Lymphology 46 (2013) 106-119

CONTRIBUTIONS OF SPECT/CT IMAGING TO THE LYMPHOSCINTIGRAPHIC INVESTIGATIONS OF THE LOWER LIMB LYMPHEDEMA

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ABSTRACT

Lymphoscintigraphy is a safe and reliable technique for investigating lymphedema. However, interpretation of delayed planar conventional imaging may be questionable due to the superimposition of soft tissues. Therefore, the aim of this retrospective study was to evaluate the contribution of single photon emission computed tomography/computed tomography (SPECT/CT) to lymphoscintigraphic investigation in a selected population with abnormal interstitial activity. Forty one patients with lower limb lymphedema either primary (n=17) or secondary (n=5), or associated with chronic venous insufficiency (n=19) underwent lymphoscintigraphy according to a standard protocol. SPECT/CT imaging that started immediately after planar imaging covered the part of the lower limbs with the most significant interstitial activity. The CT images were also analyzed separately to identify the typical honeycomb pattern of lymphedema. SPECT/CT identified additional abnormalities in vessels and soft tissues in 19 patients (46%). The additional information, primarily related to dermal collateralization of flow, dermal backflow, lymphangioma, and lymphorrhea, aided in understanding the physiopathology of edema and may have influenced management in 35 patients (85%). The honeycomb appearance of the soft tissues was noted on CT in most patients (90%). This study suggests that SPECT/CT is a promising addition to planar imaging in lymphoscintigraphic investigations of lymphedema.

Keywords: lymphedema, lymphoscintigraphy, SPECT/CT

Lower limb lymphedema is a disabling and disfiguring condition that decreases the quality of life of affected patients (1). Lymphedema is usually managed with a conservative physical treatment (2-3), and surgical approaches have also been proposed for these patients (4-5). Knowledge about tissue fluids and lymphatic structures is essential for establishing a rational, basic therapy for lymphedema.

Lymphoscintigraphy represents a relatively simple and reliable technique for demonstrating lymphatic abnormalities and dysfunction (6-10) that is useful even in very young children (11). Although lymphoscintigraphy offers remarkable insight into lymphatic (dys)function (12), the examinations depend on the application of well-standardized acquisition protocols and careful imaging interpretation (13). Quantification is dependent on multiple factors, including the type of injection, exercise during the study, injected volume, and injection site (7,14).

Lymphoscintigraphic abnormalities suggestive of lymphedema include primarily delayed visualization or absence of visualization of lymph nodes and/or lymphatic vessels and the presence of dermal activity. The presence of lymphatic vessels and lymph nodes of the deep lymphatic system and of the collateralization vascular lymphatic pathways represent other findings in lymphedematous patients. With regard to dermal activities, which are usually better depicted on delayed images (15), these findings are usually interpreted as the result of dermal backflow, a reverse spread of lymph fluid due to incompetent valves or obliterated lymphatics (7) or extravasation (diffusion) of the blocked tracer. The interpretation of these images may be less clear because accurate localization of interstitial activity is not possible with planar imaging due to the activity of deep structures and/or masking of normal underlying lymphatic vessels by superficial tissue activity. Distinguishing between localized dermal backflow and extravasation, assessing lymphangiectasia, and interpreting activity spots are especially difficult without corresponding anatomical information. One of the drawbacks of planar lymphoscintigraphy is its failure to provide detailed information regarding anatomy which can assist in understanding the physiopathology of the edema.

SPECT/CT is currently used in lymphoscintigraphy to localize the sentinel node in breast cancer (16). The aim of our study was to evaluate whether SPECT/CT imaging improves the interpretation of lower limb lymphoscintigraphy in patients with abnormal interstitial activity.

MATERIALS AND METHODS

Study Population

Lymphoscintigraphy was used in the context of routine assessment of lymphedema; data were retrospectively and anonymously analyzed for the purpose of this study. In accordance with French and Belgian Laws on Medical Scientific Research, approbation of Ethics Committee was not required.

A total of 41 patients (7 males and 34 females) with a mean age of 67 years (range: 9-84 years) underwent lymphoscintigraphy with SPECT/CT for evaluation of lower limb lymphedema. All patients had abnormal activity of soft tissues using planar imaging. Twenty-seven patients had bilateral edema. The patients were divided into three groups according to their clinical history, physical examination findings, and the results of complementary investigations.

Group 1 consisted of 17 patients with primary lymphedema; they had no particular history or significant insult to the lymphatic system, except erysipelas in four patients and minor meniscal surgery in one patient. Two patients had a subcutaneous mass involving the thigh. A 9-year-old boy had Gorham disease, a severe form of lymphangiomatosis with massive osteolysis involving the lower limb. Two patients had an intercurrent disease: acute dermo-epidermitis in one patient with morbid obesity and an arterial leg ulcer in another case.

Group 2 included five patients with secondary lymphedema who had undergone radiosurgical therapy for uterine cancer.

Group 3 included 19 patients with lymphedema associated with chronic venous insufficiency. Ten patients had previous venous stripping, and lymphedema occurred after stripping in three of these patients. Eight patients (including one patient with previous venous stripping) developed superficial leg ulcers, which oozed in six cases. One patient had morbid obesity and heart failure. Another patient had suffered from large varicose veins since childhood.

Tracer and Image Acquisition

99mTc-labeled human serum albumin nanosized colloids (Nanocoll*, GE Healthcare SAS) were used. A total of 111 MBq in a volume of 0.2-0.3 ml was injected subcutaneously in the first interdigital space of each foot. Lymphoscintigraphy was performed in the same manner in all patients using a hybrid gamma-camera (Symbia T2, Siemens). Immediately after injection, dynamic anterior images covering both legs were recorded for 40 min (1 frame per min). In the supine position, the patient was instructed to move his or her toes during the last 20 minutes of recording. Localized planar images of the lower limbs, pelvis, and thorax were acquired 40 minutes and 4 hours after injection. A whole body scan was also performed at the end of the examination.

SPECT/CT was performed immediately after late planar imaging. The patients were carefully positioned in order to obtain the most significant interstitial activity in the field of view. Based on the findings from the planar images, 36 patients underwent SPECT/CT imaging of the legs (calves only in 32 cases, calves and ankles in 4 cases), and the thighs and pelvis were imaged in the other 5 patients. The full SPECT/CT study lasted 45 min. Image reconstruction resulted in images with a slice thickness of 5 mm.

Image Analysis

Upon completion of lymphoscintigraphy, planar and SPECT/CT images were studied successively and the information provided by both techniques compared. Imaging was interpreted by the consensus of two experienced reviewers. In order to simplify the comparison of planar and tomographic imaging, the comparative study was limited to the limb with the most abnormal soft tissue activity.

Interpretation of lymphoscintigraphy included the results of dynamic, early, and delayed images. Interpretation of planar imaging was based on the evaluation of lymph vessels (activity, number, caliber, evidence of collaterals), lymph nodes (number, distribution), and soft tissue activity.

Interpretation of SPECT/CT was based on the appearance of soft tissue activity: homogeneous or heterogeneous; regularity of its limits; its location in the epidermis or superficial, deep, or whole dermis; and its extension along the perimuscular aponeurosis and/or intermuscular septa. Scattered spots were analyzed and interpreted as lymph nodes, interstitial foci, or lymphatic vessels.

Abnormalities of SPECT/CT imaging were categorized as follows: tortuous lymphatic vessels as lymphatic varicosis; saccular dilations of the main lymphatic vessels as lymphangiectasia; circumscribed dermal lesions with a cluster of interconnected multiple spots or large lymph spaces that may spread into the dermis, muscle, and bone as localized or diffuse lymphangioma; morphological abnormalities that resemble a small sack of lymph fluid (lymph collection attached to the surface of the lymphatic vessel by a thin neck) as lymphatic saccular aneurysms; a lymphatic collection that results from injury (an accumulation of lymph outside the lymphatic system) as lymphocele; lymphatic reflux at any level into superficial lymphatic collaterals with localized dermal activity, usually anterior and involving only subepidermal lymphatics as lymphatic dermal backflow; lymph diversion from the injection site thorough collateral dermal routes, diffuse dermal activity (usually circumferential, inhomogeneous, and involving the whole derma) as lymphatic dermal collateralization of flow; and leakage of lymph from the skin with subtle communication between lymphatic channel activity and the epidermis as lymphorrhea. Lymph nodes are activity foci that are usually round in the three-dimensional space and along the vascular pathways, and other activity foci that can spread in deep dermal layers along muscular fascia were considered activity spots.

TABLE 1
Primary Lymphedema (n=17 patients)

Number of patients	Pertinent history	Planar imaging interpretation	SPECT/CT imaging contribution
9		Flow collateralization: 4	**Localization** circumferential: 4
	Erysipelas (1) Meniscal surgery (1)	Dermal backflow: 2	**Localization** anterior: 2
	Erysipelas (2) Morbid obesity (1)	Equivocal: 3	**Diagnosis** dermal backflow: 3 **Localization** antero-internal: 1, anterior: 2
1	Oozing arterial ulcer	Activity areas along lymphatic vessels	**Diagnosis and localization** dermal backflow: internal, connected to lymphangiectasia
2	Mass involving the thigh (1)	Localized dermal activity:1	**Diagnosis and localization** lymphangioma: 1
	Mass involving the thigh (1)	Dermal backflow that spreads to the pelvis: 1	**Localization** anterior: 1
1	Gorham disease	Several large activity areas	**Diagnosis and localization** lymphangiomatosis in bone and soft tissues
3	Erysipelas (1)	Lymph collection slung to the vessel: 3	**Localization** saccular aneurysm: 3
1	Morbid obesity + acute dermo epidermitis	Subtle dermal activity	**Diagnosis and localization** deep foci associated with muscular necrotic areas

The CT images were analyzed separately to identify changes in soft tissue density, such as subcutaneous enlargement with stranding lines parallel and perpendicular to the skin and the presence of a honeycomb pattern, which is a usual aspect of subcutaneous tissues in lymphedema (17).

RESULTS

Analysis of Planar and 3D Imaging in Primary Lymphedema

The characteristics of the patients in group 1 are presented in *Table 1.*

In nine patients, abnormal dermal activity on delayed planar imaging was interpreted as dermal collateralization of flow from the injection site in four cases, as dermal backflow in two cases, and as equivocal in three cases. In the first six patients, SPECT/CT confirmed and localized dermal backflow and dermal collateralization. In the three uncertain cases with dermal activity in the lower part of the leg, SPECT/CT identified dermal backflow.

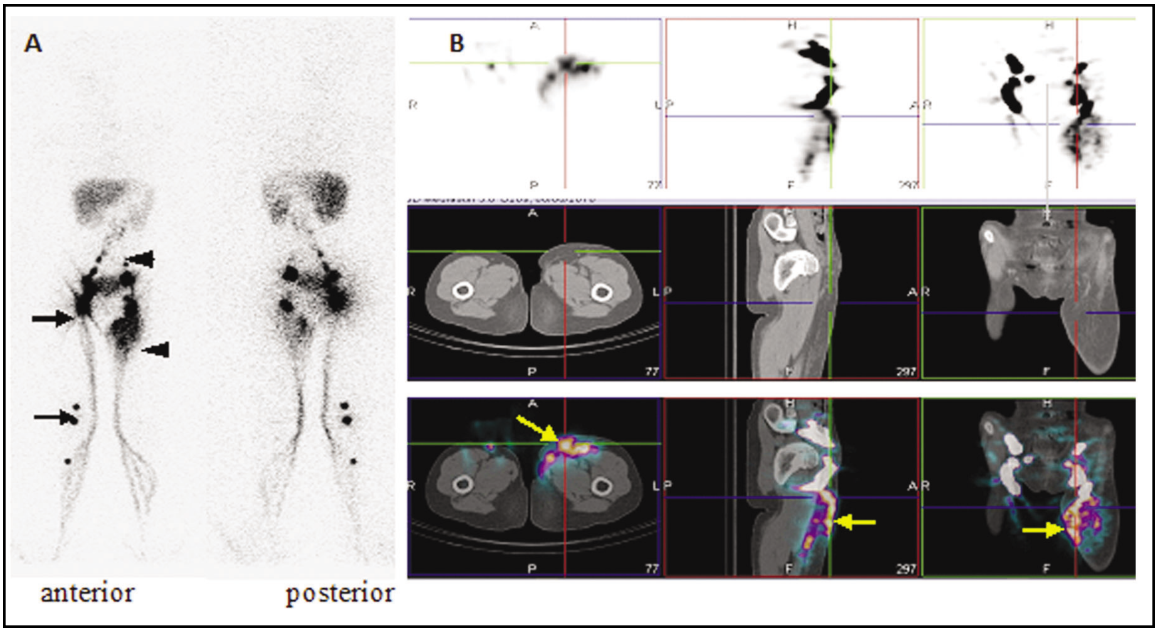

Fig. 1. Primary lymphedema of the left lower limb in an 11-year-old girl. The lymphedema began with a mass involving the left thigh. (A) Whole body imaging 4 hours after injection, anterior and posterior views. Right, normal activity is seen in the lymphatic trunks and ilio-inguinal nodes (upper arrow), popliteal nodes (lower arrow) indicating impaired lymphatic drainage. Left, normal activity is seen in the lymphatic vessels, with a slight decrease in ilio-inguinal node activity (upper arrowhead) and localized dermal activity in the internal part of the thigh (lower arrowhead). (B) SPECT/CT imaging of the pelvis and left calf 4 hours after injection. SPECT (top), CT (middle) and SPECT/CT (bottom): transaxial, sagittal and coronal images. A circumscriptum cluster of dilated lymphatic channels in the whole derma (arrows) indicates lymphangioma.

In one patient with an arterial ulcer, the latest images had two large foci of activity along the lymphatic vessels, suggesting dilated vessels or areas of dermal backflow. SPECT/CT identified several areas of localized dermal backflow next to lymphangiectasia.

In the two patients with lymphedema and a mass involving the thigh, dermal activity was observed in the internal part of the thigh. In one patient SPECT/CT displayed a circumscribed dermal lesion with interconnected spots, suggesting lymphangioma (*Fig. 1*). CT showed only a faint localized trabecular aspect in the dermis, and MRI confirmed lymphangioma. In the other patient, the results of delayed planar imaging suggested complex dysplasia; upper iliac nodes were absent, medullary and hepato-splenic activity indicated prominent venous activity and lympho-venous anastomoses, and dermal activity at the level of the internal part of the thigh was associated with dermal backflow that spread to the pelvis. SPECT/CT imaging did not reveal lymphangioma; however, it helped localize the extensive dermal backflow at the level of both thighs and the abdomen with prominent dermal backflow at the site of thigh tumefaction, and to differentiate dermal and nodal activities (*Fig. 2*). MRI was normal in this patient.

In the child with Gorham's disease, imaging displayed several large activity areas in the lower limb with high activity in the ankle. SPECT/CT localized dilated lymphatic spaces in the dermis, muscle, and bone.

In three patients, the main abnormality was a collection of lymph connected to a vessel in the calf noted as soon as the vessel

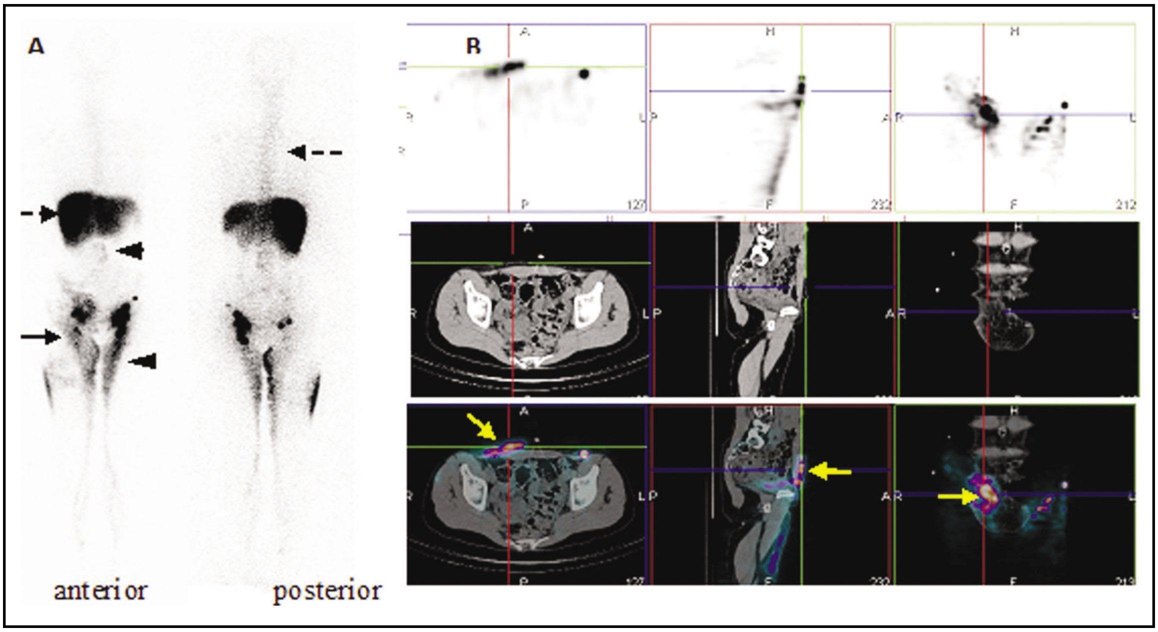

Fig. 2. Primary lymphedema in a 30-year-old woman. The patient had an intermittent mass in the internal part of the left thigh. (A) Whole body imaging 4 hours after injection, anterior and posterior views, showing prominent hepato-splenic and medullary activity (discontinuous arrows) and an absence of upper iliac node (upper arrowhead). Right, dermal backflow that spreads to the pelvis (lower arrow). Left, dermal activity in the internal part of the thigh (lower arrowhead). (B) SPECT/CT imaging of the pelvis and left thigh 4 hours after injection. SPECT (top), CT (middle) and SPECT/CT (bottom): transaxial, sagittal and coronal images: dermal backflow that involves the superficial derma in the abdomen (arrows).

was visualized. SPECT/CT confirmed a saccular aneurysm and helped to more precisely localize it in the vessel.

In the patient with morbid obesity and attacks of acute dermo-epidermitis, an absence of lymphatics suggested aplasia of the peripheral lymphatic vessels associated with minimally diffuse activity at the level of the calf. SPECT/CT displayed unexpected multiple muscular foci along the perimuscular aponeurosis, and these foci were associated with muscular necrosis on CT.

In the soft tissues of 14 patients, CT imaging revealed a “honeycomb” appearance that was not correlated with lymphatic dermal activities. This “honeycomb” aspect was not investigated in three patients with edema localized in the foot, which was not included in the SPECT/CT field of view.

Analysis of Planar and 3D Imaging in Secondary Lymphedema

The characteristics of the patients in group 2 are presented in *Table 2*.

In three of the five patients with lymphedema secondary to radiosurgical treatment for uterine cancer, the first planar images showed rapid lymph transport in lymphatic channels with multiple collaterals and dermal activity. On delayed images, ilio-inguinal node activity was either absent or limited to small nodes, and the images displayed massive dermal collateralization of flow in three patients and dermal backflow in two patients. In one patient the dermal backflow spread to the thighs, the lower abdomen, and the pelvis. In all patients, the abnormalities were confirmed and better localized by SPECT/CT (*Fig. 3*). In addition,

TABLE 2
Secondary Lymphedema (n = 5 patients)

Number of patients	Pertinent history	Planar imaging interpretation	SPECT/CT imaging contribution
5	Uterine cancer therapy	Flow collateralization: 3	**Localization**
			circumferential: 3
		Dermal backflow: 1	**Localization**
			circumferential : 1
		Dermal backflow that spreads to the pelvis: 1	**Diagnostic and localization**
			lymphocele and anterior: 1

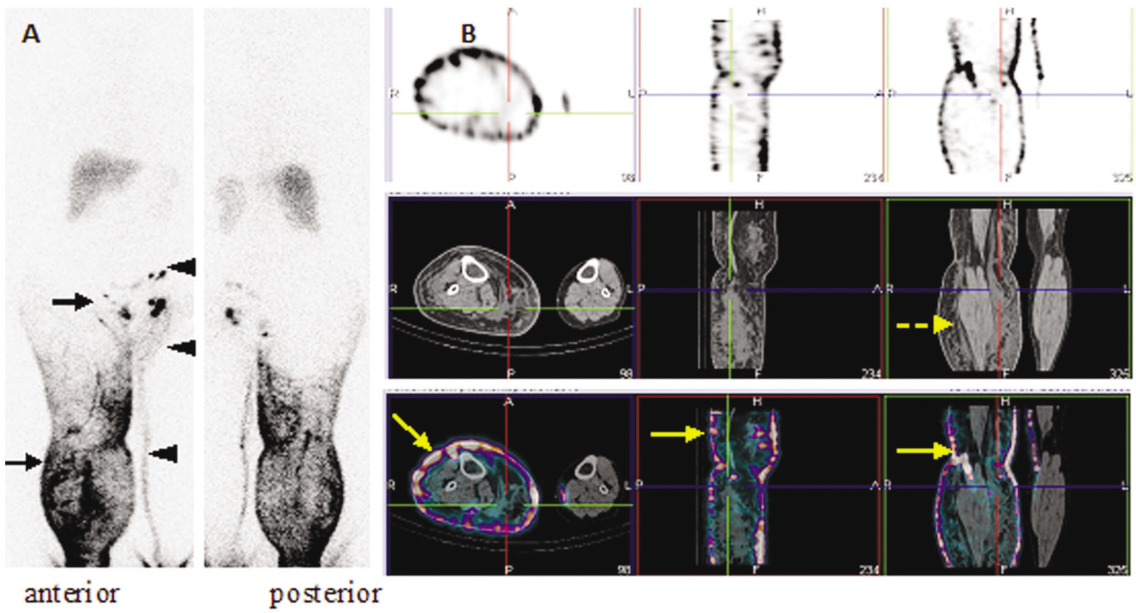

Fig 3. Secondary lymphedema in a 70-year-old woman. The patient had undergone radiosurgical therapy for uterine cancer 30 years earlier. (A) Whole body imaging 4 hours after injection, anterior and posterior views. Right, faint ilio-inguinal node activity (upper arrow) and extensive dermal collateralization of flow (lower arrow) are visible. Left, hypoactive ilio-inguinal nodes (upper arrowhead), slight thigh dermal backflow (middle arrowhead), and normal lymphatic vessels (lower arrowhead) are evident. (B) SPECT/CT imaging of the right calf 4 hours after injection. SPECT (top), CT (middle) and SPECT/CT (bottom): transaxial, sagittal and coronal images. Marked circumferential dermal collateralization of flow that involves the whole derma with extension along the muscular aponeurosis (arrows) is visible, as well as a marked honeycomb pattern (discontinuous arrow).

SPECT/CT allowed us to individualize a lymphocele associated with dermal backflow in one patient.

SPECT/CT imaging revealed a "honeycomb" appearance in the soft tissues of all patients. As in primary lymphedema,

TABLE 3 Lymphedema and Chronic Venous Insufficiency (n=19 patients)			
Number of patients	**Pertinent history**	**Planar imaging interpretation**	**SPECT/CT imaging contribution**
10	Venous stripping (5) Venous ulcer (2)	Dermal backflow: 7	**Localization** internal or antero-internal: 5 internal or antero-internal: 1 anterior: 1
	Oozing ulcer (1)	Dermal backflow: 1	**Diagnosis and localization** lymphorrhea and posterior: 1
	Venous ulcer, oozing, and venous stripping (1)	Flow collateralization: 1	**Diagnosis and localization** lymphorrhea and circumfer-ential: 1
	Venous stripping (1)	Equivocal: 1	**Diagnosis and localization** dermal backflow and anterior: 1
1	Early varicose veins	Activity areas along dilated vessels	**Diagnosis and localization** dermal backflow: internal
5	Oozing venous ulcer: 4 (1+ obesity) Venous stripping + obesity and heart failure: (1)	Localized dermal activity next to vessel: 5	**Diagnosis and localization** lymphorrhea: 5
2	Obesity (1) Stripping (1)	Lymph collection along vessel: 2	**Diagnosis** varicosis: 2
1	Venous stripping	Lymph collection bulging from the vessel	**Localization** saccular aneurysm

abnormalities in the density of soft tissues did not correlate with dermal lymphatic activity.

Analysis of Planar and 3D Imaging in Lymphedema and Chronic Venous Insufficiency

The characteristics of the patients in group 3 are presented in *Table 3*.

On planar images, ilio-inguinal node activity was present in all patients. The lymph flow was increased in 17 of the 19 patients and decreased in 2 patients (1 case with morbid obesity). The lymphatic vessels were tortuous with multiple collaterals in 12 patients.

Ten patients exhibited abnormal dermal activity, which was already obvious during the dynamic recording in five patients and interpreted as dermal backflow in eight cases, dermal collateralization of flow in one case, and as equivocal in the tenth case. Dermal backflow was confirmed in all eight cases by SPECT/CT. It predominated in the internal part of the leg in seven patients (including five cases with previous venous stripping)

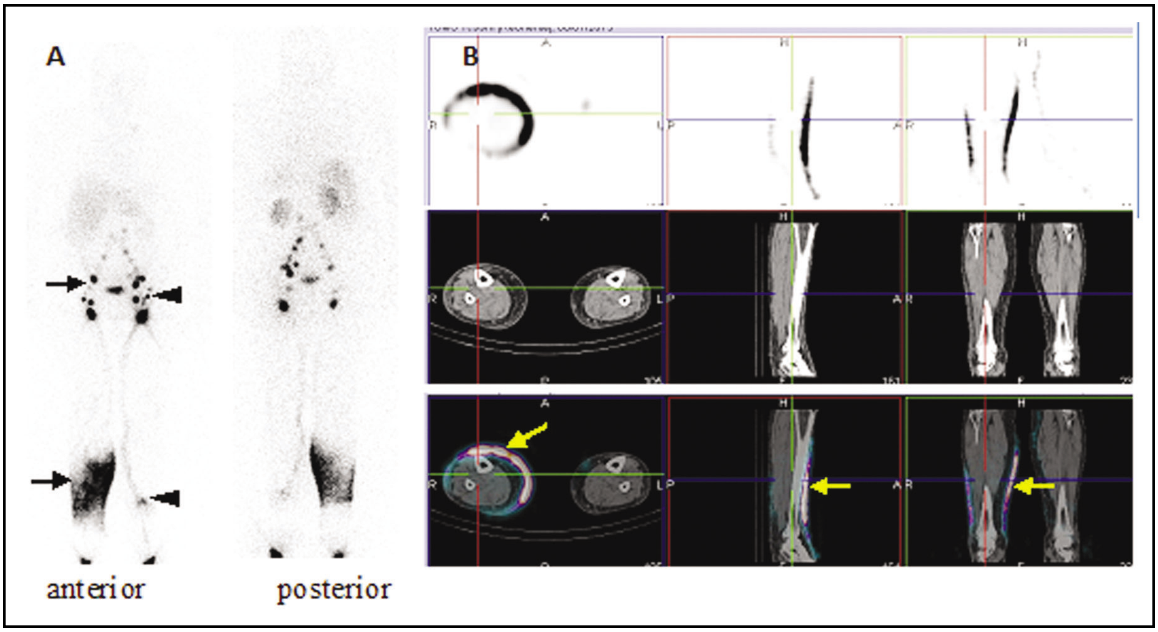

Fig 4. Lymphatico-venous edema in a 65-year-old woman. The edema occurred a few weeks after right venous stripping. (A) Whole body imaging 4 hours after injection, anterior and posterior views. Right, slightly decreased activity in the ilio-inguinal nodes (upper arrow) and localized dermal backflow in the third middle of the calf, predominantly in the internal part of the limb (lower arrow). Left, normal activity in the ilio-inguinal nodes (upper arrowhead) and normal lymphatic vessels except for an activity focus adjacent to the vessel (lower arrowhead). (B) SPECT/CT imaging of the right calf 4 hours after injection. SPECT (top), CT (middle) and SPECT/CT (bottom) : transaxial, sagittal and coronal images. Dermal background in the superficial dermis, predominantly in the anterior and internal part of the calf (arrows).

(*Fig. 4*). In a patient with oozing ulcer, SPECT/CT located dermal backflow and the site of the lymph escape from the vessel (*Fig. 5*). Associated deep nodes were revealed in three cases. In another patient with an oozing venous ulcer, SPECT/CT confirmed dermal collateralization and showed activity crossing the outline of the calf, which was interpreted as lymph discharge. In the uncertain case with dermal activity in the lower part of the leg, SPECT/CT identified a dermal backflow.

In a patient with venous varicosis since childhood, early images displayed dilated lymphatic vessels and delayed imaging displayed intense dermal activity. SPECT/CT allowed us to identify areas of dermal backflow connected to dilated vessels. In five other patients (four with an oozing venous ulcer), dermal activity was localized next to one lymphatic vessel. SPECT/CT identified and localized a leakage of lymph from the lymphatic channel to the epidermis in all cases.

In two patients with tortuous lymphatic vessels on dynamic imaging, delayed imaging displayed an intense focus of activity along the vessel, suggesting dilatation or extravasation. SPECT/CT imaging allowed us to identify lymphatic varicosis. In another patient, planar imaging displayed a lymph collection attached to the vessel. SPECT/CT helped us evaluate the site of a saccular aneurysm.

A "honeycomb" appearance of the soft tissues was noted in all patients except for the patient with varicosis since childhood. As in other groups of patients, no correlation was

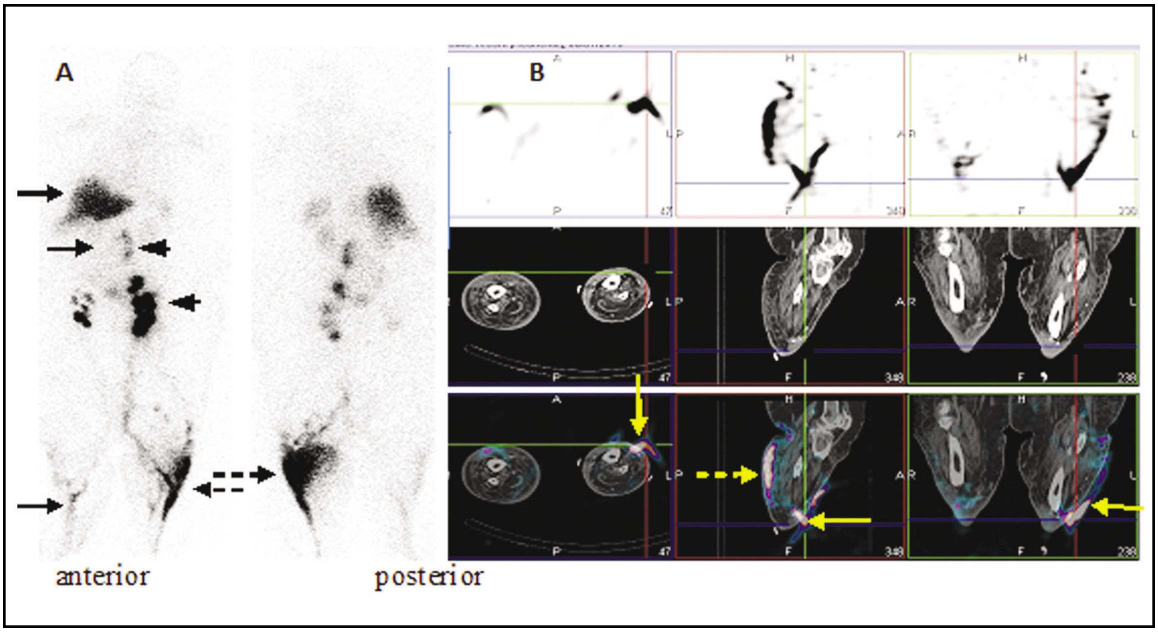

Fig. 5. Lymphatico-venous edema in a 76-year-old woman with an oozing ulcer. (A) Whole body imaging 4 hours after injection, anterior and posterior views, showing prominent hepatic activity (upper arrow). Right, absence of iliac node (middle arrow) and faint radioactivity in tortuous lymphatic vessels (lower arrow). Left, faint radioactivity uptake in iliac nodes (upper arrowhead), normal inguinal node activity (middle arrowhead) and localized dermal backflow (discontinuous arrows). (B) SPECT/CT imaging of the left calf 4 hours after injection. SPECT (top), CT (middle) and SPECT/CT (bottom): transaxial, sagittal and coronal images. Leakage of lymph (arrows) from the lymphatic vessel, and dermal background in the superficial dermis, predominantly in the posterior part of the calf (discontinuous arrow).

found between the honeycomb pattern and the distribution of lymphatic activity in soft tissues.

Summary of Additional 3D Imaging Findings

In all patients, the spatial distribution of activity was clearly depicted by SPECT, and the anatomical localization was provided by hybrid imaging. In 6 patients, SPECT/CT allowed localization of sacular aneurysm or identification of lymphatic varicosis that are simple morphological abnormalities. In the other 35 patients (85%), SPECT/CT provided significant additional information regarding vessel and soft tissue activity.

SPECT/CT had, in fact, a direct diagnostic contribution in 19 patients (46%). In 6 patients, diagnosis of dermal backflow or dermal collateralization of flow which was doubtful in planar imaging was made by SPECT/CT. In 7 patients, lymphorrhea was demonstrated by SPECT/CT. Using SPECT/CT, other lymphatic lesions; lymphangioma (n = 1), lymphangiomatosis (n = 1), muscular fascia lymphatic crossing (n = 1), lymphocele (n = 1) and lymphatic varicosis (n = 2) were revealed.

SPECT/CT also enabled us to differentiate between dermal backflow and dermal collateralization of flow. Dermal backflow was anterior, internal, or antero-internal in 17 of 19 patients, posterior or circumferential in the other two patients; it only involved the superficial dermis in 15 patients. On the other hand, dermal collateralization of flow, which was always circumferential, involved the whole dermis in six of eight patients.

Finally, the usual "honeycomb pattern" (with its trabecular structures) described with CT in lymphedema patients was observed in 37 cases. The present series showed no correlation with the distribution of the lymphoscintigraphic activities in the tissues, underlining the fact that these CT structural changes (although secondary to lymphatic diseases) do not represent lymphatic abnormalities.

DISCUSSION

SPECT/CT imaging is widely used to identify sentinel nodes. In a model of lymph node transplantation in minipigs, Blum evaluated SPECT/CT as a tool for documenting lymphatic regeneration (18). To our knowledge only one study reported the additional value of SPECT/CT in the investigation of lymphedema. Pecking found by using both conventional lymphoscintigraphy and fusion imaging obtained from a hybrid detector in patients with lower limb lymphedema that CT is useful to assess the tissues changes related to lymphedema, and the combination of a clinical, lymphoscintigraphic, and CT staging could be predictive of the treatment efficacy (19). Our work demonstrates that the three-dimensional space allows for a better localization in depth of lymphatic vessels and lymph nodes and a better analysis of dermal activities. In most cases, SPECT/CT helped us describe the physiopathology of edema and might influence prospective patient management.

The detailed SPECT/CT analysis of abnormalities allowed better understanding of individual patients. In 27 patients, CT imaging allowed anatomical assessment of the functional dermal lymphatic circulation. SPECT/CT imaging localized dermal activity in three dimensions in regards to the circumference and extension to the depth of the limb. This spatial analysis helped us differentiate between dermal backflow in 19 patients and dermal collateralization of flow in 8 patients. Dermal backflow was localized and involved the superficial dermis in the majority of patients (79%). In contrast, dermal collateralization of flow was always circumferential and involved the whole dermis in most patients (75%). These SPECT/CT observations are consistent with the definition of these functional abnormalities involving dermis. Dermal backflow represents, at any level of obstruction, a reflux of lymph from lymph nodes and/or lymphatic vessels through dermal lymphatic collaterals and towards the superficial dermal collateralization network. Dermal collateralization of flow represents a collateral route of enhanced drainage in/through the dermal lymphatic collateralization network from the injection site (20).

The internal predominance of dermal backflow in patients with previous venous stripping (83% vs 30%) suggests injury of the lymph vessels (21).

In the patient with obesity and acute dermo-epidermitis, the pattern of multiple sparse activity spots in the whole derma and along the muscular fascia could be the consequence of the low resistance of the connective tissue fibers (22). Muscular lymphedema is not present because the tight fascial binding that surrounds the skeletal muscle offsets capillary filtration (9).

In seven patients, SPECT/CT identified lymphorrhea. The pathogenesis of venous ulcers and lymphorrhea is complex (23). In patients with an oozing venous ulcer, SPECT/CT imaging allowed us to document continuity between the lymphatic vessel and skin surface. In six patients, SPECT/CT also indicated dermal activity, specifically varicosis in two cases and better localization of the saccular aneurysm in four cases.

SPECT/CT Lymphoscintigraphy in the Management of these Patients

In the patients with an oozing ulcer and in whom SPECT/CT identified lymphorrhea, the localization of lymph escape from the lymphatic vessel was a relevant abnormality that could guide local therapy. On the other hand, the diagnosis of circumscriptum lymphangioma or extensive lymphangioma allowed treatment options to be discussed. In the child with Gorham disease, SPECT/CT clearly localized the lymph spaces and recognition of these abnormalities without invasive biopsy helped manage this extensive cystic lymphangiomatosis.

SPECT-CT may be of particular interest for the microsurgical treatment of lymphedema, which include anastomosis between lymphatic vessels and veins, or between lymph nodes and veins (5). The reconstruction of "lymphatic" pathways using interposition, of either one vein or one lymphatic vessel, represents alternatives to these anastomotic procedures (24). Another surgical approach proposed clinically where no functional lymph nodes can be found is lymph node grafting (25). For these operations, identifying functional lymphatic vessels and/or lymph nodes under areas of dermal backflow should be of the utmost interest for surgeons. The techniques of lymphatic reconstruction are delicate and require a dedicated team with experience in microsurgery (5).

Another operative treatment, liposuction, is used to reduce excess fat deposition in lymphedematous limb. In techniques of liposuction (26), SPECT/CT could be used before surgery to assess the tissue changes related to the lymph stasis. Moreover, it could also be used after surgery to understand the functional state of the lymphatic system despite this surgical resection (26).

Apart from these surgical approaches, which are infrequently applied, the treatment of lymphedematous limbs is usually based on manual lymph drainage, the use of compression system devices, and the application of multi-layered semi-rigid bandages (2-3). Manual lymphatic drainage maneuvers have several potential main aims: they push the interstitial liquids and proteins in the initial lymphatics, move these fluids and proteins in the lymphatic vessels, facilitate the opening of lymphatic collaterals, and they drain the fluids and proteins toward collaterals, which can be induced or spontaneously opened, and/or towards normally functioning lymphatic vessels. With regard to the last goal, these lymphatic collaterals can cross lymphatic watersheds (zones) and be directed to unaffected areas (27). In our patient with primary lymphedema and no functional upper iliac node, the lymph was drained through abdominal lymphatic collaterals, but the delimitation of the areas with dermal backflow may also have implications for these maneuvers. The interest of these topographical and functional information was recently emphasized (28). The normal lymphatic vessels surrounding these edematous areas with dermal backflow might be stimulated by higher pressure than the pressure applied during these maneuvers on the smaller vessels forming the superficial collateral network. Notably, this superficial collateral lymphatic network has no valves (the lymph can be pushed freely in all directions), and high pressure has been reported to damage these small lymphatic vessels (29). The demonstration of dermal collateralization in which the whole dermis is involved might also allow physical therapists to apply higher pressures to these areas during their manual maneuvers and/or use of compression system devices.

Lymphoscintigraphy and Other Imaging Modalities

Multiple imaging modalities such as ultrasound, magnetic resonance imaging (MRI), and CT, have been used to evaluate abnormalities of the lymphatic system and the nature of tissue alterations in chronic lymphedema but fail to assess the functional status of the lymphatic circulation. For example, the common CT findings in lymphedema include calf skin thickening, thickening of the subcutaneous compartment, increased fat density, and thickened perimuscular aponeurosis (17). A typical honeycomb appearance is seen in most patients, representing pockets of fat surrounded by fluid or fibrous tissue (17). Our findings argue against the hypothesis that the rim-like halos represent lymph within dilated lymphatic vessels. High resolution cutaneous ultrasonography is able to analyze dermal changes (30) and high resolution MRI (hrMRI) has also been used to demonstrate water and fat distribution in the skin and subcutis in lymphedema, but hrMRI does not allow visualization of lymphatics inside the dermis (31). On the other hand, interstitial MR lymphography after intradermal injection of a contrast agent as gadodiamide has been shown to be able to localize tissue edema and visualize the functional lymphatic system in lymphedematous patients, but with concomitant venous enhancement (32). However, this technique is not commonly used in the investigation of lymphedema. Finally, dynamic lymphofluoroscopy using subcutaneous injection of a fluorescent substance, such as indocyanine green, has been recently introduced to study functional lymphatic vessels but the technique has a major drawback; it allows study of only the superficial lymphatic network (33). From this short review, it appears that, except for interstitial MR lymphography, planar and SPECT/CT lymphoscintigraphic imaging is the only image modality that allows assessment of the functional status of the lymphatic system and localization of fluid edema in soft tissues.

CONCLUSION

This study proposes that SPECT/CT represents a significant advance in lymphoscintigraphy with new potential applications for lymphedema management. Hybrid imaging supplements the knowledge obtained from lymphoscintigraphy or CT and generates a variety of information, to understand the physiopathology of lymphedema and influence its management. Lymphedema is a chronic condition. Additional knowledge about the localization of the lymphatic vessels and dermal collateralization could contribute to establishing a rational and "patient tailored" physical therapy for lymphedema and attenuate patients' discomfort.

REFERENCES

1. Szuba, A, WS Shin, HW Strauss, et al: The third circulation: Radionuclide lymphoscintigraphy in the evaluation of lymphedema. J. Nucl. Med. 44 (2003), 43-57.
2. Foldi, E, M Foldi, H Weissleder: Conservative treatment of lymphoedema of the limbs. Angiology 36 (1985), 171-180.
3. Badger, CM, JL Peacock, PS Mortimer: A randomized, controlled, parallel-group clinical trial comparing multilayer bandaging followed by hosiery versus hosiery alone in the treatment of patients with lymphedema of the limb. Cancer 15 (2000), 2832-2837.
4. Campisi, C, E Da Rin, C Bellini, et al: Pediatric lymphedema and correlated syndromes: Role of microsurgery. Microsurgery 28 (2008), 138-142.
5. Lee BB, J Laredo, R Neville: Current status of lymphatic reconstructive surgery for chronic lymphedema: It is still an uphill battle. Int. J. Angiol. 20 (2011), 73-80.
6. Ter, SE, A Alavi, CK Kim, et al: Lymphoscintigraphy. A reliable test for the diagnosis of lymphedema. Clin. Nucl. Med.18 (1993), 646-654.
7. Weissleder, H, R Weissleder: Lymphedema: Evaluation of qualitative and quantitative lymphoscintigraphy in 238 patients. Radiology 167 (1988), 729-735.
8. Witte, CL, MH Witte, EC Unger, et al: Advances in imaging of lymph flow disorders. Radiographics 20 (2000), 1697-1719.
9. Moshiri, M, DS Katz, M Boris, et al: Using lymphoscintigraphy to evaluate suspected lymphedema of the extremities. Am J Roentgenol. 178 (2002), 405-12.
10. Williams, WH, CL Witte, MH Witte, et al: Radionuclide lymphangioscintigraphy in the evaluation of peripheral lymphedema. Clin. Nucl. Med. 25 (2000), 451-464.
11. Baulieu, F, L Vaillant, N Gironet, et al: Contribution of lymphoscintigraphy in the exploration of lymphedema in children. J. Mal. Vasc. 28 (2003), 269-276.
12. International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema: 2013 Consensus Document of the International Society of Lymphology. Lymphology 46 (2013), 1-11.

13. Scarsbrook, AF, A Ganeshan, KM Bradley: Pearls and pitfalls of radionuclide imaging of the lymphatic system. Part 2: Evaluation of extremity lymphoedema. Br. J. Radiol. 80 (2007), 219-226.
14. Bourgeois, P: Scintigraphic investigations of the lymphatic system: The influence of injected volume and quantity of injected volume and quantity of labelled colloidal tracer. J. Nucl. Med. 48 (2007), 693-695.
15. Larcos, G, DR Foster: Interpretation of lymphoscintigrams in suspected lymphoedema: Contribution of delayed images. Nucl. Med. Commun. 16 (1995), 683-686.
16. Pecking, AP, M Wartski, R Cluzan et al: SPECT/CT fusion imaging radionuclide lymphoscintigraphy: Potential for limb lymphedema assessment and sentinel node detection in breast cancer. Lymphology 135 (2007), 79-84.
17. Monnin-Delhom, ED, BP Gallix, C Achard, et al: High resolution unenhanced computed tomography in patients with swollen legs. Lymphology 35 (2002), 121-128.
18. Blum KS, WH Radtke, WH Knapp, et al: SPECT-CT: A valuable method to document the regeneration of lymphatics and auto-transplanted lymph nodes fragments. Eur. J. Nucl. Med. Imaging 34 (2007), 1861-1867.
19. Pecking, AP, JL Albérini, M Wartski, et al: Relationship between lymphoscintigraphy and clinical findings in lower limb lymphedema (LO): Toward a comprehensive staging. Lymphology 41 (2008), 1-10.
20. Stanton AWB, WE Svensson, RH Mellor, et al: Differences in lymph drainage between swollen and non-swollen regions in arms with breast-cancer-related lymphedema. Clin Sci. 101 (2001), 131-140.
21. Földi M, G Idiazabal et al: The role of operative management of varicose veins in patients with lymphedema and/or lipedema of the legs. Lymphology 33 (2000), 167-171.
22. Partsch, H, C Stöberl, A Urbanek, et al: Clinical use of indirect lymphography in different forms of leg edema. Lymphology 21 (1988), 152-160.
23. Fernandez, AP, M Miteva, B Roberts, et al: Histopathologic analysis of dermal lymphatic alterations in chronic venous insufficiency ulcers using D2-40. J. Am. Acad. Dermatol. 64 (2011), 1123:e1-12.
24. Baumeister, RG, S Siuda, H Bohmert, et al: A microsurgical method for reconstruction of interrupted lymphatic pathways: Autologous lymph-vessel transplantation for treatment of lymphedemas. Scand. J. Plast. Reconstr. Surg. 1986 (20), 141-146.
25. Becker, C, JV Vasile, Levine JL, et al: Microlymphatic surgery for the treatment of iatrogenic lymphedema. Clin. Plast. Surg. 39 (2012), 385-398.
26. Brorson, H, P Höijer: Standardised measurements used to order compression garments can be used to calculate arm volumes to evaluate lymphoedema treatment. J. Plast. Surg. Hand Surg. 46 (2012), 410-415.
27. Bruna, J: Collateral lymphatic circulation. Eur. J. Plast. Surg. 23 (2000), 321-325.
28. Giacalone, G, JP Belgradon, P Bourgeois, et al: A new dynamic imaging tool to study lymphedema and associated treatments. Eur. J. Lymphol. 62 (2011), 10-14.
29. Eliska, O, M Eliskova: Are peripheral lymphatics damaged by high pressure manual massage? Lymphology 28 (1995), 21-30.
30. Naouri, M, M Samimi, M Atlan, et al: High-resolution cutaneous ultrasonography to differentiate lipoedema from lymphodema. Br. J. Dermatol. 163 (2010), 296-301.
31. Idy-Peretti, I, J Bittoun, FA Alliot, et al: Lymphedematous skin and subcutis: In vivo high resolution magnetic resonance imaging evaluation. J. Invest. Dermatol. 110 (1998), 782-787.
32. Lohrmann, C, E Földi, JP Bartholomä, et al: MR imaging of the lymphatic system: Distribution and contrast enhancement of gadodiamide after intradermal injection. Lymphology 39 (2006), 156-163.
33. Giacalone, G, JP Belgrado, P Bourgeois, et al: A new dynamic imaging tool to study lymphedema and associated treatments. Eur. J. Lymphol. 62 (2011), 10-14.

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