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

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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.

CASE REPORT

The patient was an 87-year-old woman. She 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.

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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
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; however, 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 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.
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