What do we know about lymphedema? Review Article

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ABSTRACT

Lymphedema can cause by a congenital anomaly, an infectious disease, chronic inflammation, connective tissue disease, and cancer. The most common presenting symptoms are swelling of the affected limb, difficulty wearing clothes, and disturbances to daily life activities. Most of the time, patients have a high chance of developing a soft tissue infection that will jeopardize the quality of their life and socioeconomic status. As to management of the disease, it necessary to make a precise diagnosis and clinico-pathological staging in order to guide the treatment plan and yield optimum results. Currently, surgical management for lymphedema is based on the use of 1) physiological treatment, and 2) reductive or ablative procedures. Conservative treatment (especially for complete decongestive therapy) is still the mainstay for the management of lymphedema.

Keywords: Lymphedema; lymphatic obstruction; lymphatic reconstruction; lymphatic surgery; lymphaticovenous anastomosis; lymph node transfer (Siriraj Med J 2021; 73: 293-304)

INTRODUCTION

The lymphatic system performs three main functions: 1) draining excess fluids from body tissues, 2) fat-absorption, and 3) the production of immune cells. Intercellular fluid is the fluid that leaks from the circulatory system, and 90% of it is reabsorbed by the venous circulatory system. The remaining 10% of this protein-rich fluid accumulates between cells and flows into the lymphatic system (Fig 1); once this fluid enters the lymphatic system, it is termed "lymph". It is transported through the collecting lymphatic vessels and filtered through the lymph nodes, through which approximately 2-3 liters of circulating lymph passes daily. The difference between the accumulated lymphatic and capillary lymphatic pathways is the presence of smooth muscle on the lymph vessel walls that results in compression. Intermittent valve blocking also forces lymphatic flow in one direction. Consequently, a loss of drainage ability (whether caused by a blockage of the lymphatic tract or by the lymphatic system not growing) causes lymph to accumulate between cells, with a subsequent swelling of soft tissue, inflammation, and fibrosis. This adverse condition is called "lymphedema".[1,38,39]

Anatomy and pathophysiology of lymphatic system

The lymphatic system is divided into lymph capillaries, which drain much of the intercellular fluid from the dermal layer. This fluid is subsequently passed to pre-collector and collecting vessels located in the subcutaneous fat layer before moving into the lymph nodes. The lymphatic flow is one direction because there is a valve blocking period (Fig 2).

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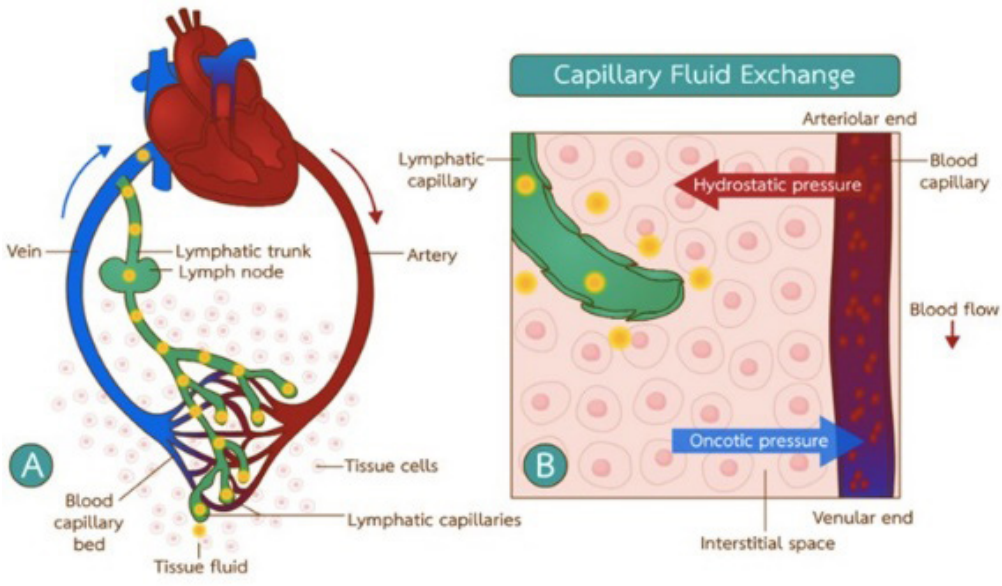

Fig 1. Lymphatic system

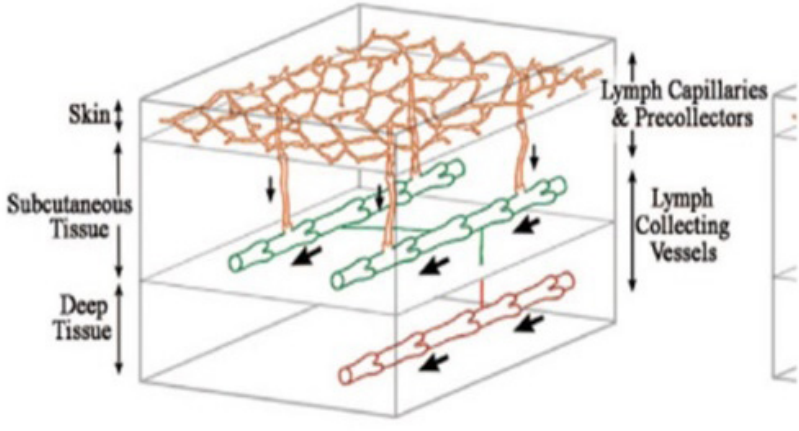

Fig 2. Anatomy of lymphatic system[2]

The etiology of lymphedema

Primary lymphedema

Primary lymphedema is the type of lymphedema that occurs from an inherited abnormality (not a consequence of other conditions). The cause is an abnormal growth of the lymphatic tract (aplasia, dysplasia, or malformation). Primary lymphedema can be subdivided into the following 3 groups, based on their etiology and the onset of the disease.

1. *Congenital lymphedema (Milroy's disease)*
   - The second most common type of primary lymphedema (10%-25%)
   - Occurs within first 2 years of age
   - Usually presents as bilateral extremity edema
   - Autosomal dominant, inherited disorder caused by an inactive mutation of VEGFR-3 tyrosine kinase (VEGFR, vascular endothelial growth factor receptor)
2. *Familial lymphedema praecox (Meige's disease)*
   - The most common form of primary lymphedema (65%–80%)
   - Incidence is about 1:100,000 in the population, with a 4:1 female/male ratio
   - Typically presents during puberty (adolescence), and usually as a unilateral edema (especially of the foot and calf)
   - Transfers through autosomal dominant inheritance, and can associate with multiple anomalies, such as a double row of eyelashes (distichiasis), vertebral and cerebrovascular malformations, and hearing loss
3. *Lymphedema tarda*
   - The rarest form of primary lymphedema (< 10%)
   - Usually occurs after 35 year of age (adulthood)
   - Histological findings of this lymphedema type are usually tortuous and hyperplastic, with an absence of competent valves

Secondary lymphedema

Secondary lymphedema is the type of lymphedema that occurs from adverse events related to other conditions. These include cancer, infectious diseases, inflammation, obesity, and postoperative tumor extirpation with lymph node surgery and/or radiotherapy (Table 1).

Epidemiology and risk factors

Worldwide, the most common cause of lymphedema is filariasis, which results from an infection by the parasitic worm, Wuchereria bancrofti.[4] However, in developed countries, its major cause is cancer and post-cancer treatment (postoperative tumor extirpation with lymph node surgery and/or radiotherapy).[5]

The etiology of lymphedema induced by cancer and post-cancer-treatment can be explained by many mechanisms. For instance, there may be a blockage of the lymphatic ducts from which the cancer is directly pressed, or a cancer may have spread directly into the lymphatic system (lymphangitic carcinomatosis). In addition, surgery for lymph node removal and radiotherapy may have injured the lymphatic partway.

Studies have shown that the incidence of upper extremity lymphedema in breast cancer patients is about 17%. Most patients who undergo axillary lymph node dissection develop symptoms of lymphedema within 3 years of the surgery.[6] Other forms of cancer have been reported to have an overall lymphedema incidence of 15.5%.[7]

Adjuvant radiotherapy after surgery significantly increases the risk of lymphedema. A systematic study in 2001 found that patients who had a mastectomy and received radiotherapy at the axilla subsequently developed lymphedema more frequently than patients who only underwent surgery (41% versus 17%, respectively). Other risk factors for lymphedema include older age and obesity; these populations are at risk of developing a greater level of lymphatic fluid formation and have a higher chance of presenting with symptoms than the general population.[9]

In 2010, Helyer et al. studied the relationship between obesity and the occurrence of lymphedema in breast cancer patients. They found that patients with a body mass index > 30 kg/m^2 had a higher chance of developing lymphedema than those with an index < 25 kg/m^2 (odds ratio, 2.93; 95% CI, 1.03–8.31).[10]

Diagnosis

History and physical examination

Patients with lymphedema often present with unilateral arm or leg edema, and they usually describe a feeling of heaviness around the affected limb. Some patients may present with abnormal skin changes, such as thicker, stiffer, and/or orange-peel-like skin (Paul d'orange).

A physical examination can establish the difference in circumference of the limbs and size will gradually grow equally entire the affected limb. In the early stage of lymphedema, the affected limb can still be depressed

TABLE 1. Causes of lymphedema.[3]

Primary lymphedema
Congenital
Praecox (adolescence)
Tarda (adulthood)
Secondary lymphedema
Cancer
Recurrent cellulitis
Connective tissue disease
Infectious disease (filariasis)
Contact dermatitis
Lymphatic drainage (surgery, radiation therapy, burn, etc.)

when pressure is applied to the skin; however, depression is no longer possible once nonpitting edema forms during the late stage of the disease. The specific physical examination for lymphedema draws upon the "Kaposi-Stemmer sign". This is looked for by trying to pinch the skin on the dorsum of the second toe into a fold (alternatively, the procedure can be performed on the index finger of the hand). If a fold cannot be made, the patient is considered positive for lymphedema (Fig 3). As to the circumference measurement (Fig 4), the patient should be in a standard position; the circumference size is used to calculate the volume of the limb by using the truncated-cone formula (Fig 5). The volume measurement obtained by using this anatomical-landmark circumference method is more accurate than the volume determined by water displacement.[11]

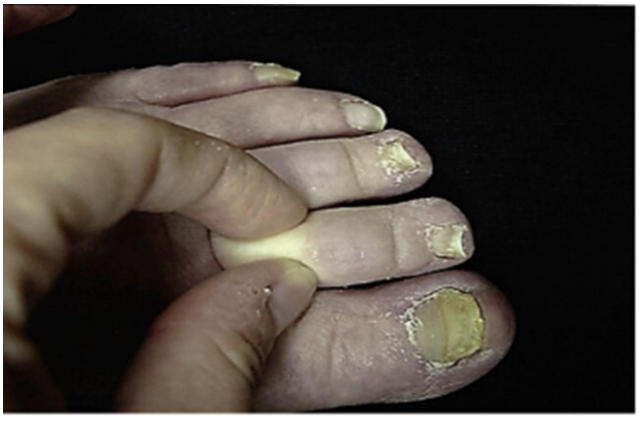

Fig 3. Kaposi–Stemmer sign[1]

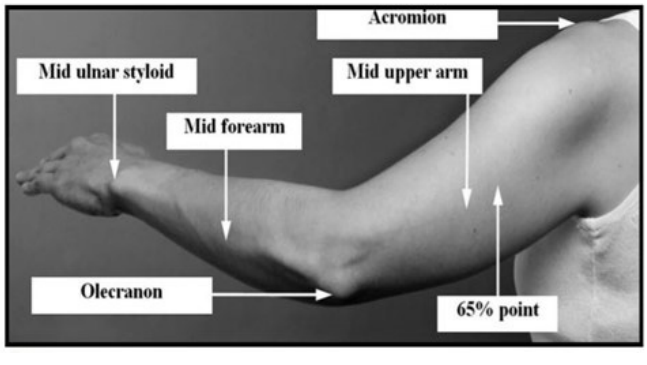

Fig 4. The truncated-cone formula[11]

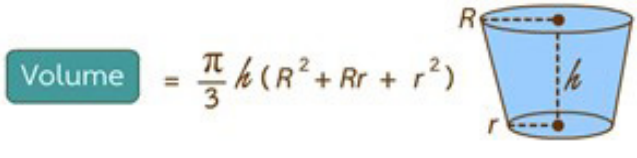

Fig 5. Anatomical landmark[11]

Differential diagnosis

1. *Venous insufficiency*

Lymphedema has some clinical features that mimic chronic venous degeneration. To differentiate them, the limb that has venous insufficiency usually has accompanying symptoms, such as varicose veins, a reddish-brown skin color (from hemosiderin deposition), and possibly ulcerative lesions above the medial malleolus area. The limb swelling that has caused the venous insufficiency often presents as pitting edema, which can be reduced in size by elevation.

2. *Deep vein thromboembolism (DVT)*

Unilateral limb swelling is also the presenting sign and symptom of DVT. However, DVT usually presents during the acute phase with rapid disease progression. Some patients with DVT may present with severe and unexplained pain, or a throbbing and cramping pain (especially at the calf), redness of the skin, and warmth in the affected limb.

3. *Lipedema*

This condition is caused by an accumulation of adipose tissue around the extremities, and it frequently occurs in young women. Normally, lipedema usually presents on both side of the extremities. The affected area is often painful when pressed, which can be used to distinguish it from a lymphatic obstruction (Table 2).

Investigation

1. *Lymphoscintigraphy*

This investigation is used to assess the lymphatic drainage of both the superficial and the deep lymphatic systems, which drain from distal to proximal to the regional lymph node basin. The test involves injecting a radioactive substance (Technetium-99m sulfur colloid) intradermally at the web space of the affected limb; serial radiographic measurements are subsequently used to detect the pattern of lymphatic flow over a period from 15 to 240 minutes.[12,13] This noninvasive investigative technique is relatively safe due to the very low radiation exposure; it also has very good accuracy (sensitivity, 96%; specificity, 100%).[14] The common findings of lymphedema from lymphoscintigraphy are:

- Not found, or a delayed lymphatic drainage
- An absence of, or a decrease in the number of, lymph nodes at the regional lymphatic basin
- A reverse flow of radioactive substance in the dermis (dermal backflow)

TABLE 2. Key clinical differences between lipedema and lymphedema of the lower extremities.[1]

Lipedema	Lymphedema
Almost always female patients	Both males and females
Spares the foot	Foot involved
Usually bilateral	Usually unilateral
Negative Kaposi–Stemmer sign	Positive Kaposi–Stemmer sign
No pitting	No pitting when it becomes chronic
Tender	Usually not tender
Soft	Firm/tense

2. *Computed tomography (CT) scan/magnetic resonance imaging (MRI)*

Both investigative techniques facilitate the evaluation of the fluid accumulation in tissues. The findings of lymphedema from a CT-scan or MRI are:

- Thickening of the skin layer (skin thickening)
- Swelling of the subcutaneous layer (subcutaneous edema)
- A honey-combed appearance

3. *Indocyanine green (ICG) fluorescence lymphography*

ICG is a near-infrared dye that is injected intradermally to facilitate the identification of the superficial lymphatic tract beneath the skin. After injection, the substance binds to albumin before being drained proximally via the lymphatic channel through the regional node basin. This method can be used to assess lymphatic leakage, pumping capacity, and lymph reflux into the dermis.[15] Moreover, ICG lymphography can be utilized to grade the severity of the disease and guide the selection of an appropriate choice of treatment.

4. *Duplex ultrasound*

While not used specifically as a diagnostic tool, it provides benefits in terms of excluding deep venous thromboembolism and venous insufficiency, and it is able to investigate a space-occupying lesion that may be compressing the lymphatic channel. Many surgeons also use it to locate and map the superficial lymphatic vessels and superficial veins before performing a lymphaticovenous anastomosis procedure.

5. *Ankle-brachial pressure index (ABI)*

As with duplex ultrasound, ABI is not used for the diagnosis of lymphedema. However, it is recommended for patients with a history of, or with suspected, peripheral arterial disease. Because of the lymphedema, patients almost always need to do compression therapy, which might affect their peripheral blood circulation. If the ABI value is < 0.5, compression therapy is contraindicated for patients.

Staging of lymphedema

There are currently many clinical staging systems for the grading of lymphedema severity. However, the most commonly used worldwide are the staging system of the International Society of Lymphology (ISL) and the Campisi staging system. The details of each are listed in Tables 3 and 4.[16]

TABLE 3. International Society of Lymphedema (ISL) stagings.

ISL stage	Description
0	Subclinical state; swelling is not evident despite impaired lymph transport
I	Accumulation of tissue fluid (higher protein content), which subsides with limb elevation
IIa	Limb elevation alone rarely reduces swelling, and pitting is manifest
IIb (late stage)	Limb may or may not be pitted as fat and tissue fibrosis is more evident
III	Lymphostatic elephantiasis; the tissue is hard (fibrotic), and pitting is absent. Skin (changes) thickening, hyperpigmentation, increased skin folds, fat deposits, and warty overgrowths develop

TABLE 4. Campisi stagings.

Campisi stage	Description
Ia	No overt swelling despite impaired lymph drainage
Ib	Reversible swelling with limb elevation
II	Mild, persistent swelling with elevation
III	Persistent swelling, with recurrent lymphangitis
IV	Fibrotic change with column-like limb
V	Elephantiasis with limb deformation, including widespread lymphostatic warts

Lymphedema management

Chronic lymphedema is an irreversible process if left untreated. The mainstay of treatment is a conservative protocol. If the clinical status does not improve within 6 months of the commencement of therapy, surgical management is recommended.

The conservative treatment protocol consists of general measures of self-care, compression therapy, and physiotherapy.

1. *Self-care*

This aims to reduce swelling and slow the progression of disease. The measures are comprised of the following.

1.1 Self-monitoring. The size of the swollen arm or leg should be monitored, with observations made of the feeling of the skin, the skin color, and changes in skin appearance.

1.2 Limb elevation. This helps to reduce swelling of the affected limb in the early stages of the disease. The patient should be advised to avoid postures that cause the limbs to fall with gravity, such as standing for long periods of time or sitting cross-legged.

1.3 Diet and exercise. Being obese is not only a risk factor for lymphedema, but it also greatly hampers compression therapy. The patient should therefore be advised to exercise regularly, control food intake, and wear a pressure garment. A study on breast cancer patients with upper extremity lymphedema, divided the patients into two groups: first, those who are advised to control food and lose weight. Second, a group that provides general dietary recommendations. At 12 weeks of follow-up, the first group showed a significant loss weight of arm (P-value = 0.02) and a significant decrease in swelling and arm volume (P-value = 0.03).[9] For exercise by lifting weights in patients with undergoing axillary lymph node dissection without lymphedema. The study did not find that lifting weights made the lymphedema more severe.[17] Additionally, in the lymphedema group, the lifting of weights reduced the pain and swelling in the affected arm, with the incidence of swelling declining from 29% to 14%.[18]

1.4 The avoidance of skin infection. Regular skin and nail care can help to prevent the cracking that leads to skin infections. If there are piercings or abrasions on the skin, an antibiotic cream or ointment should be applied. The use of a sunscreen should also be recommended if the affected limb is likely to be exposed to the sun. In addition, as exposure to extremely hot environments (such as saunas and hot springs) can cause swelling, the patient should be advised to avoid such situations.

1.5 The avoidance of local limb concussion. Wearing tight-fitting clothing or performing local constriction procedures (such as the measurement of blood pressure) exacerbates lymphedema by stimulating the production of lymph while causing a narrowing of lymphatic ducts. This differs from the use of a compression garment (discussed below): it provides a firm and even pressure from the distal to proximal limb, thereby improving the flow of lymph.

2. *Compression therapy*

2.1 Stockings and sleeves. Wearing arm or leg restraints, such as a compression sleeve, is an appropriate treatment for the early stage (ISL I) and should be employed in conjunction with skin care, exercise, and elevation. As the compression apparatus typically has a pressure range of 20-50 mmHg, it is able to stimulate lymphatic return by exerting greater force on the distal than the proximal limb. The firmness of the particular material to be selected depends on the condition of the patient's arteries and, more importantly, the patient's ability to tolerate the proposed compression garment. Evaluation

of the patient's treatment should therefore be undertaken early, after 4-6 weeks' usage of the compression sleeve. Further reviews should be conducted every 3-6 months if the condition has stabilized. In addition, the compression device should be replaced every 3-6 months, or even earlier if it appears to be starting to slacken.

2.2 Multilayer lymphedema bandaging. An elastic bandage is used to treat intermediate-stage lymphedema (ISL II), which is when the limb is so large that stockings or compression sleeves cannot be worn. The bandage is used in conjunction with skin care, limb elevation, and short-stretch bandages. Force is applied to the limbs by the elastic bandage only when the affected muscles are contracted; the pressure that is generated compresses the lymphatic vessels and increases lymph flow, resulting in decreased swelling. The appropriate ankle sub-bandage pressure is 45 mmHg. During the first week of treatment, the bandage should be changed every day; after that, changing it 2-3 times a week is acceptable.

The contraindications to the use of multilayer lymphedema bandaging are:
- ABI < 0.5
- Uncontrolled heart failure
- Severe peripheral neuropathy

2.3 Intermittent pneumatic compression device. The efficacy of intermittent pneumatic compression is still controversial. It involves the placement of cuffs around an affected limb; they are then filled with air. In turn, the cuffs squeeze the limb, compressing it from the distal to the proximal region while applying a pressure of 30-60 mmHg. It is recommended that an intermittent pneumatic compression device be used for 30-120 minutes per day, with a newer generation, multichambered device being preferable.

The contraindications to the use of intermittent pneumatic compression are:
- Untreated, nonpitting, chronic lymphedema
- Deep vein thrombosis
- Pulmonary embolism
- Acute cellulitis
- Uncontrolled heart failure
- ABI < 0.5
- Active tumor at the affected region

3. Physiotherapy

3.1 Manual lymphatic drainage. This massage technique aims to stimulate fluid flow in the lymphatic system. The force produced by the massage causes the lymph to flow from the distal to the proximal. After the massage, the patient still needs to wear a pressure garment during daily activities. A massage of at least one hour per day is recommended. Although the efficacy of manual lymphatic drainage has not yet been clearly identified, this technique is still recommended as a component of complete decongestive therapy (discussed below) during the treatment phase.

The contraindications to manual lymphatic drainage are:
- Acute cellulitis in the position to be massaged.
- Unstable hypertension
- Uncontrolled heart failure
- Tumor at the affected part

3.2 Complete decongestive therapy. This multi-modality treatment aims to reduce the swelling of the limbs in two phases:

3.2.1 ***Treatment phase.*** This comprises 1) skin and nail care, 2) exercise, 3) manual lymphatic drainage or massage, and 4) compression (bandage therapy). Patients must perform these procedures five days a week for 2-4 weeks. During the treatment phase, it is recommended that the patients take circumference and volume measurements themselves once weekly to facilitate the assessment of the treatment outcomes.

3.2.2. ***Maintenance phase.*** The treatment in this period consists of wearing a compression garment (during the day), bandaging (at night), maintaining skin care, and exercise. Lymphatic squeezing can be performed on its own after the patient has received appropriate training. During the maintenance phase, patients should measure the circumference and volume every 6 months to monitor the treatment progress.[19]

The absolute contraindications to complete decongestive therapy are:
- Infection
- Active cancer
- Heart attack
- Acute deep vein thrombosis

The relative contraindications to complete decongestive therapy are:
- High blood pressure that has not been controlled
- Diabetes
- Asthma
- Paralysis

4. Pharmacotherapy

The use of medications to treat edema is not recommended. Some studies investigated the use of diuretics to reduce limb swelling, but the results were not as good as expected. Apart from diuretics, coumarin (a benzopyrone) has been reported to reduce the incidence of cellulitis or lymphangitis.[20] However, recent studies have found that the use of this drug resulted in a reduction in the volume of swollen limbs compared with a placebo, with an incidence of hepatic toxicity of approximately 6%.[21] So, The use of medications to treat edema is still not recommended.

5. Experimental therapy

Low-level laser therapy (or cold laser therapy) has been investigated in patients with lymphedema after mastectomy. The therapy is believed to reduce fibrosis, stimulate macrophages in the immune system, and result in the formation of new lymphatic vessels (lymphangiogenesis). The results of one study showed that 1 in 3 patients who underwent laser therapy demonstrated a reduction in the volume of their swollen arm at their 3-month follow-up visit.[22] Moreover, low-level laser therapy produced a better limb-swelling reduction than pneumatic compression therapy after 12 months of treatment.[23]

6. Surgical management

Surgery is an ideal treatment option for patients with localized disease, a failed conservative treatment, recurrent cellulitis or lymphangitis, leakage of lymph to externally, or a significantly diminished quality of life.

Preoperative assessment

1. Assess degree of lymphedema

Evaluation of the degree of lymphedema is based on the difference in the circumference and volume of the affected limb relative to the contralateral, normal limb.

2. Lymphedema staging

Assessment of the stage of the disease is undertaken in order to select a suitable treatment option. The most commonly used staging system is the ISL system.[24]

3. Venous duplex ultrasound

In patients who plan to undergo surgery, venous duplex ultrasound might be required to rule out venous thrombosis, venous insufficiency, and valvular incompetency.

Surgical treatment

Surgical treatment can be divided into two broad approaches: reductive or ablative procedures, and physiological treatment.

1. Reductive or ablative procedures

1.1 Direct excision. In 1912, Dr. Charles wrote a book entitled "Elephantiasis Scroti", which describes how to treat lymphedema around the scrotum. The principle of the surgery is to remove the swollen tissue of the scrotum and then cover the wound with a skin graft from the thigh.

In 1940, Dr. Macey from the Mayo Clinic applied the Charles procedure to surgery on extremities lymphedema.[25] The benefit of this surgical technique is that it totally removes the swelling and fibrotic tissues. Nevertheless, there are still many postoperative complications, such as surgical site infection, hematoma, graft loss, and scars. Therefore, the procedure is usually recommended only for late-stage lymphedema patients, or for patients with wounds on the affected limb that are significantly disturbing their quality of life.

1.2 Liposuction. This treatment involves the insertion of a steel canula into the subcutaneous layer; the cannula is connected to a vacuum that suctions the fibrofatty tissue via negative pressure. O'Brien et al.[26] reported that this treatment reduced the volume of the swelling by 20% - 23%. The advantages of this treatment are, firstly, it only leaves a very small incisional scar and, secondly, patients recover rapidly (approximately 48 hours). The disadvantage, however, is that there may be injury to the lymphatic tract during the liposuction procedure; consequently, it is recommended that the canula is kept parallel to the limbs to reduce injuries. Another consideration is that, after liposuction, patients need to permanently wear compression devices.

2. Physiological treatment

This treatment principle aims to creates a new lymphatic channel in order to increase the ability of the lymph to flow. These surgical procedures are only suitable for the early stages of lymphedema (ISL stages I or II)[27], being ineffective in late-stage patients. The physiological treatment procedures are comprised of 4 main types, as described below.

2.1 Flap interposition. The procedure uses a flap with good blood vessels and lymphatic vasculature obtained from another site of the body. The flap is placed in the

area where the lymphatic flow is blocked or disrupted, and then anastomosis of the blood vessels and lymphatic vessels is performed.

In 1935, Gills and Fraser[28] were the first doctors to use this procedure to treat a patient with leg edema. Flaps taken from the arms were pasted to the thighs and body of the patient; the flaps became bypasses that allowed lymphatic fluid to cross the obstructed areas.

In 1974, Goldsmith et al.[29] reported the use of a greater omental flap to treat patients with lymphedema. The flap was inset in a subcutaneous layer, thereby allowing lymph in an arm or leg to drain into the lymphatic system. Twenty-two patients from their study reported satisfactory results. Nonetheless, this surgery is not popular because it has a relatively high number of complications, such as intestinal obstruction, blood clots, atherosclerosis, and hernia.

2.2 Lymphatic bypass procedure. The principle of this surgery is to create a link between distal lymphatic vessels and lymphatic vessels above the point of an obstruction. Alternatively, a bypass from the obstructed lymphatic channels into the venous system is created.

Before surgery, the functional lymphatic vessels should be identified by specific dyes transported through the lymphatic channels[27], for example, isosulfan blue or indocyanin green.

The indications for this surgery are:
- No response to conservative treatment
- Recurrence of skin infection
- Disease significantly affecting the quality of life and daily activities

The limitations of lymphatic bypass surgery are:
- Tissue fibrosis
- Late stage lymphedema
- Inferior surgical outcomes for venous hypertension or venous insufficiency patients
- Recurrence of cancer
- Patients unable to take care of themselves after surgery
- Uncooperative patient

2.2.1 ***Lymphatic-lymphatic bypass.*** An attempt was made to bypass the problematic lymphatic tract by connecting the distal lymphatic vessels to the proximal lymphatic vessels above the area of obstruction.

In 1990, Baumeistier and Suida[30,31] performed a series of lymphatic reconstructions to manage arm lymphedemas by using lymphatic vessels from thighs. Lymphatic vessels were harvested from the patients' thighs and then implanted in the subcutaneous fat layer between the upper arm and shoulder area, above the clavicular bone. In the case of lower extremity lymphedema, the surgery was performed by harvesting contralateral, normal lymphatic vessels and moving them to the groin of the affected leg. The procedure was performed on 55 patients. The treatment outcome was reductions of up to 80% in the volume of the affected areas during the 3-year follow-up period.

2.2.2 ***Lymphovenous bypass and lymphaticovenous anastomosis.*** In 1962, Jacobson et al. attempted to connect lymphatic vessels to veins by conducting an experimental study in an animal model. After that, Yamada et al. applied the technique to treat lymphedema patients by using a saphenous vein connection to an obstructed lymphatic tract. However, some concern had been expressed about using a high-pressure gradient large vein, which might cause problems if there is a poor lymphatic flow.

Consequently, Yamada et al. modified the protocol so that venules with a diameter of 0.8 mm or less were used.[32] The outcomes of lymphaticovenous anastomosis were studied in 100 patients with lymphedema of the arms or legs. The results showed clinical improvements for 96% of the patients, and a volume reduction for 74% of the cases. The overall lower-limb-volume reduction at 12 months was 42%; the decline was greater for early-stage patients (61%) than late-stage patients (17%).[33]

The effect of lymphaticovenous bypass surgery has been studied at the cell level by skin biopsy. The findings revealed a decline in the white-blood-cell and CD4 + values of the affected limb, and tissue fibrosis.[34]

Fluorescence lymphangiography is currently been used to identify the location of the lymphatic tract in real time.[15] It is also used to stage the disease. With the early stage, the lymphatic tract is seen to have a clear linear pattern. In contrast, the late stage shows a diffuse stain of substance due to obstruction and a reversed lymphatic flow. If good lymphatic vessels are identified, lymphaticovenous anastomosis is performed. The superficial lymphatic vessels are localized again using isosulfan blue dye during surgery conducted under a surgical microscope.

2.3 Vascularized lymph node transfer (VLNT). The procedure involves harvesting a free lymph node flap from outside the affected region, implanting it into the affected limb, and anastomosing it to recipient vessels via a microsurgical technique (without connecting the

lymphatic tract). Two mechanisms explain the effect of VLNT:

- Bridging mechanism. The transplanted lymph node flap secretes vascular endothelial growth factor C (VEGF-C), which stimulates the formation of a new lymphatic tract.
- Pumping mechanism. The difference in the pressure gradient between arterial anastomosis and venous anastomosis acts like a pump suctioning excess lymph back to the systemic circulation system (like lymphatic-venous drainage).

In 1982, Clodius et al.[35] reported the results of 2 cases of VLNT to manage lower extremity lymphedema, with the lymph node flap being obtained from the groin. Although the swelling rapidly subsided during the early post-operation period, the edema had returned by the 6-month follow-up session.

In 2006, Becker et al.[36] reported the long-term effects of free lymph node flap transfers using inguinal lymph nodes to manage 24, post-mastectomy, upper extremity lymphedema patients, sixteen of who had postoperative lymphoscintigraphic evaluations. The results showed that 5 out of the 16 patients (who had lymphoscintigraphy) had functional lymph nodes and lymphatic tract regeneration.

In 2012, Saaristo et al.[37] performed vascularized lymph node transfer in conjunction with autologous breast reconstruction in 9 patients with post-mastectomy lymphedema. There was an improved lymphatic circulation in 5 out of 6 patients, and 3 out of the 9 patients no longer needed to use a pressure garment after the surgery. Additionally, an increase in endogenous lymphatic vessel growth factors was demonstrated, suggesting that new lymphatic regeneration in the axilla had been stimulated.

The indications for vascularized lymph node transfer are:

- Segmental dermal backflow or a non-functioning lymphatic vessel detected by lymphoscintigraphy
- ISL stage II with repeated cellulitis
- No acute cellulitis
- Follow up > 12 months

There are two principles for lymph node implantation: 1) orthotopic (anatomical) placement, and 2) heterotopic (nonanatomical) placement.

2.3.1 ***Anatomical placement.*** The lymph nodes are implanted in the area where the obstruction occurs, such as the axilla or groin.

The advantages of anatomical placement are:

- Removal of the fibrosis that caused the lymphatic tract obstruction
- Nearby tissue can be sewn or closed without any skin grafting
- Less postoperative scarring

2.3.2 ***Nonanatomical placement.*** The lymph nodes are implanted in the distal limb, with the transplanted lymph node acting like a lymphatic pump.

The advantages of nonanatomical placement are:

- Avoidance of surgery in the area of fibrosis

The disadvantages of nonanatomical placement are:

- Bulkiness of lymph node flap in the distal limb
- Often need to do skin grafting

If a scar cannot be properly removed, it is recommended that the lymph nodes be implanted in an area that will produce less scarring. Many studies have demonstrated that VLNT can relieve symptoms in 100% of cases, reduce the volume in 91% of cases, and allow 78% of patients to stop using pressure garments.

As to complications, lymphatic leakage develops in 15% of cases, postoperative infection arises in about 8%, and a need to reoperate occurs with 3% of patients.

2.4 Lymphatic microsurgical preventive healing approach (LYMPHA). This procedure aims to connect lymphatic vessels to a branch of the axillary vein simultaneously with axillary lymph node dissection. One study found that, after 4 years of follow-up, only 3 (4%) out of 74 patients continued to have lymphedema in the arm that had been operated on.[20] However, this new technique needs further long-term studies to prove its efficacy and to determine any adverse outcomes, such as cancer recurrence.

CONCLUSION

Lymphedema is a condition caused by an obstruction in the lymphatic system arising from a congenital anomaly, infectious disease, chronic inflammation, connective tissue disease, or cancer. Patients who are faced with this disease usually have a poor quality of life due to infection and limits to their ability to perform daily activities. Consequently, it is critical to provide early diagnosis and treatment as these are key to managing and conquering the lymphedema. A multidisciplinary team approach yields the best solutions and long-term outcomes for patients.

What is already known on this topic?

Lymphedema is a congenital and acquired disease with can cause swelling of the limbs. The most common symptoms are limb swelling and recurrent cellulitis of the limbs.

What this study adds?

It reviews the related clinical presentations, physical examinations, radiological studies, and new treatment options.

Potential conflicts of interest

The authors declare that there are no conflicts of interest related to this study.

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