considered a "benign" consequence of malignant disease. In contrast, various malignancies can produce secondary lymphedema through direct neoplastic invasion or through extrinsic compression of the vessels by the tumor mass. In addition to the flow-limiting effect of tumor compression, this mechanism may also predispose to bacterial lymphangitis, with additional attendant compromise. In men, the most common tumor involvement is reported with prostate cancer; in women, it is lymphoma [30].

Additional causes: Other conditions have been associated with acquired obstruction of lymphatic flow leading to edema. These include rheumatoid arthritis, pregnancy, and contact dermatitis [31–33]. Autoimmune destruction of the lymphatics has been hypothesized but not directly demonstrated. Repeated subcutaneous injection of sclerosing drugs, such as pentazocine hydrochloride, can lead to lymphatic obstruction, as is the case in factitious edema induced by self-inflicted cellulitis.

DIFFERENTIAL DIAGNOSIS

The chief entity that poses confusion with chronic lymphedema is chronic venous insufficiency, primarily because the edematous limb in venous insufficiency is exposed to a sustained increase in lymphatic load (see earlier discussion) that can ultimately predispose to the development of secondary lymphedematous changes, once the lymphatic transport capacity of the involved limb is overwhelmed. In the absence of this series of events, there should be little confusion. Chronic venous insufficiency is characterized by a soft pitting edema, often in association with stasis changes, cutaneous hemosiderin deposits, and superficial varicosities. When the differential diagnosis is in question, imaging can be useful. The diagnostic modality most commonly employed is indirect radionuclide lymphoscintigraphy [34••]. In addition to its ability to distinguish lymphatic causes of edema, the intervention has been suggested as a prognostic indicator of the responsiveness of lymphedema to physiotherapeutic interventions [35]. MRI and ultrasound may also provide useful information in selected clinical settings [20].

The myxedema of hypothyroidism can, at times, superficially resemble lymphedema. The abnormal mucinous deposits in the skin lead to the development of edema. As hyaluronic acid-rich protein accumulates in the dermis, the skin's structural integrity is compromised and elasticity declines. The skin texture becomes rough, especially in the elbows, knees, palms, and soles, accompanied by a yellowish discoloration. In thyrotoxicosis, this process is localized to the pretibial region. Myxedema is characterized by roughening of the skin of the palms, soles, elbows, and knees; brittle, uneven nails; dull, thinning hair; yellow-orange discoloration of the skin; and reduced sweat production.

Lipedema is a condition that affects women almost exclusively, although it can be seen in men with a feminizing disorder. The edema, caused by abnormal adipose deposits in the subcutaneous regions, is typically observed between the pelvis and the ankle, with sparing of the feet. Although the pathophysiology of lipedema is uncertain, it does involve an increase of subcutaneous adipocytes with structural alterations in the small vascular structures within the skin. It is postulated that regional abnormalities of the circulation may cause the initial accumulation of fat in the affected regions. Symmetric swelling of the legs, with sparing of the feet, should suggest the correct diagnosis. Most often, lipedema appears within 1 to 2 years after the onset of puberty. In addition to the nearly lifelong history of heavy thighs and hips, affected patients often complain of painful swelling and easy bruising, perhaps a result of increased fragility of capillaries within the adipose tissue.

Malignant lymphedema must always be considered when, in the differential diagnosis of lymphedema, recurrence of cancer is a possibility. A malignant substrate should also be considered whenever a patient with postneoplastic lymphedema shows evidence of unheralded exacerbation. In malignant lymphedema, obstruction of lymphatic channels can accompany the spread of tumor cells through this circulation. Extrinsic obstruction of the lymphatics by tumor can also occur. Clinically, malignant lymphedema is characterized by rapid development and relentless progression [36]. In addition, pain, generally absent in benign lymphedema, may be a feature. Central distribution of edema and absence of pitting, even at the outset, further serve to distinguish malignant from benign presentations.

INDICATIONS FOR HOSPITALIZATION

Cellulitis with pronounced systemic toxicity is an indication for hospitalization, particularly if parenteral antibiotic therapy is warranted. Severe untreated edema that substantially limits patient mobility is an indication for inpatient, intensive decongestive physiotherapy.

Treatment

Diet and lifestyle

- There is little evidence that diet directly affects the appearance of lymphedema or alters its course.
- There are limited data to suggest that therapeutic augmentation of dietary flavenoids and restriction of long-chain triglycerides in the diet favorably affect the manifestations of lymphedema.

- The effects of exercise are largely unknown. It is conjectured that isometric muscular exertion and heavy lifting may exacerbate the condition, but little, if any, prospectively derived data are available.
- Airline travel has been reported to be a precipitating factor in patients who are predisposed to the development of lymphedema [21]. Prophylactic external compression of the limb at jeopardy using elastic-fitted garments may be warranted, but the benefits are unproven.
- Leg elevation can be employed as a temporizing measure, until more complete therapeutic interventions are instituted.

Pharmacologic treatment

- Pharmacologic therapy of lymphedema is controversial; few, if any, agents are available.

Coumarin

Standard dosage	90 to 135 mg/d.
Contraindications	Hepatic dysfunction.
Main drug interactions	Not known.
Main side effects	Hepatic dysfunction.
Special points	Coumarin has been reported to provide benefit in lymphedema [37], but the salutary effects of the drug are not universally acknowledged. Its benefit has been ascribed to its effect on cutaneous macrophages and, thereby, on local proteolysis. This drug also stimulates other cellular elements of the immune system and may promote protein reabsorption. Despite some encouraging early trials, this agent must still be considered to have an experimental role in the therapy of primary lymphedema.
Cost/cost-effectiveness	The cost-effectiveness of coumarin is not known.

Surgery

- Surgical therapy can be entertained in a select population of patients with lymphedema [38].
- One goal of surgery is to debulk the chronically enlarged limbs.
- An additional goal is the creation of lymphatico-lymphatic, lymphatico-veno-lymphatic, lymphaticovenous [39], or lymph node-venous anastomoses.

Debulking

Standard procedure	Removal of redundant skin and subcutaneous tissues.
Contraindications	No absolute contraindications.
Complications	Potential for further damage to existing cutaneous lymphatics; skin necrosis; papillomatosis; edema exacerbation.
Cost/cost-effectiveness	No data available.

Surgical liposuction

Standard procedure	Removal of redundant subcutaneous adipose tissue [40,41].
Contraindications	Significant pitting edema.
Complications	Potential for infection.
Cost/cost-effectiveness	No data available.

Construction of omental pedicles and myocutaneous flaps

Standard procedure Use of the pedicle or flap to create lymphatic anastomoses [42].

Contraindications Distal forms of obstructive lymphedema.

Complications Complications are the same as for debulking surgery, in addition to sensorineural damage, hypertrophic scarring, ulceration, graft necrosis, and exophytic keratosis.

Cost/cost-effectiveness No data available.

Other therapies

- Meticulous control of lymphedema is reported to reduce the incidence and severity of soft tissue infections.
- Decongestive lymphatic therapy has been widely demonstrated to be an effective maneuver to reduce limb volume and restore function [43•]. In decongestive lymphatic therapy, specialized massage techniques (manual lymphatic drainage) enhance lymphatic contractility and augment and redirect lymph flow through the nonobstructed cutaneous lymphatics. This complex form of physical therapy integrates meticulous skin care, massage, exercise, and the chronic use of compressive elastic garments [6].
- Decongestive lymphatic therapy can not only affect an acute reduction in limb volume, but can also ensure long-term maintenance of the accrued therapeutic benefits.

Decongestive lymphatic therapy

Standard procedure Manual lymphatic drainage, bandaging, exercise, skin care, and elastic-fitted garments are employed, at times supplemented with the use of intermittent pneumatic compression pumps [44,45].

Contraindications Pumps and tight-fitting garments may be relatively contraindicated in severe peripheral vascular insufficiency; decongestive physiotherapy is relatively contraindicated in the setting of acute cellulitis or if there is an unresolved question of recurrent malignancy.

Complications None, with proper utilization and patient education.

Cost/cost-effectiveness There are no formal studies available.

Endovascular restoration of venous patency

Standard procedure Chronic lymphedema that arises after surgical or radiotherapy commonly produces combined lymphatic and venous obstructive edema [46•]. If the latter is detected, the impact of the edema on structure and function can be remarkably ameliorated through restoration of venous patency through thrombolysis, balloon venoplasty, and/or the deployment of appropriate endovascular stents.

Contraindications Inability to use anticoagulant and antiplatelet regimens, or intolerance of radiocontrast administration.

Complications Standard complications of thrombolysis and endovascular interventions, including bleeding, vascular trauma, and radiocontrast-induced anaphylaxis.

Emerging therapies

Low level laser therapy

Standard procedure Repetitive external treatment with low level carbon dioxide laser [47,48].

Contraindications None known.

Complications None.

Cost/cost-effectiveness Unknown.

Lymphocyte injection therapy

Standard procedure	Intra-arterial injection of autologous lymphocytes [49].
Contraindications	None known.
Complications	None reported.
Special points	Activity of L-selectin, a lymphocyte-specific adhesion molecule, reportedly increases with therapy.
Cost/cost-effectiveness	Unknown.

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