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REFERENCES

1. Steinberg AD, Steinberg SC. Long-term preservation of renal function in patients with lupus nephritis receiving treatment that includes cyclophosphamide versus those treated with prednisone only. *Arthritis Rheum* 1991;34:945–950.
2. Felson DT, Anderson J. Evidence for the superiority of immunosuppressive drugs and prednisone over prednisone alone in lupus nephritis. *N Engl J Med* 1984;311:1528–1533.
3. Gladman DD. Prognosis of systemic lupus erythematosus and the factors that affect it. *Curr Opin Rheumatol* 1991;3:789–796.
4. Schur PH. Clinical features of SLE. In: Kelley WN, Harris ED, Ruddy S, Sledge CB, eds. *Textbook of rheumatology*. Philadelphia: WB Saunders; 1993:1017–1042.
5. Shibasaki T, Ishimoto F, Sakai O, Joh K, Aizawa S. Clinical characterization of drug-induced allergic nephritis. *Am J Nephrol* 1991;11:174–180.
6. Linton AL, Richmond JM, Clark WF, Lindsay RM, Driedger AA, Lamki LM. Gallium-67 scintigraphy in the diagnosis of acute renal disease. *Clin Nephrol* 1985;24:84–87.
7. Linton AL, Clark WF, Driedger AA. Acute interstitial nephritis due to drugs. *Ann Intern Med* 1980;93:735–741.
8. Ganeval D, Noel L-H, Preud'homme J-L, Droz D, Grunfeld J-P. Light chain deposition disease; its relation with SL-type amyloidosis. *Kidney Int* 1984;26:1–9.
9. Randall RE, Williamson WC Jr, Mullinex F, Tung MY, Still WJS. Manifestations of systemic light chain deposition. *Am J Med* 1976;60:273–299.
10. Tan EM, Cohen AS, Fries J. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271–1277.
11. Wallace DJ, Podell TE, Weiner JM. Lupus nephritis: experience with 230 patients in a private practice from 1950–1980. *Am J Med* 1982;72:209–220.
12. Abrass CK, Nies KM, Louie JS, Border WA, Glassock RJ. Correlation and predictive accuracy of circulation immune complexes with disease activity in patients with systemic lupus erythematosus. *Arthritis Rheum* 1980;23:273–282.
13. Lin WY, Lan JL, Cheng KY, Wang SJ. Value of gallium-67 scintigraphy in monitoring the renal activity in lupus nephritis. *Scan J Rheum* 1998;27:42–45.
14. Cruzado JM, Poveda R, Mana J, et al. Interstitial nephritis in sarcoidosis: simultaneous multiorgan involvement. *Am J Kidney Dis* 1995;26:947–951.
15. Pagniez DC, MacNamara E, Beuscart R, Wambergue F, Dequiet P, Tacquet A. Gallium scan in the follow-up of sarcoid granulomatosus nephritis. *Am J Nephrol* 1987;7:326–327.
16. Wood BC, Sharma JN, Germann DR, Wood WG, Crouch TT. Gallium-67 citrate imaging in noninfectious interstitial nephritis. *Arch Intern Med* 1978;138:1665–1666.
17. Bakir AA, Lopez-Majano V, Hryhorczuk DO, Rhee HL, Dunea G. Appraisal of lupus nephritis by renal imaging with gallium-67. *Am J Med* 1985;79:175–182.
18. Tsan M. Mechanism of gallium-67 accumulation in inflammatory lesions. *J Nucl Med* 1985;26:88–93.
19. Tsan M, Scheffel U. Gallium-67 accumulation in inflammatory lesions. *J Nucl Med* 1979;20:173–179.
20. Fraenkel L, Mackenzie T, Joseph L, Kashgarian M, Hayslett JP, Esdaile JM. Response to treatment as a predictor of long-term outcome in patients with lupus nephritis. *J Rheumatol* 1994;21:2052–2057.
21. Levey AS, Lan SP, Crowin HL. Progression and remission of renal disease in the Lupus Nephritis Collaborative Study: results of treatment with prednisone and short-term oral cyclophosphamide. *Ann Intern Med* 1992;116:114–123.
22. Laitman BS, Glicklich D, Sablay LB, Grayzel AL, Barland P, Bank N. Effect of long-term normalization of serum complement levels on the course of lupus nephritis. *Am J Med* 1989;87:132–138.
23. Appel GB, Cohen DJ, Pirani CL, Meltzer JI, Estes D. Long-term follow-up of patients with lupus nephritis: a study based on the classification of the World Health Organization. *Am J Med* 1987;83:877–885.
24. Cronin ME, Leair DW, Jaronski S, Lightfoot RW. Simultaneous use of multiple serologic tests in assessing clinical activity in systemic lupus erythematosus. *Clin Immunol Immunopathol* 1989;51:99–109.
25. Smeenk R, Hylkema M. Detection of antibodies to DNA: a technical assessment. *Mol Biol Rep* 1992;17:71–79.
26. Smeenk RJ, van-den-Brink HG, Brinkman K, Termaat RM, Berden JH, Swaak AJ. Anti-dsDNA: choice of assay in relation to clinical value. *Rheumatol Int* 1991;11:101–117.

Scintigraphic Localization of Lymphatic Leakage Site After Oral Administration of Iodine-123-IPPA

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Chylothorax can occur secondary to traumatic lesions of the thoracic duct caused by chest injuries, surgical procedures involving the pleural space, neoplasms or malformations of the lymphatics. **Methods:** Lymphatic leakage sites were localized by scintigraphy after oral administration of the ^{123}I-labeled long-chain fatty acid derivative iodophenyl pentadecanoic acid (IPPA). We report on three patients with different lymphatic leakage sites and on one normal control subject. **Results:** IPPA scintigraphy localized the lymphatic leakage site correctly in all three patients. In two of them, the method even guided the successful surgical treatment of the leakage. **Conclusion:** This approach is suitable for detecting lymphatic leakages of intestinal origin.

Key Words: thoracic duct; lymphatic leakage; iodine-123-iodophenyl pentadecanoic acid

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The thoracic duct originates from the cisterna chyli, enters the chest through the aortic hiatus, curves around the right side of the aorta, continues on the anterior surface of the vertebral column and crosses the posterior surface of the aorta to the left at the level of the fifth thoracic vertebra (T5) finally merging into the venous system at the left jugulosubclavian junction (Fig. 1). This anatomy explains how injuries below the level of T5–6 usually cause a right-sided chylothorax, whereas injuries above this level result in a left-sided effusion. Indeed, the anatomical location of the thoracic duct tends to vary greatly from individual to individual.

Depending on the frequency of food intake and fat content, leakage can have a flow rate of 1.5 ml/kg of body weight per hour. Clinically, leakage involves an accumulation of chyle in the pleural space associated with compression of the ipsilateral lung and mediastinum and can lead to dyspnea, fatigue and discomfort. Biochemically, up to 2500 ml of fat, protein, fat-soluble vitamins and antibodies can be lost over a period of 24 hr.

Before the first successful surgical closure of the leakage (*1*), the mortality of chylothorax ranged between 15% and 50%. Currently, mortality is less than 10% due to multimodal surgical approaches. Conservative therapy consists of thoracostomy including placement of tube drainage and correction of both fluid losses and electrolyte imbalance.

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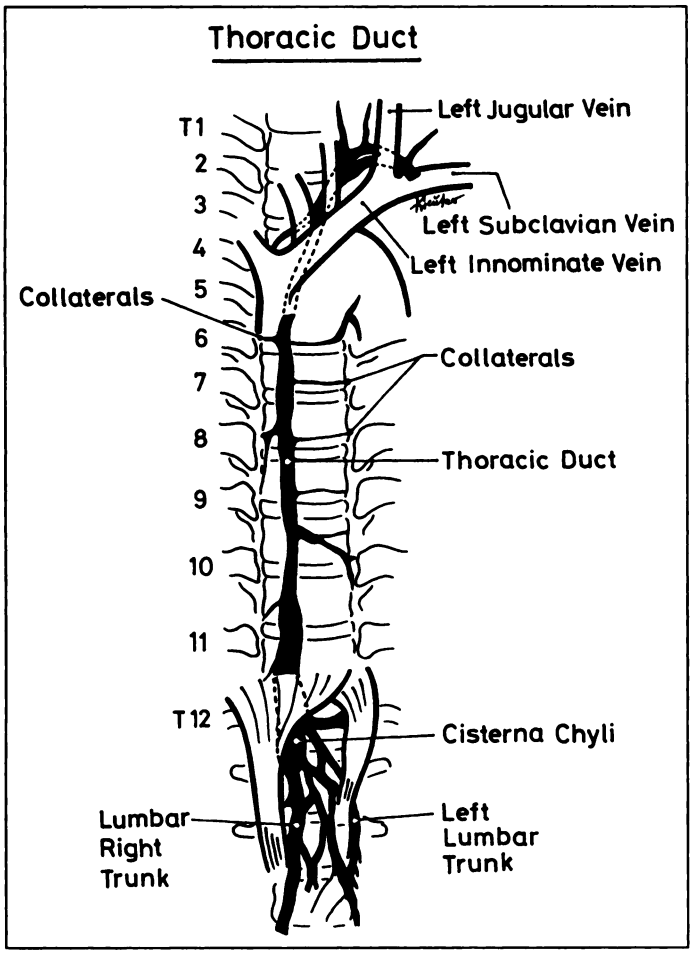

FIGURE 1. Anatomic location of thoracic duct.

Parenteral feeding involves administration of small-chain fatty acids (less than 10 carbon atoms) that are directly absorbed by the venous blood. Only long-chain fatty acids are absorbed by the intestinal lymphatics. This mode of treatment is adequate but limited to 14 days at the most. Then the crucial decision about whether surgical intervention is indicated has to be made (*2,3*). Correct localization of the lesion is prerequisite to defining the surgical strategy. In other words, there is a clinical indication to explore the thoracic duct or other lymph vessels in patients with chylic effusions.

The aim of this study was to localize leakage sites in the lymphatic vessels by the administration of radioactive food

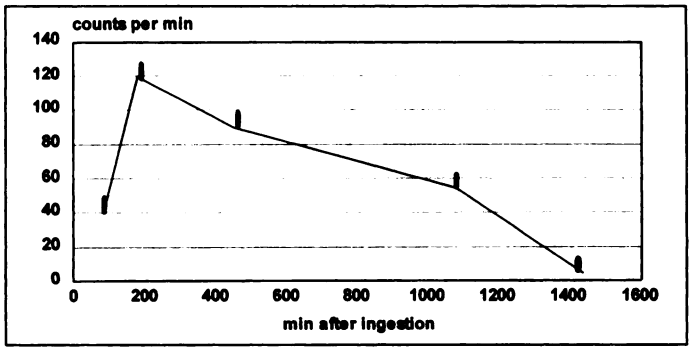

FIGURE 2. Blood-pool activity curve of ^{123}I-IPPA in a normal control subject. Time points at which blood samples were drawn are indicated by markers.

absorbable through the intestinal lymphatics. The oral administration of the ^{123}I labeled long-chain fatty acid derivative iodophenyl pentadecanoic acid (IPPA), a standard tracer in nuclear cardiology, appears to meet the criteria required of a tracer suitable for visualization of the thoracic duct and/or lymphatic leakage sites.

MATERIALS AND METHODS

We studied one normal control subject and three patients with lymphatic leakages of unknown origin. All studies were performed using a large-field-of-view, dual-head gamma camera (Multi-SPECT2; Siemens, Erlangen, Germany), an all-purpose, parallel-hole collimator and a 256 × 256 pixel matrix size for the static images.

The patients fasted for 6 hr and were given a liquid meal (200 ml) containing 260 MBq ^{123}I-IPPA (Amersham, Cygne Eindkeven, The Netherlands). A sequence of static images each lasting 10 min was taken for up to 24 hr with increasing intervals. At the beginning of the study, the intervals between the imaging sequences did not exceed 30 min. After the first 3 hr, images were produced every 1 to 4 hr. Additionally, blood samples were taken from the normal control subject.

RESULTS

The blood-pool activity curve of the normal control subject indicated that the orally-ingested ^{123}I-IPPA had entered the blood stream within 2 hr (Fig. 2). The scintiscans of the normal control subject in the anterior view are shown in Figure 3. Two hours after ingestion, the activity had reached the lymph fluid. Blood-pool activity and faint uptake in the liver and intestine were seen after 7 hr.

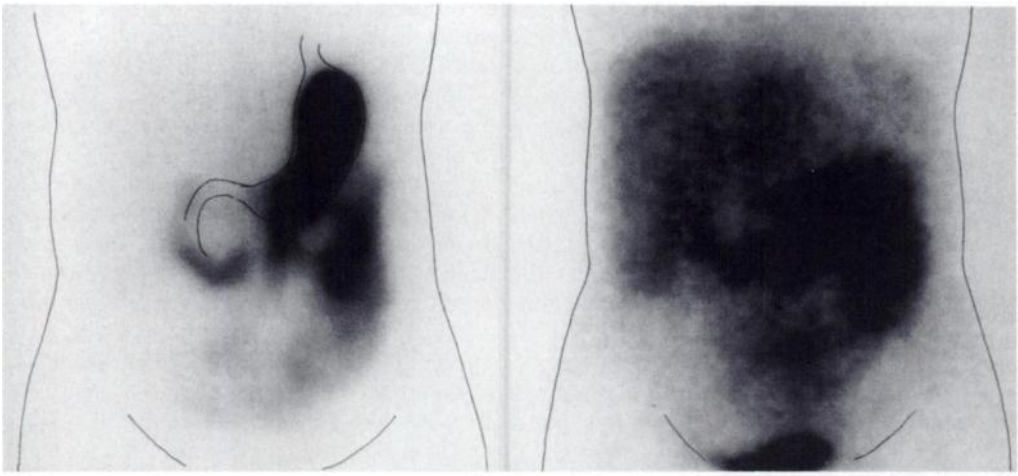

FIGURE 3. Anterior view of abdomen of a normal control subject. Orally ingested activity is seen in bowel at 2 hr (left) and in blood pool/lymph vessels at 7 hr (right).

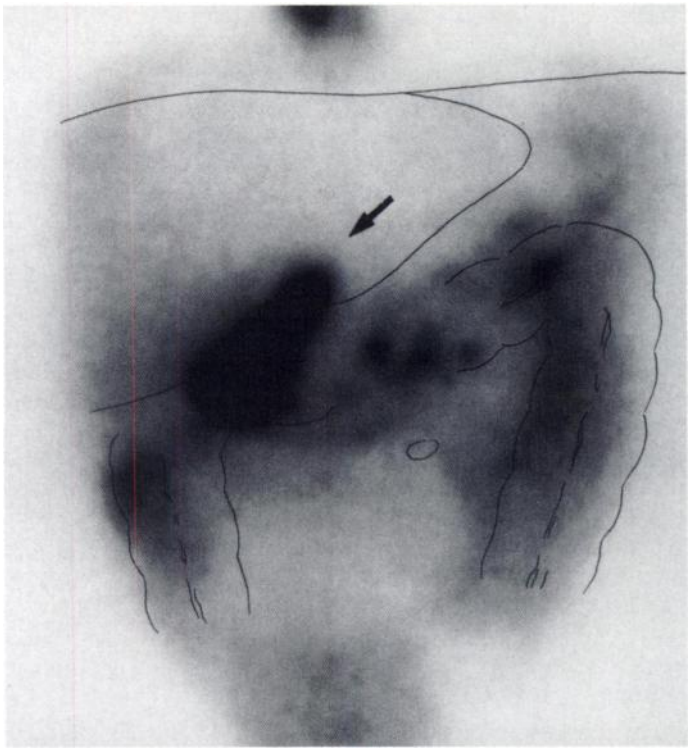

FIGURE 4. Patient 1. Anterior view of abdomen 7 hr after ingestion. Increased uptake in right upper abdomen (arrow), which was confirmed as lymphatic leakage at surgery.

Patient 1

A 52-yr-old man with esophagus carcinoma had undergone abdominothoracic esophageal resection with "level two" lymphadenectomy, i.e., the mediastinal and abdominal lymph nodes that drain this area as well as the suprapancreatic lymph nodes adjacent to the coeliac trunk were removed. Postoperatively, the patient developed a severe chyloperitoneum indicating a leakage of abdominal lymphatics from an unknown site. The patient was referred to our nuclear medicine department for localization of the leakage site. Seven hours after administration of the radiolabeled fatty acid meal through a stomach tube, a clearly higher activity accumulation was visible in the right upper abdomen adjacent to the liver (Fig. 4). Based on the scintigraphic findings, laparotomy was done with successful exploration of the lymphatic fistula approximate to the coeliac trunk and closed by a suture.

Patient 2

A 62-yr-old man with tongue carcinoma was treated by neck dissection to the left. In this patient, a leakage developed in the neck, which produced a loss of lymph fluid amounting to 1500 ml/day as assessed by drainage (Fig. 5). The leakage was obviously the result of an injury to the upper thoracic duct. Surgical intervention to close the leakage by a fibrin stick was unsuccessful. The diagnostic questions addressed to the nuclear physician were: "Is the lymph fluid of intestinal origin?" and "Are there connections to the pleural cavity or to the mediastinum?" The thyroid was not blocked intentionally for more convenient anatomical landmarking (Fig. 5). No activity appeared in the chest. A faint activity accumulation in projection to the left jugulosubclavian junction was observed 4 hr after IPPA ingestion (Fig. 5). Revision surgery led to successful sealing of the leakage.

Patient 3

A 12-yr-old boy with known malformation of the lymph vessels and chylothorax on the right underwent surgery due to

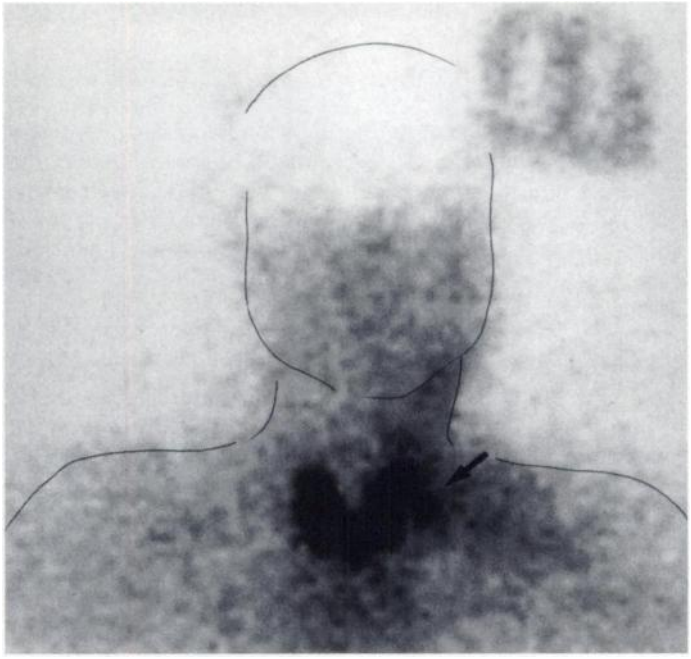

FIGURE 5. Patient 2. Anterior view of head and neck 2 hr after ingestion. Thyroid was intentionally not blocked for better anatomical landmarking of abnormal lymphatic fistula (arrow). Activity visualized to left of patient's head represents lymph fluid collection system.

compression of the right lung. Surgical exploration failed to find a thoracic duct. To prevent recurrent chylothorax, the patient was treated by drainage and nutritional support with mid-chain fatty acids. The patient was referred to our nuclear medicine department for localization of the thoracic duct and/or the lymphatic leakage site to the right lung. Surprisingly, 2 hr after IPPA ingestion, there was no activity accumulation documented in the right pleural cavity, but there was activity in the left pleural cavity (Fig. 6). This finding led to a change in therapeutic management, because it was no longer necessary to

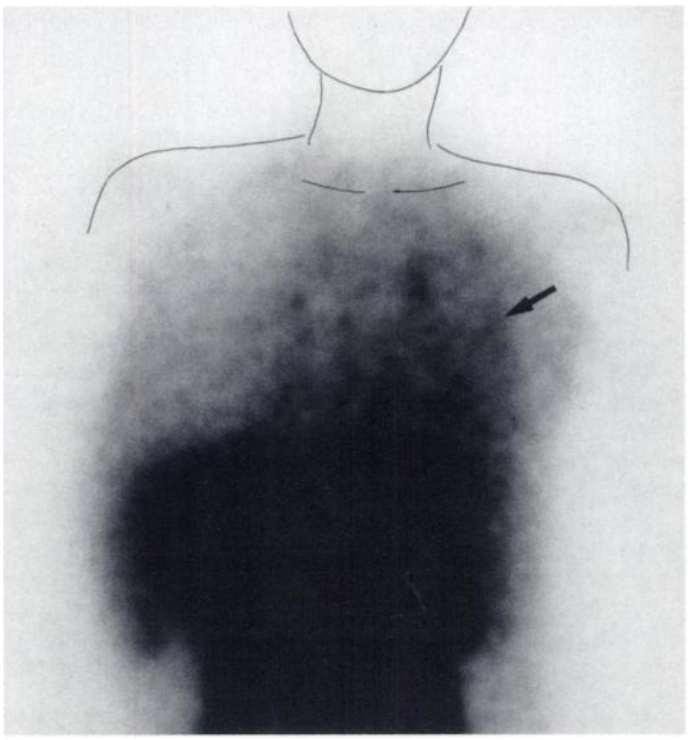

FIGURE 6. Patient 3. Anterior view of chest 3 hr after ingestion showing diffuse uptake in left pleural cavity indicating chylothorax.

prevent the patient from being treated with long-chain fatty acids.

DISCUSSION

Diagnostic imaging of injuries to the thoracic duct by contrast lymphography after invasive cannulation of an afferent lymph vessel on the dorsum of a foot is well known (*4,5*). This invasive procedure is limited to visualization of retroperitoneal lymph drainage, requires fluoroscopy resulting in higher radiation exposure and is not appropriate in patients with very fast and unpredictable lymph passage.

In nuclear medicine, various radiopharmaceuticals have been used for imaging the lymphatic system (*6–10*). Hodges et al. (*10*) used perianal injection of ^{99m}Tc-dextran for visualization of the greater lymphatics in dogs. Wang et al. (*11*) were able to localize thoracic duct injury intraoperatively in dogs using ^{131}I peanut oil.

In humans, lymphoscintigraphy of the thoracic duct has been described previously (*12–16*). The first article describing visualization of the thoracic duct using ^{123}I-heptadecanoic acid described a patient with a growing mesenteric chylic cyst (*15*). The literature includes analyses of normal anatomy in seven healthy control subjects (*16*). The thoracic duct was visible in all of them 60–90 min after ingestion of ^{123}I-heptadecanoic acid mixed with 10 ml of 20% fat emulsion. Simultaneously, an increase of activity in the peripheral blood was found (*16*).

There are three different activity distribution spaces visible after oral administration of IPPA. In the first phase, ingested activity is located intraintestinally in the upper gastrointestinal tract. It then enters the lymph vessels and moves from the intestinal lymphatics through the afferent lymphatics and the thoracic duct into the blood pool at the left jugulosubclavian junction.

Because of the biokinetics of ^{123}I-IPPA, the diffuse activity accumulation in the abdomen 7 hr after ingestion was interpreted as blood-pool/lymph-vessel activity. After intestinal absorption into the lymph and then into the blood pool, IPPA is eliminated from the blood with a half-life of 1–2 min and accumulates mostly in liver and muscle cells. In the liver, IPPA is metabolized to ^{123}I-benzoic acid and excreted through the intestinal/urinary tract.

For localizing a lymphatic lesion in the thorax, early images are necessary since the passage of radioactivity through the jugulosubclavian junction would otherwise result in diffuse blood-pool activity. The acquisition time interval depends on the leakage site. If abdominal lymphatic leakage is suspected, early and late images have to be acquired to avoid missing the leakage site. We propose a sequence of acquisitions with early images starting at 10 min and continuing up to 7 hr after ingestion.

The articles detecting traumatic leakages (*15,16*) were consistent with the findings in Patients 1 and 2 (Figs. 3 and 4). These cases of surgically induced lymphatic leakage were localized precisely before reintervention. The decision to reoperate was based mainly on the results of scintigraphy.

Not only is this method suitable for the diagnostic localization of lymphatic leakage, but it can also be used to discover the origin of lymph fluid accumulating in a distinct region. Patient 3 provided an example of this. The known right-sided pleural effusion confirmed by radiograph (left side was not suspicious of an effusion) caused this patient to develop clinically important dyspnea by mediastinal shift.

Because this right-sided pleural effusion most likely originated from the intestine, long-chain fatty acids were avoided. Because the lymph fluid of the right pleural effusion was not visualized after the ingestion of long-chain fatty acid ^{123}I-IPPA, it can be concluded that the lymph fluid originated from the lymph vessels of the right arm or of the head and neck and not from the intestine. Therefore, this patient would no longer benefit from avoiding long-chain fatty acids being drained through the abdominal lymph vessels. The accumulation of the activity in the left pleural cavity was not expected. It was rather unlikely that the left-sided effusion was caused by injury or disruption of malformed lymph vessels above level T5–6 and that the right fistula sealed spontaneously (common in about 50%). The possibility that the radiolabeled food had direct access to the left pleural region during food intake through an esophageal fistula was excluded since the early images showed no activity in this region. Thus, it was obvious that the activity in the left pleural region was caused by malformations of the lymphatic vessels.

CONCLUSION

Our findings suggest that oral administration of radiomarkers, i.e., through the physiological pathway, is more appropriate and that ^{123}I is superior to the ^{198}Au, ^{113m}In or ^{131}I markers used for imaging purposes in the early period of lymphoscintigraphy (*6–9*).

Our experience has shown that lymphoscintigraphy with orally administered ^{123}I-IPPA is easy to perform and avoids lymphatic cannulation. We did not encounter any side effects in our use of IPPA. The method proved superior to other scintigraphic approaches in visualizing thoracic and intestinal lymphatic leakages.

REFERENCES

1. Lampson RS. Traumatic chylothorax. *J Thorac Surg* 1948;17:778–782.
2. Selle JG, Synder WH, Screiber JT. Chylothorax: indications for surgery. *Ann Surg* 1973;177:245–249.
3. Williams KR, Burford TH. The management of chylothorax. *Ann Surg* 1964;160:131–139.
4. Müller KHG. Technik der Darstellung des Lymphsystems In. Heuk G, ed. *Lymphgefäßsystem, Lymphatisches Gewebe*. Stuttgart–New York: Springer-Verlag; 1995:17–21.
5. Irmer W, Baumgartl F, Grewe HE, Zindler M. Allgemeine diagnostische und therapeutische Maßnahmen In: Irmer W, Baumgartl F, Grewe HE, Zindler M, eds. *Dringliche Thoraxchirurgie*. Heidelberg–New York: Springer-Verlag; 1967:133–134.
6. López OL, Rodriquez-Maisano M, Delavaux JL. Thoracic duct malformations. Lymphoscintigraphic diagnosis. *Clin Nucl Med* 1986;11:479–481.
7. Balieu F, Balieu JL, Mesny J, et al. Visualization of the thoracic duct by lymphoscintigraphy. *Eur J Nucl Med* 1987;13:264–265.
8. Gates GF, Dore EF, Kanchanapoom V. Thoracic duct leakage in neonatal chylothorax visualized by ^{198}Au lymphangiography. *Radiology* 1972;105:619–620.
9. Woolfenden JM, Struse TB. Diagnosis of chylothorax with iodine-131 triolein. Case report. *J Nucl Med* 1977;18:128–129.
10. Hodges CC, Fossum TW, Komkov A, Hightower D. Lymphoscintigraphy in healthy dogs and dogs with experimentally created thoracic duct abnormalities. *Am J Vet Res* 1992;53:1048–1053.
11. Wang YJ, Liu K, Zhang GC, Cai ZJ. Intraoperative determination of thoracic duct injury with iodine-131 fat. An experimental study on dogs. *Chin Med J (Engl)* 1989;102:86–90.
12. Bykov SA, Grishakov SV, Bebiia NV, Bykova GV. Radionuclide diagnosis of disorders of the central lymph dynamics in thoracic duct pathology. *Med Radiol Mosk* 1989;34:27–29.
13. Bykov SA, Kanaev SV, Melnikov RA, Artiushkin AV, Matveev BV. Radionuclide visualization of the thoracic duct in patients with stomach cancer. *Vopr Onkol* 1985;31:36–42.
14. Balieu F, Balieu JL, Alison D, Barsotti J, Itti R. Use of lymphoscintigraphy in traumatic chylous ascites. *Lymphology* 1987;20:93–95.
15. Hvid-Jacobsen K, Nielsen SL, Jensen VJ, Thomsen HS. Demonstration of the thoracic duct by ^{123}I-heptadecanoic acid. Report of a case. *Acta Radiol* 1987;28:783–784.
16. Hvid-Jacobsen K, Thomsen HS, Nielsen SL, Kamper AL, Vestbo J. Scintigraphic demonstration of the thoracic duct following oral ingestion of ^{123}I-heptadecanoic acid. *Gastrointest Radiol* 1989;14:212–214.