Diagnostic application of lymphoscintigraphy in the management of lymphoedema

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Abstract

Lymphoedema (LOE) is an under-diagnosed condition which can cause severe incapacitating swelling of the extremities. Misdiagnosis and/or delayed diagnosis are common and the goal of further evaluation is to confirm the cause and determine the type and site of lymphatic obstruction. Lymphoscintigraphy (LSG) is a minimally invasive way of evaluation of the lymphatic system and can be used in the management of the LOE patients. However, many aspects of this useful diagnostic procedure are not fully explained in the medical literature. In this article we briefly explain the etiology and pathophysiology of LOE. Methodology and applications of LSG for the evaluation of this disease are extensively reviewed.

Introduction

Lymphoedema (LOE) is a chronic disease of the lymphatic system which can cause severe incapacitating swelling of the extremities. It is also a common disease especially the secondary type [1-4]. Although LOE is not associated with pain it can have a significant impact on the quality of life [5]. Despite the common belief that the treatment of LOE is not effective, there are several treatments which can decrease the patients' suffering significantly [6]. Early and correct diagnosis of LOE can be very helpful and lymphoscintigraphy (LSG) is a non-invasive tool in this regard [7]. In addition to aiding the diagnosis, LSG can determine the severity of LOE, predict treatment efficacy and be used for follow-up of the patients to evaluate response to treatment [6, 7].

Pathophysiology and etiology

The underlying pathology of LOE is dysfunction of the lymphatic transportation system. Any pathological process that disrupts the lymphatic systems can cause LOE, these include trauma, surgery and radiotherapy, infection, and congenital abnormalities [6, 8].

According to the underlying pathology, LOE is traditionally classified into two main categories: primary and secondary. The etiology of primary LOE is usually congenital abnormalities in the lymphatic system. On the other hand the underlying etiology of secondary LOE is obstruction or interruption of the normal lymphatic tract [8]. More recent classifications focus on the clinical stage of LOE [9] or emphasize the underlying anatomic abnormality of the lymphatic system in an attempt to plan treatment [10, 11].

The primary lymphoedema

Primary LOE can be divided into several categories depending on the age of onset. Milroy disease is the autosomal dominant form of primary LOE with the very early age of onset [12]. The underlying pathology in this disease is agenesis of the lymphatic system and it is typically bilateral. Lymphoedema praecox is characterized by the age of onset of 1-35 years. The etiology of this kind of LOE is hypoplastic lymphatic system and is usually unilateral [7, 12]. Lymphoedema tarda usually starts after 35 years of age and there is much debate regarding its etiology [7].

A very rare cause of primary LOE is valvular incompetence and resulting chylous reflux, which is associated with severe leg swelling [6, 13].

The secondary lymphoedema

The cause of the secondary LOE is extrinsic damage of the lymphatic system. This can be iatrogenic due to surgery and/or radiotherapy or as a result of, trauma, or infection [14, 15]. Axillary lymph node dissection for breast cancer staging is one of the most common causes of secondary LOE. In some developing countries, filariasis is the most common cause of LOE [1].

Diagnosis

Usually the diagnosis of LOE is made on the clinical basis. This is especially true for the patients with severe LOE. However diagnosis of early stage LOE can be very hard to make which may lead to delay in treatment [6].

Lymphoscintigraphy is a non-invasive procedure which can be very helpful for diagnosis of LOE. Unfortunately this diagnostic test has not been fully evaluated in the medical literature and textbooks. In the rest of this article, we discuss this procedure in detail.

Lymphoscintigraphy

Since its introduction in 1950s, LSG has become an invaluable tool for evaluation of lymphatic system and has almost replaced lymphangiography [16]. In this procedure after injection of a particulate radiotracer into the soft tissue of the organ being examined, imaging is performed to evaluate the lymphatic system and lymph nodes. Almost all aspects of LSG

like the type of the radiotracer, the site of injection, the time of imaging, etc are controversial and each institution needs to have its own protocol considering the local and logistical issues.

Radiotracers

Several radiotracers are in use for lymphoscitigraphy. These tracers are usually bound to technetium-99m (^{99m}Tc), which is an ideal radioisotope for imaging. Technetium-99m-antimony sulfide colloid (^{99m}Tc-SbSC) [17-19], ^{99m}Tc-sulfur colloid (^{99m}Tc-SC) [6] filtered [20] or unfiltered, ^{99m}Tc-human serum albumin (^{99m}Tc-HSA) [21, 22], ^{99m}Tc-dextran [23, 24], and many others are among these tracers. Technetium-99m-SbSC is readily available and used as the main radiopharmaceutical in the Institution of the first two authors [25].

The main difference between these tracers is the size of their particles. Small particles could penetrate the blood vessels and would increase the background activity and large particles would not enter the lymphatic system at all [6]. The best particle size for LSG imaging is believed to be 50-70nm [26]. Particle size in ^{99m}Tc-SC is usually larger than that of other radiotracers and this can result in slow transit of the tracer in the lymphatic system and non-visualization of the lymph channels [20]. Smaller particle size in ^{99m}Tc-SbSC and ^{99m}Tc-HSA ensures a more rapid study and better visualization of the lymphatic channels [6, 7, 20]. Lymph nodes are usually visualized earlier after injection (15-20min) with these radiotracers [7]. These tracers with smaller particle size are usually preferable for quantitative studies [27, 28].

Injection, techniques and dosage

Subcutaneous, intradermal, and sub-facial injections have all been used for LSG. However the best site for injection is still debatable. Many prefer the subcutaneous technique [29-31], and others believe that intradermal injection is the best [7, 28, 32, 33]. In our department, we use the subcutaneous technique which is not that painful compared to the intradermal technique [34]. Some authors suggest that the injection technique should be chosen according to the type of the tracer used, while the subcutaneous injection is probably the best for colloidal and intradermal injection for non-colloidal tracers [35]. O'Mahony et al. (2006) recommended the intradermal injection of the tracer for assessment of LOE in breast cancer patients because of direct access of the tracer to dermal lymphatics [36, 37].

Others suggested that for differentiation of post-thrombotic leg swelling from LOE, both epifascial and subfacial lymphatic systems should be evaluated since in LOE-in contrast to the former- both of these systems are defective [38, 39].

The dose of the tracer also differs in different studies. Others used intradermal injection of 18.5MBq ^{99m}Tc-HSA in the second web space of the foot or hand [7]. Others used 18.5MBq of this tracer in two divided doses in the second and third web spaces of each foot or hand [6]. It is worth mentioning that in both extremities, affected and non-affected limbs should be injected, for comparison, unless chylous reflux is suspected in which only the unaffected limb should be injected [13, 40].

Imaging techniques

Some authors recommended dynamic imaging after injection of the radiotracer [7, 41, 42]. Others recommended only whole body imaging in different intervals post injection. Usually two sets of images are taken: early at 10-30min post injection and at delayed 3-4h post injection [6, 7]. Others reported that early images could be normal, despite proven LOE in some patients, and recommended performing delayed imaging even with a normal set of early images [43]. Another set of image, at 1-2h is also recommended by some authors [6]. A few studies recommended single photon emission tomography of the affected limbs as well [44-46]. In our department we perform an early at 10-30min post-injection and a delayed at 3-4h post-injection, imaging.

The images should be taken by a high resolution low energy collimator with the photopeak centered at ^{99m}Tc energy. It is desirable that the speed of the whole body imaging is slow: 10cm/min, to ensure the detection of minute amount of tracer in the lymphatic channels. Some authors recommend a stress activity after the first set of images. This activity can be walking, massage, squeezing a ball, etc [17, 23, 29, 30, 47]. A change in the lymphatic pattern after stress can predict good response to physical treatment.

Quantitative LSG can also be performed with good results. It is claimed to be more sensitive for detection of LOE [29, 48-50]. Regional lymph node uptake [35, 41, 49], clearance of the tracer from the injection site [6, 51] and an even rate of appearance of the soluble molecules in blood [51] have all been used for quantitative purposes. Modi et al. (2007) in an excellent review of this condition, presented the removal rate constant of the tracers from the interstitial tissues in the best quantitative method for LSG [52].

Indications of lymphoscintigraphy in the management of lymphoedema

Diagnosis of lymphoedema

Lymphoscintigraphy is a non-invasive procedure for differentiation of LOE from other causes of limb edema [7, 53, 54]. Differential diagnosis of a swollen limb constitute systemic causes such as cardiac failure, lipoedema, deep vein thrombosis, and many others which can be readily differentiated LOE by LSG [7, 55]. The sensitivity and specificity of LSG for the diagnosis of LOE are reported to be high [19, 55]. It should be considered that some authors have reported that LSG can be abnormal in patients with chronic venous insufficiency, which can be due to lymphatic impairment in this condition [56].

The normal pattern of LSG is symmetric movement of the tracer in the extremities, discrete lymphatic channels, early visualization of regional lymph nodes: within 15-20min [7], and visualization of liver in 1h [41] (Fig. 1). In the lower limb, popliteal lymph nodes are reported to be seen in normal studies [29]. Other studies disagree and stated that popliteal nodes

visualization after superficial injection of the radiotracer is the sign of lymphatic dysfunction [30]. Our experience corroborates the latter. Figure 2 shows normal LSG of a patient.

Abnormal findings in LSG are reported to be: asymmetric visualization of the regional lymph nodes (Fig. 3) or even non-visualization in severe cases, dermal backflow, which is attributed to small collateral lymph vessels [7], interrupted, dilated and/or collateral lymph channels, and decreased number of regional nodes [6, 19, 31]. Figure 4 shows an abnormal LSG of a patient with primary LOE. Although some authors claimed that the pattern of LSG is different in primary and secondary LOE [7], most studies stated that these two entities can not be differentiated by LSG [41].

Lymphoscintigraphy can also be performed for the diagnosis of chylous reflux from the normal extremity to the abnormal one. In this situation only the normal limb should be injected with the radiotracer [13, 40, 57] (Fig. 5).

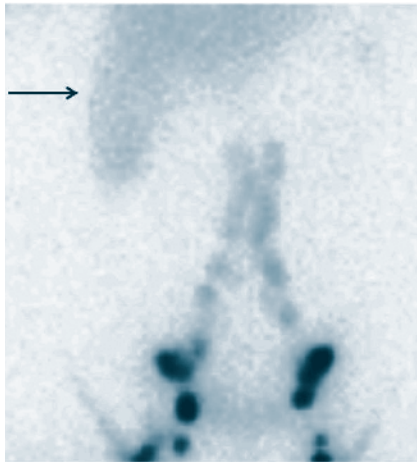

Figure 1. Abdominal and pelvic 1h view of a normal lymphoscintigram. Usually two to ten inguinal lymph nodes are seen on each side. Note the clear visualization of the liver (arrow).

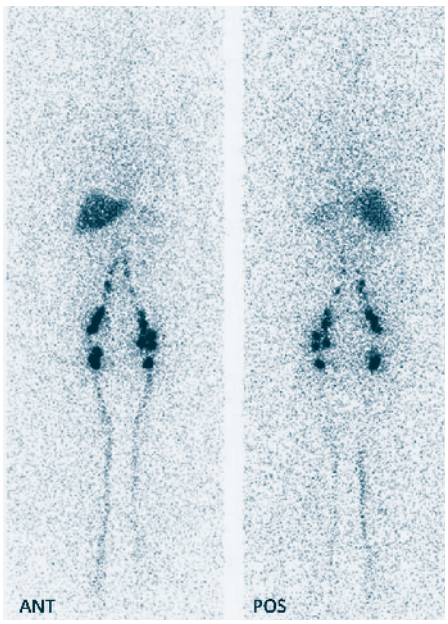

Figure 2. Normal 4h lymphoscintigram. Note the clear visualization of lymphatic channels, inguinal lymph nodes, and liver.

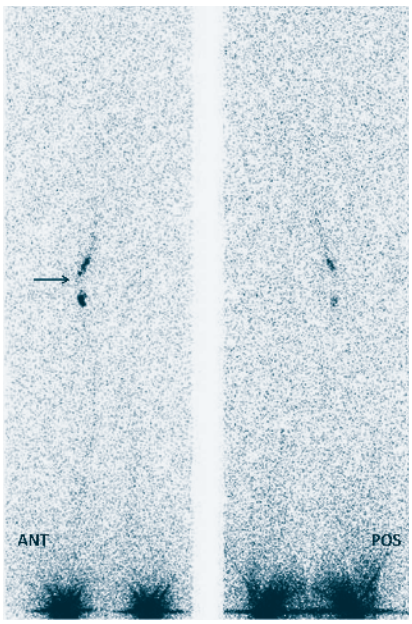

Figure 3. Abnormal 20min lymphoscintigram of a patient with left lower extremity lymphoedema. Note visualization of the inguinal lymph nodes only on the unaffected side (arrow).

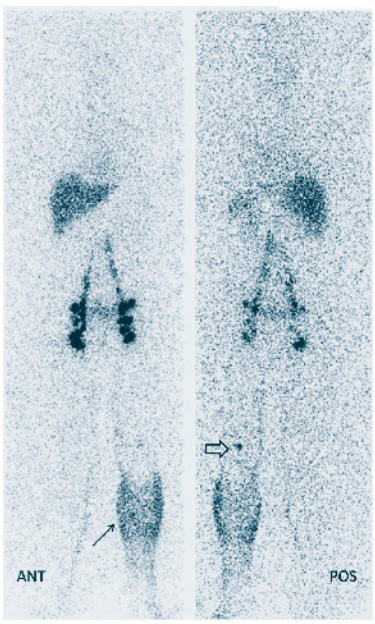

Figure 4. Four hour lymphoscintigram of a patient with left lower extremity lymphoedema. Note significant dermal backflow (arrow) in the calf, and visualization of a popliteal lymph node on the left side (hollow arrow).

The thoracic duct is not usually well seen on the LSG images, however this technique has been used to evaluate thoracic duct abnormalities with some limited success [58]. Lymphatic leakage can also be seen easily by LSG [59, 60].

Assessment of response to treatment

Several studies have evaluated LSG for the follow up of the lymphoedematous patients after various treatment protocols [45, 61-65]. Improvement of the lymphatic drainage has been confirmed after treatment in these studies. In contrast, others did not find any significant change in the LSG pattern even after effective treatment of LOE [24]. Lymphoscintigraphy has also been reported to predict the response to treatment in LOE patients [49, 50, 66].

Prediction of development of lymphoedema

Lymphoedema development is a major health concern in breast cancer patients undergoing axillary lymph nodes dissection. Several studies have evaluated the

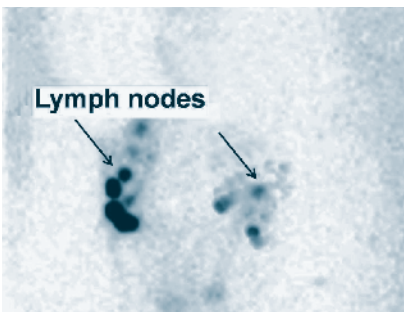

Figure 5. On hour pelvic view of a patient suspicious of lymphatic reflux to the left lower extremity. The tracer was injected only to the unaffected (right) limb. Note the visualization of the lymph nodes on both sides (arrows) which is due to reflux from the normal limb to the lymphoedematous one.

application of LSG for the prediction of this condition in the post-surgical state [67-70]. These studies stated that with LSG, patients with high risk of LOE development can be indentified, which can help in treatment planning.

In conclusion, LSG is an invaluable imaging procedure for diagnosis and follow-up of LOE patients and should be used as a first line investigation of this condition. In order to have high quality easily and interpretable studies choosing and applying the proper technique is mandatory.

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