Lymphoscintigraphy of chylous anomalies: chylothorax, chyloperitoneum, chyluria and lymphangiomatosis. Fifteen year experience in a pediatric setting and review of the literature

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Running head: Lymphoscintigraphy for chylous effusions
ABSTRACT

Objective: In the pediatric setting, lymphoscintigraphy is mostly used for the evaluation of lymphedema. Only a few cases of chylous anomalies and lymphatic malformations imaged with lymphoscintigraphy, have been reported in the literature. The aim of this study was to review the use of lymphoscintigraphy in those pathologies.

Methods: All lymphoscintigraphies obtained between 2001 and 2017 in our hospital for chylous anomalies, were retrospectively reviewed. Results were correlated to clinical and radiological findings. Lymphoscintigraphy consisted of sequential imaging after injection of 100-250 μci 99mTc-filtered sulfur colloid at the level of the feet and/or hands.

Results: Twenty-five studies were performed in 21 patients. Fourteen studies were obtained for the evaluation of chylothorax. Eleven were performed for chyloperitoneum, chyluria, chylopericardium, exsudative enteropathy or lymphangiomatosis. Ten studies were positive for lymphatic leak, 1 was dubious. After correlation with radiological findings and follow-up, there were seven true negative and five false negative (previous 67Ga interfering activity in 1, injection on the hands only in 3, low lipid diet in 1). One study became positive after injecting on the feet and another one after switching to a high lipid diet.
Conclusion: Lymphoscintigraphy is an useful tool to image lymphatic anomalies in children. To optimize results, it is suggested to inject the 4 extremities, to have the patient under a high lipid diet, to withhold octreotide and use single photon emission tomography with computed tomography (SPECT/CT).

Keywords: lymphoscintigraphy; children; chylothorax; chyloperitoneum; lymphangiomatosis.
Introduction

Lymphatic anomalies are globally rare in newborns and children but in some cases can lead to significant morbidity and mortality. Of interest are the chylous effusions that can occur in the thorax, the abdomen, the pericardium or the urinary tract. In a tertiary pediatric setting, chylothorax and chyloperitoneum are encountered more and more frequently as patients have surgeries from a very young age for congenital heart disease. Patients with vascular or lymphatic congenital malformations are also referred in a tertiary pediatric center and may need imaging. The purpose of our study was to review our experience with such patients in the last fifteen years.

Material and Methods

Between 2001 and 2017, 171 lymphoscintigraphic studies were performed in our hospital. After excluding patients evaluated for lymphedema, Klippel-Trenaunay and sentinel node mapping, twenty five studies in 21 patients were done for lymphatic anomalies chylothorax, chylopericardium, chyloperitoneum, chyluria, lymphangiomatosis or lymphangiectasia as clinical presentation.

The study was approved by the Medical Affair Direction, allowing the conduction of this retrospective study on file without the patient’s and parental consents.

After explanation of the procedure to the patient and parents, 3.7 MBq (100 uci) in infants and toddlers using a 27G x 0.5 inch needle to 9.25 MBq (250 uci) in the older children using a 25 G x 0.5 inch needle of 99mTc-filtered sulfur colloid were injected using a tuberculin syringe, under sterile conditions, at the level of the feet and/or
hands. Injected volume was between 0.1 to 0.25 cc. In most cases, intradermal
injections were performed at the level of the first interdigital spaces but some very tiny
patients had subcutaneous injections. We were not able to inject some patients in the
four limbs due to their clinical condition and/or the presence of a saturometer device or
IV access. Lymphoscintigraphy consisting of anterior and posterior sequential dynamic
images of the regions of interest were performed for 60-120 minutes followed by
delayed imaging if needed, including 24 hours study (Figure 1). If present, the drain
casing was also imaged.

Lymphoscintigraphy results were correlated to clinical and paraclinical data and
to follow up. Studies were considered false negative if the abnormalities were proven
to be present at time of lymphoscintigraphy by other modalities or clinical findings.

**Results**

Out of our 21 patients, 6 were 4 month old and younger, 7 between the ages of
10 months and 5 years and the remaining were 8 years and older (Table 1). No patients
was receiving octreotide at the time of examination. However, drains were present in
some patients and some children were parentally fed.

Patients 1 to 7 developed chylothorax following cardiac surgery for congenital
heart disease - mostly Fontan and Damus-Kaye-Stansel procedures - or cardiac
transplantation in one patient. We had only 2 studies demonstrating pleural
accumulation, in patients 2 and 7. Another study, in patient 6 was equivocal for left
sided chylothorax. Two studies (patient 1 and 3) were true negative. Two studies (patients 4 and 5) did not show any abnormal uptake and were considered false negative. However the patients were injected only on the hands due to clinical instability. Patients 8 to 11 presented themselves with congenital chylothorax. The lymphoscintigraphy was negative in patients 8 to 10. However, patient 8 was injected only on the hands. Patient 10 diagnosis was changed from congenital chylothorax to pseudochylothorax following pneumonia during follow-up. In patient 11, a one-month-old baby also known for gastroschisis, the lymphoscintigraphy was normal after injection on the hands. However, it was positive after injection, a few days later, on the feet (Figure 2).

Patients 12 to 14 were known for lymphangiomatosis and chylothorax. Patient 12 was a 15-year-old boy with Gorham's disease. He was evaluated for recurrent chylothorax and the study was positive after injection in both hands. (Figure 3). Patient 13 lymphoscintigraphy was non diagnostic due to 67Ga interference from a previous study. Patient 14 was imaged three times between age 12 and 15. She had a history of congenital chylothorax and hydrops fetalis. At age 12, she was evaluated for chylothorax and the study was a true negative. At age 15, she was imaged again for lymphatic malformations and chylopericardium necessitating drainage. After a normal lymphoscintigraphy, the patient was switched from a normal diet to a high lipid diet. Control lymphoscintigraphy demonstrated soft tissue lymphangiomatosis but while there was no frank accumulation in the pericardium, some activity was demonstrated in
the drainage bag (Figure 4). Patient 15 had a history of recurrent chylothorax and chyloperitoneum since birth. The underlying pathology was also lymphangiomatosis. She was imaged twice and her lymphatic studies were true negative.

Patient 16 to 20 were evaluated for chyloperitoneum and/or for the possibility of intestinal lymphangiectasia. Patient 16 was a ten-month-old patient with complex cardiopathy, status post Damus-Kaye-Stansel and Right Ventricle - Pulmonary Artery conduit cardiac surgery and gastrostomy. He developed chyloperitoneum which was demonstrated on the lymphoscintigraphy after injection in the four extremities (Figure 5). Patient 17 was also a ten-month-old patient with recurrent chyloperitoneum following sclerotherapy. After injection in both feet, extravasation of the tracer was demonstrated in the region of the cisterna chyli. Abnormal dysplasic lymphatics with intra-abdominal leak were confirmed by lymphography (Figure 6).

Finally, patient 21 was evaluated for chyluria, without history of previous cancer, surgery or filariasis. No leak was demonstrated on lymphoscintigraphy.

Investigation over a period of three years did not establish the origin of the chyluria.

Discussion

The thoracic duct is the main collecting system of the body's lymph and chyle. Lymph originating from the abdomen and lower extremities drains through lumbar lymph nodes to the cisterna chyli located in front of L2. The thoracic duct then travels in the retrocrural space on the right side of the aorta, then crosses the midline at the
level of T5, through the aortic arch to drain in the left subclavian vein \((1,2,3,4)\). The right side of the upper body and the head drains into the right lymphatic duct which empties in the right subclavian vein \((\text{Figure 7})\). Anatomical variations are frequent \((3)\).

Chyle is responsible for ingested fats' transport, most of it originating from the liver and gastrointestinal tract. Chyle flow increases significantly after a meal, depending on the diet, potentially influencing lymphoscintigraphy \((2,4,5)\). Transport along the thoracic duct is mediated by pressure gradient between the thorax and the abdomen, tissue hydrostatic pressure and Bernoulli's effect at the entrance of the subclavian vein \((3,5)\). More than 2 liters of lymph empty in the circulation each day.

Chyle is responsible for the transport of lipids from the GI tract into the circulation but also for the transfer of fluids, proteins and lymphocytes between the interstitial and the intravascular compartments \((6)\).

Chylothorax is probably the most frequent type of abnormal chylous accumulation. It can be caused by non iatrogenic trauma, surgery, invasive diseases and finally it can be congenital \((3,5,7)\). Congenital chylothorax is found in the neonatal period and can be associated malformations such as Noonan's disease or Down's syndrome, hydrops fetalis, congenital lymphangiectasia or lymphangiomatosis. It is suggested that the presence of a congenital weakness associated with the trauma of birth may cause congenital chylothorax in some patients \((3)\).

Due to the localization of the thoracic duct, post traumatic chylothorax is more frequent on the right side in adults \((8)\). However, in children, it can be found on the
left side, following cardiac surgery involving the aortic region (esophageal atresia repair, aortic coarctation repair, Blalock-Taussig ....) (9). It is most frequent following heart transplantation and Fontan procedures and chyloperitoneum may also occurs (10).

Post surgical chylothorax is rare in adults, as a complication of 0.25 to 0.5% of intrathoracic procedures but more frequent in children, between 2.5 and 4.7% (5,10).

Finally, mostly in adults, chylothorax may complicate lymphoma, esophageal cancer, tuberculosis, filariasis, lymphangioleiomyomatosis and Gorham’s disease as in some of our patient.

For the evaluation of chylous effusion, the lymphoscintigraphy procedure is similar to the one used for lymphedema. However, the 4 extremities must be injected, which can be difficult in very young patients or in intensive care patients. Due to the lack of availability of 99mTc antimony, 99mTc Dextran and 99mTc nano-albumin, the radiotracer of choice is Tc99-m filtered sulfur colloid. Intradermal injections in the interdigital spaces are usually used but can be replaced by subcutaneous ones. Injected activities range from 3.7 to 9.25 MBq in small volumes around 0.1 ml. More invasive subfascial injections, allowing the evaluation of the deep lymphatic system are not used in our institution(1). Treatment options include parenteral low fat diet and octreotide to reduce the intestinal chyle production, drainage and thoracic duct ligation (4,10).

Withholding medication or reintroducing a high fat diet may be needed to decrease the possibility of false negative results as in patient 14.
Only a few cases of lymphoscintigraphies performed in very young patients are found in the literature: a 2 months old boy with congenital chylothorax (11) and a neonate with chylothorax following cardiac surgery (12). We had 9 patients less than one year old in our population and some of those patients were more of a challenge to inject.

Chylothorax is differentiated from pseudo chylothorax by its high triglyceride contents (4), the latter being a complication of long standing exudate rich in cholesterol due to fatty degeneration of cells (7,8). Pseudochoylothorax following lung infection was eventually demonstrated in patient 10.

Among rare causes of chylothorax, we can include lymphangioleiomyomatosis and haemangiomatosis (4). Lymphangioleiomyomatosis is characterized by smooth muscle proliferation in the lungs, lymph nodes and thoracic duct. It is found almost exclusively in women and leads to respiratory failure. A majority of patients will present themselves with chylothorax (4,7). Haemangiomatosis or Gorham’s disease is characterized by vascular and lymphatic proliferation in the bones or in the soft tissues. Intrathoracic lesions, such as in one of our patient, are found in less than 1% of cases (4,13). Complications include chylothorax, disseminated intravascular coagulation, infection and malnutrition.

Some of our patients had chyloperitoneum, most of the time associated with other pathologies. Chyloperitoneum can be exsudative, with chyle retrodiffusion, following central obstruction by malignancy, infection or fistulous with the presence
of enlarged retroperitoneal lymphatics (14). Chyloperitoneum may also occur following trauma or surgery as in patient 16 or be congenital in origin, associated with intestinal lymphangiectasia as in patient 15 or with lymphangiomatosis as in patient 17 (15).

Primary intestinal lymphangiectasia is characterized by intestinal megalymphatics and protein-losing enteropathy and lymphoscintigraphy can demonstrated abnormal accumulation of the tracer not only in the digestive tract but in various effusion as shown in 41 patients by Wen et al (16).

Chyluria (14) is secondary to a fistula between the para aortic lymphs nodes and the kidney, with backflow toward the renal lymph nodes and extravasation in the collecting system. It is associated with filariasis, cancer, abdominal surgery, including live-donor nephrectomy, renal transplantation and oncological procedures (17,18,19). or lymphangiitis (20). Forty-one patients with chyluria were imaged using 99mTc-Dextran and only the early appearance of kidney or pelvis activity was indicative of lymphourinary fistula (20). We did not find any early urinary leak in our last patient imaged, even after using SPECT/CT to improve visualization of the thoracic duct (21).

Chylopericardium is very rare, either secondary to congenital malformations or as consequence of trauma, surgery, Gorham's disease or tumors (22). Chylopericardium could not be clearly demonstrated in patient 15.
One of the largest study using lymphoscintigraphy in chylothorax, chyloperitoneum and chyluria was published in 1998 (23). As the study originated from Asia, 11 out the 18 patients presented themselves with chyluria secondary to filiaris. The authors used 99mTc-Dextran or 99mTc-Antimony. There were no children in their cohort. Five studies were normal and the remaining 6 demonstrated obstruction (5) or lymphorenal fistula (1). The remaining 7 patients presented a combination of chylothorax / chyluria/ chyloperitoneum of various but non malignant etiologies. Enhanced lymph flow was found in one, lymph reflux in another patient and obstruction in the remaining 5. Lymphoscintigraphy was conclusive in 72% of their patients.

In an European study of 16 adult patients (14), diagnosis was obtained by lymphoscintigraphy in 4, CT scan in 6 and combination of both modalities in 6. Five patients had chyluria, 8 chylothorax and 4 chyloperitoneum. Only 2 of 5 cases of chyluria were secondary to filiaris. Nine patients had chyle leak following surgery for neoplasia and 2 secondary to tuberculosis. A traumatic origin was therefore the most frequent and not filiaris.

The only large pediatric study using lymphoscintigraphy included 5 neonates and 10 patients between 1.5 yo and 8 yo (24). The population was different from ours as most of the children affected had lymphatic dysplasia, including congenital aplasia and hypoplasia, with lymphedema. Chylous effusion were present but not the main clinical pattern in most.
Single-photon emission computed tomography with computed tomography (SPECT-CT) has shown to improve localization is suggested and we have started to use SPECT-CT in some of our more recent patients (21, 25, 26) with proper immobilization precluding the use of sedation. More recent equipment may improve even detection of small leakage (27). An alternative would be to fuse the SPECT images with contemporary diagnostic CT or magnetic resonance imaging.

**Conclusion:**

Lymphoscintigraphy can be performed in children in a variety of settings such as chylothorax, chylopericardium, chyloperitoneum, chyluria, lymphangiectasia and lymphangiomatosis. While technically challenging in babies due to their small size, the test is minimally invasive, with low radiation exposure and no side effects, in infants and children that otherwise undergo major morbidity. We recommend to inject the four limbs, to have the patient under a fatty diet, without octreotide and use SPECT-CT to improve diagnostic accuracy.

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**Conflicts of interest:**
Sophie Turpin: No conflict of interest to declare

Raymond Lambert: No conflict of interest to declare
References:


Figure 1: Normal lymphoscintigraphy after injection in the upper and lower extremities
Figure 2: Congenital Chylothorax. No abnormal accumulation after injection in both hands: (A) anterior view (top) and posterior view (bottom) of the thorax with activity in the axillary lymph nodes. Thoracic accumulation of the tracer (arrows), including in the thoracic canal region after injection in both feet: (B) anterior view (top) and posterior view (bottom) with visualization of the ilio-inguinal lymph nodes.
Figure 3: Gorham's disease. Abnormal accumulation of tracer in the mediastinum (arrow) after injection on both upper and lower extremities (A). Magnetic Resonance Imaging: diffuse infiltration of the mediastinum (arrow) secondary to lymphangiomatosis (B) and presence of loculated chylothorax (arrow)(C).
Figure 4: Lymphangiomatosis in patient with chylopericardium necessitating drainage.

Normal study with standard diet: injection in the upper (A) and lower (C) extremities.

No activity in the collecting bag (E). Left shoulder and right inguinal region lymphangiectasia (thin arrows) on lymphoscintigraphy performed after switching the patient to high fat content diet: injection in the upper (B) and lower (D) extremities.

Activity (thick arrow) in the collecting bag (F).
**Figure 5:** Chyloperitoneum. After injection in the 4 extremities, abnormal accumulation of tracer in the abdomen at 1 hour: anterior view (A), left lateral view (C) and at 5 hours: anterior view (B) and left lateral view (D).
Figure 6: After injection in the lower extremities, lymphoscintigraphy image at 1 hour demonstrating leak (arrow) (A). Diffuse intra-abdominal accumulation at 5 hour post injection (B). Conventional lymphography showing dysplastic lymphatics (arrow) and intra-abdominal leak (C).
Figure 7: Anatomy of the lymphatic system. *Adapted from Wikimedia Commons*
**TABLE 1: Patients Characteristics:** TN = True Negative; TP = True Positive; FN = False Negative; F = female; M = male.

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