Review Article

A review on lymphoedema – causes, confusions and complications

Prasad PVS¹, P K Kaviarasan¹*, Kannambal K¹

¹Dept. of DVL, Rajah Muthiah Medical College Annamalai University, Chidambaram, Tamil Nadu, India

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A B S T R A C T

Introduction: Lymphoedema is a chronic, progressive debilitating disorder of lymphoreticular system, characterized by abnormal collection of excessive proteins, oedema, chronic inflammation and fibrosis.

Classification: Primary lymphoedema, associated with underlying, but inherent malfunction of lymphatic channels, unilateral or bilateral. It can be further subdivided into congenital lymphoedema, lymphoedema praecox and lymphoedema tarda. Depends on the age of onset or manifestation. Another genetic disorder of lymphatic dysfunction is Milroy disease. It is an autosomal dominant condition due to VEGFR3 mutation characterised by lymphatic hypoplasia. Secondary lymphoedemas are more frequent than primary to dysfunction of lymphatics. Mostly localised, following recurrent infections, trauma, surgery, obesity and malignancy.

Pathophysiology: Inadequate drainage of lymphatics, leads to accumulation of lymph, interstitial fluid and proteins in skin and subcutaneous tissue. Elastic tissue disruption, fibroblast stimulation occurs and the resulting hypoxia causes chronic inflammation and fibrosis. Later adipocyte remodelling occurs and proinflammatory cytokines secreted.

Clinical Features: Starts as pitting non tender pedal oedema, later skin thickening and fibrosis which results in non-pitting oedema. Squared off appearance and Kaposi Stemmer sign are characteristic features. May develop lymphorrhoea and secondary infections may supervene. Confusions: Chronic venous insufficiency, lipoedema, myxedema.

Complications: Vicious cycle of infections and lymphedema.

Diagnosis: Lymphoscintigraphy, lymphofoouroscopy- gold standard.

Treatment: Depends on severity. Pneumatic compression garments, Low level light therapy (LLLT), Extracorporeal shock wave therapy (ESWT). Advanced stages may require surgical debulking, lymphatic reconstruction. But the results are mostly unsatisfactory, recurrences are inevitable. Combined multidisciplinary approaches will be helpful and that should be continued throughout their life.

1. Introduction

Lymphoedema is a chronic debilitating progressive disorder of lymphoreticular system characterized by peripheral edema, persistent swelling secondary to impairment of regional lymphatic drainage. International Society of Lymphology (2020) lymphoedema is “an abnormal collection of excessive proteins, oedema, chronic inflammation and fibrosis”¹. The term edema is defined as an increase in interstitial fluid volume that is enough to produce clinically palpable swelling.²

World Health Organization’s weekly epidemiological report (2019), 538.1 million people were treated for lymphatic filariasis (LF) in 38 countries the implementation of mass drug administration (MDA) campaigns for populations at risk of the disease. The Global Programme to Eliminate Lymphatic Filariasis (GPELF) has delivered over 8.2 billion cumulative treatments to more than 923 million people since 2000. India accounts for more than 40% of the global filariasis burden. WHO in 2017 introduced new
lactescent to eliminate filariasis through a combined regimen of ivermectin, diethylcarbamazine citrate and albendazole (IDA) on transmission of the parasites. In spite of all extensive coverage with IDA all around the world, the prevalence of filarial lymphoedema is still high. Filariasis is another disorder become very difficult to treat and consumes several million dolors which is a neglected tropical diseases undergone several decades of medical treatment.

Inherent malfunction of lymph carrying channels seen in primary lymphoedema. Whereas, secondary lymphoedema follows post traumatic dysfunction of lymphatic network following the sequelae secondary to post palliative surgery and radio therapy of malignancies of skin, breast, endometrium, and internal organs. Recurrent infections, injuries, drugs, metastatic and recurrences of malignancies also cause secondary lymphoedema. The definition can be further refined as “a localized form of tissue swelling caused by excessive retention of lymphatic fluid in the interstitial compartment.

1.1. Pathophysiology

Skin plays an important role in lymphoedema. Skin has an extensive presence of lymphatic capillaries. Circulating lymph transports various antigens and activated antigen presenting cells to the lymph nodes to initiate the immune response. Interstitial fluid represents fluid that leaks from capillaries into the tissue spaces. More than 90% of this fluid gets reabsorbed via venous micro circulation which finally enters the blood stream. The remaining 10% interstitial fluid has a high concentration of proteins gradually of drained by blind- ended lymphatic capillaries. This protein rich fluid is known as ‘lymph’. The lymphatic system has three main functions. Which include:

1. Drainage of excessive interstitial fluid
2. Fat absorption
3. Immune surveillance throughout the body

Lymph is actively getting transported via collecting lymphatic vessels, filtered at lymph nodes and reenters the circulatory system near the point where the peripheral venous blood enters the right heart. Unlike the lymphatic capillaries, the collecting lymphatic vessels have smooth muscle walls which contract and propel the lymphatic fluid forward.

Accumulation of lymph in primary lymphoedema can be both unilateral and bilateral. Whereas secondary lymphoedema mostly localized restricted to the affected limb. Inadequate drainage of lymph or retention of fluid, transient edema of limbs follows the direct causes include lymphatic aplasia, hypoplasia, valvular insufficiency, obliteration / disruption of lymphatic vessels. Primary impairment of contractility of lymphatics also a primary cause of this condition. Gradual retention of lymph further leads to lymphatic hypertension and reduced contractility. Accumulation of lymph, interstitial fluid, proteins, glycosaminoglycans take place within skin and subcutaneous tissue. Which in turn stimulates collagen production by fibroblasts. Reduced oxygen tension also can leads to chronic inflammation and reactive tissue fibrosis.

In addition, elastic fibers are disrupted, activation of keratinocytes, adipocytes, fibroblasts cause thickening and fibrosis of skin and its appendages. Lymph retention and deposition of cellular metabolites rise colloid tissue osmotic pressure. Which enhance accumulation of water further increase interstitial hydrostatic pressure further damages the lymphatic vessels. Patients with lymphoedema are more prone to skin infections and chronic lymphoedema may change into malignancies.

Azhar et al in a review stated and proposed a new hypothesis that impaired drainage of lymph, protein, and lipids accumulate in the interstitial space cause extensive architectural changes and deposition of adipose tissue and fibrosis. Adipose tissue remodeling cause dysregulation of adipokine production, metabolic stress, low grade inflammation, secretion of pro inflammatory cytokines like TNF Alpha, IL-6, MCP-1, IL-8 pro-inflammatory cytokines causes adipose tissue hyper trophy. Leptin and adiponectin level are elevated in patients with lymphoedema. Which further damage the lymphatics.

1.2. Diagnosis

Clinical presentation of lymphoedema can be classified as primary (hereditary) and secondary forms (acquired). Primary lymphoedema occurs to as a result of genetic mutations which leads to underdevelopment of lymphatic vessels and malfunction of lymphatic drainage capacity. Primary lymphoedema is further classified into lymphoedema of congenital origin (clinically apparent by 2 years), lymphoedema praecox (at manifests puberty but mostly before 35 years of age) and lymphoedema tarda (above 35 years of age). It affects the lower extremities and is common in women.

Milroy’s disease is a primary familial autosomal dominant skin condition which occurs due to mutations in the VEGFR3 gene leading to lymphatic hypoplasia. It primarily involves legs and feet. In rare cases Milroy’s disease can present with congenital chylous ascites. Recurrent scrotal swelling, protein losing enteropathy, bilateral pleural effusion along with non-pitting edema, fibrosis of affected skin and impaired wound healing after trauma. Though the malignant transformation of such congenital lymphoedema can a rare event, they may progress to lymphangiosarcomas and squamous epidermoid carcinomas. Fifty percent of patients with Milroy’s may die within 24 months of diagnosis.

Secondary lymphoedema is more frequent than primary lymphoedema. It occurs due to damage or obstruction
of previously normal lymphatics by disease processes. Recurrent infections, trauma, surgery, obesity (>50 kg/m²), or as consequence of therapeutic interventions like radical extensive surgeries, excision of regional lymph nodes, radiotherapy. Other rare causes of lymphoedema include rosacea and herpes virus infections. Phlebo-
lymphoedema refers to lymphoedema caused by chronic venous disease.6–10

1.3. Infections and infestations

Recurrent streptococcal infections like erysipelas and cellulitis can damage the cutaneous lymphatics and cause unilateral lymphoedema whereas filarial lymphoedema starts in one limb and progressively involves both limbs in advanced state but asymmetrical.11 (Figure 1) Genital lymphoedema occurs following recurrent urinary tract infections, sexually transmitted infections, carcinoma cervix, endometrial carcinoma and ovarian carcinoma.

Intertrigo secondary to candidiasis is also more frequent as the fibrotic thick skin of swollen toes will be difficult, to separate. Macerated intertriginous skin, enhances the penetration of pathogenic microorganisms cause ascending cellulitis and recurrent lymphadenitis which further worsen the lymphoedema.12 These can be prevented by frequent drying of web spaces to sunlight, moisturizer usage, early institution of antifungal and antibiotic preparations. Among the sexually transmitted infections lymphogranuloma venereum (LGV) caused by Chlamydia trachomatis can cause lymphoedema of the external genitalia Other causes of infections being herpetic whitlow and scrofula of the neck.13

Lymphatic filariasis (also known as elephantiasis) is the most common infestation causing secondary lymphoedema worldwide. It is acquired infestation caused by mosquito borne nematode round worm or Wuchereria bancrofti. According to WHO statistics March 2017, more than 120 million were affected filariasis with lymphoedema associated disfigurement in 40 million individuals. Wuchereria bancrofti, is responsible for 90% of the cases.Brugia malayi, which causes most of the remainder of the cases.2

Podoconiosis is condition caused by chronic exposure to irritant clay soil containing silica micro particles through bare feet walking. It is the second most common cause of chronic lymphoedema worldwide. It is endemic in Africa and India.14

Morbid obesity is also an high risk comorbid condition in developing lymphoedema. A body mass index of more than 50 (average 70) kg/m² has been linked to impaired lymphatic flow and presents with lymphoedema than those with less than 42 kg/m². In addition, increased amount of adipose tissue causes obstruction to lymphatic vessels. Sedentary life style, along with lack of physical activity results in failure of the calf muscles (peripheral heart) pumping out the fluid in the leg cause lymphoedema.15 Obesity is a major contributor of the development of secondary lymphoedema. Multiple comorbidities like obesity, vasculitis are also responsible for lymphoedema.(Figure 2)

1.4. Dermatological manifestations of lymphoedema16,17

Transient non tender pitting oedema occurs initially. There will be sense of heaviness or discomfort at the end of the day. Over the time skin develops pitted and peau d’ orange appearance. Skin becomes indurated and leathery due to thickening, fibrosis and scaring (Figure 3). Nonpitting stage indicates irreversible stage of lymphoedema. Lower limb lymphoedema manifests as swelling in the dorsal surface of the foot with a characteristic blunt “squared –off” appearance of the digits. Inability to pinch the fold of skin at the base of second toe is called as “Kaposi- Stemmer” sign and is characteristic of lymphoedema.

Lymphoedema progresses proximally. Chronic lymphoedema associated with papillomatous verrucous lesions labelled as elephantiasis nostras verrucosa, very poor response to treatment. They are prone to shows a fissures which change into ulcers. Oozing of yellow fluid (lymphorrhea) occurs in severe cases at an early stage of disease. Chronic long-standing cases lymphangiectasia like transient vesicles can occur. Secondary bacterial infection like impetigo and fungal infections like dermatophyte infection and candidiasis may occur.18

Rarely malignancies like cutaneous angiosarcoma may develop on chronic lymphoedema. Similarly, several infections and vasculitic disorders also mimics lymphoedema such as facial swelling angioedema, orbital cellulitis (Figure 4), cushingoid syndrome, renal failure. Neutrophilic dermatoses may present with purpuric lesions. Pyoderma gangrenosum is a vasculitis affecting lower extremities, and may present with non-healing ulcers. Morbid obesity with metabolic syndrome in association with vasculitic ulcers with lower limb edema cases should be worked up extensively. (Figure 5)

1.5. Confusions

Chronic venous insufficiency and lipomatosis of the legs are always confused with lymphoedema. Pitting nature of oedema can occur in both in the early stages, though filarial lymphoedema manifests as non-pitting oedema later. In chronic venous insufficiency, oedema is caused by increased capillary hydrostatic pressure, and also extravasation RBCs, pigmented purpuric dermatoses. Whereas in filarial lymphoedema, hydrostatic pressure is normal. The swelling of limb reduces with overnight foot elevation whereas filarial lymphoedema does not reduce.19,20
**Fig. 1:** A case of Unilateral filarial lymphoedema, (entire lower limb, grade 2 b ), diffuse edema.

**Fig. 2:** Morbid obesity associated with bilateral lymphoedema secondary to vasculitis.

**Fig. 3:** Atrophic Scarring complicating filarial lymphoedema

**Fig. 4:** Diffuse edema of the face complicated by orbital cellulitis in type 2 diabetes mimicking idiopathic angio edema, secondary lymphoedema following lymphadenectomy, anthrax and rhinoentomophthoromycosis

**Fig. 5:** Asymmetrical secondary lymphoedema complicated by pyoderma gangrenosum and non healing ulcer foot in an obese patient.
Lipoedema is a distinct entity, occurs secondary to abnormal deposition of subcutaneous fat associated with edema. It should be categorized under lipodystrophy. Commonly seen in females. Both legs are affected and known as lipomatosis of the leg. It is rather a chronic progressive disorder of the adipose tissue which mimics like lymphoedema. It also have swelling, pain, tenderness on prolonged standing. Swelling stops at the level of malleoli. Lipoedema can cause lymphatic obstruction at later stages. Various studies proved that there is direct correlation between lipoedema and primary abnormality of venous or lymphatic channels.19

Other conditions causing lymphoedema cause fluid retention due to sodium overload, renal dysfunction, and vascular hyper permeability. Calcium channel blockers can interfere with collecting channels of pumping lymphatic vessels.21 Hypoalbuminemia produces bilateral lymphoedema. Myxedema causes obstruction of peripheral lymphatics due to mucin deposition in the dermis.22

1.6. Complications
Lymphedematous skin is more prone to develop recurrent streptococcal skin infections like erysipelas and cellulitis. Each infectious episodes worsen lymphoedema. Interdigital infections are common due to maceration of skin as the patient is not able to separate the toes it is difficult to apply the topical medications. There is 10% risk of developing angiosarcoma in patients with chronic lymphoedema lasting >10 years. Angiosarcoma is a highly aggressive tumor with poor prognosis. Other malignancies like Kaposi sarcoma, melanoma, lymphoma, Basal cell Carcinoma (BCC) or squamous cell carcinoma can occur because of impairment of local immune surveillance due to poor immunity.

Apart from all these complications lymphoedema is associated with lot of social stigma, poor quality of life as they have to depend on others for their normal routine work and finally may result in deformities.

1.7. Management
Diagnostic work up helps the treating physician to understand the depth and extent of the lymphoedema. The affected soft tissue swellings should be confirmed with Magnetic Resonance Imaging (MRI), Computed Tomography (CT), Low flow color doppler Ultrasound. Lympho-scintigraphy is 92% sensitivity and 100% specific. It is carried out by injecting colloid labelled radioisotope between first and second toe and tracing by gamma camera as it travels from the periphery towards regional and central lymphatic collections. Additionally, lympho-fluoroscopy, near infra-red imaging are helpful in visualizing the lymph vessels used to anastomose with regional veins.23

Management depends on the severity grade of lymphoedema. Very mild form of lymphoedema (Grade 0) presents as transient edema mostly sub that can resolve resolve spontaneously with or without limb elevation. Lymphatic injury is mild. Grade 1 lymphoedema resolve spontaneously with limb elevation, clinically presenting as pitting pedal edema. Grade 2 is moderately severe, non spontaneous lymphatic drainage, needs assisted compression garments. Fibrosis occurs in grade 2 b, and it is non pitting edema. Grade 3 is labelled as lymphostatic elephantiasis- (Progressive fibrosis), acanthosis, hyper keratosis, papillomatosis. Swelling not improved by elevation. Skin become hardened, non pitting, indurated, non pinchable. The verrucous papillomatous growth will be called as elephantiasis nostras verrucosa. In grade 2 b and 3 skin is more prone to develop secondary infection and lymhangitis. Tender inguinal lymphadenopathy is more common. (Table 2)

Current gold standard therapy for the management of head and neck lymphoedema is complete decongestive therapy (CDT). Intensive and long-term phases. Multilayer bandaging is the cornerstone of the CDT and kept in place for 24 hours reapplied daily. Well trained physiatrist and physio therapists should train the patients and also motivate themselves to do. It is aimed to reduce the swelling and normalize the tissue pressure. Educate the patient to care the skin of affected limb is the first line of therapy. Adequate usage of moisturizer, avoidance from trauma, and bare foot walking reduces the incidence of trauma and secondary infection.

Educate the patients to cover the limbs while gardening, watch out for mosquito bites. Repeated venesection and heat therapy can become the source of infection. Manual lymphatic drainage stimulates both lympho-kinetic activity and also functional units of the lymph vessels. At an average of 30 to 45 minutes of manual drainage of central lymph nodes beginning from neck, axilla, groin, and areas of anastomosis rich in thorax, back, lateral trunk.

Pneumatic intermittent compression pumps, negative pressure suction apparatus will be helpful for the faster drainage of lymph. Low level light therapy (LLLT), Far Infra-Red Radiation (FIR) and extracorporeal shock wave therapy (ESWT) are the non-invasive measures offering encouraging results. They promote; ymphangiogenesis stimulates lymphatic motility also improves the lymphatic out flow, reduce interstitial fibrosis.7

Massive lymphoedema cases at an advanced stage will be difficult to manage. In such cases wide excision, surgical debulking, lymphatic reconstruction or tissue transfer techniques can be tried. Procedures like debulking, liposuction and amputation are the other options requiring multi-disciplinary approach involving radiology, plastic reconstructive surgery, vascular surgery, surgical oncology, radiotherapist and of course a more experienced paramedical staff and intensive surgical care unit maintaining strict asepsis.23,24
Table 1: Differential diagnosis of Lymphoedema: 17

| Features | Lymphoedema | Lipedema | Venous Insufficiency |
|----------|-------------|----------|----------------------|
| Location | Lower extremity | Lower extremity, spares feet | Lower extremity, spares feet |
| Kaposi- Stemmer sign | Positive | Negative | Negative |
| Pain | Discomfort | Tender | Occasional aching |
| Effect on leg elevation | No change | No change | Improves with elevation |
| Skin | Nonpitting, Peau d’ orange, verrucous changes | Pitting oedema, hyperpigmentation from hemosiderin deposition, visible varicosities |

Table 2: Clinical staging (International Society of Lymphology): 24

| Lymphoedema staging | Stage | Features |
|---------------------|-------|----------|
| Stage 0 (Sub clinical lymphoedema - with impaired function of lymphatics) | Heaviness and discomfort only | No swelling |
| Stage 1 (Reversible pitting edema /no palpable fibrosis) | Swelling relived by limb elevation, induces pitting oedema |
| Stage 2a Pitting edema not reduced by elevation | Swelling not improved by limb elevation, pitting oedema may or may not be present |
| Stage 2b non pitting oedema secondary to profound fibrosis | Non pitting, fibrosed, non-pinchable |
| Stage 3 (Lymphostatic elephantiasis- Progressive fibrosis), acanthosis, hyper keratosis, papillomatosis | Swelling not improved by elevation, Skin hardening, Non pitting oedema, Verrucous changes, Recurrent soft tissue infections |

2. Conclusion

Lymphoedema is a chronic, recurrent and recalcitrant to treat. Early suspicion, diagnosis and aggressive condition involving skin and the entire lymph reticular system management can minimize the swelling as the lymphoedema is transient, pitting reversible in early stages. Irregular therapy, repeated infections, infestations like filariasis jeopardize the normal functioning of lymphatic channels often promoting malignant transformation like lymphangiosarcoma and squamous cell carcinoma. 25 Additional radiological diagnostics along with to physiotherapist intervention using compression bandages, low level laser therapy can promote lymphangiogenesis helps the patient to come out of stigma associated with neglected tropical diseases like filariasis and leprosy. Malignancies of skin and internal organs require meticulous planning and multi-specialty joint approach for radical surgeries, lymphadenectomies, chemotherapy or radiotherapy are essential to obesity management.

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4. Conflict of Interest

The authors declare they have no conflict of interest.

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Author biography

Prasad PVS, Former professor

P K Kaviarasan, Professor and HOD

Kannambal K, Associate Professor

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