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Usefulness of ^{99m}Tc-ASC lymphoscintigraphy and SPECT/CT in the evaluation of rare lymphatic disorders

Gorham–Stout disease, lymphangioma, and lymphangioleiomyomatosis

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Abstract

The purpose of this study was to investigate the role of ^{99m}Tc-antimony sulfide colloid (ASC) lymphoscintigraphy and single photon emission computed tomography/computed tomography (SPECT/CT) in the evaluation of rare lymphatic disorders, including Gorham–Stout disease (GSD), lymphangioma, and lymphangioleiomyomatosis (LAM).

Nine patients suspected to have rare lymphatic disorders were included in this retrospective study. All patients underwent ^{99m}Tc-ASC lymphoscintigraphy and SPECT/CT to evaluate the lesions. The lymphoscintigraphy results were compared with the clinical and immunopathological findings.

^{99m}Tc-ASC lymphoscintigraphy and SPECT/CT could provide lymphatic draining and anatomical information for rare lymphatic disorders. Among the 9 patients, 3 were diagnosed with GSD (1 female, 2 males; aged 15–34 years, range 27.0 ± 10.4 years), 3 with lymphangioma (1 female, 2 males; aged 17–42 years, range 32.0 ± 13.2 years), and 3 patients were diagnosed with LAM (3 females; aged 33–50 years, range 43.7 ± 9.3 years]. GSD is characterized by multiple bone destruction, including spine, ribs, ilium, pubis, ischium, and femur. The tracer uptake of involved bones and soft tissue around bone is increased, accompanied by chylothorax, chylopericardium, and chylous leakage in abdominal and pelvic cavity. Lymphangiomas present as multiple cystic lesions with increased tracer uptake in the peripancreatic, retroperitoneal, and iliac areas, and in the abdominopelvic cavity. LAM presents as multiple thin-walled cysts in the bilateral lungs and multiple retroperitoneal enlarged lymph nodes with increased tracer uptake.

^{99m}Tc-ASC lymphoscintigraphy and SPECT/CT could comprehensively and specifically detect some rare lymphatic disorders, namely, GSD, lymphangioma, and LAM. This technique is useful for the evaluation of GSD, lymphangioma, and LAM.

Abbreviations: β-CTX = β-carboxy-terminal collagen crosslinks, ASC = antimony sulfide colloid, CT = computed tomography, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, GSD = Gorham–Stout disease, LAM = lymphangioleiomyomatosis, MRI = magnetic resonance imaging, SPECT = single photon emission computed tomography, VEGF-D = vascular endothelial growth factor-D.

Keywords: Gorham–Stout disease, lymphangioleiomyomatosis, lymphangioma, lymphoscintigraphy, SPECT/CT

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Ethical approval was waived by the Ethics Committee of our hospital because this is a retrospective study.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. Introduction

Gorham–Stout disease (GSD), lymphangioma, and lymphangioleiomyomatosis (LAM) are rare lymphatic disorders.[1–7] GSD is characterized by massive osteolysis resulting from bone-replacing abnormal capillary proliferation early in the disease or fibrous hyperplasia in the later stage.[8–10] Only about 300 cases of GSD have been reported in the literature.[11] All bones could be affected, but the most common areas are the skull, shoulder girdle, pelvis, and extremities.[6,12] The osteolytic lesions in GSD are related to the local lymphatic vessel proliferation.[13] The distribution of lymphatics in GSD-affected bones is abnormal, whereas no such vessels are found in normal bones. Osteoclast activation and lymphangiogenesis are the necessary conditions for development of GSD.[14] Lymphangiomas are congenital benign tumors of the lymphatic system.[15] The exact etiology of lymphangiomas remains unknown, but they might be associated with congenital disorders in the embryological development of lymphatics, or may be caused by lymphatic obstruction secondary to lymphatic hemorrhage or inflammation.[15–18] One characteristic of LAM is a multifocal nodular proliferation[19,20] of immature smooth muscle and perivascular epithelioid cells (LAM cells),[20] which could secrete vascular endothelial growth factor-D (VEGF-D) to promote lymphatic formation.

These 3 rare diseases are usually evaluated by traditional imaging examinations, including ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI).[1–7] The role of lymphoscintigraphy, a nuclear medicine imaging method, is not fully recognized in the evaluation of these 3 lymphatic disorders due to their rarity. The procedure of lymphoscintigraphy is quite simple and safe, and only requires a subcutaneous injection of a small amount of a radiotracer. In the subcutaneous tissue, the radiotracer is taken up by the lymphatic vessels and lymphatic images are acquired by a gamma camera.[21] As lymphoscintigraphy is a specific tool for lymphatic system imaging,[22,23] we expected that ^{99m}Tc-antimony sulfide colloid (ASC) lymphoscintigraphy combined with single photon emission computed tomography/CT (SPECT/CT) might be able to provide comprehensive information of the 3 rare lymphatic disorders for the clinical physician. Accurate diagnosis and evaluation of lymphatic disorders are crucial for the therapeutic approach.[10,15,24,25]

Given the characteristics of lymphoscintigraphy and the pathological features of GSD, lymphangioma, and LAM, we investigated the role of ^{99m}Tc-ASC lymphoscintigraphy and SPECT/CT in the evaluation of these 3 rare lymphatic disorders.

2. Patients and methods

2.1. Ethical considerations

This retrospective study of existing patient data and images was approved by the institutional review board of Peking Union Medical College Hospital. The requirement for informed consent was waived.

2.2. Patients

Nine patients who were suspected to have rare lymphatic disorders and underwent ^{99m}Tc-ASC lymphoscintigraphy and SPECT/CT to evaluate the lesions from April 2015 to January 2020 were included in this retrospective study. The lymphoscintigraphy results were compared with the clinical and immunopathological findings.

2.3. GSD, lymphangioma, and LAM diagnosis

The histopathological diagnosis of GSD was based on extensive loss of bony matrix replaced by proliferation of thin-walled capillary-sized vascular channels, and at a later stage, by fibrous connective tissue.[10] Dilated lymph vessels are the typical histopathological finding of lymphangioma, which is usually present as a cystic structure on imaging.[3] According to the diagnosis guidelines, a definite diagnosis of LAM can be made based on the presence of cystic changes on high-resolution CT of the chest and any of the following confirmatory features: renal angiomyolipoma, chylous effusion, lymphangioleiomyoma, adenopathy, lymphatic vessel dilation, and either definite or probable tuberous sclerosis complex.[4]

2.4. ^{99m}Tc-ASC lymphoscintigraphy

Lymphoscintigraphy was performed 1 hour after ^{99m}Tc-ASC was subcutaneously injected into the first and second interdigital spaces of both feet (0.5 mL, 37 MBq/foot). Images were acquired with a double-head gamma camera and a low-energy high-resolution parallel whole collimator in whole-body scanning mode with a 256×1024 matrix at a scan speed of 15 cm/min. SPECT/CT (Philips, Precedence 16P, the Netherlands) fusion images of the mainly affected area were obtained 2 hours after radiotracer injection. SPECT imaging was performed using a 128×128 matrix with a spacing of 3.0 mm, 32 projections over 360°, and 40 seconds per projection. A CT scan of the same anatomical region was obtained with 110 kV, 75 mAs, and pitch 1.3. Iterative reconstruction of the SPECT data was performed using an ordered-subset maximum-likelihood expectation-maximization algorithm; 3 iterations, 8 subsets, including resolution recovery.

2.5. Image interpretation

Visual methods were applied for image analysis. The images were analyzed by 2 experienced nuclear medicine physicians, who visually evaluated the lymphatic system, including the morphology and distribution.

3. Results

3.1. Patients' characteristics

A total of 9 patients (7 females, 2 males; aged 15–50 years, mean age, 34.1 ± 12.1 years) were included. Among them, 3 patients were diagnosed with GSD (1 female, 2 males; mean age 27.0 ± 10.4 years, range 15–34 years), 3 were diagnosed with lymphangioma (1 female, 2 males; mean age 32.0 ± 13.2 years, range 17–42 years), and 3 were diagnosed with LAM (3 females; mean age 43.7 ± 9.3 years, range 33–50 years). The 3 rare lymphatic disorders involved multiple organs, including the lymphatics, bones, lungs, pleura, omentum, and subcutaneous soft tissues.

3.2. GSD

The clinical symptoms of these 3 patients included bone pain, dyspnea, abdominal distention, and limb swelling. The β-carboxy-terminal collagen crosslinks (β-CTX) level was elevated in 2 of 3 patients, whereas the serum albumin and total protein levels were normal in all 3 patients (Table 1). Lymphoscintig-

Table 1

The imaging findings and clinical characters of Gorham–Stout disease.

Patients	Age/ sex	Affected skeletal regions*	Involved surrounding soft-tissue*	Chylous effusions*	β-CTX (Reference: 0.26–0.512 ng/mL)	Serum albumin protein (Reference: 35–52 g/dL)	Serum total protein (Reference: 60–85 g/dL)	Symptoms	Diagnosis
1	15/F	Thoracolumbar vertebra and ribs	Pleurae	Pleural and pericardial effusions	2.530	43	69	Chest pain, dyspnea	Based on the clinical information, histopathologic and radiographic findings
2	32/M	Lumbosacral vertebra, ilium, pubic bone, and ischia	Omentum	Abdominal and pelvic effusions	1.020	43	72	Sacrococcygeal pain, abdominal distention	Based on the clinical information, histopathologic and radiographic findings
3	34/M	Pelvic bones and femoral heads	Subcutaneous soft tissue	Subcutaneous effusions of the lower back, hip, and left lower limb	0.360	43	70	Skeletal deformity and bone pain of pelvic bones and femoral heads, and lymphedema	Based on the clinical information, histopathologic and radiographic findings

* Positive on ^{99m}Tc-ASC lymphoscintigraphy and SPECT/CT.

raphy and SPECT/CT demonstrated multiple ^{99m}Tc-ASC uptake sites in the skeletal system, including the spine, ribs, ilium, pubic bone, ischia, and femoral heads. The images also demonstrated tracer uptake in the surrounding tissues of the affected bones, including the pleurae, omentum, and subcutaneous soft tissue. In addition, pleural and pericardial effusions, abdominal and pelvic effusions, and lymphedema in the lower back, hip, and left lower limb were also observed by lymphoscintigraphy (Fig. 1).

3.3. Lymphangioma

The clinical symptoms of patients suspected to have lymphangioma were abdominal distention, abdominal ache, weight loss, diarrhea, hematochezia, and weakness. The red blood cell count and hemoglobin level were decreased in 2 of 3 patients. The serum albumin and total protein levels were reduced in 1 of 3 patients (Table 2). Lymphoscintigraphy and SPECT/CT showed multiple clear-edged cystic masses with ^{99m}Tc-ASC uptake in the peripancreatic, retroperitoneal, and iliac areas, and in the abdominopelvic cavity. The imaging findings also revealed radiotracer uptake in the jejunoileal and colonic walls (Fig. 2).

3.4. LAM

The clinical symptom of patients with LAM was dyspnea. The VEGF-D level was elevated in two patients; patient 3 did not undergo this examination. The forced expiratory volume in 1 second (FEV1) was <80% of the predicted and the FEV1/forced vital capacity (FVC) ratio was <70% in 2 of 3 patients (Table 3). In 2 of 3 patients, lymphoscintigraphy and SPECT/CT revealed multiple thin-walled cysts in the bilateral lungs with ^{99m}Tc-ASC uptake, which was more intense in the 2 lower lobes. In addition, the images showed enlarged lymph nodes in the retroperitoneum with intense ^{99m}Tc-ASC uptake (Fig. 3).

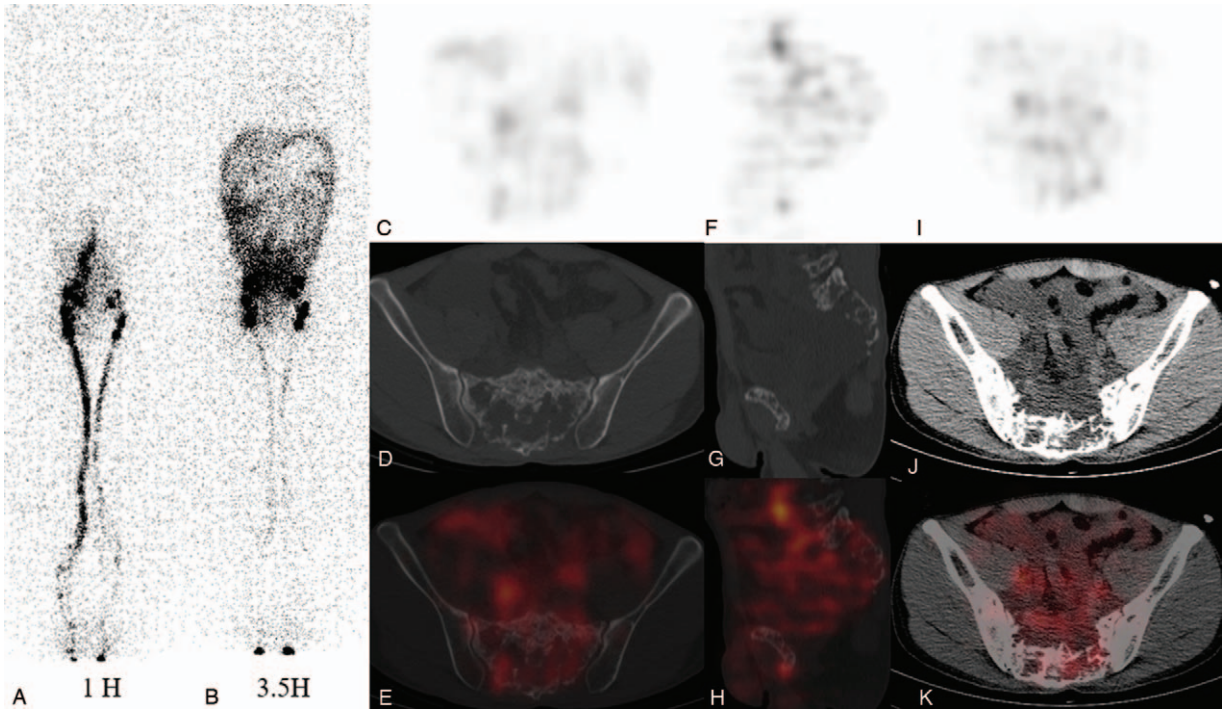

Figure 1. Representative images of Gorham–Stout disease in patient 2. (A) Anterior image of lymphoscintigraphy obtained 1 h after ^{99m}Tc-ASC injection; (B) anterior image of lymphoscintigraphy obtained 3.5 h after ^{99m}Tc-ASC injection; (C–E) Axial SPECT, CT, and fusion images of the pelvis (bone window); (F–H) sagittal SPECT, CT, and fusion images of the pelvis (bone window); (I–K) axial SPECT, CT, and fusion images of the pelvis (soft-tissue window).

Table 2

The imaging findings and clinical characters of lymphangioma.

Patients	Age/ sex	The location of lymphangioma*	Symptoms	Red blood cell count	Hemoglobin	Serum total protein (Reference: 60–85 g/dL)	Serum albumin protein (Reference: 35–52 g/dL)	Diagnosis
4	37/M	Peripancreatic area and jejunoileal wall	Abdominal distention, weight loss	4.98 (Reference: $4.00–5.50 \times 10^{12}$/L)	146g/L (Reference: 120–160 g/L)	68	46	Based on the histopathologic results and imaging findings
5	17/M	Retroperitoneal and iliac area, colonic wall	Stomachache, hematochezia, diarrhea	3.98 (Reference: $4.00–5.50 \times 10^{12}$/L)	74 g/L, (Reference: 120–160 g/L)	41	25	Based on the histopathologic results and imaging findings
6	42/F	retroperitoneal area, abdominopelvic cavity	Weakness, bellyache	3.00 (Reference: $3.50–5.00 \times 10^{12}$/L)	91g/L (Reference: 110–150 g/L)	72	47	Based on the histopathologic results and imaging findings

* Positive on ^{99m}Tc-ASC lymphoscintigraphy and SPECT/CT.

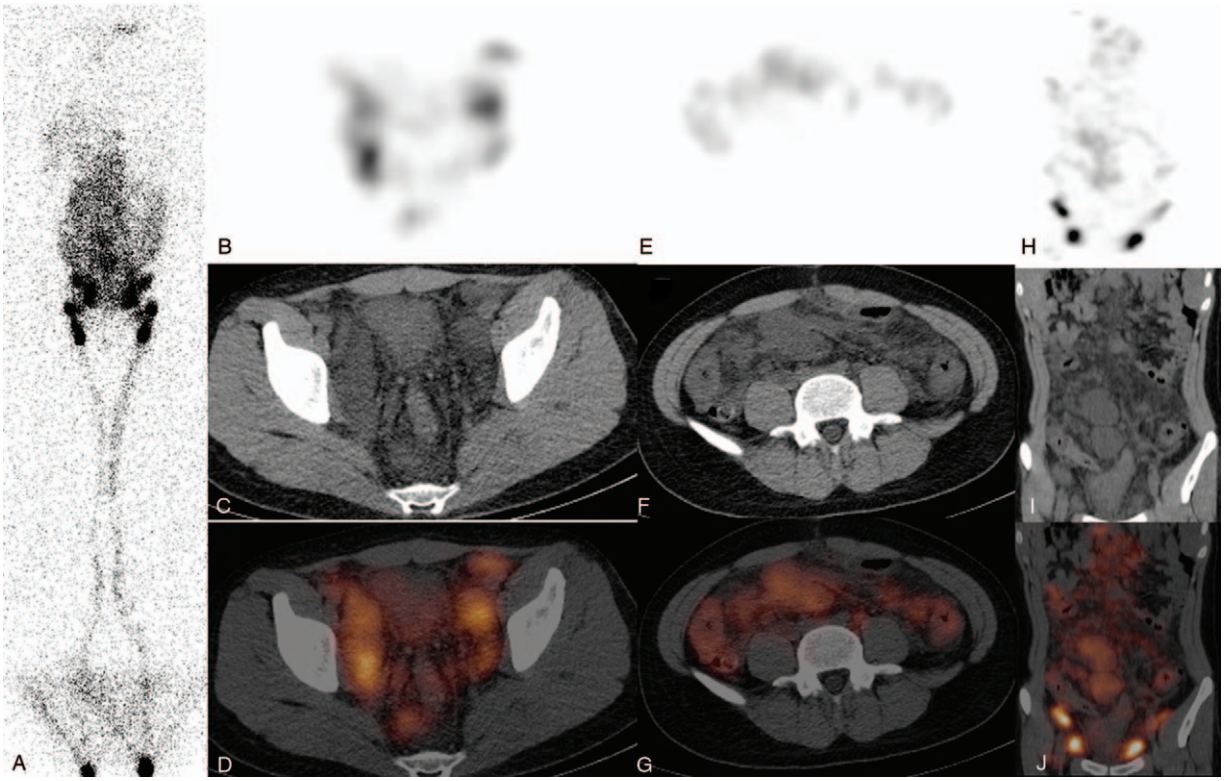

Figure 2. Representative images of lymphangioma in patient 5. (A) Anterior image of lymphoscintigraphy obtained 1 h after ^{99m}Tc-ASC injection; (B–D) axial SPECT, CT, and fusion images of the pelvis; (E–G) axial SPECT, CT, and fusion images of the abdomen; (H–J) coronary SPECT, CT, and fusion images of the abdominopelvic region.

Table 3

The imaging findings and clinical characters of LAM.

Patient	Age/sex	Involved organs*	Symptoms	FEV1 (%pred)	FEV1/FVC (%pred)	VEGF-D, pg/mL	Diagnosis
7	33/F	Negative	Dyspnea	41.7	40.37	3244.21	Based on the criterion of American Thoracic Society Guidelines of 2016
8	50/F	Lung, lymph glands	Dyspnea	126.4	85.14	3137.317	Based on the criterion of American Thoracic Society Guidelines of 2016
9	48/F	Lung	Dyspnea	73.0	69.59	Not available	Based on the criterion of American Thoracic Society Guidelines of 2016

%pred = the percentages of predicting value, FEV1 = forced expiratory volume in 1 s, FVC = forced vital capacity, VEFG-D = vascular endothelial growth factor-D.
* Positive on ^{99m}Tc-ASC lymphoscintigraphy and SPECT/CT.

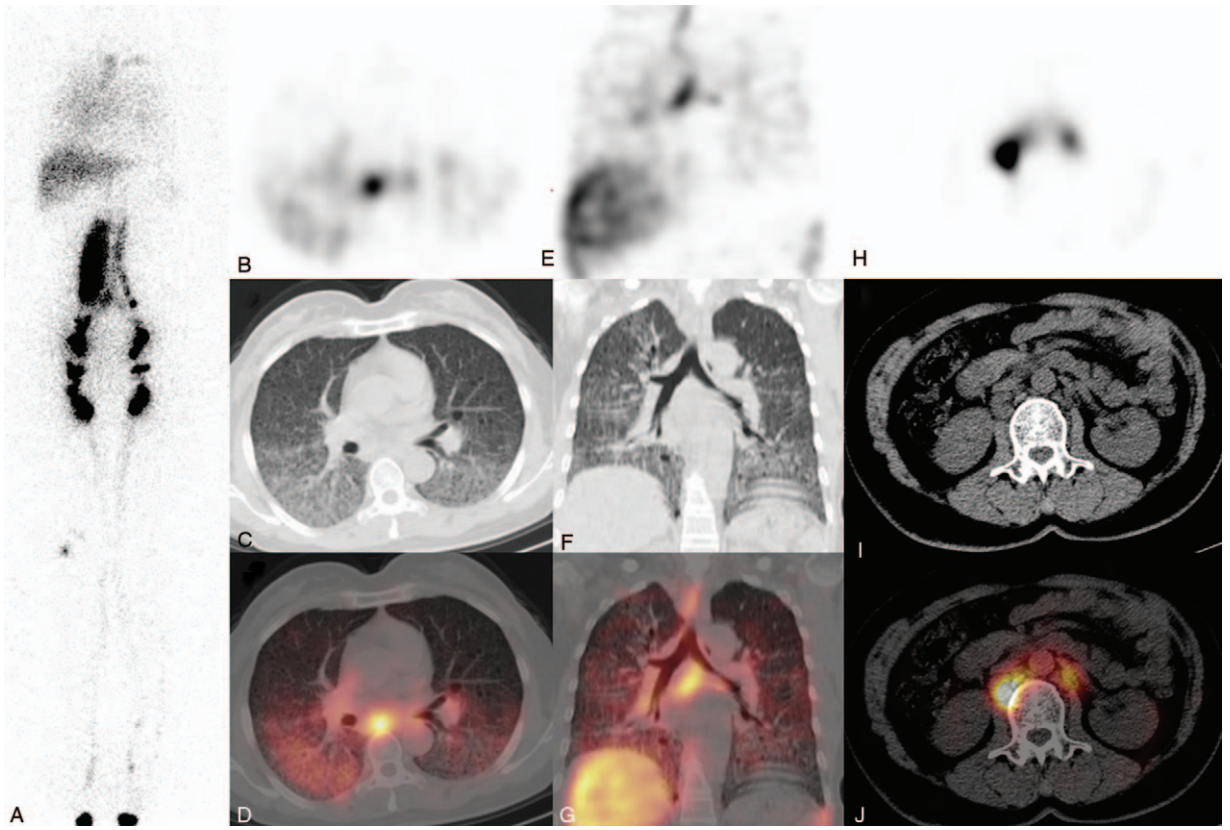

Figure 3. Representative images of lymphangioleiomyomatosis in patient 8. (A) Anterior image of ^{99m}Tc-ASC lymphoscintigraphy after 1-h injection; (B–D) axial SPECT, CT, and fusion images of chest; (E–G) coronary SPECT, CT, and fusion images of chest; H-J, axial SPECT, CT, and fusion images of the abdomen.

4. Discussion

The evaluation of lymphatic disorders is difficult using CT and MRI, which only provide anatomical information, without a functional status. The lymphatic system imaging method, lymphoscintigraphy, should be specific for lymphatic disorders, particularly in rare diseases. In this study, we investigated the role of ^{99m}Tc-ASC lymphoscintigraphy and SPECT/CT in the evaluation of these rare diseases and found that this method enabled comprehensive evaluation of rare lymphatic disorders.

4.1. GSD

The mechanisms behind the osteolysis in GSD are not clear, but it is known that the osteolytic lesions in GSD are related to local lymphangioproliferation.[13] The distribution of lymphatics in GSD-affected bones is abnormal, whereas no such vessels are found in normal bones. Accordingly, we expected that lymphoscintigraphy might have a potential to evaluate GSD. The diagnosis of GSD is mainly based on the clinical information and the histopathologic and radiographic findings.[26] The commonly used radiological examinations for the evaluation of GSD are X-ray, ultrasound, CT, bone scan, and MRI.[5,14,27–29] As lymphoscintigraphy was found to be helpful for the diagnosis of lymphedema and chylous effusion,[22,23] and GSD is a lymphatic disorder, lymphoscintigraphy might play a role in the evaluation of GSD.

The clinical manifestations and complications of GSD depend on the invasion of the affected bones and surrounding tissues.[30] When the ribs, thoracic vertebrae, or scapula are affected, chylothorax may be caused by the expansion and/or rupture of lymphatics into the chest or the invasion through the thoracic duct,[27] as was seen in our patient 1.

β-CTX is a piece of collagen released into the blood after degradation in the process of bone remodeling. The increase of β-CTX content reflects the degree of bone absorption and the increase of bone loss, leading to the occurrence of osteoporosis and deformable osteopathy,[31] such as GSD. β-CTX is a commonly used biomarker of osteoclastic bone resorption for the prediction of bone mass loss.[32] In our study, the β-CTX level was elevated in 2 of 3 patients (2 of 3, 75%). The serum albumin and total protein levels were normal in all 3 patients, indicating that these patients in this study did not have protein loss.

^{99m}Tc-ASC lymphoscintigraphy combined with SPECT/CT might outperform the planar image of lymphoscintigraphy alone in the evaluation of GSD because SPECT/CT could supply the lymphatic draining and anatomical information for accurate and systematic evaluation.

4.2. Lymphangioma

Lymphangiomas, most commonly found in children, usually occur in the head, axillary regions, and the neck.[33,34] Less than 1% of patients present with cystic lymphangiomas in the greater omentum, mesentery, and retroperitoneum.[34–37] Lymphangiomas in the retroperitoneal and iliac regions are very rare.[38] In our study, lymphangiomas were found in the peripancreatic, retroperitoneal, and iliac areas, and in the abdominopelvic cavity.

In addition, we also found lymphangioma in the jejunoileal and colonic walls. The clinical symptoms of lymphangioma were reported to be abdominal distention, abdominal pain, diarrhea, gastrointestinal bleeding, and hypoproteinemia.[3,39,40]

Imaging studies are important for diagnosing lymphangioma.[3] CT or MRI can localize the lesion and reveal its cystic structure, suggesting the possibility of lymphangioma,[1,7] but nontumorous cystic lesions, including abscesses and tumorous cystic lesions such as mesothelioma, should be differentiated.[41] At CT or MRI, lymphangiomas and other cystic lesions are often difficult to differentiate. Radionuclide studies may be useful to further characterize tumors and investigate tumor-related pathophysiology.[3,38,42] In particular, lymphoscintigraphy is useful to diagnose lymphangioma and demonstrate the communication between the tumor and the lymphatic system.[3] Accurate diagnosis and evaluation of lymphangioma are important for the surgical treatment and prognosis because recurrence rates after incomplete resection are higher than those after complete resection (35–64% vs 17–24%).[15,24,25]

4.3. LAM

In this study, all 3 patients were diagnosed with LAM according to the 2016 American Thoracic Society Guidelines.[4] In these patients, dyspnea, pneumothorax, and hemoptysis are common manifestations, while chylothorax, chylous ascites, and lymphangiomyoma are also frequently seen.[43] As lymphoscintigraphy was found to be helpful for the evaluation of lymphatic disorders,[22,23] we investigated the role of ^{99m}Tc-ASC lymphoscintigraphy and SPECT/CT in the evaluation of LAM.

The rate of positive LAM findings on ^{99m}Tc-ASC lymphoscintigraphy and SPECT/CT was 75%. As a functional imaging method, lymphoscintigraphy could reveal the pulmonary and extrapulmonary LAM lesions and might play an alternative role in the diagnosis and evaluation of LAM.

As a whole-body imaging method,^{99m}Tc-ASC lymphoscintigraphy could comprehensively evaluate the lymphatic drainage function, particularly in rare lymphatic disorders whose diagnosis and evaluation on CT and MRI is challenging. The combination of ^{99m}Tc-ASC lymphoscintigraphy and SPECT could accurately reveal the sites of lymphatic malformation, which is important for the treatment schedule. In addition, this study adds to the clinical cognition of rare lymphatic disorders and the role of lymphoscintigraphy, which may be helpful for clinical physicians to diagnose and evaluate those diseases.

In this study, we found that the VEGF-D level was elevated in two patients (2/2, 100%; this test was not performed on patient 9). The promoting lymphangiogenic growth factor, VEGF-D, has been proposed as a potential diagnostic marker for LAM.[44] Serum VEGF-D level is elevated (> 800 pg/mL) in approximately 70% of patients; however, a negative serum VEGF-D result does not exclude a diagnosis of LAM.[45–47] The FEV1 was <80% and FEV1/FVC ratio was <70% in two of three patients (patients 7 and 9), indicating that these patients had obstructive ventilatory defects.[48]

The main limitation of this study is the limited sample size of patients with GSD, lymphangioma, and LAM, which greatly affects the analysis of the results. Therefore, in this manuscript, we mainly describe the performance of the disease on SPECT lymphoscintigraphy and focus on the characteristics of the images of these unusual lymphatic disorders. More cases should be included in further studies to investigate the role of ^{99m}Tc-ASC lymphoscintigraphy and SPECT/CT in assessing the three rare lymphatic disorders systematically and comprehensively.

5. Conclusion

^{99m}Tc-ASC lymphoscintigraphy and SPECT/CT could comprehensively and specifically evaluate rare lymphatic disorders, namely, GSD, lymphangioma, and LAM. This technique is useful for the evaluation of GSD, lymphangioma, and LAM.

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References

[1] Wunderbaldinger P, Paya K, Partik B, et al. CT and MR imaging of generalized cystic lymphangiomatosis in pediatric patients. AJR Am J Roentgenol 2000;174:827–32.
[2] Tanaka Y, Fujii S, Kusaka T, et al. Effective use of EUS for diagnosing a jejunal lymphangioma accompanied with hemorrhage. Gastrointest Endosc 2020;91:199–200.
[3] Okizaki A, Shuke N, Yamamoto W, et al. Protein-loss into retroperitoneal lymphangioma: demonstration by lymphoscintigraphy and blood-pool scintigraphy with Tc-99m-human serum albumin. Ann Nucl Med 2000;14:131–4.
[4] McCormack FX, Gupta N, Finlay GR, et al. Official American Thoracic Society/Japanese Respiratory Society Clinical Practice Guidelines: lymphangioleiomyomatosis diagnosis and management. Am J Respir Crit Care Med 2016;194:748–61.
[5] Lo CP, Chen CY, Chin SC, et al. Disappearing calvarium in Gorham disease: MR imaging characteristics with pathologic correlation. AJNR Am J Neuroradiol 2004;25:415–8.
[6] Liu Y, Zhong DR, Zhou PR, et al. Gorham-Stout disease: radiological, histological, and clinical features of 12 cases and review of literature. Clin Rheumatol 2016;35:813–23.
[7] Charruau L, Parrens M, Jougon J, et al. Mediastinal lymphangioma in adults: CT and MR imaging features. Eur Radiol 2000;10:1310–4.
[8] Liu SZ, Zhou X, Song A, et al. Gorham-Stout syndrome. QJM 2018;111:911–2.
[9] Galiay L, Simon F, Levy R, et al. Temporomandibular joint anomalies in pediatric craniofacial Gorham-Stout disease. J Craniomaxillofac Surg 2018;46:1179–84.
[10] Jiang Y, Hou G, Cheng W. 99mTc-SC lymphoscintigraphy and SPECT/CT findings in a case report of Gorham-Stout disease presenting with chylothorax and bone pain. Medicine (Baltimore) 2019;98:e15023.
[11] Dellinger MT, Garg N, Olsen BR. Viewpoints on vessels and vanishing bones in Gorham-Stout disease. Bone 2014;63:47–52.
[12] Lala S, Mulliken JB, Alomari AI, et al. Gorham-Stout disease and generalized lymphatic anomaly: clinical, radiologic, and histologic differentiation. Skeletal Radiol 2013;42:917–24.
[13] Hagendoorn J, Yock TI, Borel Rinkes IH, et al. Novel molecular pathways in Gorham disease: implications for treatment. Pediatr Blood Cancer 2014;61:401–6.
[14] Ozeki M, Fukao T. Generalized lymphatic anomaly and Gorham-Stout disease: overview and recent insights. Adv Wound Care (New Rochelle) 2019;8:230–45.
[15] Losanoff JE, Richman BW, El-Sherif A, et al. Mesenteric cystic lymphangioma. J Am Coll Surg 2003;196:598–603.

[16] Antoniades K, Kiziridou A, Psimopoulou M. Traumatic cervical cystic hygroma. Int J Oral Maxillofac Surg 2000;29:47–8.
[17] Ohhashi T, Kawai Y. Proposed new lymphology combined with lymphatic physiology, innate immunology, and oncology. J Physiol Sci 2015;65:51–66.
[18] Perkins JA, Manning SC, Tempero RM, et al. Lymphatic malformations: current cellular and clinical investigations. Otolaryngol Head Neck Surg 2010;142:789–94.
[19] Hou G, Xu W, Jiang Y, et al. Lymphangioleiomyomatosis revealed by (68)Ga-NOTA-Evans Blue PET/CT. Eur J Nuclear Med Mol Imaging 2020;47:2469–70.
[20] Johnson SR, Cordier JF, Lazor R, et al. European Respiratory Society guidelines for the diagnosis and management of lymphangioleiomyomatosis. Eur Respir J 2010;35:14–26.
[21] Yoshida RY, Kariya S, Ha-Kawa S, et al. Lymphoscintigraphy for imaging of the lymphatic flow disorders. Tech Vasc Interv Radiol 2016;19:273–6.
[22] The diagnosis and treatment of peripheral lymphedema: 2016 Consensus Document of the International Society of Lymphology. Lymphology 2016;49:170–84.
[23] Pui MH, Yueh TC. Lymphoscintigraphy in chyluria, chyloperitoneum and chylothorax. J Nucl Med 1998;39:1292–6.
[24] Amodeo I, Cavallaro G, Raffaeli G, et al. Abdominal cystic lymphangioma in a term newborn: a case report and update of new treatments. Medicine (Baltimore) 2017;96:e5984.
[25] Alqahtani A, Nguyen LT, Flageole H, et al. 25 years' experience with lymphangiomas in children. J Pediatr Surg 1999;34:1164–8.
[26] Tateda S, Aizawa T, Hashimoto K, et al. Successful management of Gorham-Stout disease in the cervical spine by combined conservative and surgical treatments: a case report. Tohoku J Exp Med 2017;241:249–54.
[27] Rossi M, Buonuomo PS, Battafarano G, et al. Dissecting the mechanisms of bone loss in Gorham-Stout disease. Bone 2020;130:115068.
[28] Park SB, Choi JY, Kim SJ. Gorham-Stout disease affecting the mandible: bone scintigraphy and computed tomography findings. Clin Nucl Med 2017;42:779–81.
[29] Assoun J, Richardi G, Railhac JJ, et al. CT and MRI of massive osteolysis of Gorham. J Comput Assist Tomogr 1994;18:981–4.
[30] Johnstun J, Brady L, Simstein R, et al. Chronic recurrent Gorham-Stout syndrome with cutaneous involvement. Rare Tumors 2010;2:e40.
[31] Ross RD, Deng Y, Fang R, et al. Discovery of biomarkers to identify periimplant osteolysis before radiographic diagnosis. J Orthop Res 2018;36:2754–61.
[32] Eastell R, Hannon RA. Biomarkers of bone health and osteoporosis risk. Proc Nutr Soc 2008;67:157–62.
[33] Kosir MA, Sonnino RE, Gauderer MW. Pediatric abdominal lymphangiomas: a plea for early recognition. J Pediatr Surg 1991;26:1309–13.
[34] He W, Hao YC, Xia HZ, et al. [Perirenal cystic lymphangioma in an adult: a case report and literature review]. Beijing Da Xue Xue Bao Yi Xue Ban 2017;49:730–2.
[35] Chen D, Feng X, Lv Z, et al. Cystic lymphangioma of pancreas: a rare case report and review of the literature. Medicine 2018;97:e11238.
[36] Banerjee JK, Saranga Bharathi R, Venkatesan S, et al. Abdominal lymphangioma. Med J Armed Forces India 2016;72(suppl 1):S70–3.
[37] Huguet KL, Metzger PP, Menke DM. Colorectal lymphangioma. Am Surg 2007;73:414–6.
[38] Hou G, Li X, Hou B, et al. Lymphangioma on 68Ga-NOTA-Evans Blue PET/MRI. Clin Nucl Med 2018;43:553–5.
[39] de Perrot M, Rostan O, Morel P, et al. Abdominal lymphangioma in adults and children. Br J Surg 1998;85:395–7.
[40] Bezzola T, Buhler L, Chardot C, et al. [Surgical therapy of abdominal cystic lymphangioma in adults and children]. J Chir 2008;145:238–43.
[41] Ros PR, Olmsted WW, Moser RPJr, et al. Mesenteric and omental cysts: histologic classification with imaging correlation. Radiology 1987;164:327–32.
[42] Hou G, Jiang Y, Jian S, et al. Hemolymphangioma involving bones and bladder detected on 68Ga-NEB PET/CT: a rare case report. Medicine 2019;98:e15213.
[43] Xu KF, Lo BH. Lymphangioleiomyomatosis: differential diagnosis and optimal management. Ther Clin Risk Manag 2014;10:691–700.
[44] Moir LM. Lymphangioleiomyomatosis: current understanding and potential treatments. Pharmacol Ther 2016;158:114–24.
[45] Xu K-F, Zhang P, Tian X, et al. The role of vascular endothelial growth factor-D in diagnosis of lymphangioleiomyomatosis (LAM). Respir Med 2013;107:263–8.
[46] Mou Y, Ye L, Wang J, et al. Diagnostic and treatment monitoring potential of serum vascular endothelial growth factor-D in lymphangioleiomyomatosis. Lymphology 2016;49:140–9.
[47] Seyama K, Kumasaka T, Souma S, et al. Vascular endothelial growth factor-D is increased in serum of patients with lymphangioleiomyomatosis. Lymphat Res Biol 2006;4:143–52.
[48] Singh D, Agusti A, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: the GOLD science committee report 2019. Eur Respir J 2019;53:1900164.