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IDIOPATHIC PORTAL HYPERTENSION AND LOWER LIMB LYMPHEDEMA

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ABSTRACT

Idiopathic lymphedema is a condition where lymph accumulates in subcutaneous tissue without a clear cause. Likewise, idiopathic portal hypertension is a syndrome where intrahepatic peripheral portal branch obstruction causes portal hypertension without a clear cause. We encountered a 37-year-old man with both idiopathic lymphedema and idiopathic portal hypertension. He had a history of right lower limb edema and epigastric varices since childhood with repeated cellulitis in the affected limb. Lymph accumulation and dilation of collateral lymph pathways in the right lower limb were observed by indocyanine green and lymphoscintigraphy, and a serpentine thoracic duct was observed using MRI. Idiopathic portal hypertension and idiopathic lymphedema were diagnosed, and peripheral lymphaticovenous anastomosis was performed for treatment of lymphedema. The limb circumference improved, and the frequency of cellulitis decreased. It is postulated that an abnormality in the embryonic cardinal vein before lymph vessel differentiation could be a possible mechanism of the dual pathologic conditions.

Keywords: idiopathic lymphedema, idiopathic portal hypertension, magnetic resonance-thoracic ductography (MRTD), lymphatico-venous anastomosis (LVA), ICG, lymphoscintigraphy

Lymphedema is a condition where lymph accumulates in subcutaneous tissue due to an inadequate lymph return. Most cases are secondary in nature caused by lymph node dissection for treatment of malignant tumor or filarial infection. Gene aberrations of VEGFR3 and FOXC2 have been identified in some cases of primary lymphedema (1-4), but the cause is unclear in many cases, and these are termed idiopathic lymphedema. As the condition becomes chronic, cellulitis can repeatedly develop in the affected region (5-6) and markedly impairs quality of life. Generally, complex physical therapy is performed for treatment of lymphedema. However, surgical treatments such as lymphatico-venous anastomosis (LVA) and lymph node transplantation have also been reported (7-12).

Idiopathic portal hypertension is the term used for a syndrome in which obstruction of the intrahepatic peripheral portal branch causes portal hypertension without a known cause (13-16). Reduction of one or more types of circulating blood cells (cytopenias), mild liver dysfunction, splenomegaly, and esophageal varices occur. Autoimmunity, splenogenic effects, infection, and intrahepatic peripheral portal thrombois

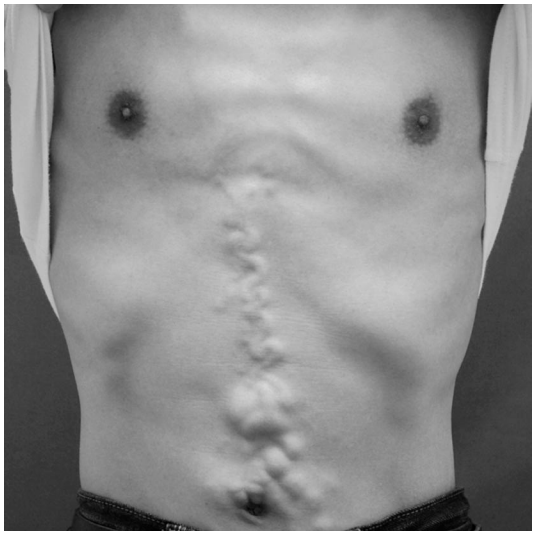

Fig. 1. Photograph before operation showing marked venous dilation in the abdominal wall.

have all been suggested as underlying causes, but the specific etiology is unclear.

We encountered a patient with concomitant idiopathic lymphedema and idiopathic portal hypertension. Such a patient has not been previously reported, and investigation of this case may contribute to elucidation of the unknown pathogenesis of these conditions. The purpose of this paper is to report this uncommon presentation of coexisting idiopathic lymphedema and idiopathic portal hypertension.

CASE REPORT

The patient is a 37-year-old man who experienced edema in the right lower limb and epigastric varices since childhood. Edema in the right lower limb increased at 14 years of age, and cellulitis repeatedly occurred approximately every six months. He consulted with a local physician who diagnosed primary lymphedema following examination. At 27, he started to wear an elastic stocking on the right lower limb. Splenomegaly was observed on abdominal CT at 33, and esophageal varices were detected at 35, but only course observation was performed for both lesions. The patient also had a medical history of appendicitis at 14 and a ureteral stone at 26. He had never visited an endemic filarial region such as Southeast Asia and the southern part of Japan, and there is no relevant familial medical history.

TABLE
Blood Data Before Surgery

Item	Value*
WBC	3600/μl ↓
RBC	444 $\times 10^4$/μl
MCV	87.8 fl
MCH	32.0 pg
MCHC	36.4 g/dl
Hb	14.2 g/dl
Hct	39.0%
PLT	4.8×10^4/μl ↓
Alb	4.2 g/dl
LD	210 IU/l
AST(GOT)	25 IU/l
ALT(GPT)	14 IU/l
γ-GTP	16 IU/l
ALP	276 IU/l
T-Bil	2.2 mg/dl ↑
D-Bil	0.7 mg/dl ↑
T-Cho	108 mg/dl
PTs	12.7 sec
PT%	88.0%
PT-INR	1.05

* Arrows indicate values that were abnormally elevated or reduced

The patient first visited the Department of Gastrointestinal Medicine and Department of Plastic and Reconstructive Surgery of the University of Tokyo Hospital for right lower limb edema at age 36. On the initial examination, marked pitting edema in the right lower limb and varices on the abdominal wall were observed (*Fig. 1*). No edema was noted in the left lower limb or any other region. Blood tests showed pancytopenia and mild liver dysfunction (*Table*). Abdominal CT

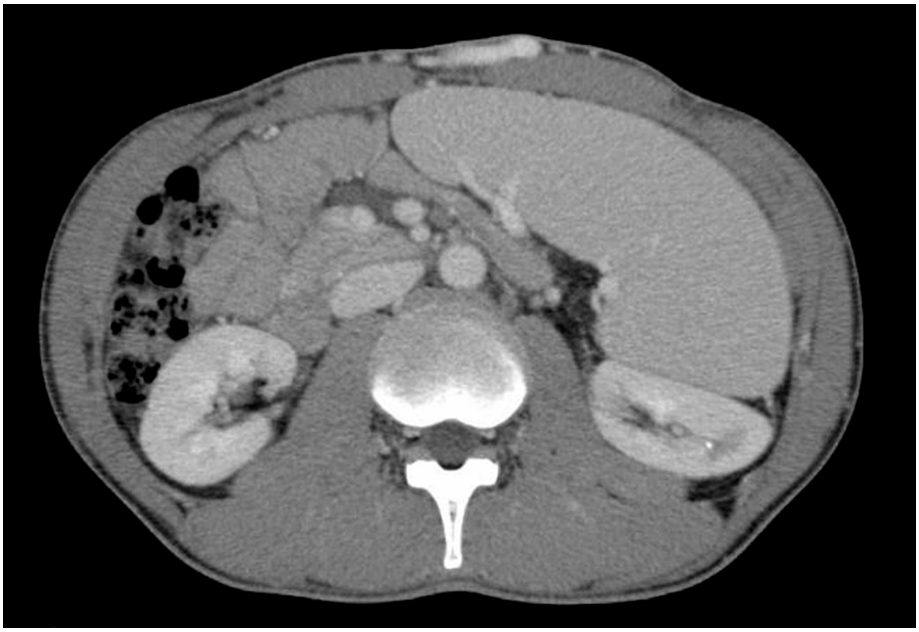

Fig. 2. Abdominal contrast CT showing severe splenomegaly measuring 15 cm and venous dilation in the abdominal wall.

indicated splenomegaly measuring 15 cm and marked dilation of the splenic vein over the portal vein, with formation of a collateral pathway from the paraumbilical vein to the femoral vein through the epigastric superficial and inferior epigastric veins (*Fig. 2*). Mild liver deformity was observed. Endoscopy of the upper digestive tract showed varices at a site 20 cm from the incisor over the cardioesophageal junction. No reddening was noted, and there was no abnormality in the stomach or duodenum.

Based on the clinical and laboratory findings, idiopathic portal hypertension and idiopathic lymphedema were diagnosed. Idiopathic portal hypertension was subjected to a course of observation in the Internal Medicine Department, while surgical treatment was planned for the lymphedema in Plastic and Reconstructive Surgery.

Indocyanine Green (ICG) Test

ICG (0.2 ml; Diagnogreen 0.5%, Daiichi Pharmaceutical, Tokyo, Japan) was injected intracutaneously into the first interdigit on both feet. Imaging was performed using a photodynamic eye (PDE) system (Hamamatsu Photonics, Hamamatsu, Japan) 24h after ICG injection. In the right lower limb, transport from the dorsum of the foot to above the calf was not visualized and diffuse patterns were noted in the thigh. In the left lower limb, linear patterns were noted from the dorsum of the foot to above the thigh, but many serpentine lymph vessels, which are not normally observed, were present in the anterior calf (*Fig. 3*).

Lymphoscintigraphy

A 99mTc-labeled nanocolloid was injected subcutaneously (~20 MBq in 0.1 mL per limb) into the dorsum of the first web space of the feet. Half-body anterior and posterior images from the upper abdomen to the toes were obtained with a large-field-of-view gamma camera, commencing 90 minutes after tracer injection. Tracer retention was observed in the medial and

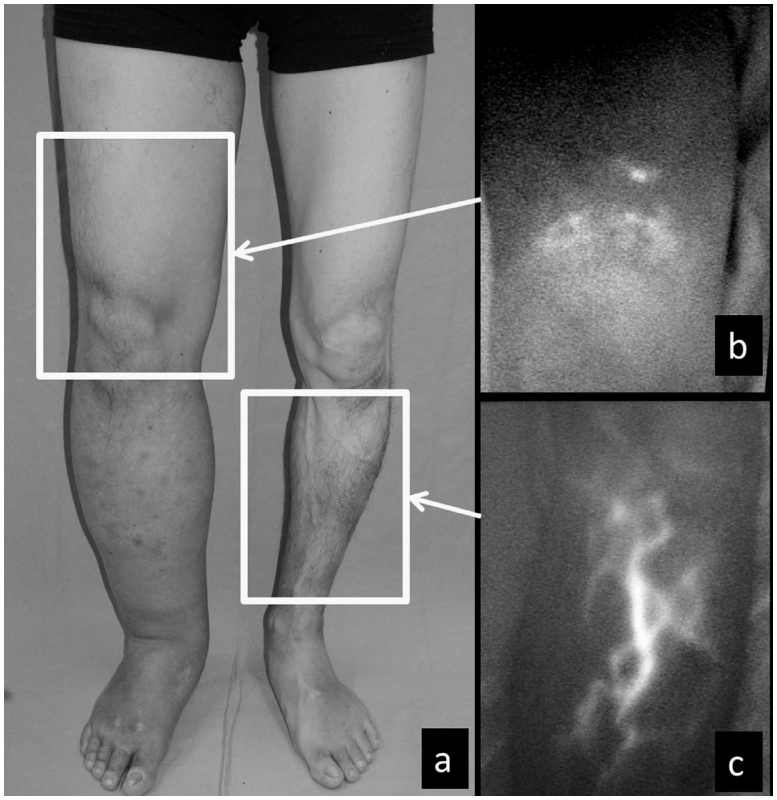

Fig. 3. ICG fluoresence lymphography before surgery. (a) Edema in the right lower limb, but no apparent edema in the left lower limb. (b) Stardust patterns in the edematous right thigh. (c) Many dilated and serpentine lymph vessels were present in the left calf, which was not edematous.

lateral regions of the right thigh (*Fig. 4*). Collateral lymph pathways were present on the lateral side of the left calf, indicating lymph flow alteration, despite no apparent edema in this region. This finding suggested preclinical lymphedema.

Thoracic Duct MRI (Magnetic Resonance Thoracic Ductography, MRTD)

Thoracic duct MRI was performed as previously described (17,18) using a 1.5T MRI system (Intera Master unit; Philips Medical Systems, Eindhoven, The Netherlands). MRTD images were acquired using the imaging sequence for magnetic resonance cholangiopancreatography (MRCP) applied to the mediastinum. No contrast agent was used. The thoracic duct ascended on the right side of the aorta and moved into the left venous angle (*Fig. 5*). A moderate serpentine distribution was noted over the whole length in an oblique image.

Lymphatico-Venous Anastomosis (LVA)

LVA was performed for bilateral lower limb lymphedema under local anesthesia in a supine position. The operation time was 2h 56 min, and the blood loss was minimal. In the right lower limb, 4 anastomoses were applied at 4 sites in the dorsum of the foot, ankle, knee joint, and inguinal regions, using an operating microscope and 11-0 nylon suture. Severe subcutaneous fibrosis was noted in the dorsum of the foot and ankle

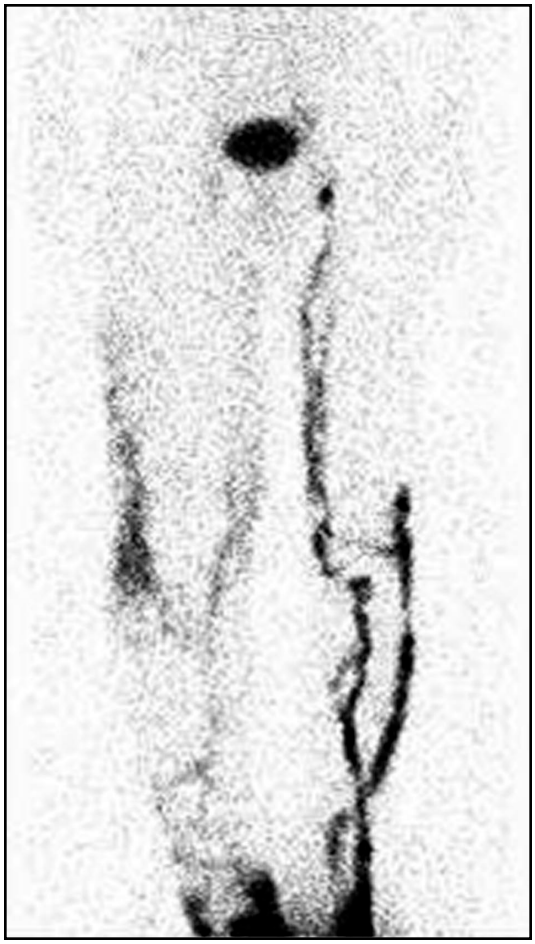

Fig. 4. Lymphoscintigraphy before operation, showing lymph retention in the right thigh (left side of the picture) and dilated collateral lymph pathways in the lateral region of the left calf.

joint. The collecting lymph vessel in the inguinal region was thick (1.6 mm) and flow was favorable, but the lymph vessel wall was markedly thickened. There was no edema in the left lower limb, but lymph retention was observed on the ICG test, for which an anastomosis was applied at one site in the ankle joint. No subcutaneous fibrosis was noted, but the collecting lymph vessel was dilated to 0.8 mm, reflecting lymph stasis in the left lower limb.

Postoperative Course

Wearing of an elastic stocking was re-started 2 weeks after surgery. The circumference of the calf was markedly improved 1 year after surgery, especially in the lower leg (-7 cm at the lower leg and -3 cm at the ankle) (*Fig. 6*). Mild erythema occurred in the right lower limb only once during the 1-year period, but he experienced no systemic symptoms or fever after the operation.

DISCUSSION

There have been no previous reports of concomitant idiopathic portal hypertension and idiopathic lymphedema. LVA was applied for lymphedema, and the circumference of the calf was markedly improved at 1 year after surgery. The elevated portal pressure may have been associated with elevated venous pressure in the lower limbs, and compression by wearing of elastic stockings after surgery may have improved venous circulation and possibly enhanced the effect of LVA. The pressure of elastic stockings is about 40 mmHg, which is higher than the venous pressure. Improvement in the circumference of a limb affected by lymphedema requires time because fibrosis of subcutaneous tissue does not change quickly, and the circumference may continue to improve. Further follow up may provide enhancement of success due to the LVA or the relatively high pressure compression stockings. The frequency of cellulitis also decreased. Fever higher than 38.5°C developed with cellulitis before surgery, but cellulitis accompanied by systemic fever did not occur after surgery, suggesting that lymph flow was improved.

It is of interest to consider whether idiopathic lymphedema and idiopathic portal hypertension were derived from the same cause or co-incidentally developed concomitantly through different mechanisms. If lower limb edema is directly caused by elevated portal pressure, venous edema may occur in both lower limbs through a patent pre-umbilical vein connection (19). In this

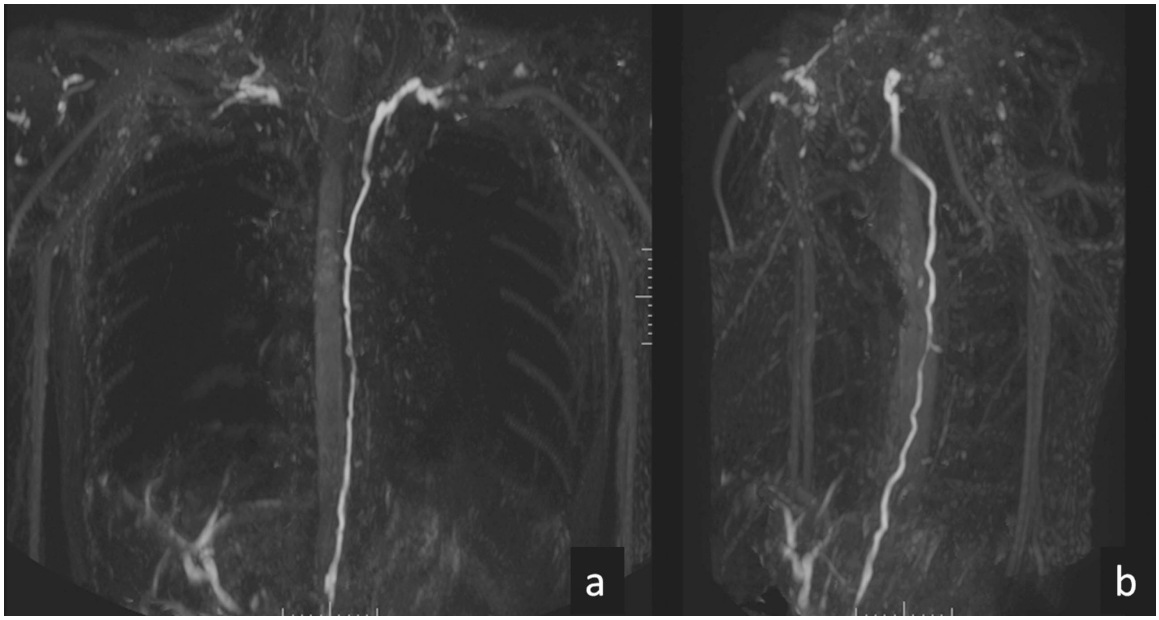

Fig. 5. Magnetic resonance-thoracic ductography (MRTD). (a) Frontal view. (b) Right oblique view. The thoracic duct ascended in a serpentine pattern.

patient, a component of venous edema cannot be ruled out, but the presence of lymphedema was substantiated by the findings of lymphoscintigraphy and ICG fluorescence lymphography. The incidence of idiopathic portal hypertension peaks in patients in their 40s and 50s, and this condition may be caused by autoimmunity, splenogenic effects, or intrahepatic peripheral portal thrombus (20). However, epigastric varices were present in this patient since childhood, suggesting another mechanism.

Lymphatic vessels differentiate from veins in the developmental process through Prox1 and platelet aggregation activities (21-24). It is postulated that the embryonic cardinal vein, at the origin of lymph vessels, was occluded or narrowed due to an abnormality before lymph vessel differentiation, and that this abnormality simultaneously caused the two disorders, or that valve insufficiencies occurred in the cardinal vein and lymph vessels differentiating from this vein. The thoracic duct ascended in a serpentine pattern on MRTD, suggesting the presence of a structural abnormality such as smooth muscle or valve insufficiency of the thoracic duct although overload of the thoracic duct from increased production of intestinal (and presumably also hepatic lymph) from portal hypertension may also be a contributing factor as previously documented in thoracic duct and regional hepatosplenic lymph studies in patients with portal hypertension from hepatic cirrhosis (25). The central lymphatic system disturbance could have then been transmitted to both the edematous right lower limb and the thoracic cavity, suggesting that an abnormality was present in the cardinal vein before venous and lymph vessel differentiation. Alternatively, these two entities could have arisen independently of each other. Further investigation by genetic analysis and histological examination of lower limb lymph vessels may be helpful in exploring these hypotheses.

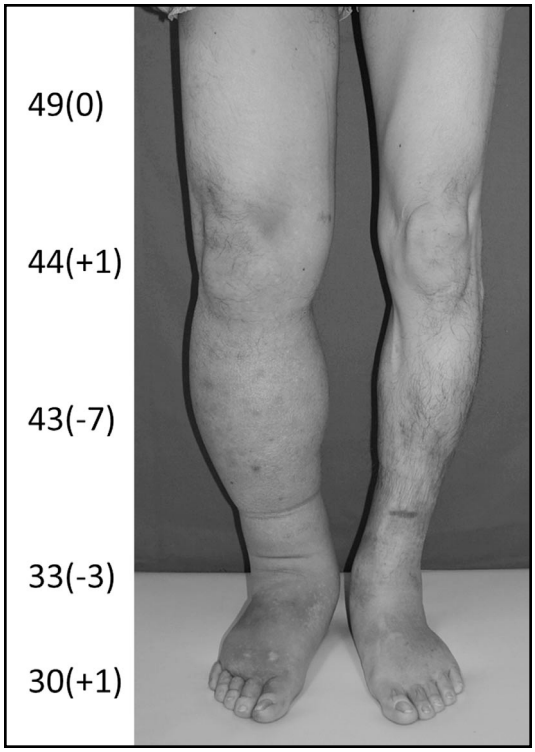

Fig. 6. Photograph after operation. The leg circumferences (cm; with change from pre-operation) were measured at sites 10 cm above the knee, just above the patella, 10 cm below the knee, at the ankle joint, and at the dorsum of the foot. The circumference of the calf was markedly improved.

CONCLUSION

We describe a patient with concomitant idiopathic portal hypertension and idiopathic lymphedema. An abnormality in the cardinal vein before lymph vessel differentiation may be a possible cause of both pathologic conditions.

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