

Lymphatic system

Anatomy and physiology of the lymphatic system

Functions

1. Removes water, electrolytes, low-molecular-weight moieties (polypeptides, cytokines, and growth factors) and macromolecules (fibrinogen, albumen, globulins, coagulation and fibrinolytic factors) from the interstitial space and returns them to the circulation.
2. Permits the circulation of lymphocytes and other immune cells,
3. Intestinal lymph (chyle) transports cholesterol, long-chain fatty acids, triglycerides and the fat-soluble vitamins (A, D, E and K) directly to the circulation, bypassing the liver.

Development and macroanatomy

Lymph from the lower limbs and abdomen drain via the cisterna chyli, lying between the aorta and azygos vein, into the thoracic duct. This duct is a major lymph channel which passes cephalad on the left of the bodies of the thoracic vertebrae to enter the left side of the neck, where it drains into the left internal jugular vein at its confluence with the left subclavian vein. Lymph from the head and right arm drains via a separate lymphatic trunk, the right lymphatic duct, into the right internal jugular vein. Lymph nodes develop as condensations along the course of these lymphatic highways.

Lymphatics accompany veins everywhere in the body except in the cortical bony skeleton and central nervous system, although the brain and retina possess analogous systems (cerebrospinal fluid and aqueous humour, respectively). The lymphatic system comprises lymphatic channels, lymphoid organs (lymph nodes, spleen, Peyer's patches, thymus, tonsils) and circulating elements (lymphocytes and other mononuclear immune cells).

Microanatomy and physiology

Lymphatic capillaries

Lymphatics originate within the interstitial space either from specialised endothelialised capillaries (initial lymphatics) or from nonendothelialised precapillaries. In the resting state initial lymphatic capillaries are collapsed. When interstitial fluid volume and pressure increase, the space expands and the lymphatic capillaries and their pores are held open to facilitate increased lymphatic drainage.

Terminal lymphatics

Lymphatic capillaries drain into terminal (collecting) lymphatics which possess bicuspid valves and endothelial cells rich in the contractile protein actin. Larger collecting lymphatics are innervated and surrounded by smooth muscle. Valves partition the lymphatic into segments termed lymphangions which are believed to contract sequentially in order to propel lymph into the lymph trunks.

Lymph trunks

Terminal lymphatics lead to lymph trunks which have a structure that is similar to veins: a single layer of endothelial cells, lying on a basement membrane overlying a media comprised of smooth muscle cells that are innervated with sympathetic, parasympathetic and sensory nerve endings. The distribution of fluid and protein between the vascular and interstitial spaces depends on the balance of hydrostatic and oncotic pressures between the two compartments (Starling's forces), together with the relative impermeability of the blood capillary membrane. In health there is net capillary filtration into the interstitial space of 2—4 litres per 24 hours which is removed by the lymphatic system. Disease processes which disturb Starling's forces lead primarily to oedema that is low in protein, whereas diseases which primarily impair lymphatic drainage lead to high-protein oedema (lymphoedema).

In the normal limb, lymph flow is largely due to intrinsic lymphatic contractility, although exercise, limb movement and external compression do increase lymphatic return. However, in lymphoedema, where the lymphatics are constantly distended with lymph, these forces assume a much more important functional role and this explains the success of physical therapy.

Acute inflammation of the lymphatics

Acute lymphangitis occurs when a deep or superficial infection, often due to *Streptococcus pyogenes* or *Staphylococcus aureus*, spreads to the draining lymphatics and lymph nodes (lymphadenitis) where an abscess may form. Eventually this may progress to bacteraemia or septicaemia. The normal signs of infection are present and a red streak is seen in the skin along the line of the inflamed lymphatic.

Treatment

The part should be rested, elevated to reduce swelling and the patient treated with intravenous antibiotics based upon actual or suspected sensitivities. Failure to improve within 48 hours suggests inappropriate antibiotic therapy, the presence of undrained pus either in the lymph nodes or at the site of primary infection. The lymphatic damage caused by acute lymphangitis may lead to recurrent attacks of infection and lymphoedema.

Lymphoedema**Defination**

Oedema is due primarily to defective lymphatic drainage in the presence of (near) normal net capillary filtration.

Pathophysiology

Lymphoedema is the end result of insufficient lymphatic outflow due to aplasia, hypoplasia, primary decreased lymphatic contractility or inflammatory obliteration. Lymphatic hypertension occurs and leads to distension with secondary impairment of contractility and valvular competence. Lymphostasis leads to the accumulation of fluid, proteins, growth factors and other active peptide moieties, glycosaminoglycans and particulate matter, including bacteria. As a consequence, there is increased collagen production by fibroblasts, an accumulation of inflammatory cells (predominantly macrophages and lymphocytes) and activation of keratinocytes. The end result is protein-rich oedema fluid, increased deposition of ground substance, subdermal fibrosis, and dermal thickening and proliferation.

Classification

- ✓ Lymphoedema was originally classified by Allen in 1934 who subdivided it into primary lymphoedema, in which the cause is unknown (or at least unproved), and secondary lymphoedema, in which there is a clear aetiology.
- ✓ Primary lymphoedema is usually further subdivided on the basis of age of onset and the presence of a family history.
- ✓ Lymphoedema may also be classified on the basis of lymphangiographic findings and clinical severity regardless of the underlying cause.

Aetiology and classification of lymphoedema***Primary lymphoedema***

- Congenital
- Praecox
- Tarda

Secondary lymphoedema

- Parasitic as filariasis
- Fungal as tinea pedis
- Exposure to foreign body materials as silica particles
- Primary lymphatic malignancy
- Metastatic spread to lymph nodes
- Radiotherapy to LN
- Surgical excision of LN
- Trauma particularly degloving injuries
- Superficial thrombophlebitis
- DVT

Clinical classification of lymphoedema

| Grade | Clinical features |
|----------------------|--|
| Subclinical (latent) | There is excess interstitial fluid and histological abnormalities in lymphatics and LN but no clinically apparent lymphoedema. |
| I | Oedema pits on pressure and swelling largely or completely disappears on elevation and bed rest. |
| II | Oedema does not pit and does not significantly reduce upon elevation. |
| III | Oedema is associated with irreversible skin changes i.e. fibrosis, papillae. |

Risk factors for lymphoedema

Upper limb/trunk

- Axillary LN dissection
- Scar formation, fibrosis and radiodermatitis following radiotherapy
- Drain/wound complications or infection
- Seroma formation
- Advanced cancer
- Obesity
- Congenital predisposition
- Trauma
- Chronic skin disorders and inflammations
- Hypertension
- Taxane chemotherapy
- Insertion of pacemaker
- Arteriovenous shunt
- Air travel
- Living in or visiting an area for endemic lymphatic filariasis
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Lower limb

- Inguinal LN dissection
- Radiotherapy
- Recurrent soft tissue infection at the same site
- Obesity
- Varicose vein stripping
- Congenital predisposition
- Advanced cancer
- Orthopedic procedures
- Thrombophlebitis and chronic venous insufficiency
- Any unresolved asymmetric oedema
- Chronic skin disorders and inflammations
- Concurrent illness as phlebitis, hyperthyroidism, renal or cardiac disease
- Immobilization
- Living in or visiting an area for endemic lymphatic filariasis

History

The age of onset of painless swelling, together with the presence or absence of a family history or coexistent pathology, will allow differentiation of primary from secondary lymphoedema to be made in most cases.

Signs

Unlike other types of oedema, lymphoedema characteristically involves the foot. The contour of the ankle is lost through infilling of the submalleolar depressions, a 'buffalo hump' حذبة جاموس forms on the dorsum of the foot, the toes appear 'square' owing to confinement of footwear and the skin on the dorsum of the toes cannot be pinched because of subcutaneous fibrosis. Lymphoedema usually spreads proximally to knee level and less commonly affects the whole leg. Lymphoedema will pit easily at first but, with time, fibrosis and dermal thickening prevent pitting except following prolonged pressure. Chronic eczema, fungal infection of the skin and nails, and fissuring, are frequently seen in advanced conditions.

Frank ulceration is rare except in the presence of chronic venous insufficiency. Ulceration can also develop after minor trauma and be slow to heal.

Primary Lymphoedema**Pathophysiology****✚ Non familial primary lymphoedema**

It has been proposed that all cases of primary lymphoedema are due to an inherited abnormality of the lymphatic system, sometimes termed 'dysplasia in utero'. However, it is more likely that many sporadic cases occur in the presence of a (near) normal lymphatic system. It is likely that most nonfamilial primary lymphoedema is due to chronic injury over many years due to seemingly trivial (but repeated) bacterial and/or fungal infections, insect bites, barefoot walking, deep venous thrombosis or episodes of superficial thrombophlebitis. *Primary lymphoedema is much more common in the legs than the arms.* This may be due to gravity and the fact that the lymphatic system of the leg is less well developed than that of the arm or the increased susceptibility of the lower extremity to trauma and/or infection.

✚ Familial primary lymphoedema

In familial cases it is assumed that there must be some genetic susceptibility of the lymphatic system to such injury. ***This may be:***

- A structural problem such as aplasia or hypoplasia
- A functional problem such as defective lymphatic contractility;
- An immune deficiency.

However, at the present time, the exact mechanisms causing familial primary lymphoedema remain uncertain.

Lymphoedema congenita

Congenital lymphoedema (onset at or within a year of birth) is more common in males, more likely to be bilateral and to involve the whole leg, and accounts for less than 5 per cent of primary lymphoedema. Milroy's disease describes familial lymphoedema that is present at birth or is noticed shortly thereafter.

Lymphoedema praecox

Lymphoedema praecox (onset from 1 to 35 years of age) is three times more common in females than males, has a peak incidence shortly after menarche, is three times more likely to be unilateral than bilateral, usually only extends to the knee and accounts for about 20 per cent of primary lymphoedema. The

familial form is referred to as Meige's disease and represents about one-third of all cases.

Lymphoedema tarda

Lymphoedema tarda develops after the age of 35 years but, in practice, is a disease of middle age. It is often associated with obesity and, histologically, lymph nodes are replaced with fatty and fibrous tissue. The cause is unknown. Lymphoedema developing for the first time in later life should prompt a thorough search for underlying malignancy, particularly of the pelvic organs, prostate and external genitalia; such malignancy may be found in up to 10 per cent of patients.

Secondary Lymphoedema

This is the most common form of lymphoedema. There are several well recognised causes.

Filariasis

This is the commonest cause of lymphoedema worldwide, affecting up to 100 million individuals. It is particularly prevalent in Africa, India and South America where 5—10 per cent of the population may be affected. The viviparous nematode *Wucheria bancrofti*, whose only host is humans, is responsible for 90 per cent of cases and is spread by the mosquito. The disease is associated with poor sanitation. The parasite enters lymphatics from the blood and lodges in lymph nodes where it causes fibrosis and obstruction. Proximal lymphatics become grossly dilated with adult parasites. The degree of oedema is often massive, in which case it is termed 'elephantiasis'.

Diagnosis

- 1) Immature parasites (microfilariae) enter the blood at night and can be identified on a blood smear, a centrifuged specimen of urine or in lymph itself.
- 2) A complement fixation test is also available and is positive in present or past infection.
- 3) Eosinophilia is usually present.

Treatment

Diethylcarbamazine destroys the parasites but does not reverse the lymphatic changes. Once the infection has been cleared treatment is as for primary lymphoedema.

Malignancy and its treatment

This is the most common cause of lymphoedema in developed countries. Hodgkin's and non-Hodgkin's lymphoma may present with lymphoedema, as may malignant melanoma which has metastasised to regional lymph nodes and malignancy of the pelvic organs (ovary, uterus, bladder), anus, prostate, testes and breast (peau d'orange).

More often lymphoedema is a result of treatment, either surgical excision of draining lymph nodes and/or radiotherapy.

Trauma

Especially seen after degloving injuries of the extremities.

Acute cellulitis

Acute bacterial lymphangitis is a frequently observed triggering event for secondary lymphoedema.

Other causes

Rare, but well-documented, causes of secondary lymphoedema include :

1. Tuberculosis
2. Rheumatoid arthritis (chronic inflammation and lymph node fibrosis)
3. Snake and insect bites.
4. Deep venous thrombosis, chronic venous insufficiency and superficial thrombophlebitis.

Investigation of lymphoedema

Many clinicians diagnose lymphoedema purely on the basis of history and examination, especially when the swelling is mild and there are no apparent complicating features. Severe swelling, with unusual features, or where there may be more than one pathology contributing to the clinical picture usually warrants further investigation.

Routine' tests

A full blood count, plasma urea and electrolytes, creatinine, liver function tests, chest radiograph.

Contrast lymphangiography

It is now generally reserved for preoperative evaluation of patients with megalymphatics who are being considered for bypass or fistula ligation.

Isotope lymphoscintigraphy

This has largely replaced contrast lymphangiography and is used in most centres as the primary diagnostic technique.

Computerised tomography

The main role of CT is to exclude pelvic or abdominal mass lesions. Although lymphoedema itself can be visualised on CT, it is of little diagnostic value in this respect.

Magnetic resonance imaging

Magnetic resonance imaging can provide clear images of lymphatic channels and lymph nodes, and can also distinguish venous and lymphatic disease as the cause of a swollen limb. However, it cannot at present provide the information available from lymphoscintigraphy, and as a cross-sectional imaging technique it appears to have little advantage over CT.

Pathological examination

In cases where malignancy is suspected, samples of lymph nodes may be obtained by fine needle aspiration, needle core biopsy or surgical excision.

Management of lymphoedema**Physical methods**

The patient should elevate the foot above the level of the hip when sitting, elevate the foot of the bed when sleeping and avoid prolonged standing. Various forms of massage are effective at reducing oedema. Single- and multiple-chamber intermittent pneumatic compression devices are also useful. Pressures exceeding 50 mmHg at the ankle may be required to control

oedema. Below-knee stockings are usually sufficient. The patient should put the stocking on first thing in the morning when the leg is at its least swollen.

Drugs

Diuretics are of no value in pure lymphoedema. Their use is associated with side effects including electrolyte disturbance. Antibiotics should be prescribed promptly for cellulitis; **penicillin V** 500 mg four times daily for streptococcal infection and **flucloxacillin** 250 mg four times daily for staphylococcal infection are suitable. In severe cases there should be no hesitation in admitting the patient to hospital, elevating the limb and administering antibiotics intravenously. Antibiotics should be continued for at least 7 days or until all signs and symptoms have abated. **Erythromycin** is a reasonable alternative for those who are allergic to penicillin. In patients who suffer recurrent spontaneous episodes of cellulitis, long-term prophylactic antibiotic therapy may be indicated. Fungal infection (tinea pedis) must be treated aggressively; **topical clotrimazole 1 per cent or miconazole 2 per cent** used regularly is sufficient in most cases, but in refractory situations systemic **griseofulvin** 250—1000 mg daily may be required. The feet must be dried after washing and the skin kept clean and supple with water-based emollients to prevent entry of bacteria.

Surgery

Only a small minority of patients with lymphoedema benefits from surgery. Operations fall into two categories: **bypass procedures and reduction procedures.**

Bypass procedures

In less than 2 per cent of patients with primary lymphoedema, lymphangiography will demonstrate proximal lymphatic obstruction in the ilio-inguinal region with essentially normal distal lymphatic channels. Such patients might benefit from lymphatic bypass. A number of methods have been described, including the omental pedicle, anastomosing lymph nodes to veins, and, more recently, direct lymphovenous anastomosis with the aid of the operating microscope.

Limb reduction procedures

These are indicated when a limb is so swollen that it interferes with mobility and livelihood. These operations are not 'cosmetic' in the sense that they do not create a normally shaped leg and are usually associated with significant scarring.

Four operations have been described:

1) Sistrunk

A wedge of skin and subcutaneous tissue is excised and the wound closed primarily. This is most commonly employed to reduce the girth of the thigh.

2) Homan

Skin flaps are elevated and subcutaneous tissue is excised from beneath the flaps, which are then trimmed to size to accommodate the reduced girth of the limb and closed primarily. This is the most satisfactory operation for the calf

3) Thompson

One denuded عاري skin flap is sutured to the deep fascia and buried beneath the second skin flap (the so-called buried dermal flap). This procedure has

become less popular as pilonidal sinus formation is common, the cosmetic result is no better than that obtained with Homan's procedure and there is no evidence that the buried flap establishes any new lymphatic connection with the deep tissues.

4) Charles

This operation was initially designed for filariasis and involved excision of all the skin and subcutaneous tissues down to deep fascia with coverage using split skin grafts. This leaves a very unsatisfactory cosmetic result and graft failure is not uncommon.

Chylous ascites and chylothorax

The diagnosis may be obvious if accompanied by lymphoedema of an extremity. However, some patients develop chylous ascites and/or chylothorax in isolation, in which case the diagnosis can be confirmed by aspiration and the identification of chylomicrons in the aspirate. Cytology for malignant cells should also be carried out. CT scan may show enlarged lymph nodes and CT with guided biopsy, laparoscopy or even laparotomy and biopsy may be necessary to exclude lymphoma or other malignancy. Lymphangiography may indicate the site of a lymphatic fistula which can be surgically ligated. If the problem is too diffuse to be corrected surgically, a peritoneal venous shunt may be inserted, although occlusion and infection are important complications. Medical treatment comprising the avoidance of fat in the diet and the prescription of medium chain triglycerides (which are absorbed directly into the blood rather than via the lymphatics) may reduce swelling. Chylothorax is best treated by pleurodesis with either bleomycin, or tetracycline.

Lymphangiomas

Lymphangioma circumscriptum

This involves superficial proliferation of capillary sized lymphatic vessels which comprise fluid-filled vesicles on the surface and larger cisternae in the subcutaneous tissues and even adjacent muscles.

The affected skin and a generous amount of subcutaneous tissue containing the vessels may be excised if they cause symptoms.

Cystic hygroma

Cystic hygroma is an abnormal lymph-filled, often multilocular, space which usually presents in childhood as a soft, brilliantly transilluminable swelling in the base of the neck. They develop from primitive lymph cisterns. It behaves like a benign tumour and grows gradually in size, leading to cosmetic problems and compression of surrounding structures. Recurrence is common after simple aspiration and injection of sclerosant. Excision is technically challenging due to the large number of vital structures in the vicinity.

Muqdad fuad