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Review

Lymphoedema: lymphoscintigraphy versus other diagnostic techniques – a clinician's point of view

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Abstract

This paper overviews the problem of the clinical basis, diagnosis and available therapy modalities for lymphoedema. Regarding diagnostics, the measurement of circumference, volume and thickness of the limb are presented, as well as diagnostic imaging modalities. These include direct and indirect lymphography, MRI, CT, ultrasound imaging and lymphoscintigraphy, which is currently considered the leading technique in primary diagnosis of lymphoedema and its follow-up. This paper discusses the treatment of lymphoedema and the role of lymphoscintigraphy in the follow-up of patents with lymphoedema.
Key words: lymphatic oedema, diagnostic imaging, lymphoscintigraphy

Introduction

Clinical basics

Lymphoedema can be defined as the progressive, protein-rich fluid accumulation in the interstitial spaces of the skin that arises as a consequence of impaired lymphatic drainage [1, 2]. It can occurr in all parts of the body. However, limbs are most often affected.

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Lymphoedema of the lower or upper extremities is typically a chronic condition either congenital or acquired. It may be primary or secondary to the presence of other diseases or occur following surgical treatment. The disorder typically affects the dermis and spares the deeper compartments of the skin. If left untreated it will continue to progress and becomes irreversible due to the increased formation of fibres or adipose tissue [2]. Patients with lymphoedema experience extremity swelling, decreased coordination and mobility of joints — mostly elbows, knees and ankles. Approximately 30% of patients with lymphoedema complain of pain in the lower and upper limbs [3].

There is a higher risk of infections and injuries. Recurring skin and subcutaneous tissue inflammations also involve small lymphatic vessels. All these disorders lead to an increased risk of swelling and secondary scarring. Permanent movement disorders, a feeling of limbs heaviness, the necessity of everyday self-care management and psychological difficulties can lead to social changes in patients' lives [2, 4].

The disease can often be diagnosed by its characteristic clinical presentation, yet, in some cases, ancillary tests might be necessary to establish the diagnosis, particularly in the early stages of the disease and in oedemas of mixed etiology [2]. At the initial medical evaluation of patients with suspected extremity lymphoedema, it is highly desirable for physicians to define the abnormality and to establish an objective baseline. Before instituting a therapeutic plan it is very important to determine whether the suspected abnormality is ideed a lymphatic abnormailty [3, 5–7]. The differential diagnosis of extremity lymphoedema includes venous disease and systemic disease (e.g., hypoalbuminemia) [2].

Primary lymphoedema may occur at any phase of life but it most commonly appears during puberty. Lymphoedema praecox is a special type of primary lymphoedema in pediatric patients. It is usually mild but often impairs quality of life and entails risk of lymphangitis.

Secondary lymphoedema is encountered more often. The most frequent worldwide cause of lymphoedema is filariasis, which is particularly common in south-east Asian underdeveloped countries. In the USA, post-surgical lymphoedema of prevails. Radical lymphadenectomy or obliteration of lymphatic vessels by scar or following radiotherapy may lead to lymphoedema after cancer treatment. It may appear at any time after surgery.

Lymphoedema is a quite a prevalent disease. Worldwide, about 90 million people have lymphoedema, primarily because of parasitic infections. Approximately 10 million people have lymphoedema secondary to breast and pelvic cancer therapy, recurrent infections, injuries or vascular surgery. When chronic venous insufficiency is added as a case, there may be as many as 300 million cases [5,8,9]. The reported incidence of secondary lymphoedema after mastectomy varies amongst different published series from 5.5 to 80% reviewed by Szuba and Rockson [2]. In other studies, it varies between 24–49% [10, 11]. In Europe, its prevalence is up to 0–60% depending on the mode of breast cancer treatment and on different methods of measurement and definition of lymphoedema [12]. Complications of chronic limb lymphoedema include recurrent cellulitis and lymphangiosarcoma. Filarial infestation can cause massive swelling (elephantiasis) with associated infection and ulceration.

Rehabilitation is an integral part of lymphoedema treatment. It helps to minimize and limit the unwanted physical changes such as decreased mobility and muscle strength. Most patients are treated conservatively, by means of various forms of compression therapy. Prevention is important, as treatment is difficult. There is no effective pharmacological cure supporting therapy. Benzopyrones are considered as drugs that can reduce protein-rich oedema by their influence on proteolysis processes [2]. The use of diuretics is not recommended. Antibiotics are used to control the skin infection.

Surgical treatment is frequently unsuccessful. Lymphatic microsurgery (lymphatic transplants, lymphatico-venous or lymphatico-lymphatic or lymph node-venous anastomoses) is still in an experimental stage, although few centres consistently report favourable outcomes. Volume reducing surgery is performed rarely. A muscular-venous by-pass associated with ultrasound liposuction may be performed [13].

This paper overviews the radionuclide diagnostics in the detection and follow-up of lymphoedema as compared to other diagnostic methods. It also overviews the pathology and treatment of lymphoedema.

Diagnosis of lymphoedema

Clinical evaluation

Various clinical classification systems have been developed to describe the severity of lymphoedema [2]. According to one of them, there are three clinical stages of lymphatic oedema:

— 1st — reversible oedema. It disappears spontaneously, or when the limb is elevated;
— 2nd — irreversible oedema. Elevation of a limb does not decrease swelling to a considerable extent;
— 3rd — lymphatic elephantiasis with huge increase in size of the limb and hardened skin [7].

Frequently used objective measures of lymphoedema include circumferential measures of limbs at various points, volumetric measurement using limb submersion in water, recording deformation of tissue by mass (tonometry), measurement of impedance (amount of extra cellular water and total water content) and diagnostic imaging.

Measurement of limb size and shape

Circumferential measures with calculations designed to compute limb volumes and volumetric measures are used most frequently in everyday practice, but have some difficulty with reliability [14].

Tape measurement

This method provides information on localization of swelling. A measurement is made with a tape at marked points on a limb. Results are referred to values of an unaffected limb. Criteria for identification of lymphoedema differ from side-to-side difference of 1, 5 or 2.5 cm even to an increase of 5 cm [15]. Errors are usually caused by excessive tape-measure pressure on tissues, inaccurate marked points and improper measuring angle in relation to long axis of the limb [16].

Water displacement volumetry

Water displacement volumetry is a direct measurement of limb volume submerged in a scaled container of water. Arm lymphoedema is defined as an increase in volume of 10% or at least 200 ml from the preoperative measurements [15, 17, 18]. However, it is time-consuming and improper in the case of skin damage and joint movement limitation [16].

Optoelectronic volumetry

This method is based on the interruption of infrared light beams by the limb placed inside a special device with rows of infrared light emitting diodes. The volume is calculated automatically. This method is probably the most accurate way of limb volume evaluation, but the cost and size of the equipment, difficulty to use it outside the hospital and impossibility of measurement of the full length of the limb are major drawbacks [16].

Measurement of the fluid mobility

Tonometry

Tonometry is a method used for the assessment of physical characteristics of lymphoedema. The clinical pitting test is subjective evaluation made by pressing a finger on the site of the swelling. Objective determination of the depth of tissue pitting is provided by using a tonometer, which measures the depth of compression by an applied mass, and is read after a fixed period [16].

Measurement of impedance

Monitoring impedance to a small current passed through the body might give information about total extra cellular water and total body water [16]. This method is considered a very useful tool, especially in early stages of lymphoedema, but fails, when the swelling is mild. 50% of women after mastectomy with observed increase of limb volume (volumetrically measured) did not show any changes in bioimpedance measurements [15].

Diagnostic imaging of lymphoedema

Available modalities include contrast lymphography, indirect lymphography, lymphoscintigraphy, lymphatic capillaroscopy, magnetic resonance imaging, computed tomography and ultra-

sonography [2]. Lymphatic capillaroscopy is available only in specialised centres [2].

Contrast lymphography

Contrast lymphography is accomplished through the direct injection of iodine based, lipid-soluble contrast media into subcutaneous lymphatic vessels, identified prior to the study by subcutaneous injection of blue dye. It is an old technique, introduced in 1944 [19] and refined in the nineteen-fifties [20]. Its use has declined recently, superseded by lymphoscintigraphy as a primary diagnostic tool, although it is still useful in visualizing lymphatic anatomy prior to lymphatic reconstructive surgery [2]. It is also carried out in patients, when the lymphoscintigraphy results are thought to be misleading [21].

Some authors still strongly advocate this technique [22]. They argue that the unique ability of lymphography to demonstrate derangements of the internal architecture of normal-sized lymph nodes can be valuable and makes it more accurate than CT in evaluation of some lymphomas (especially Hodgkin disease) and genitourinary malignancies. They believe that lymphography and CT are complementary rather than mutually exclusive techniques for the staging of some lymphomas and genitourinary malignancies. In addition, lymphography opacifies the lymphatic channels and therefore may be a valuable tool for detection of lymphatic fistulas or lymphatic leakage. Finally, the authors believe that lymphography helps to guide subsequent therapy in patients with lymphomas, genitourinary malignancies, or disorders of lymphatic flow [22]. This may be correct, but rather in secondary, not primary lymphoedemas.

Additionally, this technique presents many technical difficulties and may exacerbate lymphoedema by the pooling and accumulation of oil-based contrast media.

Indirect lymphography

Indirect lymphography is based upon an intradermal infusion of water-soluble iodinated contrast media [23]. It is particularly useful in imaging skin lymphatics and lymphatic trunks. It is useful both as a primary diagnostic tool and prior to lymphatic reconstructive surgery.

Magnetic resonance imaging

Magnetic resonance imaging is a useful tool in differential diagnosis of limb oedema. In lymphatic oedema, there is a characteristic MRI image of a honeycomb pattern within the epifascial compartment along with thickening of the skin. In venous oedema, both the epifascial compartments are affected. In lipoedema, there is a fat accumulation without fluid [25]. Other typical findings are trabecular structures suggesting dilated collateral lymphatic vessels in the swollen subcutis [26]. Magnetic resonance imaging is also useful in lymph node imaging, visualising enlarged lymphatic trunks and identifying the underlying cases of secondary lymphoedema. Magnetic resonance imaging of lymphatic vessels may be enhanced with tissue-specific iron contrast media [27].

Computed tomography

Computed tomography's (CT) usefulness in diagnosis of lymphoedema is rather limited. It provides definition of oedema localisation (subfascial vs. epifascial), identifies skin thickening and the characteristic honeycomb pattern of the subcutaneous tissue [2, 28]. CT may be useful in monitoring the outcome of compression therapy [29]. Oedema fluid accumulation is readily demonstrated with a plain CT scan and is not present in lipoedema. Specific CT features of the subcutaneous fat and muscle compartments also allow accurate differentiation between lymphoedema and deep vein thrombosis.

Ultrasound examination

Ultrasound examination (US) plays an ancillary role in non-invasive diagnosis of lymphoedema. It shows the thickening of the cutaneous, epifascial and subfascial tissue compartments, interstitial fluid accumulation and sometimes it allows evaluation of the degree of fibrosis. High frequency ultrasound reveals characteristic patterns of cutaneous fluid localisation in various types of oedema [25, 30].

Balzarini et al. showed by US fluid accumulation in 35%, fibrosis in 26% and a mixed picture (fibrosis and fluid) in 40%. Correlation with clinical information ("soft," "medium," "hard", and "pitting" oedema) demonstrated that US documented interstitial fluid in 68.4% of soft oedema, mixed fluid and fibrosis in 64.2% of medium oedema, and fibrosis in 76.9% of hard oedema. Ultrasonography also showed that in soft and medium oedema, fibrosis might already have formed [31].

Colour Doppler ultrasound augments the findings of lymphoscintigraphy, when the two are performed together [32]. There is an influence of development of fibrosis on US results — subcutaneous tissue is more echogenic on the oedematous side, with significant hyperechogenicity at the fascial subcutaneous layer, which indicates that fibrotic tissue develops distally in the forearm [33].

Some findings substantiate the unique role of this modality in the evaluation of filariasis in secondary lymphoedema. With use of a standard transducer, Amaral et al [34] were able to detect indwelling motile adult nematodes in the groins of patients in Recife, Brazil, an endemic area for such parasites.

Fluorescein microlymphangiography

Intradermal injection of fluorescein isothiocyanate dextran allows visualization of the superficial peripheral microvasculature, including the contractility, permeability and diffusion characteristics of local blood and lymph capillaries [35, 36]. Diameters of lymph capillaries can be determined from sequential video-recorded images of the injected field. Findings indicate that patients who have had lymphoedema since childhood have aplasia of lymphatic microvessels, whereas those in whom lymphoedema first appears during puberty (lymphoedema precox) have intact lymphatic capillaries (initial lymphatic vessels) in conjunction with hypoplastic lymph trunks more proximally [36].

Lymphoscintigraphy

Today, lymphoscintigraphy is the primary imaging modality used in determining a diagnosis in patients with suspected extremity lymphoedema. Lymph node evaluation with radiotracers dates back to the 1950s [37]. This method has largely replaced

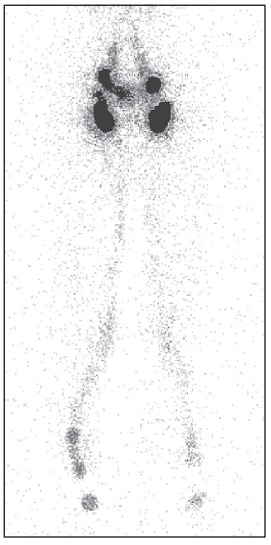

Figure 1. A normal pattern of lymphoscintigraphy of the lower limbs.

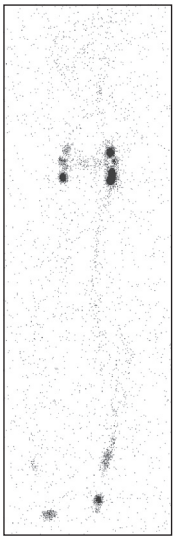

Figure 2. An abnormal pattern of lymphoscintigraphy of the lower limbs.

the more invasive and technically difficult technique of lymphography [38]. Lymphoscintigraphy has been refined over the past few decades and has proved reliable and reproducible [2]. The study is non-invasive with no known adverse effects. In addition, the radiation dose received during the examination is low, and the study can be repeated after therapy [5]. Some authors underline the high sensitivity, but — at least in some cases — insufficient specificity — which may mistakenly classify some normal legs as lymphoedematous [39].

Performing lymphoscintigraphy

Radiotracers

Early studies were performed using colloidal gold-198 [37]. Due to the high radiation burden this was subsequently replaced by technetium-99m agents: sulphur, rhenium, stannous sulphur colloids, antimony sulphide colloid, albumin colloid, microaggregated albumin and human serum albumin [40, 41]. Today, probably Millipore filtered technetium-99m sulphur colloid is the most commonly used radiotracer for lymphoscintigraphy, being inexpensive, with a very good safety profile and demonstrated clinical value, although some authors believe (99m)Tc-HIG is marginally superior to nanocolloid and sulphur colloid for this purpose [41].

Imaging

Most often, 74-296 MBq of ^{99m}Tc sulphur colloid suspended in 0.10 ml of saline is injected into the interdigital web spaces between the first and second digits on the patient's right and left lower (or upper) extremities. Intradermal injection is superior to the subcutaneous [41]. Both of the feet (or hands) are massaged for 2 minutes immediately after the injection. A high-resolution collimator is always used. The camera speed is set at 8 cm/min, and images of at least 300,000 counts are acquired. Images should be recorded with a dual-head gammacamera, using high-resolution collimators in whole-body scanning mode and a scan speed of 10 cm/min [42]. A flow study is performed, and the arrival of radionuclide delivery to the knees and groin (or to the elbows and axillary regions for the arms) is timed. Spot and whole-body images are obtained for up to 3–4 hr; the study may be also tailored to the need of individual findings [43]. Quantitative or semi-quantitative approach to lymphoscintigraphy may improve the results of the study [2, 23]. Quantitation of the regional lymph node accumulation of radiotracer is preferred [23].

Normal findings

In patients with normal lymphatic anatomy and function, a predictable sequence should be seen in lymphoscintigraphy. In the lower extremities, symmetric migration of the radionuclide should be seen through discrete lymph vessels (three to five lymph vessels per calf and one to two per thigh). Then bilateral visualization of ilioinguinal lymph nodes should occur within 1 hr, as should visualization of the liver because of the systemic circulation of the radiocolloid [1, 41, 43]. Typically, approximately one to three popliteal nodes and two to ten ilioinguinal nodes are visualized [38]. A parallel sequence should be seen in the upper extremities. A normal pattern of lymphoscintigraphy is shown in Figure 1.

Abnormal findings

On lymphoscintigrams with abnormal findings, a variety of findings can be identified, including interruption of lymphatic flow, collateral lymph vessels, dermal backflow, delayed flow, delayed visualization or nonvisualization of lymph nodes, a reduced number of lymph nodes, dilated lymphatics and, in severe cases, no visualization of the lymphatic system at all [1, 6, 38]. Purely qualitative analysis has been reported to be very accurate for confirming or excluding the diagnosis of lymphoedema, with a sensitivity as high as 92% and a specificity as high as 100% [1]. An abnormal pattern of lymphoscintigraphy is shown in Figure 2.

Despite earlier reports, most authors believe that primary lymphoedema cannot be reliably differentiated from secondary lymphoedema on the basis of lymphoscintigraphic findings alone [1, 6, 38]. Some authors have reported that lymphoscintigrams of patients with primary lymphoedema tend to show a lack of lymphatic vessels and absent or delayed transport, whereas those of patients

with secondary lymphoedema tend to show obstruction with visualization of discrete lymphatic trunks and slow transport [5]. In both primary and secondary lymphoedema, however, both dermal back-flow and a decreased number of lymph nodes can be identified [26].

Conservative therapy of lymphoedema

Despite the common opinion about treatment inefficacy, lymphoedema can and should be treated. The earlier treatment begins after the onset of the disease the better is the prognosis for the patients [49]. Treatment is aimed at reducing swelling, educating patients and families. Decreasing limb swelling improves function and reduces the risk of infections. Improvement of clinical appearance also has an advantageous influence on the mental condition of patients [50].

Lymphoedema can be treated in a number of physiotherapy techniques applied in various combinations.

Complex physical therapy (CPT) or complete decongestive therapy (CDT)

This method combines lymphatic drainage, compression, positioning, special exercises and skin care techniques performed as treatment sessions usually from 2 to 4 or 6 weeks [2, 51]. It is carried out either as outpatient or inpatient treatment.

Manual Lymph Drainage (MLD)

Manual lymph drainage is focused on draining oedematosus tissue by stimulating the lymph system, which increases normalisation of microlymphatic hypertension and prevents fibrous processes in subcutaneous tissue [45, 52]. The massage permits unblocking of the central lymphatic system and facilitates the lymph flow from peripheral lymphatics [2]. This procedure should be carried out by skilled practitioners [53, 54]. The complexity of the technique requires a special education program and the technique must be checked constantly.

Bandaging

To continue the stimulation and the shape of the limb after each session of MLD multilayer bandaging (MLB) is applied. It is fastened on the wrist area and then a narrow band goes throughout the dorsal part of the hand to the fingers, binding them up one by one. Next, a wider bandage binds up the forearm, arm and shoulder. This way of bandaging permits limb movement and stretching bandages stimulate lymph flow.

Exercise and positioning

Special exercises are always a part of CPT to supplement the compression bandages and stimulate lymph drainage by muscular movement. They are performed 2 or 3 times a day for several minutes. Leaving a limb in bandages during the exercises is an advantage. To mobilize lymph flow there should always be breathing exercises included in the program. Negative pressure oscillations in the chest induce the return of venous blood to the heart and lymph flow to the venous system [55].

Compression therapy

Once swelling is reduced compression stockings or sleeves should be applied to prevent re-accumulation of fluid. The degree of compression ranges from 30–40 mm Hg. Using of a higher compression is less tolerated by patients [2]. Combining with other modalities does not increase the reduction of swelling [56]. Other authors, however, are paying attention to the short term benefits when this method is used as a primary therapy, emphasizing benefits in reduction achieved after a few months of combined physiotherapy treatment [12].

Education

Systematic patient education is an important element of CPT. Self-help recommendations to manage lymphoedema include suitable skin care to prevent deterioration and infection. Tight clothes, jewellery, airplane flights or even using an elevator may cause or increase swelling. Proper diet and weight control are also recommended [57, 15]. Many patients point out strong physical work as a factor causing or increasing swelling. However, it has not been shown in many studies [57].

After completion of an intensive 4–6 week regimen of complex therapy, the frequency of the physical treatment sessions should progressively decrease [58]. The benefits achieved by physical therapy may decline in time [49, 59].

Intermittent pneumatic compression (IPC) or sequential intermittent pneumatic compression (SIPC)

This form of lymphoedema management can be used as a primary or with the addition of other methods. Exerting temporary compression during operation with single or multichamber pneumatic pump facilitates lymphatic drainage and removes fluid from the extremity. It is reported that forceful fluid displacement can damage lymphatic-vessels, induce lymphangiitis, increase swelling and tissue fibrosis [2].

Some studies suggest no efficacy of IPC treatment alone in the therapy of lymphoedema [60]. Recently Szuba observed good toleration and no complications after using IPC with elements of CPT. The reduction of volume was significantly greater than in the control group only with CPT treatment [61].

The role of lymphoscintigraphy in the follow-up therapy of lymphoedema

As shown above, lymphoedema is notoriously difficult to treat. Lymphoscintigraphy can be repeated after therapy to provide an objective measure of the disease status in patients [5, 45, 46]. Boris et al. reported that 30 patients whose progress was followed up for as long as 1 year after complex lymphoedema therapy had an average 86% decrease in their initial extremity volume [44]. Other authors, however, found no changes in lymphatic flow in patients treated by sequential intermittent pneumatic compression (SIPC) and assessed by lymphoscintigraphy. The authors argue that compression increased the transport of lymph fluid (i.e., water) without comparable transport of macromolecules (i.e., protein). Alternatively, SIPC reduced lymphoedema by decreasing blood capillary filtration (lymph formation) rather than by accelerating lymph return [47].

Regarding lymphatic surgery, lymphoscintigraphy is also helpful, not only in planning microsurgical treatment but also in moni-

toring the postoperative outcome [48, 62, 63], although some authors prefer using an ultrasound [64, 65]. Some believe that lymphoscintigraphy is diagnostic but cannot be repeated frequently in the follow-up [65], which can be disputed. Lymphoscintigraphy as a method of evaluation has proved to be very sensitive, reproducible and able to measure the transport capacity in follow-up study in patients with transplanted lymphatic vessels in upper [48] and lower extremities [62, 63]. In patients 8 years after microsurgical treatment of lymphatic vessels of an upper extremity, lymphatic function was reported to improve after autologous lymphatic vessel transplantation compared with preoperative findings. This could be verified by a statistically significant decrease of the transport index — TI (< 0.01), clear demonstration of lymph nodes, and a less diffuse distribution pattern of the Tc-99m-labeled nanocolloids [48]. In another study, in 122 investigations of upper and lower extremities, TI was found to be very sensitive (97.4%) with specificity 90.3% [62]. Patients with scintigraphic visualisation of the vessel graft showed a substantially better postoperative outcome than those without visualisation of the vessel graft [63]. An important role of lymphoscintigraphy has been also confirmed in coordinated imaging of the follow up percutaneous sclerotherapy of lymphangiomas, utilising doxycycline as a sclerosant [66].

Some reports deal with the pharmacological treatment of lymphoedema. Freedman et al followed-up the efficiency of diethylcarbamazine treatment on lymphatic damage in human bancroftian filariasis [67].

Conclusions

There is hope for decreased morbidity of lymphatic oedema due to the increasing role of selective surgery of lymph nodes, following the sentinel node concept. However, the impact of such a procedure on the incidence of post surgical lymphoedema has not been thoroughly assessed yet. On the other hand, the higher incidence of breast cancer and longer survival of patients is likely to cause increased prevalence of arm lymphoedema, which may develop many years after surgery. Further studies of early diagnostic methods, evaluation of lymphoedema over a period of time, development of new therapeutic techniques and finding methods to assess objectively the effects of therapy are of extreme importance. These will remain an interesting meeting-point of diagnostic imaging specialists, surgeons and physiotherapists. It will permit better understanding of physiopathology of lymphoedema, identification of individual risk factors of swelling in order to undertake preventive measures of the onset of lymphoedema and ensure appropriate care, particularly for women treated for breast cancer.

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