OPEN

PRS GLOBAL OPEN

CASE REPORT
Technology

Lymphatic Dysfunction Detected by Multi-lymphosome Indocyanine Green Lymphography and Lymphatic Ultrasound

Hisako Hara, MD, PhD
Makoto Mihara, MD

Summary: Investigation into the cause of lower extremity edema is essential for successful treatment; however, it is sometimes difficult to diagnose. In this case report, we present a patient with bilateral lower extremity edema in whom abnormalities were detected with multi-lymphosome indocyanine green (ICG) lymphography and lymphatic ultrasound. An 87-year-old woman underwent total hysterectomy and pelvic lymphadenectomy for uterine cancer when she was 55 years old. Ten years ago, she was prescribed with a diuretic agent for bilateral edema of the lower extremities; however, the edema did not subside. Conventional general examination, including blood tests, electrocardiography, echocardiography, duplex ultrasound for the legs, and lymphoscintigraphy, did not show any significant abnormalities that may occur with lower limb edema. We performed multi-lymphosome ICG lymphography by injecting ICG in the first web space of the foot, the lateral ankle, and the lateral thigh. This helped us detect lymphatic dysfunction in both lower extremities. Additionally, we performed lymphatic ultrasound and found dilated lymphatic vessels in both lower limbs, indicating lymphatic accumulation within these vessels. Injecting ICG into multiple lymphosomes appears to be useful in diagnosing the causes of lower extremity edema as well as evaluating the lymphatic function of those lymphosomes. Furthermore, lymphatic ultrasound can be used to scan the whole lower extremity because it does not rely on the flow of a contrast agent to produce an image. We believe that combining these diagnostic examinations will make it possible to diagnose patients who have previously been misdiagnosed due to insufficient screening measures. *(Plast Reconstr Surg Glob Open 2021;9:e3859; doi: 10.1097/GOX.0000000000003859; Published online 22 October 2021.)*

When determining the cause of chronic lower extremity edema, review of the patient's medical history, physical examination, and diagnostic testing are essential.[1] This diagnostic testing should include blood examination, chest radiography, duplex ultrasound, and electrocardiogram to evaluate renal, hepatic, and cardiac function as well as the presence of deep venous thrombosis.[1–3] Also, abdominal or pectoral occupying lesions should be excluded by computed tomography.

When no abnormalities are found during examination, rest, lower extremity elevation, or compression therapy are often prescribed.[4] However, these measures do not lead to improvement in all patients.

Recently, lymphoscintigraphy, indocyanine green (ICG) lymphography, or magnetic resonance lymphography have been used to diagnose lymphedema.[5–10] In recent reports, the lower extremity has been subdivided into several lymphatic territories known as lymphosomes,[11] although those examinations traditionally evaluate only one lymphosome.[5,6] We have reported the usefulness of multi-lymphosome ICG lymphography and lymphatic ultrasound for the preoperative examination of lymphaticovenous anastomosis (LVA) to detect the lymphatic vessels with good function.[12–15]

In this case report, we present a patient with bilateral lower extremity edema. Although the results of general examination by the internal medicine department, duplex ultrasound, and lymphoscintigraphy were all found to be normal, abnormalities were detected during multi-lymphosome ICG lymphography and lymphatic ultrasound.

CASE REPORT

The patient was an 87-year-old woman. She underwent total hysterectomy and pelvic lymphadenectomy

Disclosure: *The authors have no financial interest to declare in relation to the content of this article.*

From the Department of Lymphatic and Reconstructive Surgery, JR Tokyo General Hospital, Tokyo, Japan.

Received for publication December 1, 2020; accepted August 19, 2021.

DOI: 10.1097/GOX.0000000000003859

for uterine cancer when she was 55 years old. Ten years ago, she was prescribed a diuretic agent for bilateral lower extremity edema, but it did not improve. She had experienced cellulitis of the lower extremities five times.

When she consulted our department, severe edema was observed in both lower extremities (Fig. 1A). The skin of the lower legs was solid with nonpitting edema. A blood examination revealed the presence of hyperlipidemia and elevated D-dimer levels. Electrocardiography revealed a nonspecific T wave abnormality despite also showing normal cardiac function. No abdominal or pectoral occupying lesions were observed in computed tomography. No deep venous thrombosis or venous insufficiency was observed during the Duplex ultrasound. In a lymphoscintigram taken 60 minutes after the injection, dermal backflow was not observed, and lymphatic dysfunction was thought to be negative (Fig. 2). Simply put, conventional examination of any potential causes of edema revealed no significant abnormalities.

Multi-lymphosome ICG lymphography was then used to further evaluate lymphatic function in other lymphosomes. After injecting ICG into the first web space of the foot, the lateral ankle, and the superior edge of the lateral thigh, a linear pattern was found in the saphenous lymphatics, although dermal backflow was observed in the lateral calf and the lateral thigh region, indicating widespread lymphatic dysfunction (Fig. 2).

Lymphatic ultrasound was performed by the author (HH) using a Noblus ultrasound system with an 18-MHz linear probe (Hitachi Medical Corp., Tokyo, Japan), as we previously reported.[14,15] Briefly, we scanned the lower extremities according to the expected routes of the lymphatic vessels in three lymphosomes, the saphenous lymphosome, the lateral calf lymphosome, and the lateral thigh lymphosome, placing the probe perpendicular to the long axis of the lymphatic vessels to obtain short axis images. The lymphatic vessels could be distinguished from the subcutaneous veins because they did not flow into the larger veins when traced proximally. Also, the inner pressure of the lymphatic vessels was higher than that of the veins.

We performed the lymphatic ultrasound, referring to the result of ICG lymphography. In the right lower extremity, we found dilated lymphatic vessels at the lateral side of the lower leg and the lateral side of the thigh (the lateral calf and the lateral thigh lymphosomes), indicating lymphatic accumulation and increased internal pressure in the lymphatic vessels (Fig. 3). In the left lower extremity, we found dilated lymphatic vessels at the medial and the lateral side of the lower leg and the lateral side of the thigh (the saphenous, the lateral calf, and the lateral thigh lymphosomes).

Based on the findings of the aforementioned examinations, we diagnosed her with bilateral lower-limb lymphedema. As a treatment, compression therapy and LVA were performed. We performed LVA in five lymphosomes where we detected dilated lymphatic vessels and suitable subcutaneous veins nearby. We confirmed that there were dilated, but not sclerosed, lymphatic vessels in the bilateral lower legs (Fig. 1B).

DISCUSSION

In this case report, we present a case of bilateral lower-limb lymphedema in which we could not detect any

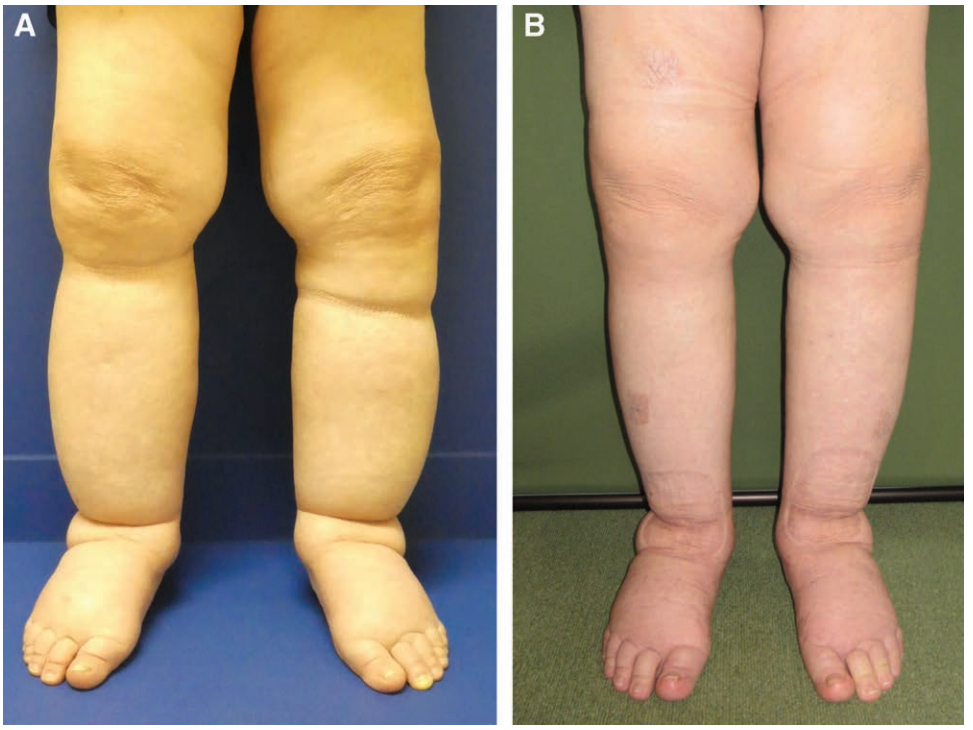

Fig. 1. Clinical images of the patient. A, Clinical picture at the first consultation. Bilateral lower extremity edema was observed. B, Clinical picture after compression therapy and lymphaticovenous anastomosis. Edema in bilateral lower extremity was improved.

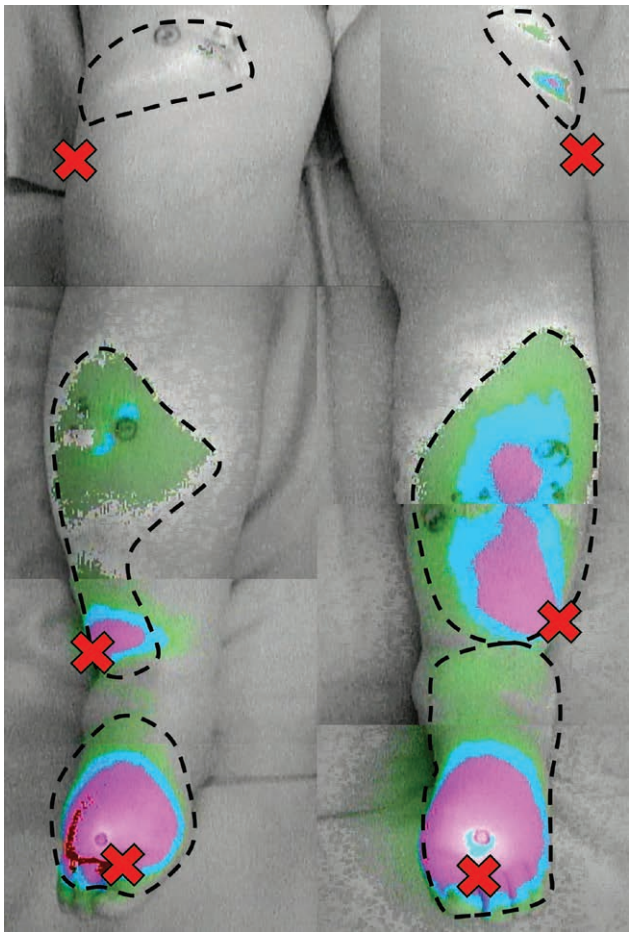

Fig. 2. Findings in multi-lymphosome ICG lymphography. ICG was injected at six points (red crosses) and dermal backflow was observed in the areas indicated with dotted lines.

abnormalities using conventional examinations, including lymphoscintigraphy. The sensitivity of lymphoscintigraphy in diagnosing lymphedema was reported to be 96%, and all of the false-negative cases were primary lymphedema.[16] We did, however, detect lymphatic dysfunction using multi-lymphosome ICG lymphography and lymphatic ultrasound. When no abnormalities are observed upon conventional examination, rest, leg elevation, and compression therapy with 20 mm Hg of pressure may be prescribed; however, in lymphedema, at least 30 mm Hg is needed.[17,18] Lymphedema is also treated with exercise rather than rest.[19]

The use of lymphoscintigraphy, ICG lymphangiography, and ultrasonography are all operator-dependent. Lymphoscintigraphy is a standard diagnostic procedure.[6] ICG lymphography is a relatively new technique, and can depict lymphatic vessels clearly in real time.[5,7] However, its disadvantage is that it is only possible to render images of the superficial lymphatic vessels. As with lymphoscintigraphy, ICG lymphography can only produce images of the lymphatic vessels through which the medical agent flows. The lymphatic ultrasound is independent of contrast agent, and a recent study reported that the findings

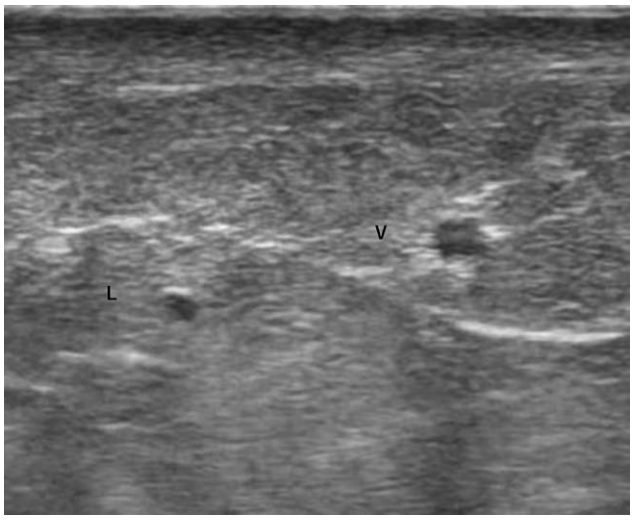

Fig. 3. Ultrasonographic image of the lymphatic vessels (L) and subcutaneous veins (V). The hypo-echoic circles indicate the lumen of the vessels. The lymphatic vessels were dilated, indicating the stasis of the lymphatic fluid within the lymphatic vessels. The hyperechoic circles around the lumen indicate the vessel walls. The walls of the lymphatic vessels are thin and do not seem to be sclerosed.

in the lymphatic ultrasound strongly correlate with their histology.[20] Also, the lymphatic ultrasound can evaluate the degeneration of the lymphatic vessels and can diagnose lymphedema.[14,21] However, the expertise for ultrasonography of lymphatic system is not widely available at the current time, and many centers will still rely on the use of traditional methods of lymphatic imaging for diagnosis.

Suami et al proposed the concept of lymphosomes.[11,22] We performed multi-lymphosome ICG lymphography as a preoperative examination for LVA to assess the functionality of the lymphatic vessels.[12,13] Because lymphatic abnormalities can appear at random, the lack of dermal backflow during conventional lymphoscintigraphy does not mean the lymphatic vessels of the lower extremities are unaffected.[23,24] The concept of lymphosomes is relatively new and the appropriate injection site for ICG lymphography is still controversial. Also, the usefulness of "dilated" lymphatic vessels in diagnosis and treatment remains in question. The other limitation of the lymphatic ultrasound is that it is examiner-dependent, just like the venous ultrasound.

CONCLUSIONS

Multi-lymphosome ICG lymphography and lymphatic ultrasound appeared to be useful in diagnosing the causes of lower extremity edema. It is our belief that combining these two diagnostic examinations will make it possible to diagnose patients who have previously been misdiagnosed due to insufficient screening measures. It is important to evaluate the lymphatic function in every lymphosome, especially when primary lymphedema is suspected, because the lymphatic dysfunction may appear at random.

Makoto Mihara, MD
Department of Lymphatic and Reconstructive Surgery
JR Tokyo General Hospital
2-1-3 Yoyogi, Shibuya-ku
Tokyo 151-8528
Japan
E-mail: mihara.plasticsurgery@gmail.com

ACKNOWLEDGMENT

This case report is approved by the institutional ethical committee (H30-08).

REFERENCES

1. Gasparis AP, Kim PS, Dean SM, et al. Diagnostic approach to lower limb edema. *Phlebology*. 2020;35:650-655.
2. Kistner RL, Eklof B, Masuda EM. Diagnosis of chronic venous disease of the lower extremities: The "CEAP" classification. *Mayo Clin Proc*. 1996;71:338–345.
3. Ad Hoc Committee, American Venous Forum. Classification and grading of chronic venous disease in the lower limbs. A consensus statement. *J Cardiovasc Surg (Torino)*. 1997;38:437–441.
4. Ely JW, Osheroff JA, Chambliss ML, et al. Approach to leg edema of unclear etiology. *J Am Board Fam Med*. 2006;19:148–160.
5. Yamamoto T, Narushima M, Doi K, et al. Characteristic indocyanine green lymphography findings in lower extremity lymphedema: The generation of a novel lymphedema severity staging system using dermal backflow patterns. *Plast Reconstr Surg*. 2011;127:1979–1986.
6. Maegawa J, Mikami T, Yamamoto Y, et al. Types of lymphoscintigraphy and indications for lymphaticovenous anastomosis. *Microsurgery*. 2010;30:437–442.
7. Mihara M, Hara H, Araki J, et al. Indocyanine green (ICG) lymphography is superior to lymphoscintigraphy for diagnostic imaging of early lymphedema of the upper limbs. *PLoS One*. 2012;7:e38182.
8. Hara H, Mihara M, Seki Y, et al. Comparison of indocyanine green lymphographic findings with the conditions of collecting lymphatic vessels of limbs in patients with lymphedema. *Plast Reconstr Surg*. 2013;132:1612–1618.
9. Mazzei MA, Gentili F, Mazzei FG, et al. High-resolution MR lymphangiography for planning lymphaticovenous anastomosis treatment: A single-centre experience. *Radiol Med*. 2017;122:918–927.
10. Liu NF, Yan ZX, Wu XF, et al. Magnetic resonance lymphography demonstrates spontaneous lymphatic disruption and regeneration in obstructive lymphedema. *Lymphology*. 2013;46:56–63.
11. Suami H, Shin D, Chang DW. Mapping of lymphosomes in the canine forelimb: Comparative anatomy between canines and humans. *Plast Reconstr Surg*. 2012;129:612–620.
12. Hara H, Mihara M. Multilymphosome injection indocyanine green lymphography can detect more lymphatic vessels than lymphoscintigraphy in lymphedematous limbs. *J Plast Reconstr Aesthet Surg*. 2020;73:1025–1030.
13. Hara H, Mihara M. Multi-area lymphaticovenous anastomosis with multi-lymphosome injection in indocyanine green lymphography: A prospective study. *Microsurgery*. 2019;39:167–173.
14. Mihara M, Hara H, Kawakami Y. Ultrasonography for classifying lymphatic sclerosis types and deciding optimal sites for lymphatic-venous anastomosis in patients with lymphoedema<sup/>. *J Plast Reconstr Aesthet Surg*. 2018;71:1274–1281.
15. Hara H, Mihara M. Usefulness of preoperative echography for detection of lymphatic vessels for lymphaticovenous anastomosis. *SAGE Open Med Case Rep*. 2017;5:2050313X17745207.
16. Hassanein AH, Maclellan RA, Grant FD, et al. Diagnostic accuracy of lymphoscintigraphy for lymphedema and analysis of false-negative tests. *Plast Reconstr Surg Glob Open*. 2017;5:e1396.
17. Partsch H, Clark M, Mosti G, et al. Classification of compression bandages: Practical aspects. *Dermatol Surg*. 2008;34:600–609.
18. Hara H, Hamanaka N, Yoshida M, et al. Variability in compression pressure of multi-layer bandaging applied by lymphedema therapists. *Support Care Cancer*. 2019;27:959–963.
19. Executive Committee of the International Society of Lymphology. Executive Committee of the International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema: 2020 Consensus Document of the International Society of Lymphology. *Lymphology*. 2020;53:3–19.
20. Bianchi A, Visconti G, Hayashi A, et al. Ultra-High frequency ultrasound imaging of lymphatic channels correlates with their histological features: A step forward in lymphatic surgery. *J Plast Reconstr Aesthet Surg*. 2020;73:1622–1629.
21. Hara H, Mihara M. Diagnosis of lymphatic dysfunction by evaluation of lymphatic degeneration with lymphatic ultrasound. *Lymphat Res Biol*. 2021;19:334–339.
22. Suami H. Lymphosome concept: Anatomical study of the lymphatic system. *J Surg Oncol*. 2017;115:13–17.
23. Hara H, Mihara M, Ohtsu H, et al. Indication of lymphaticovenous anastomosis for lower limb primary lymphedema. *Plast Reconstr Surg*. 2015;136:883–893.
24. Hara H, Mihara M, Okuda I, et al. Presence of thoracic duct abnormalities in patients with primary lymphoedema of the extremities. *J Plast Reconstr Aesthet Surg*. 2012;65:e305–e310.