LYMPHOEDEMA: PATHOPHYSIOLOGY, DIAGNOSIS AND TREATMENT OF A DIFFICULT DISEASE

A CAVEZZI AND I JAKUBIAK
Vascular Unit, "Stella Maris" Clinic, San Benedetto del Tronto (AP), Italy

INTRODUCTION

Lymphoedema is a syndrome characterised by oedema and other related tissue changes caused by an impaired lymphatic drainage, secondary to an organic disease and/or a functional deficit of the lymphatic system.

Lymphoedema of the extremities is a relatively common disease, the incidence being much greater than frequently expected. The underestimated diagnosis and the limited treatment options have resulted in a lack of interest amongst most physicians. Lymphoedema usually deserves diligent care, but treatment may give little satisfaction to the treating doctors and their patients.

From an epidemiological point of view, up-to-date information is still lacking and the latest figures are those of 1994 World Health Organisation (WHO) conference which accounted for a total of 140,000,000 cases of lymphoedema worldwide (mainly of parasitic origin). In fact, the incidence of lymphoedema could be much higher than previously estimated. Italian data confirms a high prevalence of secondary or acquired lymphoedema as well as a higher prevalence in the lower limbs than in the upper limbs.

PATHOPHYSIOLOGY

Physiologically, limb oedema is due to two different processes: I) an excess of inflow of fluids into the interstitium (oedema due to cardiac insufficiency, renal failure, venous insufficiency, etc.), II) a deficit of lymphatic drainage (the true lymphoedema). These two processes may co-exist in one patient.

Pathologically, lymphoedema may be subsequently divided into three categories: lymph stasis caused by organic disease (lymphoedema due to mechanical lymphatic insufficiency), by functional impairment of lymphatic system (dynamic lymphatic insufficiency, due to overload of the lymph flow), or by the co-presence of these two pathologic conditions (lymphoedema due to "safety valve" failure). This last condition frequently presents in conjunction with the post-thrombotic venous ulcer, where deep (and superficial) venous disease is subsequently complicated by lymph stasis due to overloading and organic disease of the lymphatic system.

Lymphoedema may be considered of primary or secondary nature. Primary lymphoedema may be congenital...
(e.g., due to aplasia or hypoplasia of lymph vessels and/or nodes, as in Milroy’s disease); may present early in life (before the twenties) or later in life (third decade or later) (Figure 1).

Secondary lymphoedema may follow parasitic infections (as in filariasis), surgery, radiotherapy, lymphangitis, erysipelas, trauma, chronic inflammatory disease such as rheumatoid arthritis, burns, malignancies in the lymphatic system (as in Kaposi’s sarcoma or other lymphomas), or malignancies elsewhere.

According to Foldi, the presence of any kind of oedema may indicate lymphatic disease and/or overloading of the lymphatic system and its related mechanisms such as proteolysis by macrophages. This clearly explains why treatment of swollen limbs should always be directed at correcting the lymphatic system decompenation.

Lymph is fluid with a protein content greater than 1g/dl. Since the lymphatic network normally reabsorbs and drains fluids and macro-molecules (especially macro-proteins), lymphoedema is a high-protein oedema which distinguishes it from other kinds of oedema caused by venous insufficiency, cardiac or renal failure, and protein metabolism alteration. This may explain the progressive and harmful fibrosis that characterises the deterioration of the lymphoedematous tissue. This transformation is reflected in the classification of lymphoedema, which is commonly considered a chronic, evolving, progressive disease with a strong propensity to cause invalidism. The disease is considered progressive as no true cure is possible in the majority of the cases, but this fact cannot justify treatment denial as appropriate therapies can help improve the patient’s condition in the long-term.
Typically, lymphoedema varies in severity and natural progression. According to the severity of oedema and the related complications a classification based on 5 stages of severity has been proposed:

- **Stage I** (subclinical). This stage is characterised by the absence of major draining lymph nodes or by localised and limited destruction of lymphatic channels. The limb is identical with its counterpart, as far as shape, volume and consistency are concerned. An example is lymphoedema of the arm following mastectomy with axillary lymphadenectomy where there is no change in the diameter of the affected arm. However, lymphoscintigraphy may demonstrate impaired lymphatic drainage;

- **Stage II**. This stage is characterised by the presence of soft oedema, usually worse in the evenings, and regressing spontaneously with the limb in the raised position. There is an increase in lymph stasis but with little fibrous tissue formation;

- **Stage III**: The oedema is constantly present (from early morning) and does not regress spontaneously in the supine position. It is harder and more fibrotic;

- **Stage IV** (Elephantiasis stage): This stage is characterised by permanent oedema and gross skin changes and thickening that deforms the structure of the limb (Figure 2). Dermatolymphangioadenitis (DLA) (erysipelas and lymphangitis) is quite frequent at this stage;

- **Stage V**: This stage is characterised by permanent oedema with serious deformation of the limb and considerable functional impairment due to relative muscular dystrophy. There are arthritic changes affecting the large joints and complicating intervening neurological disease. DLA is seen frequently and may affect the whole limb. This stage may even progress to neoplastic disease or it may easily lead to systemic infection, which explains the necessity for early intervention.

Infection of skin, lymphatic vessels and nodes (DLA), may be due to a deficient immune response in the affected limb. This may potentially result in life-threatening septicemia. Other possible complications are lymphorrea and lymphangiosarcoma. (The latter is a rare malignancy which may arise in the older patients or more advanced cases). A lymphatic ulcer may rarely develop in a lymphoedematous limb.

**DIAGNOSIS**

Diagnosis of lymphoedema relies upon a detailed history to establish the nature of lymph stasis (primary or secondary). Medical history should always take into account the possible presence of lymphoedema in the patient’s relatives, a history of trauma or infection in the affected limb, as well as previous operations. Physical examination should evaluate the degree of pitting in the oedematous region and the presence of co-existing skin changes which includes skin thickening as demonstrated by Stemmer’s sign (a failure to pick or pinch a fold of skin at the base of the second toe). Similarly the localisation of oedema should be noted (usually secondary lymphoedema does not affect the peripheral part of the limb, at least in the early stages), and signs of venous insufficiency can elucidate a venous stasis component. Although the vast majority of cases can be diagnosed clinically without other diagnostic procedures, a few of these methods may be very useful in the management of the disease, especially in complex, mixed cases.

Lymphoscintigraphy (Figure 3) is considered the most useful and feasible way to investigate lymphatic intake and transport. It helps in confirming the diagnosis and is important in guiding and monitoring the treatment. This technique is based on one or more (usually two) injections of a tiny quantity of albumin which is labelled with a radiotracer. A gamma camera depicts the drainage of albumin, which is typically reabsorbed and transported by the lymphatic system. Thus this examination may highlight possible obstructions and impediments in the macromolecular ascend along the main lymph collectors and nodes. Collateral pathways are visualised and a “dermal backflow” indicates stagnation (deficit of uptake) due to trauma or primary lymphatic disease.

A few other non-invasive diagnostic procedures have recently been proposed and developed. Colour-flow duplex imaging (CFDI) has become a mandatory tool to study arterial and venous disease, but recent applications of this method have also elicited its new role in lymphoedema imaging. When facing a swollen limb, CFDI is a reliable way to adequately diagnose and monitor therapy. There may also be certain applications for high-frequency probes in lymphoedema. In fact, CFDI may elucidate node enlargement, fluid collection, localisation and tissue characterisation. On duplex imaging fibrosis correlates with hyperechogenicity. Enlarged lymphatic vessels may also be visualised in some instances (Figure 4). Furthermore CFDI may be helpful in guiding and monitoring of the treatment (Figures 5 and 6). Magnetic Resonance Imaging (MR) and Computed tomography (CT) have enhanced lymphatic imaging capabilities, not only helping the scientific understanding of the process, but also favouring a better practical management of the lymphoedematous limb. CT may demonstrate honeycombing of subcutaneous tissues. Moreover, MR and CT adequately image non-vascular pathologies and the concomitant bone, joint, muscle, ligament deterioration associated with the advancement of the lymphatic disease.

Lymphangiography was used by the vast majority of investigators up until 15-20 years ago, but its invasiveness and harmfulness has made it obsolete and useless,
especially after the advent of lymphoscintigraphy. A recent diagnostic proposal utilising fluorescence microlymphangiography may have a scientific role, due to its ability to investigate lymphatic microcirculation.

By utilising these investigations, swelling in a limb may be attributed to lymphatic disease, and/or to venous disease. The combination of venous stasis and lymphoedema gives rise to phlebolymphoedema as in post-thrombotic syndrome or in Klippel Trenaunay’s syndrome (veno-lymphatic angiodysplasia). Similarly it has been recognised that lymph stasis is common in post-traumatic oedema (usually of high protein type), as well as in the reduced function of the plantar and calf muscle venous pump, which is typical in patients with osteo-arthropathies, and diminished mobility.

As lymphatic insufficiency may be much more common than expected, a careful diagnostic pathway should be the basis of management of a swollen limb. In the vast majority of cases, lymphatic impairment of organic or functional nature is involved, and specific treatments for lymphoedema (manual lymphatic drainage, bandaging and stocking, air pressotherapy, coumarin) may be useful.

MANAGEMENT

From the therapeutic point of view, lymphoedema is a complex disease and several modalities of treatment should always be employed. European and Australian schools have described this multi-faceted approach to lymphoedema in different terms (complex decongestive therapy, complex lymphatic therapy, complex physical therapy), but the aim has always been to manage lymph stasis by means of a holistic and integrated approach. According to the International Society of Lymphology Consensus Document, and following the subsequent innovations, a few principal treatments have been recommended.

Manual Lymphatic Drainage (MLD) (Figure 7) probably represents the cornerstone of the therapeutic approach, as it enhances protein reabsorption, improves lymphatic transport and favours the development and function of collateral pathways. Lymphoscintigraphic studies and clinical experience highlight the importance of MLD in limbs affected by lymphoedema, but its efficacy is objectively lower in the more advanced stages (stage IV and V).

Together with MLD, compression therapy has always been the most feasible and widespread form of treatment for lymphoedema. Bandaging is considered the initial method of choice stimulating protein uptake from the lymphoedematous tissue. Bandages and MLD are the two therapies which recover proteins the most. Bandaging also reduces the oedema and allows softening of the fibrotic tissues. Bandaging in lymphoedema should be of the multi-layer type, usually with short stretch bandages and utilising pads to increase or decrease the pressure according to Laplace’s law.

Elastic stockings or sleeves are usually used following intensive bandaging treatment. Stemmer stated that “bandages obtain a result, elastic dressings can maintain this result”. The use of elastic stockings and sleeves complies with patients’ expectations, thus improving their compliance; moreover these garments may maintain the results achieved during the intensive combined treatment, remodelling tissues and counterbalancing the lymph stasis. In case of lymphoedema, elastic stockings or sleeves should be of high pressure type: a 30-40, or 40-50 mmHg (at the ankle or at the wrist) garment, but in specific conditions a 20-30 mmHg, or even a 50-60 mmHg stocking may be required.
Other forms of treatment include both systemic (mainly oral) and topical medications. Coumarin has gained credibility, mainly due to studies by Casley-Smith. Topical or systemic Coumarin has been demonstrated to have a positive action on lymphatic flow, on protein lysis (macrophage activation) and protein recovery from the tissues. Flavonoids such as rutines and diosmin have been used, sometimes with satisfactory results.

Recent debate about air pumps (also called air pressotherapy) has led to a review of this physical method, which may specifically drain the fluid component of lymphoedema. Pressotherapy can be useful in low-protein oedemas as well as in lymphoedema. When dealing with lymph stasis (especially of a secondary type), it becomes mandatory to perform an adequate MLD session (or at least a sufficient inguinal or axillary lymph nodes clearance by means of MLD) before pressotherapy. This will help reduce the risk of fibrosis at the root of the limb, as pressotherapy may concentrate proteins, removing only fluid, thus resulting in a worsened condition if used as the sole method.

Every therapeutic program should also include anti-stasis exercises, such as isotonic movements and specific exercises under compression garments or bandages. Lymph needs muscle contractility to flow and adequate training may guarantee the maintenance and improvement of the initial outcomes. Physical exercise may be substituted with muscle electric stimulation that may enhance venous and lymphatic flow, even in bed-ridden or low-compliant patients (elderly, etc).

There are also literature reports about several other kinds of treatment that have never been sufficiently validated, including electric lymph stimulation, thermotherapy, immunotherapy, mercury pressotherapy and others.

Psychological help is sometimes necessary during both the intensive and maintenance periods, as most results will be lost due to patient’s non-compliance with further treatments or failure to adhere to hygiene rules which should be strictly respected to avoid DLA.

In cases of advanced lymphoedema a surgical approach may be indicated, even though its role remains controversial. Microsurgery with derivative or reconstructive operations may be beneficial in reducing advanced lymphoedemas (stage IV or V), but excision operations are still performed in selective cases. Microsurgery may include: a) the detour of lymph from lymphatic vessels and/or nodes to the venous system via micro-anastomoses, or b) the transposition of a lymphatic or venous segment along the diseased lymphatic system. These options need great skill in the operator and a delicate balance in the pressure gradients as well an adequate conservative therapy to maintain long-term results. Excisional surgery may be performed with lympholiposuction, or by the old-fashion Thompson’ or Charles’ operation.

Complications of lymphoedema include recurrent episodes of DLA highlighting the need for adequate prevention by means of cyclic usage of antibiotics such as penicillins or cyclosporins. Non-steroidal or steroidal (the latter in the worse cases) anti-inflammatory drugs may also be required. Fungal infections should be treated with appropriate anti-fungals but hygiene of the skin and great care of the extremities is highly recommended indefinitely.

The chronic disabling nature of lymphoedema and its natural deteriorating evolution may lead to a poor quality of life. Both the external appearance of the limb and the complex management of this disease make patients frustrated at most times, which explains the necessity of a multi-faceted approach. Only the synergic and chronologically correct application of different treatment modalities may lead to adequate control of lymphoedema of the lower or upper limbs.

**REFERENCES**