# Evaluation of Edema of the Extremity

4

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**Clinical Pearls**

1. The evaluation of symmetry in patients with lower extremity edema can help guide the differential diagnosis and evaluation.
2. Lymphedema is associated with chronic skin changes and a positive Stemmer sign (inability to pinch the skin at the base of the second toe).
3. Lipedema is common in obese patients and typically spares the feet.

## Introduction

Extremity edema involves the accumulation of extravascular, interstitial fluid and is influenced by a variety of factors. These include many systemic influences such as alterations in blood volume and capillary blood pressure, changes in colloid oncotic pressure, sodium and water retention, increased capillary permeability, and increase in tissue compartment pressure. A disruption in the Starling forces in the extracellular space will lead to fluid shifts which may lead to an expansion of the extracellular water volume. These forces include increased hydrostatic pressure, decreased oncotic pressure, and increased vascular permeability. Excess interstitial water will lead to findings of pitting edema, defined as the presence of an indentation in the skin after 5 s of pressure application. In addition to these major physiologic principles, adequate lymphatic outflow is an additional contributing factor for normal fluid homeostasis in the extracellular space of bodily tissues.

Alterations in capillary blood pressure within venules can occur in situations such as a deep venous occlusion. This can decrease the degree of venular fluid reabsorption, resulting in interstitial edema. Oncotic pressures are created by the concentration of electrolytes, glucose, urea, and proteins in the extracellular fluid. Oncotic fluid shifts are primarily driven by the pressure exerted by large proteins which are impermeable to the capillary wall. In the normal state, plasma contains a much higher concentration of osmotically active proteins compared to interstitial fluid. An imbalance caused by a decrease in plasma protein concentration or an increase in the protein concentration of the interstitial fluid would impair water reabsorption in the venule. Increases in capillary permeability will also affect the passage of both fluid and protein into the interstitium, leading to edema formation.

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**Table 4.1** Subdivisions of primary lower extremity edema etiologies

| Primary etiology for edema | Unilateral | Bilateral |
|---|---|---|
| Vascular | DVT[a] ↔<br>CVI[a] ↔<br>Lymphedema[a] ↔<br>Post-revascularization<br>Popliteal aneurysm<br>Vascular compression<br>Compartment syndrome<br>Vascular anomalies:<br>• KTS, Parkes-Weber syndrome | *High-risk patients* (i.e., *cancer*) *often asymmetric when bilateral secondary causes* (i.e., *malignancy*)<br>**Vascular CVH**:<br>• **Vena cava obstruction**, vena cava anomalies<br>Capillary leak syndromes:<br>• Shock, thermal injury |
| Nonvascular | **Infectious/inflammatory**:<br>• **cellulitis**, **OM**, **abscess**<br>**Trauma**<br>**Calf muscle disuse/atrophy**<br>Popliteal cyst<br>Tumor/lymphoma<br>Neurogenic causes:<br>• CRPS, neuropathy, Charcot foot<br>Hemihypertrophy<br>Retroperitoneal fibrosis[a] ↔<br>Factitial limb swelling[a] ↔ | **CHF/RV dysfunction**<br>**Nonvascular CVH**:<br>• **OSA**, **PH**, **COPD**<br>**Pseudoedema**:<br>• **Lipedema**, **Obesity**<br>**Drug induced**<br>Pregnancy<br>CKD/nephrotic syndrome<br>Cirrhosis<br>Protein deficiency<br>Hormonal imbalances:<br>• Cushing's syndrome, exogenous steroid, hypo- and hyperthyroidism (pretibial myxedema)<br>Idiopathic (cyclic) edema |

More common etiologies are listed first in each category with the most common causes in bold
*DVT* deep vein thrombosis, *CVI* chronic venous insufficiency, *KTS* Klippel-Trenaunay syndrome, *OM* osteomyelitis, *CRPS* chronic regional pain syndrome, *CVH* central venous hypertension, *CHF* congestive heart failure, *RV* right ventricle, *OSA* obstructive sleep apnea, *PH* pulmonary hypertension, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease
[a]Indicates primarily a unilateral disorder but could present with bilateral lower extremity involvement

Causes for edema can also be simplified by grouping them into vascular and nonvascular etiologies as well as unilateral versus bilateral involvement. Within these categories, there are typical physical patterns which include not only symmetry but also appearance, skin texture, onset, progression, and other skin manifestations. The presence of wounds, pain, inflammation and responses to compression, elevation, and diuresis all provide further clues. Table 4.1 reviews the causes for edema grouped by unilateral versus bilateral involvement for both vascular and nonvascular etiologies.

## Vascular Edema

### Venous Edema

Edema of the lower extremities related to localized venous hypertension often consists of low-viscosity, protein-poor interstitial fluid. This accumulation of fluid is directly related to increased capillary filtration and/or decreased venular reabsorption. If local venous pressure increases, as with either deep venous obstruction or deep valvular incompetence, localized venous pressure in that extremity increases with downstream (retrograde) transmission of pressure. The most dependent areas of the ankles (gaiter region) are affected to the highest degree, and pathways of venous incompetence can influence the accumulation of edema and related stasis skin manifestations such as hemosiderin deposition, inflammation, and skin ulceration.

Chronic venous valvular incompetence usually develops over long periods of time such that edema and hyperpigmentation follows an indolent course. Valvular dysfunction of the lower extremity deep veins is often a consequence of prior intraluminal damage from inflammation and fibrosis, due to the incomplete resolution of a prior thrombosis (the post-thrombotic syndrome). Valvular dysfunction

of superficial lower extremity veins such as the axial saphenous systems may be related to a variety of causative factors. Whether the dysfunction is related to deep, superficial, or perforator veins in the lower extremities, edema is usually first noted in the ankles with indentations created by conventional stockings. At this stage, elevation is quite effective at controlling swelling that is directly related to the degree of dependency and inversely related to the degree of calf muscle activity. Histologic evaluation at this stage reveals dilated venules and lymphatic spaces with extracellular edema and separation of collagen bundles. In time, however, dermal and subdermal inflammation develops, which can lead to extravascular fibrin deposition and sclerosis. This can lead to the obliteration of lymphatics and microvasculature, and perivascular fibrosis can result in diminished nutrition of the epidermis. Capillaries become quite dilated with tuft formation and venules will become tortuous at this stage. In all stages there is extravasation of erythrocytes with hemosiderin uptake by macrophages, leading ultimately to the typical orange to brown or even violaceous staining of the skin.

*Lipodermatosclerosis* is the term to describe the inflammation and induration in the lower third of the leg which is often described as resembling an "inverted champagne bottle" or a "piano leg" (Fig. 4.1), with edema both above and below the sclerotic tissue. When local lymphatic outflow is adversely affected to the degree that the limb begins to develop secondary evidence for lymphatic congestion (see patterns listed in the lymphedema section), the term *phlebolymphedema* is often used to describe this pattern of edema (Fig. 4.2). With this terminology, the presumed primary cause is usually listed first (phlebo) followed by the secondary vascular insult (lymphedema). Phlebolymphedema should be regarded as an end-stage manifestation of severe chronic venous insufficiency, with the aforementioned destruction of distal lymphatic vessels and the conversion of chronic edema from a more typical foot-sparing pattern in lesser stages of venous insufficiency to the involvement of the foot and toes more typical for lymphedema as depicted in Fig. 4.2.

Obstruction of the deep veins of the lower extremities as a consequence of DVT often leads

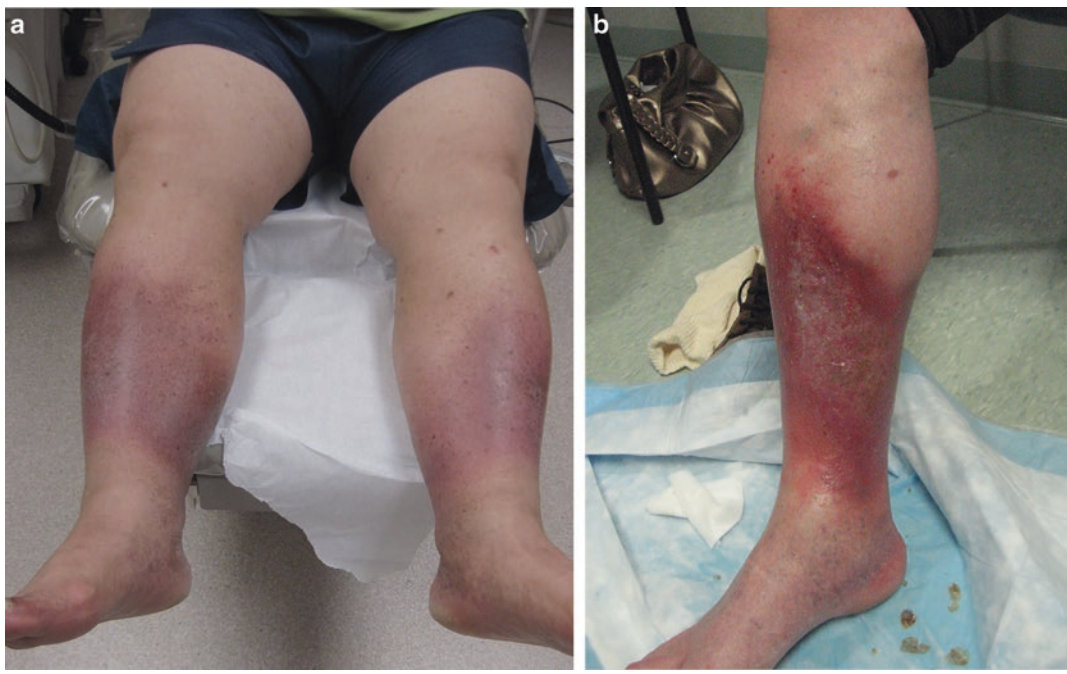


**Fig. 4.1** Lipodermatosclerosis in chronic venous insufficiency. Panel (**a**) displays typical violaceous-brown discoloration with nearly circumferential dermal thickening. In panel (**b**) there is a shiny appearance with various degrees of dermatitis at the borders. This image also displays a central papular texture with islands of atrophie blanche (class C4b)

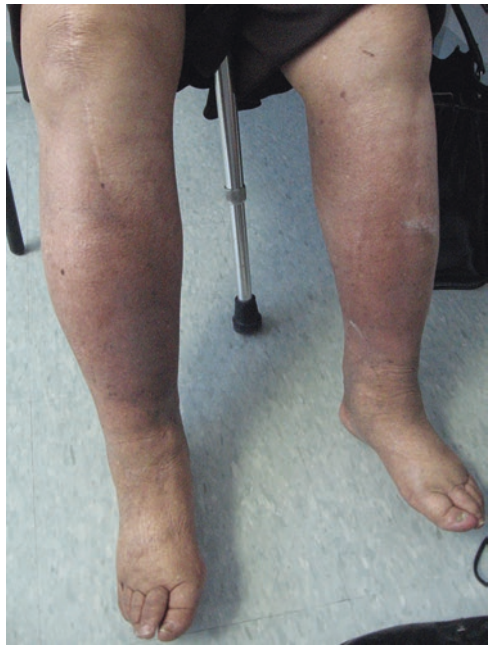

**Fig. 4.2** Phlebolymphedema. Significant stasis hyperpigmentation is present in the gaiter regions of this patient with an edema pattern on the right consistent with lymphatic congestion. Notice the involvement of the dorsum of the foot with deepening of skin fissures at the base of the toes

to painful venous congestion in the effected limb in the acute setting. In extreme cases, the edema can be tense with cyanosis of the extremity and the development of ischemia. *Phlegmasia alba dolens* reflects early diminished arterial inflow and is classically known as a "milk leg" given the white appearance and its association with the third trimester of pregnancy or postpartum DVT development. The more advanced venous congestion of *phlegmasia cerulea dolens* refers to pre-gangrenous changes often with bullae formation, intractable pain, and features which can also mimic acute limb ischemia (pulselessness, paresthesia, and paralysis) when this entity begins to develop into venous gangrene. This can be a limb-threatening condition if the severity is not recognized in a timely manner since anticoagulation and elevation alone may not suffice.

It is important to recognize that not all swelling is edema in patients with vascular anomalies. Hemihypertrophy and venous congestion of a limb due to congenital arteriovenous fistulas can be seen in Parkes-Weber syndrome. Muscular hypertrophy is also a part of the triad in Klippel-Trenaunay syndrome which also includes the presence of varicose veins and a port-wine stain. Aside from congenital malformations, spontaneous or iatrogenic arteriovenous fistulas, when large enough to increase venous pressure, can lead to chronic venous congestion and limb swelling.

Venous congestion of the upper extremities is usually associated with acute thrombosis of the deep or superficial veins but usually resolves within days to weeks after appropriate treatment with anticoagulation, elevation, and compression. One exception to this is in the case of venous thoracic outlet syndrome ("effort thrombosis"), where there is persistent extrinsic vascular compression. This will often lead to a chronically swollen limb with limited improvement with the aforementioned treatment unless the mechanical compression can be addressed through an appropriate surgical decompression based on the anatomic structures that are involved (often requiring a first rib resection).

Aside from venous obstruction and valvular dysfunction, leg muscle inactivity and weakness can be a major contributing factor of increased local venous hypertension. Such muscular inactivity of the gastrocnemius and soleal muscle groups is often referred to as "calf muscle pump dysfunction." Compared to the foot and thigh musculature, the calf muscle pump is considered the most efficient, given the ability to generate pressures that can exceed 200 mmHg during contraction [1]. Dysfunction of the calf muscle pump can be quantified with the calf ejection fraction measured with air plethysmography (APG), and it is often defined as a fraction of 40% or less of the volume of blood in the calf ejected after a standard set of repetitive plantar flexion exercises.

## Lymphedema

Lymph in the extremities consists of protein-rich interstitial fluid which is normally transported from terminal lymphatic capillaries to major collecting channels located subcutaneously and in deep limb compartments. The deep lymphatic system follows the tibial, popliteal, and femoral vessels, but the more extensive subcutaneous lymphatic system carries 80% of lymphatic fluid [2, 3]. A large percentage of subcutaneous lymphatic return in the lower extremities is along major channels adjacent to the great saphenous vein.

Like veins, unidirectional flow is partially dependent on competent bicuspid valves along major channels. However, valves are not present in the dermal capillaries. Either congenital or acquired obstruction of lymphatic flow will therefore promote the accumulation of the protein-rich fluid in the subcutaneous space, especially when local collateral lymphatic circulation is overwhelmed. Trauma, radiation, and surgery (particularly lymphadenectomy), as well as malignancy, chronic inflammation, and filariasis (the most common cause of lymphedema in non-industrialized countries), are all causes for the development of secondary lymphedema which can develop months or even years after the initial insult causing interruption of normal lymphatic flow. This latent development can also be explained by gradual lymphatic stasis from progressive dilation of lymph vessels causing valvular incompetence, increased incompetency of endothelial junctions within lymph capillaries, fibrosis of lymphatics with the loss of permeability, and the eventual exhaustion of extra lymphatic interstitial protein transport from macrophages. As a result of these processes, local immune defenses are impaired and chronic or acute bacterial or fungal infection can result in fueling the inflammatory degeneration of lymphatic structures and surrounding tissue.

Primary lymphedema can be in the form of a congenital familial disease (*Milroy Disease*), which is present at birth or becomes evident at a very early age. This disease is considered to be related to mutations in the vascular endothelial growth factor (VEGF)-3 receptor in the endothelium causing impaired lymphangiogenesis. Mutations in the FOXC2 gene have been described in the autosomal dominant form of primary lymphedema known as *Meige disease* which has a more latent presentation. Primary lymphedema can also be associated with Turner syndrome, Noonan syndrome, Down syndrome, yellow nail syndrome, and venous malformation syndromes such as Klippel-Trenaunay syndrome.

When lymphedema presents during late development around puberty into the early twenties, this form of primary, non-hereditory lymphedema is known as *lymphedema praecox*. Women are disproportionately affected with this form of lymphedema; classic series of lymphedema patients suggest a female to male ratio of 10:1 [2]. Although lymphedema in later adult life is usually secondary to an identifiable cause, primary lymphedema can still present in older individuals and is referred to as *lymphedema tarda* when diagnosed after the ages of 30–40 years old.

The clinical presentation generally begins as painless fullness in the dorsum of the foot or in the hand. At this early stage, the edema is subject to fluctuation with dependency or elevation of the limb and will often pit with a soft texture. The progression is usually from distal to proximal, although pelvic malignancies can sometimes produce a pattern of early isolated thigh edema which progresses distally. Over time, edema becomes fixed, accompanied by an array of characteristic dermal changes (see next paragraph). The forefoot will often have a dorsal "buffalo" hump with thickening of the dermis. The classic inability to pinch the skin at the base of the second toe is consistently demonstrated as a positive *Stemmer sign* in nearly all patients with lymphedema at this stage.

As the dermis thickens and becomes more fibrotic, edema becomes firmer and will no longer pit to digital compression. A velvety texture will often form on the toes, which begin to assume a squared-off appearance with deepening of the skin fissures at the base of the toes and between

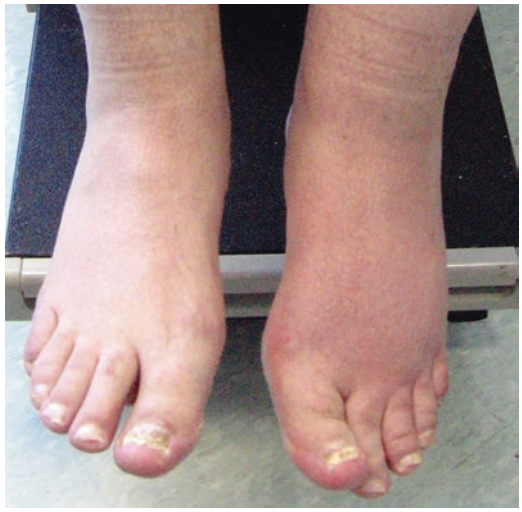

**Fig. 4.3** Early lymphedema findings. The left foot displays a "dorsal hump" with squaring of the toes and deepening of skin fissures and creases. There is a lack of such findings in the right leg of this unilateral presentation of early lymphedema tarda

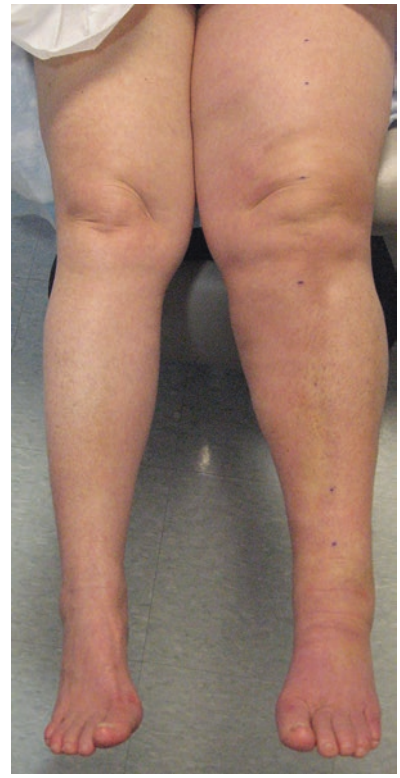

**Fig. 4.4** Stage II lymphedema. Fixed edema is present in the left lower extremity with firm, non-pitting characteristics in the ankle and foot. Notice the asymmetry which extends from the proximal thigh down to the toes in this patient

the phalanges (Fig. 4.3). Toenails will also thicken, becoming brittle and yellow in color. The velvety texture of the skin on the dorsal surface of the distal foot can progress to a cobblestone appearance with warty outgrowths with papillomas from local dermal lymphostasis. Woody fibrosis can progress proximally up into the gaiter area, and the skin may begin to resemble the peel of an orange (*peau d'orange* appearance). Hallmarks of chronic venous insufficiency such as hyperpigmentation and varices are usually absent in lymphedema unless it occurs as a secondary process of progressive degeneration of lymphatics in advanced chronic venous insufficiency. The International Society of Lymphology categorizes lymphedema into three stages based on clinical characteristics. The first stage is characterized by soft, non-fibrotic edema which can be reduced with leg elevation. The second stage is differentiated by the progression to dermal fibrotic changes which resist pitting pressure and do not reduce with elevation (Fig. 4.4). Finally, stage 3 lymphedema represents lymphostatic elephantiasis with trophic skin changes, advanced dermal fibrosis, acanthosis, and warty, nodular overgrowths (Fig. 4.5). Elephantiasis of a limb with a particularly severe nodular presentation has been termed *elephantiasis nostras verrucosa*. In some cases, limb heaviness can be reported by patients prior to the clinical development of edema, as can often occur in the upper extremities of breast cancer patients. Because of this type of subclinical presentation, some have suggested labeling this as stage 0 lymphedema. A 2013 consensus document published by the International Society of Lymphology further suggests that within each stage, functional severity can be estimated as minimal (<20% increase in limb volume), moderate (20–40% increase), or severe (>40% increase) [4].

The diagnosis of lymphedema is largely supported by the history and physical exam alone. The history should focus on the temporal development of findings and symptoms. One should

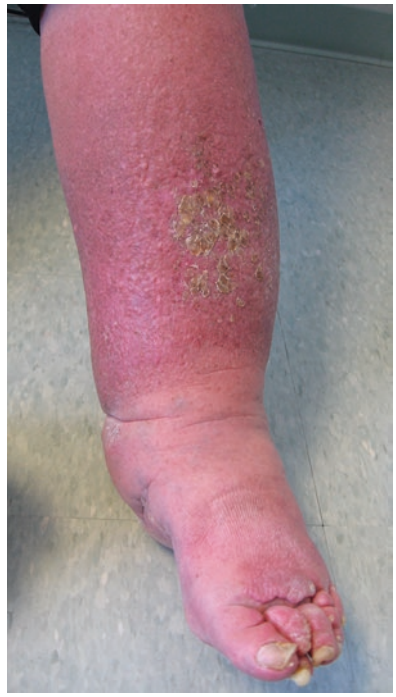

**Fig. 4.5** Stage III lymphedema. At this stage, advanced fibrotic changes are present with wart-like nodularity and hyperplastic overgrowths seen at the base of the toes

consider a potential correlation with limb injury, limb or abdominal/pelvic surgery, radiation therapy, or a history of lymph node dissection. Confounding conditions such as morbid obesity, endocrine dysfunction, and venous insufficiency may complicate the clinical picture. Obstructive causes such as a unilateral pelvic mass or visceral tumor may need to be considered. In females who have an elevated risk for pelvic malignancy, for example, a CT scan may be indicated when lymphedema develops after the age of 40. Comorbid conditions which lead to edema should also be considered, especially when the presence of such conditions (i.e., congestive heart failure) may preclude the ability to adequately elevate, compress, or manually decompress the limb. The role for imaging in lymphedema, especially as it pertains to confirming the diagnosis, determining the extent, and identifying a potential level of obstruction is discussed in the Diagnostic Workup of Edema section.

Current treatment of lymphedema is primarily focused on nonoperative therapies. Complete decongestive therapy (CDT) is supported by years of experience and is usually divided into two distinct phases. The first phase consists of intensive skin and wound care, manual lymph drainage (MLD), range of motion exercises, and multilayered bandaging. The second phase involves converting to a short-stretch bandage or graduated compression stocking, repetitive light massage, and pneumatic lymphatic pumping (usually arranged to be performed at home by the patient).

Drug therapy for lymphedema is currently limited. Diuretics should be reserved for patients with comorbid conditions that require their administration. Diuretic use solely for controlling lymphedema is discouraged because of its marginal benefit due to the concentrating effect on protein in the interstitial space which can lead to significant rebound edema. Other oral agents such as benzopyrones (including rutosides, bioflavonoids, and coumarin) have theoretical benefits by hydrolyzing tissue proteins and facilitating absorption.

Surgery is infrequently employed for very select patients who are refractory to conservative measures, especially when there are severe physical limitations because of grotesquely bulky lymphedema. Debulking, ablative, or excisional surgery can be offered to reduce the subcutaneous fat and fibrous overgrowth. Liposuction can also be employed to remove excessive adipose tissue from the epifascial compartment. Indications for surgery beyond failure to respond to standard therapy can be expanded to the development of chylous reflux or serious refractory infections which can compromise the function of the affected limb. Reconstructive surgery with microsurgical techniques such as lymphovenous anastomoses may be available in very select centers.

A particularly morbid, late complication is the rare secondary development of lymphangiosarcoma. This can present in patients with chronic lymphedema as a bruise-like lesion of the affected extremity which develops painlessly. The lesion will expand rapidly, often with central ulceration

and early metastasis. The prognosis is often poor unless early wide excision or amputation is undertaken.

## Nonvascular Edema

A variety of systemic disease states must be considered in patients with peripheral edema, especially if it presents as a bilateral manifestation. Drugs or disorders that lead to right ventricular dysfunction, cirrhosis, renal failure, or the nephrotic syndrome should be ruled out. Aside from imaging and lab testing, the history and physical exam can often be very suggestive of the cause and there are patterns of edema that may otherwise go unrecognized if the clinician is not observant. Ascites may sometimes be underappreciated in morbidly obese individuals with underlying cirrhosis causing lower extremity edema. Patients with global cardiomyopathy will often have pulmonary congestion along with peripheral edema. Right ventricular dysfunction will sometimes lead to wide or fixed splitting of the S2 heart sound or less commonly a gallop (S3 and S4 heart tones are more commonly ascribed to left ventricular etiologies). Some drugs cause edema, which will often profoundly affect the ankles and feet such as pregabalin or calcium channel blockers. Central venous pressure can also be estimated with the physical exam by knowing how to read the level of jugular venous pressure.

Unilateral causes for peripheral edema may involve compression of venous outflow such as with the May-Thurner syndrome or as a complication from a space-occupying mass such as pelvic or limb tumors, hematomas, or even a very large popliteal cyst.

Infection must be considered in the differential if there are exam findings of wounds, acute or chronic skin inflammation, or cellulitis. Even in the absence of dermal findings, a large abscess can cause vascular compression. Chronic deep tissue inflammation such as with osteomyelitis or a Charcot foot in diabetics can lead to destruction of the bony architecture of the foot, often with severe pedal edema.

Neuropathy can also lead to pedal edema likely due to secondary chronic dependency and abnormal foot and ankle mechanics which lead to inefficient priming of the venous sinusoids of the calf muscle pump. Another neuropathic cause for intermittent swelling of a limb is chronic regional pain syndrome (CRPS). The swelling associated with CRPS is episodic and exquisitely painful and tender, often with rubor and elevated skin temperature. This form of edema is often misdiagnosed as having an inflammatory cause and occurs following trauma or surgery in the effected extremity.

Bilateral edema, especially when it is symmetric in the lower extremities, often has nonvascular causation. As mentioned previously, although lower extremity lymphedema may present bilaterally, when lymphedema is symmetric, tumors, lymphoma, pelvic malignancy, or a history of pelvic irradiation should be considered as a cause.

Central venous hypertension (CVH) will often lead to bilateral symmetric edema with findings of elevated jugular pressure. Volume expansion needs to be considered in this scenario such as with biventricular failure or primary renal sodium retention. A urinalysis, blood urea nitrogen, plasma creatinine, and B-type natriuretic protein (BNP) can aide in distinguishing between underlying renal disease and heart failure. Some secondary causes for CVH are becoming more common such as right ventricular dysfunction from obesity/hypopnea syndrome or obstructive sleep apnea with the current obesity pandemic. Other less common causes for secondary pulmonary hypertension can lead to symmetric lower extremity edema such as cor pulmonale from end-stage COPD. If CVH needs to be confirmed, pressures can be estimated with echocardiography or measured with a Swan-Ganz catheter, especially if plasma volume status is in question.

Along with peripheral edema, patients with nephrotic syndrome may present with ascites or periorbital edema. Fluid retention can be ascribed to both the reduced oncotic pressure caused by hypoproteinemia and also sodium retention from often associated renal tubular disease. The

diagnosis is confirmed by documenting proteinuria which exceeds 3.5 g daily.

Patients with cirrhosis not only develop ascites but because of the dilated venous tributaries and small arteriovenous fistulae, cirrhotic patients often have an elevated total blood volume with a decreased effective blood volume. CVP is usually normal or even reduced. Low serum albumin and altered sodium and water reabsorption is often present in cirrhotic patients with peripheral edema. Hypoalbuminemia can also be caused by severe malnutrition, protein-wasting syndromes, or decreased protein synthesis leading to symmetric dependent edema.

Hormonal causes for edema are often complex and difficult to diagnose. Exogenous steroids are a more obvious cause with generalized edema that can involve all four extremities and the face. This has been attributed to the increased tubular sodium reabsorption which occurs with high concentrations of steroids with mineralocorticoid activity and is also seen in Cushing's Syndrome. Pretibial myxedema from hypothyroidism or even autoimmune hyperthyroidism (Grave's disease) causes chronic symmetric edema in the pretibial regions and dorsi of the feet which is usually non-pitting with raised, thickened dermis which may be subtly hyperpigmented. This can be attributed to the accumulation of mucopolysaccarides in the dermis. Hypothyroidism also leads to accumulation of interstitial proteins likely due to an elevation in capillary protein permeability. Excess interstitial protein and the resulting fluid in turn cannot be adequately cleared because of altered lymphatic flow in myxedema [5]. Adult-onset growth hormone deficiency (either primary or secondary to hypopituitarism) presenting with extremity edema resembles lipedema but often involves the arms as well as the legs. This is not a true edema but a condition where muscle mass is replaced with fat.

Idiopathic (cyclic) edema is a condition affecting premenopausal women which remains poorly understood. Fluid retention can occur not only in all of the limbs but also in the face and trunk. The condition is usually associated with an upright position with documented weight gain throughout the day. This weight gain will often exceed a normal 0.5–1.5 kg gain attributed to a fall in urine sodium excretion because of volume depletion from venous pooling in the legs. It should not be confused with edema associated with the menstrual cycle. Several mechanisms have been proposed such as capillary leak, secondary hypoaldosteronism, excessive secretion of antidiuretic hormone, chronic diuretic use, refeeding edema, defects in venular vasomotor tone, and others. The diagnosis is one of exclusion and therefore requires a workup to rule out renal, cardiovascular, or hepatic disorders. Therapy for this condition needs to be tailored to the individual but should include salt and free water restriction, a holiday from diuretic therapy and elevation. Many other treatments have been recommended such as treating a potential dopamine deficiency or increasing sympathetic activity [6] since the mechanisms underlying the development of edema in this cohort are likely to be heterogeneous and multiple.

Drugs which cause edema of the lower extremities may act through a variety of mechanisms. Arteriolar vasodilation is the most common mechanism leading to soft, pitting edema which resolves after the drug is withdrawn. These drugs are numerous and include hydralazine, minoxidil, dihydropyridine calcium channel blockers, and alpha blockers. Renal sodium retention can also lead to peripheral edema from a variety of medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), thiazolidinediones, insulins, estrogens, progestins, androgens, aromatase inhibitors, and tamoxifen. Some drugs are administered with either high volumes of fluids or have high sodium concentrations (carbenicillin). Increased capillary permeability may be induced through interleukin-2 therapy. Other drugs such as anticonvulsants (gabapentin and pregabalin), chemotherapy agents (cisplatin), antidepressants, and dopamine agonists (pramipexole, ropinirole) cause peripheral edema through unclear mechanisms.

Increased capillary permeability can be the result of drugs, shock, or injury to the capillary membrane. Thermal injury, with either significant heat or cold exposure, can result in damage

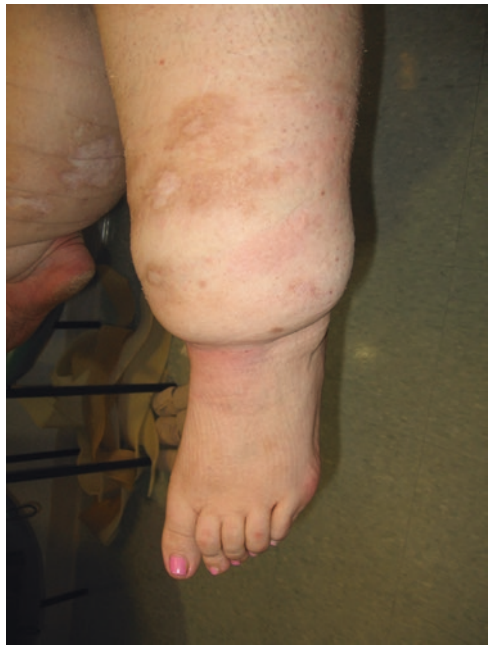

**Fig. 4.6** Lipedema. This leg displays typical features of lipedema with bilateral, symmetric globular fat distribution involving the lower legs with sparing of the feet (so called "ankle cuff sign"). Notice the scarring in the medial and posterior calf from a history of skin ulceration from friction complicated by cellulitis

to capillary membranes and produce a swollen limb from the flow of plasma proteins into the interstitial space. With severe cold exposure, edema will occur during rewarming.

Another example of a condition of an enlarged limb which is not a true edema is the underappreciated condition of lipedema. This condition is the result of a familial pattern of fat maldistribution which is amplified by obesity. Lipedema is seen predominantly in women, which has led to the proposal of a relationship with female hormones, although the nature of this relationship is not understood. Further support for this hormonal hypothesis is its development during female puberty and the fact that men with this condition often have cirrhosis or are receiving hormone therapy. The typical pattern is symmetric with involvement of the hips (sometime buttocks), thighs, and lower legs but classically spares the feet (Fig. 4.6). This was first described by Allen and Hines in 1940 but has received very little appreciation or mention in the literature over the past 75 years [7]. It occurs may be associated with heaviness of the legs and tenderness, especially if tight elastic compression is used.

Factitial limb swelling is edema caused by constrictive bands, tourniquets, or straps that are either purposely or inadvertently placed on the limb. The history may be difficult to ascertain due to a fluctuating pattern that is reported and may elude recognition for months. A major clue to factitial edema is a sharp demarcation at the edge of edema with evidence for skin marks from the device that is used as a tourniquet. Treatment for this condition will often require behavioral modification through counseling and the involvement of psychiatry.

## Diagnostic Workup of Edema

In the majority of cases, the diagnosis of edema can be made by clinical examination alone. Table 4.2 helps identify edema patterns based on history and examination. Commonly, adjunctive lab testing will be helpful to evaluate edema when a nonvascular cause is considered. Figure 4.7 outlines an algorithm to aide in the clinical workup of lower extremity edema. This often includes a metabolic profile, urinalysis, and thyroid function. System-specific testing such as looking for heart failure (BNP) or liver dysfunction (hepatic panel) may be indicated. In order to differentiate between the many etiologies of edema, however, the clinical examination is not always sufficient, and imaging can be helpful. Imaging may also be necessary to define management options in cases of venous edema and edema with mixed etiology.

Duplex ultrasound still remains the first-line test in the diagnostic workup of patients with limb edema. Duplex ultrasound identifies acute and chronic venous obstruction, the presence and extent of venous reflux, and the presence of vascular malformations. It can help to identify some abnormalities that either cause swelling (Baker cyst) or mimic edema (intramuscular hematoma). Identification of arterial disease may also be necessary in selected cases.

**Table 4.2** Typical edema patterns

| | CVI | DVT | Primary lymphedema (praecox, tarda) | Secondary lymphedema (obstruction) | Lipedema | CHF |
|---|---|---|---|---|---|---|
| Onset | Gradual | Rapid | Slow, insidious | Variable | Gradual | Variable |
| Location | Below knee or below level of obstruction | Distal to level of thrombosis | Initially foot and toes | Initially pelvis and thighs | Spares feet | Dorsal foot hump |
| Progression | Slow | Rapid without treatment | Slow; distal to proximal | Slow; proximal to distal | Associated with weight gain | Variable; distal to proximal |
| Skin findings | Hyperpigmentation, brawny, taut skin. Lipodermatosclerosis, atrophie blanche | Tense edema | Hyperkeratosis, velvety papillomatosis, warty nodules, squaring of toes, Stemmer sign | Skin distention, stemmer sign | Loose, flabby skin folds | Doughy edema |
| Pitting | Minimal | Variable | Minimal | None | None | Marked |
| Discomfort | Ache; variable | Pain; variable. Tenderness and cramping | Heaviness | Tenderness; variable | Mild sensitivity | Heaviness. Pain with skin distention |
| Response to elevation | Reduction | Marked reduction | Minimal change | Minimal change | None | Reduction |

*CVI* chronic venous insufficiency, *DVT* deep vein thrombosis, *CHF* congestive heart failure

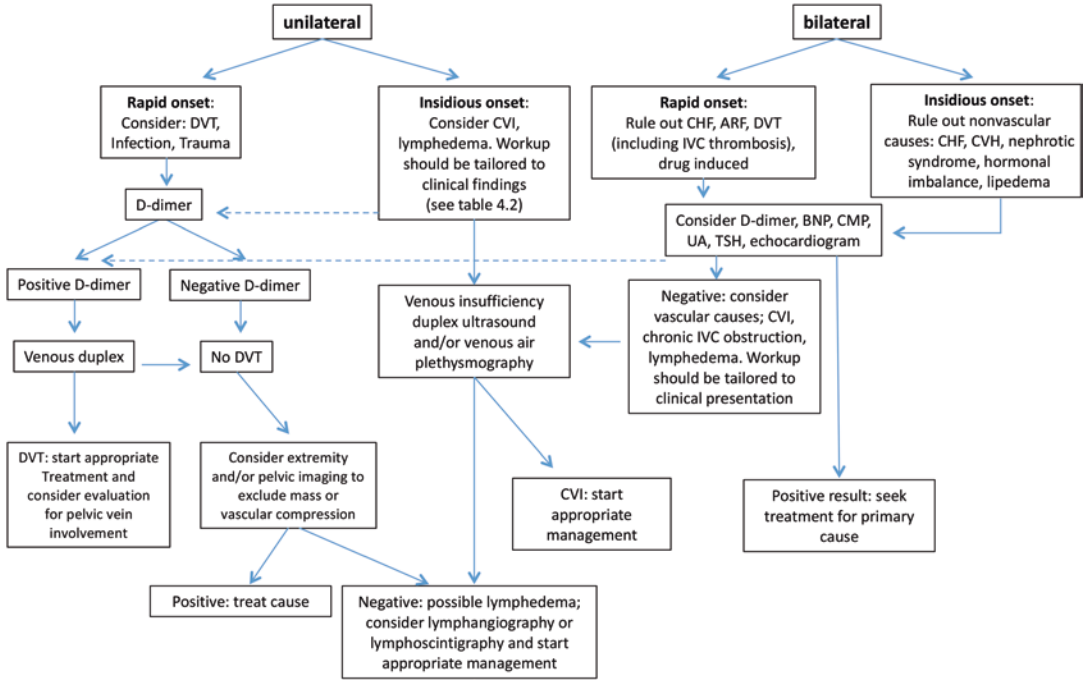


**Fig. 4.7** Basic Algorithm for the work up of lower extremity edema. *DVT* deep vein thrombosis, *CVI* chronic venous insufficiency, *CHF* congestive heart failure, *ARF* acute renal failure, *IVC* inferior vena cava, *BNP* brain natriuretic protein, *CMP* complete metabolic panel, *UA* urinalysis, *TSH* thyroid-stimulating hormone

Duplex ultrasound can be used to evaluate the severity of edema and for objective assessment of treatment success. Changes in skin thickness, subcutaneous tissue thickness, and echogenicity have been shown to be diagnostic for clinical stages of lymphedema [8]. The distribution of echo-free spaces can help to differentiate between dependent edema, early stages of lymphedema, and venous edema [9]. In the early stages of lymphedema, the echogenicity of subcutaneous tissue increases in the thigh and calf, with echo-free spaces distributed throughout the entire calf. In cases of dependent edema, the increase of echogenicity is limited to the calf, and the echo-free spaces are predominantly located in the lower lateral leg. In contrast to lymphedema, ultrasound findings in limbs affected by lipedema consist of normal skin thickness and echogenicity of subcutaneous tissues [10].

Similar to ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) provide morphological information related to skin and subcutaneous tissue. These advanced imaging modalities may provide better resolution and more quantifiable information on relative volumes of limb segments, along with the distribution of edema. They may also provide more information regarding other soft tissue structures such as lymph nodes and tumors. CT may be helpful in differentiating between lymphedema, cellulitis, and edema of other etiologies [11]. MRI is capable of visualizing lymphatic vessels, and enhancement with contrast can assess lymphatic function with accuracy similar to lymphoscintigraphy [12, 13].

Lymphoscintigraphy is performed to gain specific information on regional lymphatic function and requires radionuclide injection in the web spaces of the feet or hands. Advantages of lymphoscintigraphy are that it provides a quantitative assessment of the time of absorption and transport of the injected radiolabeled substance by the lymphatic system and a qualitative assessment of the lymphatic network pattern along with potentially identifying the level of obstruction to the lymphatic flow. Although lymphoscintigra-

phy is recommended by several guidelines as a first-line diagnostic test for lymphedema, this technique lacks strict standardization (various radiotracers, doses, injection volumes, and static versus dynamic imaging techniques) and is subject to institutional standards, complicating the relevance of the interpretation [4].

The use of fluorescence agents has opened an opportunity to visualize lymphatic vessels and assess lymphatic function in typical clinical settings. A technique using photolymphoscintigraphy with indocyanine green and near-infrared light is particularly promising. The penetration depth of up to 4 cm allows visualization and functional assessment of lymphatic vessels not only in the skin but also in subcutaneous tissue and muscle [14–16].

## Conclusion

Segregating the etiologies for vascular or non-vascular edema into bilateral versus unilateral causes aides in simplifying the workup for patients who present for consultation with peripheral edema to a vascular clinic. Many patients present, however, with multiple comorbidities with the potential for overlapping multifactorial causation for their edema. The swollen limb of a patient is not only a common problem but one which often presents a true diagnostic challenge. Diagnostic testing may be useful but is often superfluous. The clinician must therefore have proper exam and history-taking skills and an appreciation for the wide array of causes for a swollen limb. It is with this solid foundation that one can arrive at the correct diagnosis and institute appropriate, cost-effective, and timely therapy.

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