Introduction of Lower Limb Edema

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1.1 Background

Lower limb edema is the commonest peripheral edema affecting legs, ankle, and foot. The cause may be simple, sometimes like sitting for a long time on a plane or standing for too long or it may be a result of more serious underlying diseases such as systemic diseases in the form of cardiac failure, liver disease, or renal impairment. It is a manifestation leading to consultation from so many specialists like surgery, plastic surgery, orthopedics, neurology, vascular surgery, cardiology, nephrology, medicine, radiotherapy, physical medicine, and rehabilitation. Lower limb edema may be trivial, temporary, transient, or terrible sometimes not responding to treatment. Cellular fluid balance disruption and accumulation in the interstitial space with gravitational pull effect driving fluid in dependent parts is the culprit in lower limb edema. Peripheral edema is common in older adults and pregnant women, but it can occur in any age group including children. It may affect one or both legs and may be acute or chronic.

Swelling of the lower limb is a frequent finding in clinical practice and often harmless, but the cause should always be identified to avoid irreversible changes over the skin and subcutaneous tissue of lower extremity. Apart from harmless causes manifesting as edema, sometimes underlying serious systemic diseases need immediate attention. The pathophysiology of edema is mainly based on disturbances in the microcirculation. However, the differential diagnosis for lower limb

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swelling is always broader, and it may be multifactorial in etiology. In systemic disorders, medications of the underlying pathology are central in the management while localized underlying causes such as chronic venous disorder, lymphedema, deep vein thrombosis, cellulitis, and trauma may need intervention and meticulous follow-up from time to time. Patients with lower limb swelling may suffer from functional as well as cosmetic compromises requiring lifelong treatment and psychological support.

1.2 Introduction

Edema can be described as accumulation of fluid in tissues caused by an expanded interstitial fluid compartment due to vascular leakage with or without decreased lymphatic drainage [1].Water accounts for approximately 60% of the body weight in an adult out of which the intracellular fluid occupies three-fourths and the rest is extracellular fluid. Extracellular fluid is further constituted by three-fourths of the interstitial compartment while only one-fourth comprises the plasma which accounts for about 5% of the lean body weight. This microcirculatory homeostasis is meticulously maintained by the Starling forces which include capillary hydrostatic pressure, interstitial hydrostatic pressure, capillary oncotic pressure, and interstitial oncotic pressure. Any alternation or disturbance in this mechanism either due to local causes or systemic diseases can lead to edema which can cause clinical symptoms and signs. Edema can be exudative with high protein content and transudative with decreased protein content. Albumin makes up for most of the protein content in the body and any level below 2 g/dl can precipitate edema [1, 2].

1.3 Etiology and Classification

Multifactorial association in lower limb edema always needs evaluation locally as well as systemically, but as a rule unilateral edema is mostly due to underlying local causes such as chronic venous disease, deep vein thrombosis, cellulitis, lymphedema, and trauma while systemic diseases such as cardiac failure, renal failure, hepatic failure or pulmonary hypertension, anemia, and myxedema manifest as bilateral and generalized swelling of the body. Impaired activity of either cardiac muscle or calf muscle may manifest ultimately in edema. Both venous and lymphatic systems must act to prevent accumulation of fluid in extracellular space. The basic mechanism in edema is either underperformance of the venous system and lymphatic system in local pathological conditions such as chronic venous disease, lymphedema, and deep vein thrombosis or overload of the fluid not returned by the normal veno-lymphatic system in systemic diseases leading to fluid overload.

RISK FACTORS [3, 4]

1. Physiological	(i) Age	Incidence increases with increasing age due to incompetent vessels
	(ii) Pregnancy	• Increased plasma volume and retention of fluid • Pressure on the venous system causing decreased return to the heart
	(iii) Menstrual hormonal changes	• Impaired venous return and retention of fluids • Increased plasma volume leading to increased capillary hydrostatic pressure
2. Lifestyle related	(i) Immobility	• In the absence of normal muscle function, venous and lymphatic drainage is hampered • Stasis leads to edema in dependent parts owing to gravity
	(ii) Obesity	Pressure on vessels in the groin leads to decreased lymphatic and venous return
	(iii) High sodium intake	Edema due to water retention
3. Drugs	(i) Vasodilators	Increased capillary hydrostatic pressure
	(ii) Calcium channel blockers	Selective arteriolar vasodilation leading to increased capillary hydrostatic pressure
	(iii) Estrogen-based drugs	Fluid retention
	(iv) Steroids	Sodium retention
	(v) NSAIDs	PGE2 inhibition causing increased sodium reabsorption
4. Systemic diseases	(i) Congestive cardiac failure	• Increased capillary hydrostatic pressure • Decreased renal blood flow
	(ii) Cirrhosis	Decreased protein synthesis leading to decreased plasma oncotic pressure
	(iii) Renal failure	Sodium water retention
	(iv) Malnutrition	Decreased protein in the body leading to decreased plasma oncotic pressure
	(v) Chronic venous insufficiency	Regional venous hypertension causing increased capillary hydrostatic pressure
	(vi) Deep vein thrombosis	
5. Lymphatic obstruction	(i) Filariasis	
	(ii) Cancer surgeries	
	(iii) Radiotherapy	
6. Others	(i) Cellulitis	Increased capillary permeability
	(ii) Burns	
	(iii) Trauma	

CLASSIFICATION:

(I) **BASED ON SITE OF INVOLVEMENT**

1. UNILATERAL: involving only one limb
2. BILATERAL: involving both the limbs

(II) **BASED ON THE VESSEL INVOLVED**
1. VENOUS: Increased capillary filtration that cannot be drained by normal lymphatic drainage results in a low viscosity, transudative collection.
2. LYMPHATIC: Lymphatic dysfunction leads to exudative edematous fluid within the skin and subcutaneous tissue. It is of two types.
   (i) Primary—Present at birth
   (ii) Secondary—Acquired due to lymphatic system abnormality
3. LIPEDEMA: A fat-rich collection; it is sometimes considered as a form of fat maldistribution rather than a true edema.

(III) **BASED ON DURATION OF SYMPTOMS**
1. ACUTE: less than 72 h
2. CHRONIC: more than 72 h

(IV) **BASED ON ETIOLOGY**
1. LOCAL CAUSES: Trauma, infections, etc.
2. SYSTEMIC CAUSES: Heart failure, renal failure, liver failure, diabetes, etc.
3. POST-SURGERY: Cancer surgeries and lymph node dissections often lead to lymphedema.

(V) **BASED ON REACTION TO PRESSURE**
1. PITTING: Fluid drains to the surrounding areas on application of pressure, thus leaving a depression that can be visualized even after the pressure is released.
2. NON-PITTING: Fluid is pushed along the lymphatic vessels when pressure is applied and fills up rapidly as soon as the pressure is removed.

1.4 Pathophysiology

The basic physiological forces responsible for maintaining fluid balance between the capillaries and interstitium are defined by Starling. The basic mechanisms involved in the production of edema include:

1. Difference between intracapillary blood pressure and extravascular hydrostatic pressure (ΔP)
2. Differences in oncotic (colloid osmotic) pressure ($\Delta\pi$)
3. The permeability of the blood vessel wall (K_f)

According to Starling, net fluid movement (F_M) across a semipermeable membrane is $\mathbf{F_M = K_f\,(\Delta P - \Delta\pi)}$.

Hence the factors causing pedal edema are:

1. Increased intravascular/intracapillary hydrostatic pressure
2. Decreased plasma oncotic (colloid osmotic) pressure
3. Increased vascular permeability
4. Increased osmotic pressure in the interstitial space

Along with this, other factors causing pedal edema are:

- Impairment of lymphatic drainage in congenital or inflammatory diseases of lymphatics
- Local injury and infection causing damage to capillary endothelial barrier (causing increased permeability)
- Drugs leading to bilateral edema mostly

1.5 Diagnosis

Diagnosis of limb swelling includes the history, examination, and radiological imaging.

History includes the duration of the edema whether acute or chronic. Acute presentation is when the edema has appeared in less than 72 h. Deep vein thrombosis and cellulitis are strongly considered if the onset is acute [5].

However, even after 72 h, DVT cannot be ruled out merely on the basis of the history of duration of symptoms and concomitant examination and imaging must be carried out. History related to trauma and post-surgery edema is also essential for the diagnosis. Painful swelling is usually seen in deep vein thrombosis and reflex sympathetic dystrophy [6].

It may also be present in cellulitis. Pain will be low grade in chronic venous insufficiency. Lymphedema is usually painless [7].

History related to systemic diseases like heart, liver, or kidney disease, etc., and drugs like calcium channel blockers, prednisone, and anti-inflammatory should be taken as they are common causes of leg edema [8, 9].

History related to pelvic/abdominal neoplasm or radiation can also cause lower limb edema. Sleep apnea history should also be elicited as it can cause pulmonary hypertension, which is a cause of leg edema. Sleep apnea includes snoring or apnea during sleep, daytime somnolence, or a neck circumference of more than 17 inches. Obesity is also a risk factor for swelling and lipedema.

Venous edema improves overnight as compared to lymphedema due to elevation of the leg at the level of the heart [10].

The elicitation of history is very important to approach a patient with edema. The duration of edema will point out about acute (<72 h) or chronic onset. If acute onset, the most likely diagnosis is deep vein thrombosis, but it may be considered even in chronic onset edema if clinical findings are compatible. The presence of pain favors diagnosis of deep vein thrombosis and reflex sympathetic dystrophy. Low grade pain in the presence of edema points toward chronic venous insufficiency, while lymphedema is usually painless. The history of the presence of systemic diseases such as cardiac, renal, and hepatobiliary system should be ruled out by clinical examinations and investigations. Any history of radiation exposure and abdominal surgery for malignant disease again favors deep vein thrombosis. If edema of legs improves during night, it is most likely venous in origin.

In determining the cause of swelling, a thorough physical examination is just as important as a thorough clinical history. Even though the complaint may be unilateral, it is critical to evaluate both lower limbs for complete diagnosis and further management.

The other limb is frequently swollen, and this can reveal information about the reasons of swelling in the more affected limb. It is important to pay attention to how the swelling is distributed.

Despite the fact that the primary symptom is in the lower limbs, a thorough examination of the heart, lungs, and abdomen is necessary to rule out any systemic etiologies or contributing factors. Heart failure, a bloated belly with ascitic fluid, or crackles in the lungs may cause increased jugular venous distension or crackles in the lungs.

The skin of the lower extremities should be inspected extensively. Erythema and increased temperature can accompany infection and thrombophlebitis.

Varicose veins (Fig. 1.1), particularly those with a gaiter distribution of hemosiderin staining, eczematous dermatitis, or atrophy blanche, are all signs of venous insufficiency[11]. Systemic illness evaluation is required, especially in older

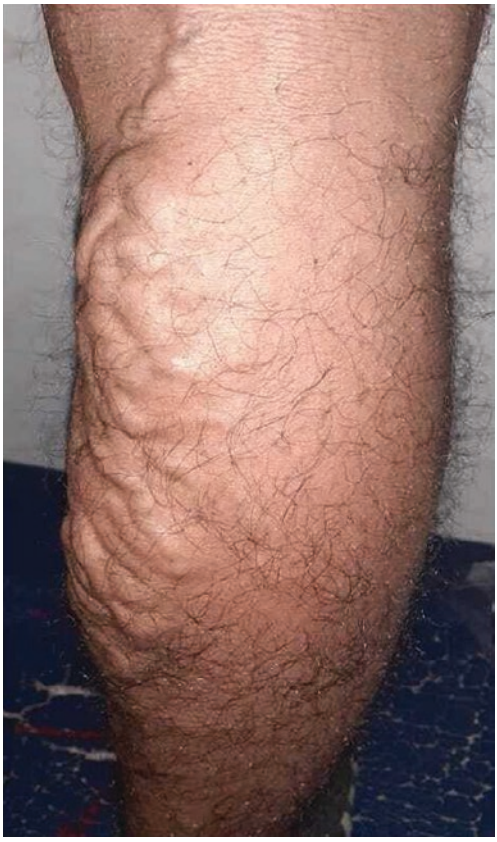

Fig. 1.1 This patient presented with swelling of the right lower limb and after evaluation was diagnosed as varicose veins

Table 1.1 Clinical findings and possible diagnosis

Clinical findings	Possible diseases
BMI > 35(obesity)	Venous insufficiency
Unilateral leg edema	Deep vein thrombosis, venous insufficiency, lymphedema
Bilateral leg edema	Systemic diseases (cardiac, renal, and hepatic) Local: Abdominal malignancy compressing both femoral veins
Generalized without involvement of the dorsum of feet	Lipedema
Predominant edema of the dorsum of feet	Lymphedema
Tender edema	Deep vein thrombosis, lipedema
Nontender edema	Lymphedema
Edema with periorbital puffiness	Renal diseases
Pitting edema	Deep vein thrombosis, venous insufficiency, early phase of lymphedema
Non-pitting edema	Myxedema, late phase of lymphedema
Varicose vein	Chronic venous insufficiency
Positive Kaposi-Stemmer sign	Lymphedema
Brownish induration of skin with papillomatosis	Chronic lymphedema
Brown hemosiderin deposits of legs and ankles	Venous insufficiency
Warm tender skin with profuse sweating initially followed by thin shiny and cool skin	Reflex sympathetic dystrophy
Dry atrophic skin with flexion contracture	Reflex sympathetic dystrophy
Raised JVP, bilateral basal crackles, significant murmur/rub over the pericardium, and tender hepatomegaly	Cardiac diseases
Clubbing, gynecomastia, spider nevi, jaundice, and ascites	Chronic liver disease

individuals with several concomitant disorders that may be contributing to their largely bilateral leg edema. An underlying cause may be the onset or aggravation of cardiac, renal, hematological, hepatic, or endocrine problems.

Malignant venous compression can be diagnosed by a history of unexplained weight loss or adenopathy.

The relevant findings of clinical examination with their interpretation are mentioned in Table 1.1.

1.6 Management and Outcome

Depending on the underlying suspected cause, a complete blood count, a metabolic panel including creatinine, urinalysis, thyroid function test, atrial natriuretic peptide, and liver function tests be done first in cases of acute edema which may detect the underlying abnormalities [11]. In some circumstances, a D-dimer level can be useful in suggesting DVT which can be confirmed with Duplex scan [12, 13].

Table 1.2 Investigations in patients with edema

First line	Second line
• CBC • Serum electrolytes, creatinine • Blood sugar • Serum total protein/ albumin • Thyroid function tests • Routine urine and microscopy	• Deep vein thrombosis: D-dimer and color Doppler study • Heart failure: ECG, 2D echocardiogram, chest X-ray, NT-proBNP • Liver failure: ALT, AST, albumin, bilirubin total and direct, PT, APTT • Renal failure: Complete urine analysis, blood urea, serum creatinine, and electrolytes, USG-KUB • Serum lipid profile: Useful in nephrotic syndrome • Malignancy: Abdominal/pelvic CT • Lymphedema: Abdominal/pelvic CT • Lymphoscintigraphy: To distinguish lymphedema from venous edema

The recommended investigations with their interpretations are mentioned in Table 1.2.

Patients should weigh themselves nude and with an empty bladder before food or fluids in the morning and at bedtime. A mean weight gain >0.7 kg is consistent with idiopathic edema. Water load test is another way to detect idiopathic patients with idiopathic edema; less than 55% of water load is excreted in the upright position and more than 65% in the recumbent position.

The most commonly advised initial imaging modality in edema of the lower extremity is Duplex scan (DUS) [11] to detect deep vein thrombosis which needs immediate attention and proper treatment to prevent progression and pulmonary thromboembolism which has a high mortality rate. With the Duplex ultrasound, the vein diameters are measured which is important for further deciding the modality of intervention, and reflux times are assessed in every case with the patient examined in reverse Trendelenburg using Valsalva maneuver. Distal compression of the vein helps in detecting the reflux. The severity of the reflux is classified as follows: 0.5 to 2 s is mild, 2 to 5 s is moderate, and >5 s or continuous flow with Valsalva is severe [14].

If additional abdominal or pelvic imaging is required after DUS, contrast-enhanced venous phase computed tomography (CT) or magnetic resonance (MR) imaging are options. It is simple to see the mass effect of a tumor or larger lymph nodes, iliocaval compression/obstruction, and overall venous architecture.

Additional benefits of MR imaging can also be utilized to assess musculoskeletal or neurologic causes where no venous, arterial, or lymphatic disorder is identified.

Investigating is not only to confirm the diagnosis but also to exclude a potentially lethal condition, such as DVT. Diagnosis of lower limb edema is a clinical diagnosis but history is most important to detect the underlying cause. Chronic venous insufficiency is the commonest cause of lower limb edema in the age group of above 50 years. In female patients, it is quite common in the age group of below 50 years age group observe premenstrual edema and pregnancy induced edema but a group of females also have idiopathic edema which is managed with conservative treatment [15].

Most individuals with primary lymphedema and lipedema have normal venous imaging. Both disorders are often diagnosed based on a patient's medical history and physical exam findings. It is crucial to note, however, that these basic signs do not appear in all cases. When the normal appearance of lymphedema is not apparent or when surgical therapy is being considered, lymphatic imaging may be useful to plan further intervention. By excluding substantial venous illness in cases with subcutaneous fluid or excessive adipose tissue accumulation, DUS can help identify patients with lymphedema and lipedema.

1.7 Deep Vein Thrombosis

Deep vein thrombosis is an acute emergency and if undiagnosed leads to pulmonary embolism, superior vena cava syndrome, and sudden death. It is a common cause of unilateral leg edema but may be bilateral. The edematous limb may be warm, erythematous, painful, and tender (Fig. 1.2). Homan's sign may be positive. The risk factors of deep vein thrombosis are congenital deficiency of protein C, S, and antithrombin III, homocystinuria, factor V laden mutation, dysfibrinogenemia, prolonged immobilization of limbs (hemiplegia or paraplegia), polycythemia, SLE, anti-phospholipid antibody syndrome, indwelling catheter in femoral vein, septicemia, paroxysmal nocturnal hemoglobinuria, nephrotic syndrome, and pelvic malignancy. Wells score is used to predict the probability of DVT.

The increased level of D-dimer indicates high probability of deep vein thrombosis but not diagnostic in patients with intermediate or high risk [16]. Patients with

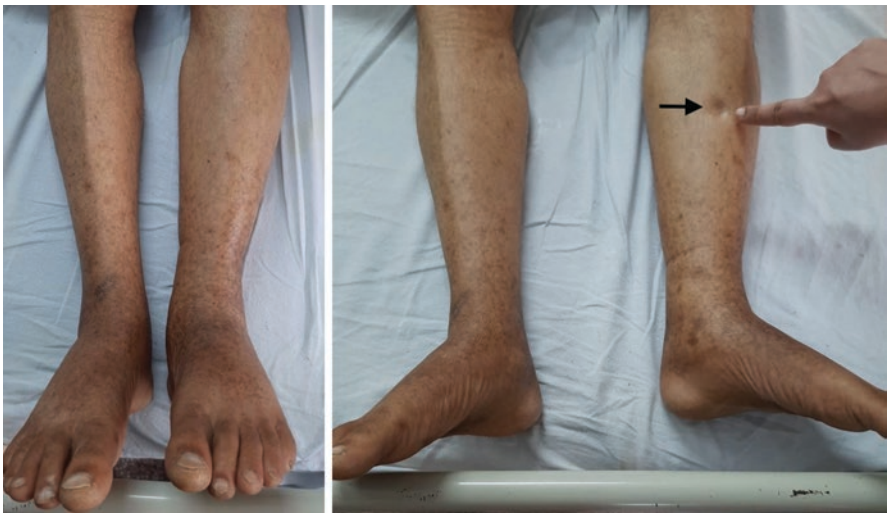

Fig. 1.2 Unilateral (left lower limb) pitting pedal oedema. A case of deep vein thrombosis of left lower limb

high probability of DVT should be immediately subjected to Doppler flow study. If the D-dimer is positive and Doppler flow study is negative, phlebography should be done in 3–7 days.

1.8 Lymphedema

The diagnosis is suggested by clinical manifestations e.g. increase in the girth of limbs, USG of affected parts, lymphangiography, computed tomography (CT), and magnetic resonance imaging (MRI) [7].

The primary objective of management is to halt the progression of disease, reduce the size of the affected extremities, alleviate the symptoms, and reduce the risk of infection. The brief outline of approach to such patients is mentioned below.

1. Conservative: skincare, lymph drainage, compressive stocks.
2. Drugs: flavonoids (effective in the venous stasis).
3. Surgery: Debulking or bypass procedures should be considered if other modalities of therapies are ineffective, effective provided the venous system is patent, continent, and the lymphatic system is functioning properly [7].

The treatment of lymphedema should be decided by a physician who is having knowledge in the field concerned. The above conservative approach may be helpful, but some form of treatment is always necessary to mobilize the excess fluid present in the tissues. The most acceptable approach to lymphedema treatment is called complex decongestive physiotherapy (CDPT), which is focused over reducing the size of the affected limb. Essential components of CDPT comprise manual lymphatic drainage with multilayer bandage to decrease the size and volume of the limb. The treatment is prolonged, time-consuming, and labor intensive but effective [17, 18].

Manual lymphatic drainage (MLD) increases the contraction of lymphatic channels. Light-touch skin stimulation in MLD opens the lymphatic capillaries. MLD should be performed by a trained lymphedema team with a trained therapist. CDPT is then followed by application of compression garments to augment the effect of MLD. Another option is an intermittent pneumatic compression device that can also be a helpful adjunct to compression garments.

1.9 Conclusion

Edema is common in all ages and presents several different pathologies.

Bilateral leg swelling is often related to systemic diseases (heart, liver, and/or renal), but venous insufficiency in the elderly or idiopathic edema in young women should be ruled out.

In case of rapid onset edema, either unilateral or bilateral, and if soft tissue infections have been ruled out, deep vein thrombosis should be considered.

USG with Doppler flow study (Duplex Ultrasongram) is useful in localized edema as well as in detecting DVT and inferior vena cava obstruction.

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