Lymphoscintigraphic Abnormalities in Venous Thrombosis

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CASE PRESENTATION

A 50-yr-old male presented to the Mayo Clinic for evaluation of bilateral leg edema and a nonhealing ulcer over the right lateral malleolus.

CLINICAL HISTORY

The patient first developed superficial leg ulcers at the age of 16. In the previous year, bilateral superficial thrombophlebitis had been diagnosed clinically. Over the next 34 yr he was admitted to hospitals on numerous occasions for management of recurrent cellulitis and limb ulcers. Clinical examination over this time reportedly revealed bilateral leg edema which was attributed to deep venous thrombosis. Therapy consisted of antibiotics, limb elevation and bed rest. Split thickness skin grafts were undertaken on three occasions for treatment of his leg ulcers. Laboratory investigation failed to identify a predisposing systemic etiology. There was no history of malignancy, ilioinguinal surgery or radiotherapy. He had not traveled outside the United States. The patient was receiving treatment for essential hypertension and gout and was self-employed as a milk truck driver. He was a nonsmoker and consumed alcohol on social occasions only.

On examination, the patient was an obese white male weighing 137 kg. His temperature was 36.0°C. His lower limbs revealed changes characteristic of stasis eczema. There were varicosities extending from the feet to the lower abdomen. A 4 × 5 cm superficial ulcer was located over the right lateral malleolus; several eschars were located at the base, which was otherwise covered by granulation tissue. Significant nonpitting edema was present bilaterally; the skin over the dorsum of the feet was indurated and imparted a "doughy" sensation. There was no evidence of cellulitis or lymphangitis. The peripheral pulses were normal with the exception of the posterior tibial artery bilaterally, which was considered impalpable due to edema. Clinical examination was otherwise unremarkable.

A number of investigations including lymphoscintigraphy, bilateral leg and inferior vena cava (IVC) venography, duplex ultrasound, and impedence plethysmography were undertaken in order to determine the: (1) relative contribution of lymphedema to the patient's limb swelling and (2) potential benefit of perforating vein ligation on leg ulceration. Lymphoscintigraphy was performed following the subcutaneous administration of 11 MBq (410 μCi) of ^{99m}Tc-antimony trisulfide colloid (Sb_2S_3) into the second web space bilaterally. Images were acquired using a large field of view gamma camera equipped with a low energy all purpose collimator. A 20% window was placed symmetrically around the 140-keV photopeak of ^{99m}Tc. Dynamic anterior images (12 × 5 min frames) of the groin were obtained over the first hour. Subsequently, anterior views of the feet, calves, thighs and abdomen were acquired for 5 min each. A foot ergometer was employed during the first hour so as to exercise the feet at regular intervals. At 1 hr, no activity was visualized in the lymph channels or inguinal lymph nodes (Fig. 1). The patient was encouraged to ambulate prior to the 3-hr images; the latter revealed activity bilaterally in the inguinal lymph nodes and lymph channels within the legs. However, the vessels in the right calf were numerous and somewhat prominent. In addition, only faint activity was noted proximal to the inguinal lymph nodes (Fig. 2).

Venogram studies revealed an occlusion of the IVC at the level of the first lumbar interspace. There was filling proximal to this point, but the IVC showed irregularity and linear lucencies suggestive of previous thrombosis and recanalization (Fig. 3). Large varicosities were noted in both lower extremities with no opacification of the common femoral and iliac veins, consistent with chronic thrombosis (Fig. 4). The distal popliteal and tibial veins showed no valves and incompetence was confirmed by impedence plethysmography. Duplex ultrasound was considered technically unsatisfactory due to body habitus and edema.

Bilateral ligation of perforating veins and resection of calf varicosities were subsequently undertaken. The patient's ulcer resolved after about 5 mo. There was no significant change in leg edema.

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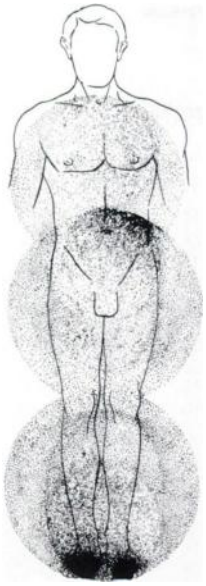

FIGURE 1. Anterior lymphoscintigram of the lower extremities, groin, and trunk after 1 hr, revealing no migration of tracer from the injection site bilaterally.

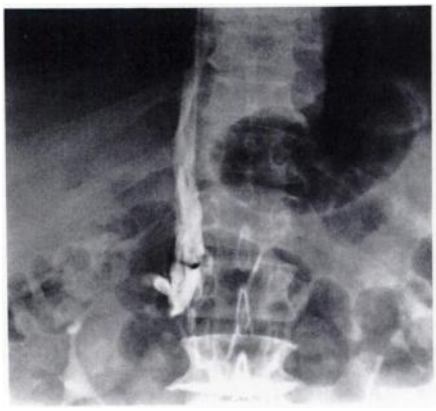

FIGURE 3. Venogram of the inferior vena cava depicting no opacification below the first lumbar vertebra and lucencies within the vessel lumen.

DISCUSSION

Lymphoscintigraphy in Extremity Edema

In recent years, lymphoscintigraphy has become the imaging modality of choice for the noninvasive investigation of suspected lymphedema (*1–8*). This technique enjoys considerable popularity as it conveniently provides a functional assessment of lymph transport capacity and identifies major morphological abnormalities of the lymphatic system. Further, there are no specific contraindications and radiation burden is low (*2*). These attributes allow lymphoscintigraphy to be performed periodically in order to evaluate the effect of treatment or monitor the course of disease.

The radionuclide technique is particularly beneficial in patients with chronic extremity edema in whom clinical history and physical examination have been diagnostically inconclusive. It has been suggested that lymphoscintigraphy can accurately discriminate between lymphedema and other causes of limb swelling including venous obstruction (*3,6–11*). This case demonstrates however, that in some patients the distinction between such disorders may be less clear, as abnormal lymph flow may occur in venous thrombosis.

The Normal Lymphoscintigram

Following subcutaneous injection of ^{99m}Tc-Sb_2S_3, activity normally appears in the lymphatic bundle along the

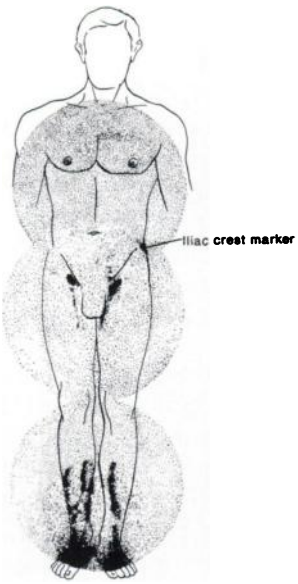

FIGURE 2. Anterior lymphoscintigram of the lower extremities, groin, and trunk at 3 hr, demonstrating uptake in the inguinal lymph nodes bilaterally, with visualization of lymph channels in the calves. Tracer is noted faintly in the iliac region, but there is no hepatic activity.

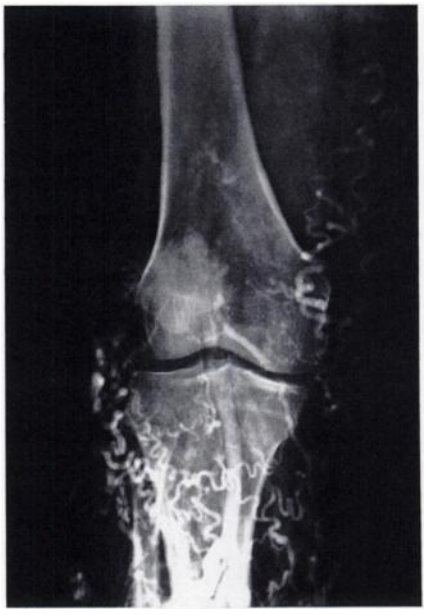

FIGURE 4. Venogram of the right leg showing numerous collaterals in the calf with no opacification of the common femoral vein.

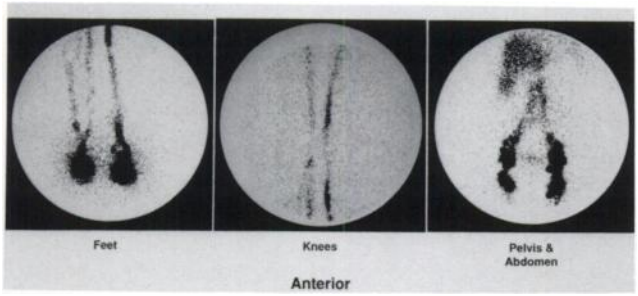

FIGURE 5. Anterior 3-hr lymphoscintigram of the lower extremities and trunk showing normal lymph vessels and regional lymph nodes as well as activity in liver and urinary bladder (faintly).

anteromedial aspect of the leg. Several channels may be identified in the calf, but usually only one lymph vessel is seen in the thigh (*12*). Radiocolloid should be clearly visualized in inguinal nodes within 1 hr. Hepatic uptake, as well as activity in urinary bladder and paraortic and iliac lymph nodes may also be identified at this stage. These should all increase in intensity on later views (Fig. 5). Tracer which is only faintly visualized in inguinal nodes at 1 hr or not seen until 3–6 hr is considered indicative of lymph transport delay (*3*).

The time taken for activity to appear in regional lymph nodes has been variably defined depending in part on the physical characteristics of the imaging agent. For example, small particles such as ^{99m}Tc human serum albumin may appear in pelvic nodes within 10 min (*12*), whereas larger agents including rhenium and Sb_2S_3 colloid should arrive within 30 min (*7*) or 1 hr (*13*) respectively. Inadvertent venous injection however, invalidates results and the study should be repeated at a later date. The importance of muscular exercise during lymphoscintigraphy has also been stressed (*12,13*). This maneuver not only enhances lymph flow but allows the formulation of reproducible parameters.

An important limitation of lymphoscintigraphy lies in its inherently poor visualization of the deep lymphatic system (*6*). In general, web space injections highlight the superficial system only. Deep lymph channels originating posterior to the malleoli and coursing to the popliteal lymph nodes and along the superficial femoral vein are usually not identified. This anatomical division of the lymphatic circulation has prompted Golueke et al. (*6*) to propose multiple injections within an extremity as a means of improved lymph system characterization. However, this approach has not met with widespread acceptance.

Classification of Lymphedema

The subdivision of lymphedema into primary and secondary disorders has been based classically on underlying etiology (*14*). In primary lymphedema, aplastic or hypoplastic lymphatic trunks are postulated to occur secondary to embryological maldevelopment or an acquired event (*11,14*). Such disorders may arise rarely on a familial basis as in Milroy's disease (autosomal dominant with incomplete penetrance) (*14,15*) or form part of a wider entity [Turner's syndrome (*1,14*), or neurofibromatosis (*16*)]. Nonfamilial forms of lymphedema are more common and are designated praecox and tarda. These disorders are characterized by less severe lymph vessel hypoplasia and are distinguished by age at disease onset (praecox prior to and tarda over 35, respectively) (*1*). Females are affected up to 4 times as often as males (*14*). Lower limb lymphedema constitutes the majority of cases; however, edema may also involve the face, hands or genitalia. Rarely, protein losing enteropathy may occur (*14*). As in our patient, excess protein rich fluid in the subcutaneous tissues promotes a recurring cycle of inflammation and fibrosis (*2*).

Secondary lymphedema has been reported to occur in up to 50% of patients following mastectomy (*2*). Other common causes include malignancy, irradiation, pelvic or inguinal surgery, and recurrent inflammation (*14*). Filariasis is endemic in many parts of Africa and Asia and is another important cause of secondary lymphedema. In this disorder, repetitive inflammation following invasion of the lymphatics by microfilaria produces thickened and obstructed lymph vessels (*17*).

Scintigraphic Findings in Lymphedema

Primary and secondary causes of lymphedema are associated with certain abnormalities on lymphoscintigraphy. These include a delay in transport from the injection site, the presence of large collaterals, extravasated activity, "cross-over" pattern, fewer visualized lymph nodes and dermal backflow (*12,13*) (Fig. 6). In primary lymphedema, it may be possible to distinguish aplasia from hypoplasia by imaging early in the evolution of the disease. In the former, there is usually little or no: (1) removal of tracer from the injection site, (2) tracer in regional lymph nodes on 1- and 3-hr images, (3) dermal backflow and (4) visualized lymph channels. In hypoplasia, these scintigraphic features may be variably present. Regardless of etiology, lymphatic vessels of normal caliber are not seen in longstanding lymphedema (*12*).

Qualitative interpretation of images has resulted in excellent sensitivity (92%) and specificity (100%) for the diagnosis of lymphedema (*3*). Quantitative criteria may improve detection of early disease (*12*), but results have been controversial (*3,13*). Neither the image pattern nor quantitative parameters can reliably distinguish primary from secondary lymphedema (*12,13*).

Lymphoscintigraphy in Venous Thrombosis

The lymphatic system develops from lymph sacs during the first trimester of pregnancy and grows in proximity to main veins (*18*). As well as being closely related anatomically, the lymphatic and venous circulations have been shown to be functionally interdependent in human subjects and animal models. Field and Drinker (*19*) and Taylor et al. (*20*) reported that in conditions of tissue inflammation and venous obstruction the lymphatic ves-

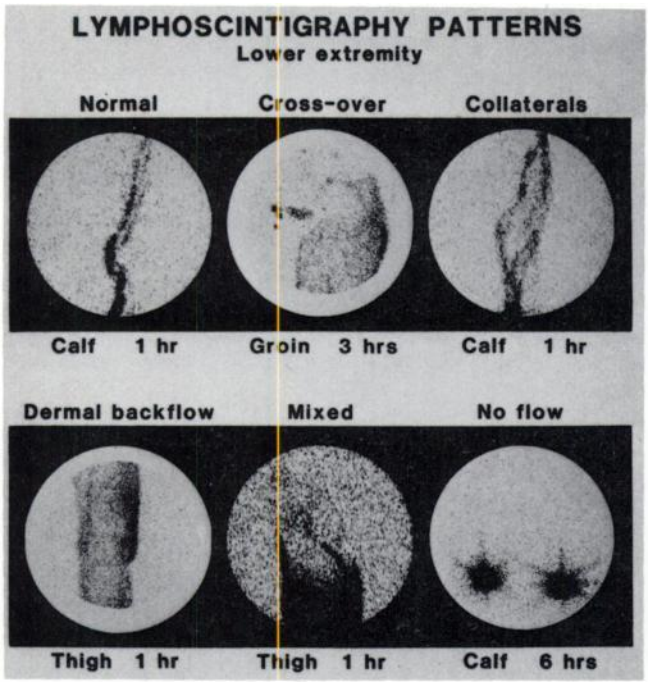

FIGURE 6. Lymphoscintigrams demonstrating normal caliber lymph vessels (top left) and typical abnormalities encountered in lymphedema (reprinted by permission of reference 13).

sels may serve as an alternate pathway for erythrocytes and plasma. The clinical implications of superimposed lymphatic disruption were first recognized by Homans (*21*).

Limb swelling due to venous thrombosis has been variably included as a cause of secondary lymphedema. Of 91 patients with secondary lymphedema, Weissleder et al. (*12*) reported that 34 had chronic venous insufficiency. This group had similar scintigraphic features to patients with primary lymphedema. Rijke et al. (*22*) employed time activity curve analysis and demonstrated that chronic venous obstruction was accompanied by prolonged migration of tracer within the affected limb. Further, this phenomenon has been identified not only in patients with chronic venous stasis, but in those in whom veins have been harvested for surgical procedures (*5,23*).

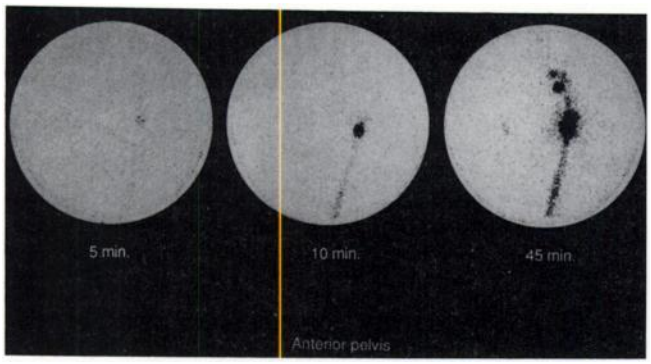

FIGURE 7. Lymphoscintigraphy was performed in a 47-yr-old male with a history of left leg edema and stasis pigmentation, and deep venous thrombosis 3-yr previously. Anterior views of the groin disclose rapid ascent of radiocolloid on the left, with activity appearing in 5 min. Inguinal activity is noted on the right at 45 min.

By contrast, several other groups have noted either normal or increased lymph flow in patients with venous insufficiency (*3,6–11*) (Fig. 7). Stewart and colleagues (*7*) studied the appearance time of activity in the inguinal lymph nodes of patients with primary lymphedema, venous edema and normal volunteers. All patients with venous edema demonstrated rapid lymphatic transport, with greater than 2% of injected activity appearing in ilioinguinal lymph nodes at 30 min. This compared with less than 0.05% uptake in patients with lymphedema. Golueke et al. (*6*) were able to reliably discriminate between lymphedema and other causes of extremity swelling using both hepatic uptake of ^{99m}Tc Sb_2S_3 at 3 hr and lymph drainage patterns in the limb. Carena et al. (*8*) investigated a number of quantitative parameters in a heterogenous group of patients. In venous obstruction, the mean clearance from the injection site at 6 hr was similar to normal volunteers.

Chronic Venous Stasis

How can this discrepancy in venous edema be explained? Several authors (*24,25*) have emphasized that chronic venous stasis is a complex disorder, with a multitude of clinical and radiologic manifestations. In one form (dependent venous edema with ulceration), lymphatic flow increases as a consequence of venous hypertension (*25*) and in accordance with Starling's hypothesis. Szabo et al. (*26*) described increased lymph flow in a canine model following the acute onset of venous constriction. Tosatti et al. (*27*) provided lymphangiographic correlation of this phenomenon by demonstrating an increase in the number and caliber of deep lymph vessels in a small series of patients with the post-phlebitic syndrome. Thus, an efficient collateral circulation develops.

Lipodermatosclerosis is another recognized variant of chronic venous stasis. This disorder is characterized by skin induration, hyperpigmentation, ulceration and capillary proliferation of the lower leg and ankle, notably along the medial aspect (*25*). These clinical manifestations were features of our patient. In lipodermatosclerosis, tissue fibrinolytic activity is profoundly reduced and vascular proliferation promotes increased fibrin deposition. A semipermeable barrier is formed over time which impairs local diffusion of oxygen (*28*). Further, the fibrotic process also involves lymphatic channels, thus contributing to lymphedema (*25*). Injection of tracer into the edge of these ulcers reveals a lack of migration into regional lymph nodes whereas activity administered more distantly is relatively unaffected (*29*). This impairment in local lymph transport capacity has been termed "lymphatic microangiopathy" (*30*). An analogous situation has been postulated to occur in postsurgical lymphedema; wound scar formation may

contribute to lymph stasis in this setting through reduced permeability and altered vessel compliance (*31*).

In the present case, there was no clearance of radiocolloid from the injection site within 1 hr. This pattern may be seen in either primary or secondary lymphedema (*12, 13*). However, the lymph channels and inguinal nodes on the 3-hr images were relatively normal in appearance and number, which are unusual features in established lymphedema. These findings therefore may alert the clinician to causes of limb swelling other than lymphedema. In our patient specifically, this pattern suggested dysfunction of the distal lymphatic vessels, consistent with lipodermatosclerosis.

Combined Venous and Lymphatic Obstruction

An important differential diagnosis in adult patients developing mixed venous and lymphedema is underlying malignancy. Locally infiltrative prostatic and cervical carcinoma have been reported to obstruct both lymphatic and venous channels (*14*). Neoplasm was excluded in our patient by abdominal and pelvic computed tomography scanning as well as the long duration of symptoms without sinister manifestations. Although rare, consideration should also be given to "mixed vascular" abnormalities, the most widely known of which is the Klippel-Trenaunay syndrome (*14,23*). In this disorder, unilateral limb hypertrophy is associated with skin naevi and varices, and lymphangiography reveals hypoplastic lymph vessels (*14*).

CONCLUSION

In summary, venous thrombosis may be associated with a variety of patterns on lymphoscintigraphy. After an initial phase of accelerated flow, lymph stasis and obstruction develop and the lymphoscintigram may mimic primary or secondary lymphedema. Delayed (3–24-hr) views may allow improved characterization of lymphatic system abnormalities. Diagnosis of patients with combined venous and lymphatic obstruction requires a careful history and examination, with consideration of malignancy in adults. Imaging of the venous system remains an important first step in the assessment of leg edema, as venous disorders are most common (*11*). In patients with chronic venous stasis, lymphoscintigraphy is a valuable adjunctive tool in the evaluation of secondary lymphatic dysfunction.

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