REVIEW

Lower extremity lymphedema

Update: pathophysiology, diagnosis, and treatment guidelines

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Lower extremity lymphedema is an important medical issue which causes morbidity and is frequently seen by dermatologists. The subject has not been adequately addressed in dermatologic literature for many years. Primary lymphedema is caused by an inherent malfunction of the lymph-carrying channel, in which no direct outside cause can be found. Secondary lymphedema is caused by an outside force, such as tumors, scar tissue after radiation, or removal of lymph nodes, which results in dysfunction of the lymph-carrying channels. Treatment is based on rerouting the lymph fluid through remaining functional lymph vessels. This is accomplished through elevation, exercises, compression garments/devices, manual lymph drainage, and treatment is combined with good skin care practices. (J Am Acad Dermatol 10.1016/j.jaad.2008.04.013.)

ETIOLOGY AND PATHOPHYSIOLOGY OF LOWER EXTREMITY LYMPHEDEMA

Dermatologists frequently encounter patients with lymphedema of the lower extremities, often caused by chronic venous insufficiency and recurrent cellulitis. Although this is a relatively common problem, it has rarely been addressed in the dermatology literature. In this article, we will provide a concise review on definitions, causes, diagnosis, and treatment strategies in lymphedema.

Lymph vessels and lymph drainage

The lymph drainage system parallels the venous drainage system. The lymph drainage moves through the lymphatic vessels in a one-way directional path to return protein, colloids, and particulate matter to the systemic venous circulation. The smallest lymphatic vessels are the lymphatic capillaries which drain into the larger precollector vessels. The precollectors then drain into the larger collecting lymphatic vessels. The collecting lymphatics are the major lymphatic vessels of the limbs, and they provide flow of the lymph drainage to the lymph nodes.[1-3]

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The lymph drainage from the initial lymphatics (the lymphatic capillaries and the precollectors) is dependent upon compressive forces along these lymphatics. Movement of the tissues that contain these lymphatics, either by overlying surface pressure, or through underlying contraction of muscles or contact with adjacent artery pulsations, causes dilation or constriction of the initial lymphatics, thus propelling the flow of lymph forward. There are also unidirectional valves in both the initial and collecting lymphatics which prevent backward movement of the lymph fluid. The collecting lymphatics then receive the flow of lymph and send it toward the lymph nodes via an intrinsic pumping mechanism of smooth muscle contractions within the lymphatic walls. This pumping mechanism of the main collecting lymphatics is only as good as its supply of lymph from the initial lymphatics.[1]

Lymphedema and edema: The difference

Lymphedema is the result of protein-rich interstitial volume overload, secondary to lymph drainage failure in the face of normal capillary filtration. This is in contrast to edema, which is defined as an increase in interstitial fluid volume that is enough to produce clinical, palpable swelling. This occurs whenever there is an imbalance between capillary filtration and lymph drainage, no matter the etiology. Interstitial fluid volume is primarily controlled by the lymphatic system, which normally compensates for increased capillary filtration through an increase in lymph flow.[1,2] Edema that resolves after elevating the affected area overnight is likely secondary to increased capillary filtration (eg, chronic venous insufficiency).

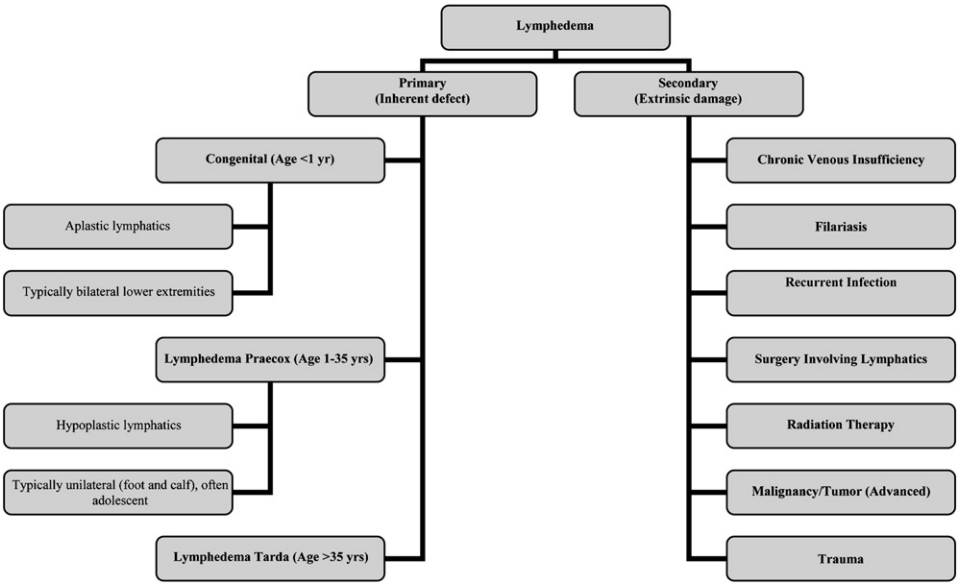

Fig 1. Causes of lymphedema.[4,5]

Edema that does not improve much with overnight elevation often indicates lymphedema because even though there is decreased capillary filtration, there is still no improvement in the failure of the lymph-conducting pathways. These physiological concepts become important when discussing the treatments of both lymphedema and chronic venous insufficiency.[2,4]

Pathophysiology

Lymphedema often occurs in the extremities, probably because of the low number of alternate lymph pathways for drainage since the outlet at the groin is narrowed by the lacunar ligament. Further accumulation of protein-rich fluid results in decreased oxygen tension and fibrosis. Lymphedema occurs when there is (1) an inherent defect within the lymph-carrying conduits, termed primary lymphedema, or (2) whenever acquired damage arises, termed secondary lymphedema (eg, pressure from tumors, scar tissue after radiation, surgical removal of lymph nodes) (Fig 1).[1,3,5]

The primary causes can be further categorized according to the age at which they first had clinical manifestations: congenital causes (age <1 year), lymphedema praecox (age 1-35), and lymphedema tarda (age >35 years).[5] The congenital type of lymphedema is either sporadic or familial. The familial form is termed Milroy disease and is thought to be linked to autosomal inheritance of a single mutated gene, vascular endothelial growth factor 3 (*VEGFR-3*).[6] This reduces the *VEGFR-3* tyrosine kinase activity, which ultimately reduces the effects of *VEGF-C* and *VEGF-D*, both of which are key players in lymphangiogenesis.[7] Congenital lymphedema tends to affect both of the lower extremities, but can also involve the upper extremities, and even the face. Histologically, the initial lymphatics are absent. The most common type of primary lymphedema is lymphedema praecox. Lymphedema praecox (Meige's disease) usually affects adolescent women, and is typically unilateral, involving the foot and the calf. Histologically, the lymphatics are hypoplastic. Lymphedema tarda occurs in individuals who have congenitally weakened lymphatics so that precipitating events such as trauma or an inflammatory reaction result in lymphedema. These breakdowns in lymphatic function are likely secondary to errors in fetal development; though late-onset primary lymphedemas may be acquired defects. Alternatively, a defect may be present from birth with the lymphatic system able to compensate, until there is an insult resulting in lymphatic transport capacity overload.[4-6]

Another way to categorize primary lymphedema is whether the lymphatics are aplastic, hypoplastic, or hyperplastic. Although these conditions can be differentiated by biopsy or lymphoscintigraphy, ultimately this is not managed with different therapies.[5]

The secondary causes are numerous; however, they are based on two basic principles: lymphatic obstruction and lymphatic interruption. The most common cause of lymphedema in the developing world is secondary to an infection by the nematode *Wuscheria bancrofti*, also known as filariasis. The most common cause of lymphedema in the industrialized world is malignancy and malignancy-associated

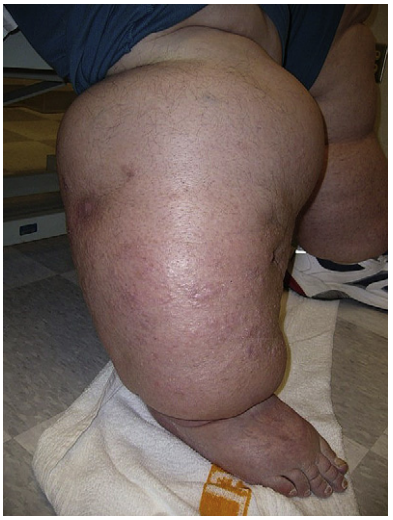

Fig 2. Lower extremity lymphedema.

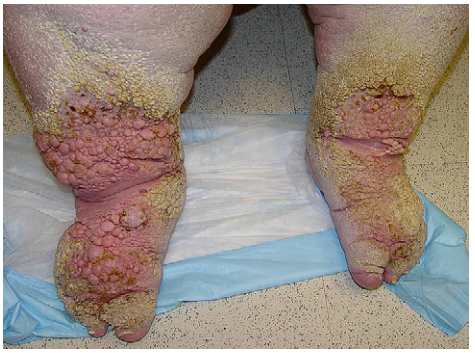

Fig 3. Skin changes associated with lymphedema.

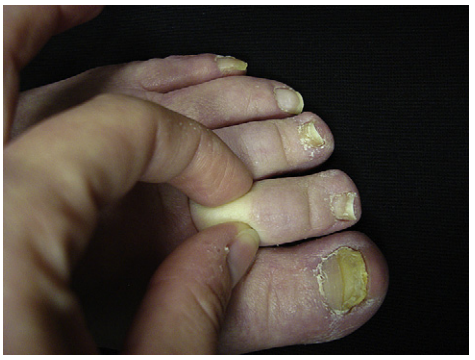

Fig 4. Kaposi-Stemmer sign.

treatments, including radiotherapy and surgery (eg, radical lymph node dissection). Other causes include trauma, recurrent bacterial infections, thyroid dermopathy, and chronic venous insufficiency.[4-6,8]

Elephantiasis verrucosa nostras is an exaggerated form of secondary lymphedema, which has been complicated by recurrent fungal and bacterial infections. These infections further damage the lymphatics and cause further progression along the continuum, ultimately resulting in diffuse, hyperkeratotic, nodular lesions. When advanced, the term "mossy foot" is used to describe the appearance of the extremity.[2,9]

The prevalence of lower extremity lymphedema is not currently known. Lymphedema is found in both sexes, but women are evaluated more often than men. It is found at any age. Two thirds of all cases are unilateral, and the distal portion of the extremity is always affected before the proximal extremity.[6]

The epidemic of obesity in the United States in the last decade has also caused a significant increase in the number of cases of lymphedema in the morbidly obese. Obesity can impede lymphatic flow and lead to protein-rich fluid accumulation in the subcutaneous tissue.[9]

CLINICAL PRESENTATION

Initially, patients with lower extremity lymphedema present with unilateral painless swelling that starts on the dorsal aspect of the foot, with eventual proximal involvement over the first year (Fig 2). The foot often has a squared-off appearance. The edema is initially a pitting edema, but over time the subcutaneous tissue becomes fibrotic, resulting in nonpitting brawny edema. The edema can then spread circumferentially if treatment is not initiated. Eventually, the involved skin becomes hyperkeratotic, hyperpigmented, and papillomatous or verrucous with increased skin turgor (Fig 3). The Kaposi-Stemmer sign is a clinical sign indicative of lymphedema, in which an examiner is unable to pinch a fold of skin at the base of the second toe on the dorsal aspect of the foot (Fig 4).[2,4,5]

Ultimately, the skin is at risk for breakdown and subsequent infection. Recurrent infections such as cellulitis, erysipelas, tinea pedis, and lymphangitis can then ensue. This inflammation worsens swelling and increases the complexity of the problem. In areas of barrier dysfunction there is risk of lymph fluid leakage, which further impairs healing. The swelling associated with lymphedema results in a sense of heaviness, discomfort, and impaired mobility of the limb. Angiosarcoma may develop in chronic lymphedematous limbs (Stewart-Treves syndrome), but is most commonly seen in the upper extremity following mastectomy with nodal dissection.[10,11] This is often referred to as lymphangiosarcoma, which is actually a misnomer, since the tumor is not derived from lymphatic vessels, but is rather derived from vascular endothelial cells within chronic lymphedema. Treatment is predominantly

radiotherapy, and surgery is reserved for those with isolated disease.[2,5,10-13]

DIFFERENTIAL DIAGNOSIS

Lymphedema should be considered with any edematous extremity without pain or inflammation. Chronic venous insufficiency can be difficult to differentiate from early lymphedema because both have pitting edema, and skin changes typical of late-stage lymphedema are not yet present. Additionally, chronic venous insufficiency is often bilateral, rather than unilateral as in lymphedema. Lymphoscintigraphy may be necessary to distinguish the two, although the distinction cannot always be made since chronic venous insufficiency can actually lead to secondary lymphedema. Similarly, a deep vein thrombosis can cause a postphlebitic syndrome, which can result in lipodermatosclerosis and chronic swelling of the limb.[4,5]

In nonfilarial regions of tropical Africa, Central America, and the Indian subcontinent, there is a condition that has a presentation similar to filariasis, called podoconiosis, or nonfilarial elephantiasis. This causes edematous feet and legs. Podoconiosis is caused by long-term inoculation of microparticles of silica through the soles of barefoot walkers.[2]

Exclusion of general medical causes of lower extremity swelling should be a priority. These causes include, but are not limited to, renal failure, protein-losing nephropathy, hypoalbuminemia, congestive heart failure, pulmonary hypertension, drug-induced edema, obesity, and pregnancy.[4,8]

Other considerations include lipedema (also known as lipomatosis of the leg), "armchair legs," and postoperative swelling. Lipedema is a syndrome of bilateral adipose deposition in the buttocks and lower extremities, causing subsequent enlargement, which stops abruptly at the malleoli, sparing the feet (helpful in distinguishing this from lymphedema). Lipedema typically affects overweight women, though it has occurred in women of normal weight and often begins during or soon after puberty. It is often associated with considerable aching and pain within the extremity, especially below the knee.[14] "Armchair legs" is a descriptive term that results from sitting in a chair all day and night with one's legs in a dependent position. The immobility results in decreased lymphatic drainage and a functional lymphedema. Postoperative swelling caused by femoropopliteal bypass grafting occurs as a result of disruption, or impaired lymphatic drainage, secondary to the surgical dissection in the thigh and popliteal areas. Swelling typically resolves within 3 months. If there is significant edema, a postoperative tibial or popliteal vein thrombosis should be considered.[5,8]

DIAGNOSIS

Whenever there is doubt regarding the clinical diagnosis, diagnostic confirmation can be accomplished with isotopic lymphoscintigraphy (considered the method of choice) or, if necessary, with radiocontrast lymphangiography.[15] Computed tomographic (CT) scanning or magnetic resonance imaging (MRI) (MRI is superior to CT scans because it can detect water) of the lower extremity can also detect a "honeycomb" pattern of the subcutaneous tissue that is not characteristic of other types of edema. Additionally, a venous duplex ultrasound is often needed to assess for deep venous thrombosis or venous disease, which can coincide with lymphedema (see Fig 4). If there is suspicion of filariasis, one can perform a blood smear (collected at night) looking for the presence of microfilariae. Antigen testing by immunochromatographic card test (Binax) or enzyme-linked immunosorbent assay (TropBio) is more sensitive than microfilariae detection; these tests can use blood collected during the day or night.[16] In addition to a thorough history and physical examination, other diagnostic studies to rule out alternative causes of lower extremity edema may include a complete metabolic profile, serum albumin, and urinalysis to screen for renal failure, hypoalbuminemia, and protein-losing enteropathy.[2,8]

MANAGEMENT

Lymphedema is associated with significant morbidity in terms of the functional, cosmetic, and emotional consequences of this chronic and potentially disabling condition. Treatment efforts are focused on minimizing the associated swelling, restoring cosmesis and functionality of the limb, and preventing potential complications associated with lymphedema (eg, cellulitis, lymphangitis). Treatments are time consuming, expensive, and involve a multidisciplinary approach among rehabilitative lymphedema therapy, dermatology, and occasionally surgery (Fig 5).[17]

Elevation

Although elevation is not considered a main treatment option in the management of lymphedema, it can be used as adjunctive therapy. The mechanism of action of elevation in lymphedema is not completely clear, but it is thought that elevating the extremity decreases intravascular hydrostatic pressure and thus reduces the amount of lymph load received. Thus, even though elevation is not stimulating lymph drainage, it is lowering the venous pressure, as well as filtration, so that lymph drainage flows unimpeded. It is not recommended that

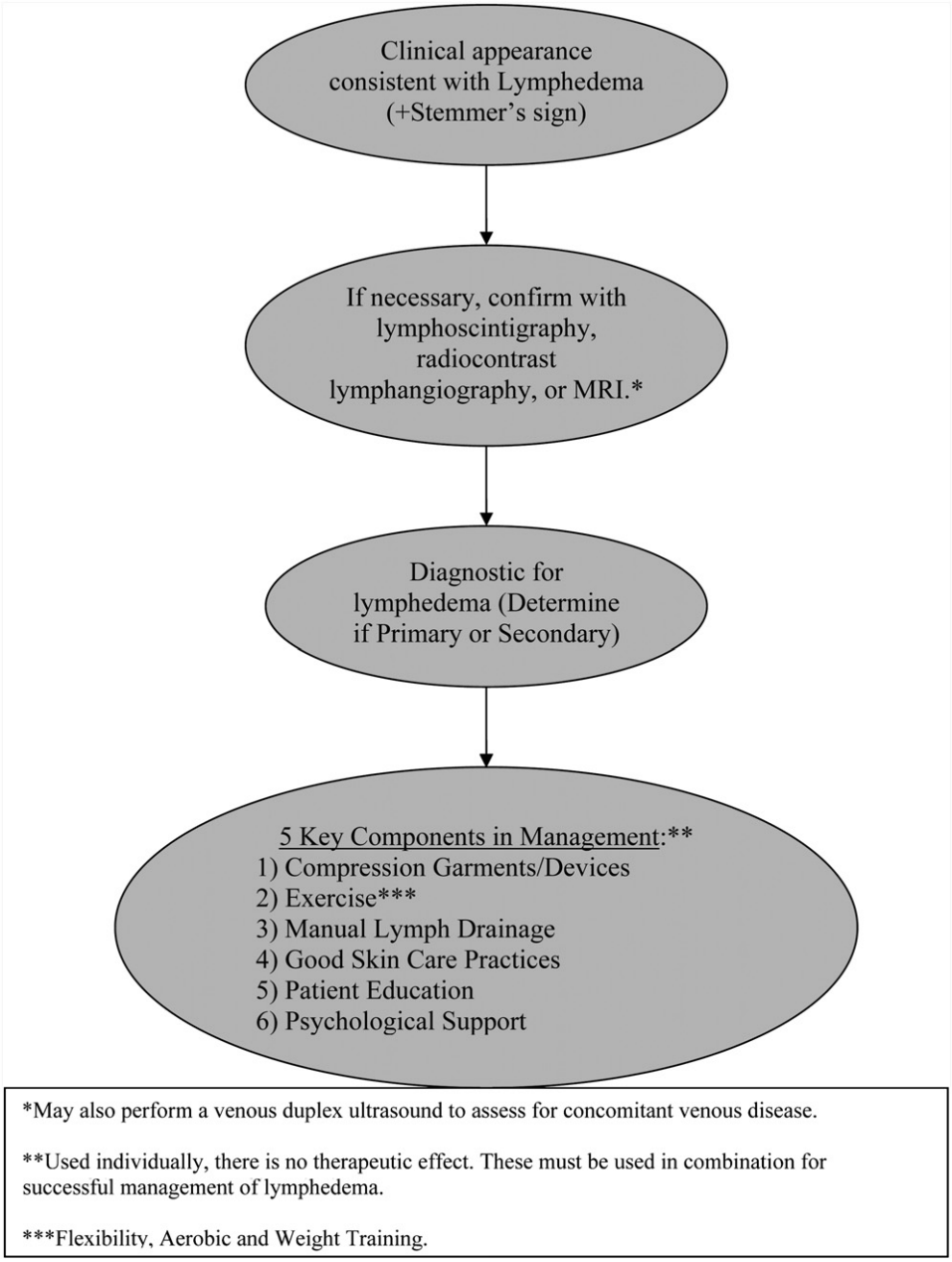

Fig 5. General diagnosis and management of lymphedema.

elevation be performed during the day, since this can not only hinder functionality, but can discourage exercise, which is ultimately more beneficial in the management of lymphedema. However, it can be attempted at night and during other times of inactivity. [8,17,18]

Exercise

Exercise is an essential element in the management of lymphedema. Studies support the notion that exercise enhances lymph flow and may even improve protein resorption. Decreasing intrathoracic pressure through the act of inspiration increases lymph flow, and it is thought that increasing pulmonary work through exercise will assist in lymph clearance. Combinations of flexibility training, aerobic training, and strengthening, during wearing of compression garments/devices, have produced considerable improvements in lymphedema. Flexibility training seems to assist in the prevention of soft tissue contractures, which can obstruct lymph flow. Having cardiac or pulmonary disease is a relative contraindication to exercise, and gradual and slow advances in exercise should be done with caution.

Weight reduction is also a key element if obesity is contributory to the lymphedema. Therapy for lymphedema without concomitant weight reduction can ultimately hamper the rehabilitation effort.[2,8,17,19-21]

Compression garments/devices

External compression is employed in lymphedema and other edematous conditions to attempt to decrease interstitial fluid production, as well as to eliminate any excess lymph fluid already accumulated in the extremity. There are multiple different methods of external compression, including multiple-layer short stretch compression bandages, elastic stockings/hosiery, adjustable, nonelastic compression leggings (eg, CircAid, CompreFit [US Patent Pending]), and pneumatic compression devices.[8]

Multiple-layer short stretch compression bandages have been found in a randomized, controlled trial to be superior as initial treatment for lymphedema patients followed by hosiery, to hosiery alone. This method achieved a greater reduction in edema volume (>20% excess limb volume) with more long-lasting results than hosiery alone (sustained over a 24-week period). On the lower limbs, a minimum of two layers of bandages were applied, the first in a spiral configuration, and the last layer in a shape of a figure eight. The bandages were left in place continuously, and replaced daily. Hosiery was started after 18 days of multilayer bandaging.[22] A typical strategy in the early, intensive phase of treatment involves the combination of multilayer bandaging, exercises, and manual lymph drainage (massage), with eventual use of compression hosiery to maintain and control reaccumulation of edema.[22,23] In our region, initial bandages cost approximately $200 per leg.

Elastic stockings/hosiery appear to be beneficial in the long-term maintenance of reduced limb circumference, particularly in secondary lymphedema, but as discussed above, compression stockings are probably not the treatment of choice as an individual therapy early in the course of the disease.[23-25] Compression hosiery opposes capillary filtration and behaves as an opposing force to the force produced by muscle contractions, which ultimately leads to decreased interstitial fluid formation, and thus decreased lymphatic load.[8] In patients who have a venous stasis component to their disease, compression hosiery also improves venous return. Elastic stockings typically provide pressures from 30 to 60 mm Hg and should be replaced every 3 to 6 months or when they begin to lose their elasticity.[16] In our area, custom hosiery costs between $500 and $600, and they are typically replaced every 4 to 6 months.

Alternatives to elastic stocking/hosiery include adjustable, nonelastic compression leggings (eg, CircAid, CompreFit [US Patent Pending]). These leggings are particularly helpful in lymphedema patients who have difficulty applying or removing the elastic stockings. They are costly, but for some patients who require continual replacement of elastic stockings due to loss of elasticity and pressure, it may be found to be more cost effective.[26]

Compliance with these compression garments is complex because they are not cosmetically appealing, are laborious to apply and remove, and can be uncomfortable. For this reason, patient education is of paramount importance. Complications associated with compression garments include skin irritation in the form of allergic or irritant contact dermatitis, as well as the induction or worsening of swelling at sites distal to the garment. An open wound or infection is not a contraindication to wearing these compression stockings, although the pain associated with the use of these garments in these conditions may preclude a patient's ability to wear the garment.[17]

Sequential intermittent pneumatic compression has been shown to be beneficial in the treatment of lymphedema; it is an excellent adjunct to our current compression therapies, and continued use in knowledgeable hands is appropriate. A study showed that when pneumatic compression is used in conjunction with established decongestive lymphatic therapies, there is an enhancement in therapeutic response.[17,27] There are not any established guidelines regarding optimal pressure ranges, inflation/deflation cycles, length or frequency of individual pumping sessions. No one pump appears to be superior to another. Recommended pressures typically range from 80 to 110 mm Hg pumping 4 to 8 hours per day, although lower pressures can be effectively used when combined with other decongestive lymphatic therapies. Pneumatic compression is relatively free of complications, but there are still concerns that these devices can worsen truncal and genital lymphedema, as well as the fear that high pressures can cause peripheral lymphatic damage. These pumps should not be used in patients with local or proximal malignancies because of concern of possible metastasis. There is also concern for worsening of congestive heart failure or induction of congestive heart failure in a patient with severe coronary artery disease.[17,28] The approximate cost of renting a compression device is $200 per month. Often, these fees include a home nurse who will periodically evaluate whether the patient is using the pump correctly and effectively, and if the patient is encountering any preventable problems.

Manual lymph drainage

Manual lymph drainage is a massage technique that causes lymph conduits to contract more often and milks or siphons lymphatic fluid away from congested regions, and subsequently toward nearby functioning lymph basins. This is used in the early, intensive phase of lymphedema therapy. This always starts with good skin care and is combined with compression bandaging immediately after manual lymph drainage, subsequently followed by a series of exercises to increase lymphatic flow through functioning collateral pathways. This combination of therapy is referred to as complete decongestive therapy or combined or complex physical therapy. The second phase of complete decongestive therapy is one of maintenance where skin care continues and elastic compression garments are worn during the day and low stretch bandages are worn overnight, combined with maintenance exercises in the morning while still wearing the bandages, before changing back into the elastic compression garment.[17,21]

Skin care

Good hygiene and prevention of infection, particularly cellulitis, lymphangitis, and erysipelas, are paramount in the management of lymphedema. The verrucous skin surface associated with lymphedema harbors microbes which produce a characteristic odor and increase the risk for infection. Infections should be treated at the first sign with antibiotics, and occasionally prophylactic antibiotics (phenoxymethyl penicillin 500 mg daily or cephalexin) are required in cases of recurrent erysipelas. Salicylic acid ointment can be used as a keratolytic and the application of eosin or antiseptic paint has been helpful in controlling skin surface microbe colonization. The control of tinea pedis, especially toe web involvement, which is a portal of entry for bacterial infections (eg, recurrent erysipelas) is also very important.[2,4]

Surgery

Surgery is held in reserve for patients who are unresponsive to traditional measures.[17] There are two categories of surgery in the management of lymphedema: reconstructive (restoring function) and debulking (reduction of fluid and tissue). Reconstructive surgeries aim to create lymph-venous shunts or perform autologous vessel transplantations. Debulking surgeries involve removing excess tissue to reduce the size and weight of the affected limb in order to improve mobility and function. Unfortunately, problems with wound healing are prevalent and create short- and long-term obstacles.[2,29,30]

Drug therapy

Drug therapy has been disappointing in the management of lymphedema. Family physicians often prescribe diuretics, but when studied, they have not been found to be helpful in lymphedema.[2,4,17] Coumarin, a benzopyrone, has been found to have a favorable effect on lymphedema. The mechanism of action is thought to be through the reduction of vascular permeability, and thus capillary filtration. Additionally, coumarin is thought to activate macrophages, which increases protein degradation, thus resulting in a reduction in fibrotic tissue. However, the trials were not considered to be of good quality, long-term data regarding treatment of lymphedema with these agents are not available, and reports of hepatotoxicity cause valid concern.[2,17,31,32]

MULTIDISCIPLINARY TREATMENT APPROACH

The diagnosis of lymphedema is one with a chronic, disabling connotation. Through the joint efforts of a multidisciplinary team of lymphedema therapists, dermatologists, nurses, and occasionally vascular surgeons, a comprehensive treatment plan can be developed (see Fig 5). A description of each type of therapy should be presented to the patient with lymphedema, and a recommendation of an overall treatment plan should be discussed in detail.

There is a lack of high-quality randomized, controlled trials to evaluate the different physical therapies (compression garments and manual lymph drainage) in lymphedema management.[25] Until then, recommendations can only be based on the data we currently know, in conjunction with clinical experience using these different modalities.

Useful, practical recommendations include elevation at night with two bed lifts placed under the foot of the bed, providing elevation of the lower extremities. Electrical medical beds can perform this function as well. Often, pneumatic compression pumps will only be covered by Medicare if all other intensive treatments (excluding surgical correction) have been tried first and have been unsuccessful.[33,34]

In our experience, one of the major obstacles to successful treatment is the lack of participation and commitment of the patient to the rehabilitation effort. Therefore social support and support groups may be helpful in improving patient engagement and motivation, analogous to support groups for obesity.

Lower extremity lymphedema, if uncontrolled, always progresses. Utilizing the approach described in this article through a multidisciplinary team, in combination with patient education and ultimately improved patient compliance, we can satisfactorily

prevent and/or control this potentially disabling disease with real functional, cosmetic, and emotional consequences.

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