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The role of radionuclide lymphoscintigraphy in extremity lymphedema

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The characteristics of lymphedema on radionuclide lymphoscintigraphy were studied, and the diagnostic value of radionuclide lymphoscintigraphy in lymphedema was evaluated. In this report radionuclide lymphoscintigraphy was performed in 110 cases of clinically suspected lymphedema. A retrospective study method was used to analyze the imaging results. The typical pattern of lymphedema on radionuclide lymphoscintigraphy was summarized. It was found that the characteristics of lymphedema on radionuclide lymphoscintigraphy were diverse. The most common pattern was increased radiotracer accumulation in the soft tissue and lymphatic webs. Surgery and infection dominated as the causes of lymphedema in this study. It was concluded that radionuclide lymphoscintigraphy is a useful noninvasive method for diagnosing lymphedema. It is easy to operate and provides reliable results.

Key words: radionuclide lymphoscintigraphy, lymphedema, ^{99m}Tc dextran

INTRODUCTION

LYMPHEDEMA is the swelling of a body part due to an abnormality in the loco regional lymphatic drainage[1] which results in an increase in interstitial volume secondary to the accumulation of lymphatic fluid. It is most common in the lower limb, about 80% of cases, but can also occur in the arms, face, trunk, and external genitalia. Lymphedema is a common and chronic lymphatic disease that is frequently misdiagnosed, treated too late, or not treated at all. Lymphedema results from impaired lymphatic transport caused by injury of the lymphatics, infection, or congenital abnormality. Patients often suffer in silence when their primary physician or surgeon suggests that the problem is mild and little can be done. However, there are effective therapies for lymphedema that can be implemented, particularly after the disorder is characterized with lymphoscintigraphy.[2]

Lymphoscintigraphy, the radionuclide technique of imaging the lymphatic system using interstitially injected radiopharmaceutical particles, was first introduced in 1953 and is now the gold standard for assessing the lymphatics.[3] Lymphoscintigraphy is a simple and noninvasive functional test for the evaluation of the lymphatic system. The safety, ease-of-performance and the benign nature of the technique have contributed to its popularity. To assess its role in managing peripheral lymphedema, we retrospectively studied the characteristics of particle distribution seen during radionuclide lymphoscintigraphy in a series of patients with clinically suspected lymphedema.

MATERIALS AND METHODS

Clinical data:

110 patients with clinically diagnosed lymphedema (62 females and 48 males; mean age, 42.6 years; range, 5–68 years) underwent radionuclide lymphoscintigraphy. 21 patients complained of upper limb and 89 of lower limb involvement. The main complaint of most of the patients was swelling of the limbs.

Methods:

The radiopharmaceutical used in this study was Tc-99m dextran (DX; Syncor, Shanghai). Tracer was injected subcutaneously in the webs between the first, second and third toes or fingers, two sites per limb, 37 MBq (1 mCi) per site. After injection patients were asked to walk for

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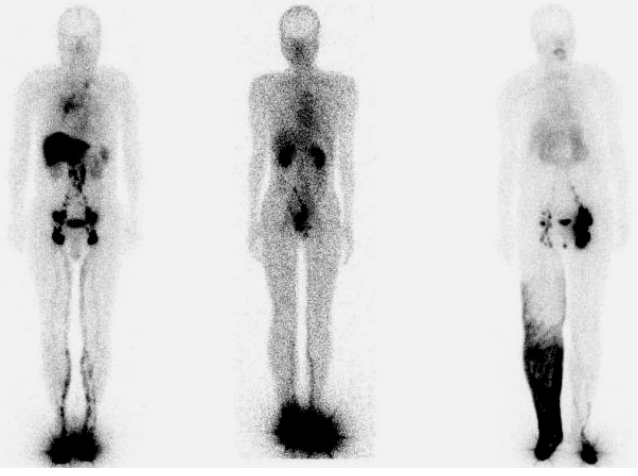
Table 1 The causes of lymphedema in 82 proved cases

Causes of lymphedema	Case No.	incidence rate (%)
Primary lymphedema	6	7.32
Filariasis	5	6.10
Infection	24	29.27
Lymphangitis	11	13.40
Trauma	8	9.76
Surgery	23	28.05
Uncertain reason	5	6.10



A B C

Fig. 1 Typical patterns in lymphoscintigraphy. A: Normal pattern. B: Primary lymphedema. C: Lymphedema, increased accumulation of radiotracer in soft tissue.

more than 30 minutes or massage the injection sites. Usually about 60 minutes post injection, whole body and spot imaging were acquired using a GE Millennium VG Hawkeye gamma camera. The findings were interpreted by two nuclear medicine physicians.

Three main diagnostic points of lymphoscintigraphy in lymphedema were used in this study. The first and most important one is whether there is increased accumulation of radiotracer in lymphatic webs and soft tissue. This pattern not only indicates the existence of lymphedema but also indicates the range and severity of the disease. The second one is, for lower limb lymphedema, whether inguinal nodes could be seen on the image. No inguinal nodes imaged indicates a more severe state of the disease. The third one is if there are abnormal lymph nodes or lymphatics branch visible on the extremities, but this is not a specific sign in lymphedema as we found some normal cases that also showed this kind of pattern. Generally, the main criteria of scintigraphic diagnosis are whether lymphatic channels could be clearly seen and accumulated radiotracer found in the soft tissue or lymphatic webs.

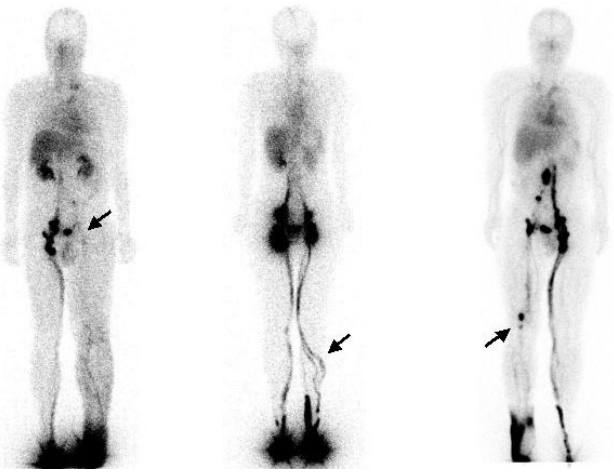


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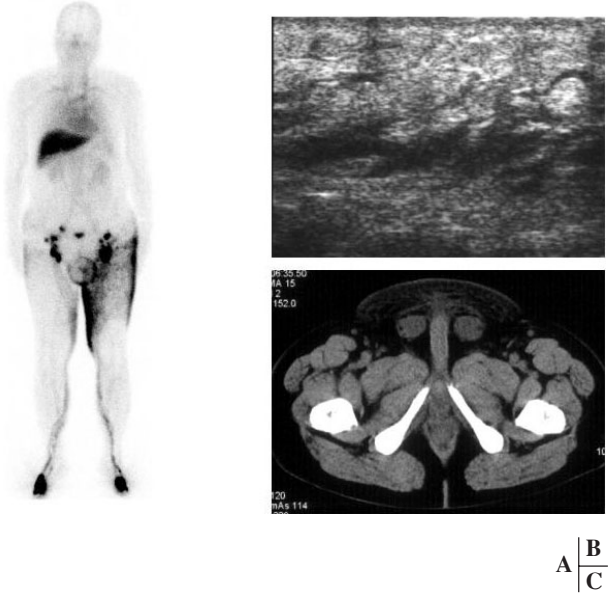
Fig. 2 Some typical signals of lymphedema in lymphoscintigraphy. A: Inguinal nodes not imaged. B: Lymphatic branches imaged. C: Abnormal lymph nodes imaged.



A | B / C

Fig. 3 A 54-year-old male with lymphedema due to colorectal cancer surgery. A: Apparent abnormality in lymphoscintigraphy. B: Volumetric changes in ultrasonography. C: Lymphedema changes in X-CT, typical honeycomb appearance.

RESULTS

After follow-up 82 cases were proved as lymphedema. Six patients with mild symptoms showed negative results and 76 cases showed positive results. All the negative scintigraphy cases (28 normal and 6 mild lymphedema cases) underwent lymphangiography and/or ultrasonography to make a differential diagnosis. The causes of lymphedema are summarized in Table 1. Among the 82 cases of proved lymphedema, infection (24 cases, 29.27%)

and surgery (23 cases, 28.05%) were the main causes of the disease.

There are many normal and abnormal patterns of lymphoscintigraphy.[4] Usually the normal pattern of lymphoscintigraphy was that tracer could be seen at the injection site, but less activity than that in lymphedema, along the lymphatic drainage, and in groin and iliac lymph nodes but usually not in axillary lymph nodes. No radiotracer accumulated in the soft tissue or lymphatic webs (Fig. 1-A). Several typical types of imaging characteristics were: tracer highly accumulated in the injection site, radioactivity in lymphatic drainage and groin lymph nodes could not be seen, no apparent accumulation of radiotracer in soft tissue or lymphatic webs; this pattern often suggest primary lymphedema (Fig. 1-B); apparent accumulation of radioactivity in soft tissue or lymphatic webs, this was the most common pattern of lymphedema and the most important diagnostic criterion (Fig. 1-C); abnormal lymph nodes imaged, cut-off or disappearance of lymphatic channels, poor or no groin nodal uptake in the diseased extremity; these patterns are not related to the cause of the lymphedema and could be seen alone or together in many cases (Fig. 2). But the more these patterns could be found in the imaging result usually indicated greater severity of the disease.

DISCUSSION

Lymphedema is found in both sexes, although women are investigated for this disease more often than men.[5] It can be seen at any age as already noted, and two thirds of cases are unilateral. The distal part of the leg is affected initially, with proximal extension occurring later. The feet are not spared.

A swollen leg may be due to local systemic causes, including congestive cardiac failure, renal failure, hypoalbuminemia, and protein losing nephropathy.[6] Local causes include primary and secondary lymphedema, lipedema, deep vein thrombosis and chronic venous disease, postoperative complications following ipsilateral surgery, cellulitis, Baker cyst and cyclical and idiopathic edema. In children, lower limb swelling is associated with arthritis but the underlying mechanism for this association is unknown. In this study, we found the most common causes of extremity lymphedema to be infection, lymphangitis, trauma, filariasis and post-surgical complications. In China, especially in the southern part, about 50 years ago filariasis dominated as the cause of lymphedema. Because of the hardwork of epidemiologists' preventive steps, filariasis is rare in China at this time. The weather in Shanghai is hot and wet, and also ringworm infection of the feet is another main cause of lymphedema, especially in the population with poorer sanitation conditions or personal habits. Recently the lymphedema caused by surgery has increased secondary to lymph node dissection in breast or pelvic cancer, with an estimated frequency of 5%–30%. If combined with radiotherapy, the risk of lymphedema is higher, as fibrous scarring reduces regrowth of ducts. Although lymphovenous bypass surgery is an ideal method for the therapy of some cases of severe lymphedema, some cases worsen after such surgery.

The main aims of treating patients with lymphedema are to prevent the progression of the disease, to achieve mechanical reduction and maintenance of limb size, to alleviate the symptoms arising from lymphedema, and to prevent skin infection. Hence, treatment depends on the symptoms and the severity of the condition. The treatment can be divided into conservative, pharmacologic, and surgical.[1]

Injection of radiolabeled tracers with subsequent gamma camera monitoring has been used to study the lymphatic system since the 1950's.[7] Lymphoscintigraphy is useful in the evaluation of primary and secondary lymphedema, lymphangioma with lymphatic leakage, lymphangiectasia, chylous ascites and chylothorax. This minimally invasive procedure simply requires intradermal or subcutaneous injection of the chosen radiolabeled tracer. The method has largely replaced the more invasive and technically difficult technique of lymphangiography.[8] The protocol for lymphoscintigraphy is not standardized and differs in diagnostic centers. Differences include the choice of radiotracer, the type and site of injection, the use of dynamic and static acquisitions, and the acquisition times.

The preferred radiopharmaceutical, Tc-99m antimony colloid, is a colloid of small size (3 to 30 nm), but the FDA (Food and Drug Administration) approved manufacturer of Tc-99m antimony colloid is no longer in business. The next best available agent is ^{99m}Tc SC (sulfur colloid, 10 to 1000 nm), which can be filtered to remove the larger particles, creating a nearly uniform particle size (10–50 nm). Another often used Tc-99m labeled colloid is ^{99m}Tc albumin colloid. Albumin microcolloid has a reproducible colloid size distribution (95% is <80 nm) and ease of labeling. Its rapid clearance from the injection site makes it suitable for quantitative studies, and injections are painless. Noncolloidal tracers reported in the literature include ^{99m}Tc HSA (human serum albumin), ^{99m}Tc dextran and ^{99m}Tc HIG (human immunoglobulin). Although the noncolloidal tracers clear from the injection site, they clear by a dual mechanism, with both resorption into capillaries and transport through lymphatics. As a result, use of these agents requires different criteria for interpretation than those used for colloidal tracers. In China, ^{99m}Tc dextran (6 to 7 nm) is the most commonly used radiotracer for lymphoscintigraphy. In our experience, ^{99m}Tc dextran is adequate for the purpose of diagnosing lymphedema, but for finding the lymphatic leakage site, ^{99m}Tc SC is better. As this examination needs dynamic acquisition and it takes more time for ^{99m}Tc dextran than ^{99m}Tc SC to transport from the injection site.[9] Another

reason is its dual uptake mechanism, with resorption into capillaries greatly affecting its diagnosis specificity in lymphatic leakage finding, especially in the situation of chyluria. Another often used agent for lymphoscintigraphy is ^{99m}Tc phytate, although mostly we used it in liver scintigraphy. A recent report showed that ^{99m}Tc phytate had some advantages in sentinel lymphoscintigraphy.[10]

The technique of injection in lymphoscintigraphy is an intractable problem.[11] The basic rule is different aim and radiotracer using different technique. For searching for lymphatic leakage, subcutaneous route is better than intradermal due to its dual uptake mechanism. For sentinel lymph node detection, the technique is more complicated and controversial, outside of the lesion or inside of the lesion. This question is beyond the scope of this paper. For searching for metastatic lymph nodes, mostly deep lymph nodes, some time a deeper injection site is suggested. Both subcutaneous and intradermal injections are used in routine studies of superficial lymphatics of the extremity. In our study we used subcutaneous injection method as we chose ^{99m}Tc dextran as the radiotracer.

The routine imaging modality of lymphoscintigraphy for lymphedema is whole body scan plus another spot imaging and in fact for clinical diagnosis, the information from the whole body scan is sufficient and a spot imaging can give us more information in detail. Besides whole body scan and spot imaging, dynamic lymphoscintigraphy is another often used method usually by monitoring the time-activity curve of inguinal nodes.[12]

In the late stage of lymphedema, the diagnosis is easy as the limb symptoms provide sufficient proof. But in the early stage some imaging modalities are still necessary in the differential diagnosis. Before lymphosintigraphy became the gold standard, lymphangiography was the main technique used for visualizing the lymphatics.[13] But due to its difficult technique and potential side effects, the technique has largely been abandoned as a diagnostic tool. The ultrasound features of lymphedema are volumetric changes (Fig. 3-B), like a minimal increase in the thickness of the dermis, an increase in the subcutaneous layer, and an increase, decrease, or no change in the muscle mass and structural changes, including hyperechogenic dermis and hypoechogenic subcutaneous layer.[14] The common CT findings in lymphedema include calf skin thickening (Fig. 3-C), thickening of the subcutaneous compartment, increased fat density, and thickened perimuscular aponeurosis.[15] Features of lymphedema on MRI include circumferential edema, increased volume of subcutaneous tissue, and a honeycomb pattern above fascia between the muscle and subcutis, with marked thickening of the dermis.[16]

In conclusion radionuclide lymphoscintigraphy is a useful noninvasive method for diagnosing lymphedema. It is easy to perform and provides reliable results.

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