Vaginal discharge caused by lymphatic malformation identified by lymphoscintigraphy combined with T2-weighted magnetic resonance imaging

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ABSTRACT

Prepubertal vaginal discharge is most commonly caused by vulvovaginitis and is rarely caused by lymphatic malformations, resulting in chylous vaginal discharge. The diagnosis of chylous vaginal discharge remains a challenge because of a knowledge gap. We describe a 12-year-old girl with intermittent vaginal discharge for 10 years. Although we found a high signal in the vagina on T2-weighted magnetic resonance imaging (MRI), the final diagnosis, vaginal lymphatic leakage, was established on lymphoscintigraphy. Lymphatic leakage in the vagina on lymphoscintigraphy was the key imaging feature of chylous vaginal discharge in this patient. Moreover, diffuse radioactivity was found in the abdomen and thorax on lymphoscintigraphy, which indicated the multiple cystic lymphatic malformations and intestinal lymphangiectasia combined with T2-weighted MRI. Thus, T2-weighted MRI could be used in combination with lymphoscintigraphy to simply identify chylous vaginal discharge. (J Vasc Surg Cases and Innovative Techniques 2020;6:1-5.)

Keywords: Vaginal discharge; Lymphatic malformation; Lymphoscintigraphy; Magnetic resonance; Intestinal lymphangiectasia

Prepubertal vaginal discharge is most often caused by vulvovaginitis. It also could be caused by sexual abuse, a foreign body, labial adhesions, and vaginal agenesis.[1] It is rarely caused by lymphatic malformation on the vaginal wall, resulting in chylous vaginal discharge.[2,3]

Lymphatic malformation is characterized by dysplastic and incompetent lymphatic channels in multiple tissues and organs. It is one type of vascular malformation. Vascular malformation consists of lymphatic malformation, venous malformation, arteriovenous malformation (AVM), and arteriovenous fistula (AVF).[4] The diagnosis of chylous vaginal discharge remains a challenge because of a knowledge gap.[3] Whole-body lymphoscintigraphy has been used to evaluate lymphatic flow after subcutaneous injection of technetium-99m (^{99m}Tc) filtered sulfate colloid into the toe webs. The radionuclide traces the lymphatic flow and the lymphatic leakage (eg, chylothorax, chyloperitoneum).[5] Dynamic contrast-enhanced magnetic resonance angiography (DC-MRA) has been used to differentiate venous malformation from lymphatic malformation as well as to differentiate a high-flow vascular malformation (AVM or AVF) from a low-flow vascular malformation (lymphatic malformation and venous malformation). On DC-MRA, no enhancement is found in the lesions of lymphatic malformation, whereas slow gradual enhancement is found in the lesions of venous malformation.[6] However, the deposition of gadolinium has been found in the brain, and the gadolinium probably led to renal fibrosis.[7,8]

The purpose of this case report is to underline that whole-body lymphoscintigraphy can be combined with plain T2-weighted magnetic resonance imaging (MRI) to identify chylous vaginal discharge. The local Institutional Review Board approved this research. Consent for publication was obtained from the patient's guardians.

CASE REPORT

A 12-year-old girl complained of intermittent vaginal discharge during 10 years without vaginal bleeding, hematuria, or chyluria. Although the patient had visited several hospitals, the pathogenesis of the vaginal discharge was unclear. Examination of the vulva showed a small amount of pink-milky discharge out of the vaginal introitus as well as an iatrogenic fractured hymen. The findings on vaginal examination and vaginoscopy were unremarkable. Microscopic examination of the vaginal secretions with saline showed a small amount of inflammation cells and no malignant cells. Chemical tests for the vaginal discharge found an elevated triglyceride level (783 mg/dL), which indicated a chylous vaginal discharge. Blood tests showed hypoproteinemia (albumin level of 2.5 g/dL) and anemia (hemoglobin level of 6.7 g/dL). Abdominal ultrasound and computed tomography outside the hospital found multicystic masses in the abdomen. T2-weighted MRI showed multiple macrocystic septate lesions in the abdomen and retroperitoneum (Figs 1 and 2), multiple microcysts in the spleen (Fig 3), and irregular microcystic lesions in both the left spinal muscle and gluteus

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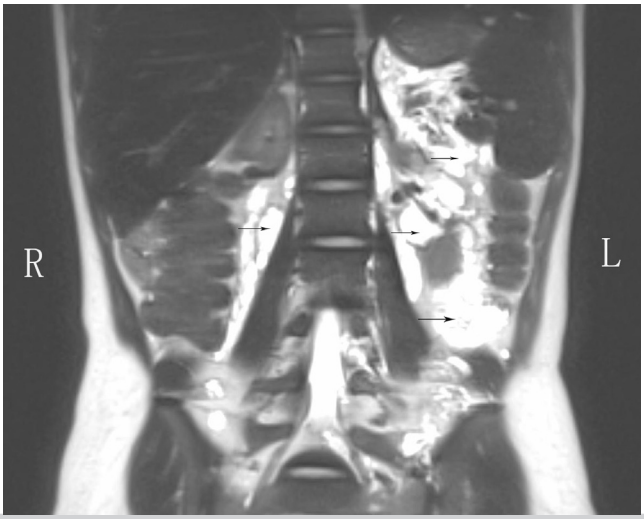

Fig 1. Coronal abdominal T2-weighted magnetic resonance image showing multiple retroperitoneal macrocystic lesions (*arrows*). This feature indicated possible lymphatic malformation, most probably the generalized lymphatic anomaly (GLA) that is a subtype of the lymphatic malformation.

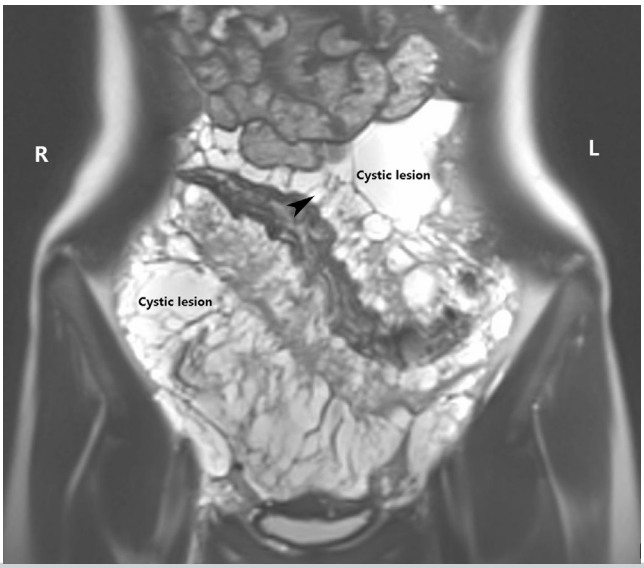

Fig 2. Coronal pelvic T2-weighted magnetic resonance image showing multiple mesenteric microcysts (*arrowhead*) and mesenteric macrocyst. These findings implied intestinal lymphangiectasia.

maximus as well as in the left brachial fat layer (Fig 4). Those findings indicated possible lymphatic or venous malformation. T2-weighted MRI also showed diffuse lesions in the whole rectovaginal septum and the whole vaginal wall (Fig 5), which implied the possible location of the vaginal discharge, and a large area of bright signal in the intestine, which implied intestinal lymphangiectasia (Fig 2). Putting the imaging findings and the chemical tests together, the radiologists suggested that the lesions were most probably lymphatic malformation or venous malformation.

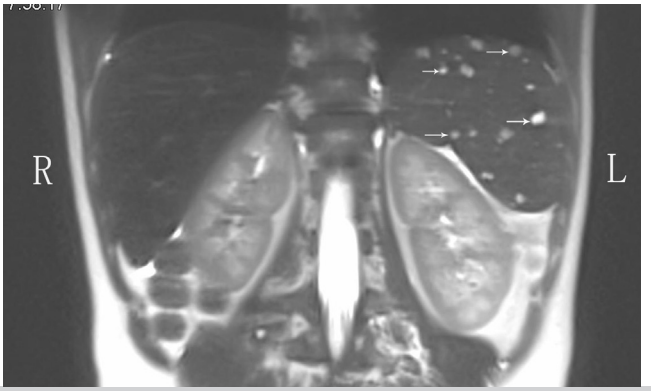

Fig 3. Coronal upper abdominal T2-weighted magnetic resonance image showing multiple microcysts (*arrows*) in the spleen, which implied the generalized lymphatic anomaly (GLA).

The patient next underwent laparoscopy at an outside hospital, but no correlation between the radiologic findings and the vaginal discharge was found. She was transferred to our institute to undergo lymphoscintigraphy. Two subcutaneous injections of 0.5 mCi of ^{99m}Tc filtered sulfur colloid were simultaneously administered into the toe webs. Whole-body lymphoscintigraphy, using a scan speed of 10 cm/min, was performed at 40, 60, 120, and 300 minutes after the radionuclide injection. Lymphoscintigraphy showed a diffuse abdominal-pelvic distribution of the radiotracer (Fig 6), which indicated lymphatic malformation, most probably generalized lymphatic anomaly (GLA). It also showed a lymphatic leakage in the vagina (Fig 6), under the bladder, which indicated a chylous vaginal discharge. Radioactivity was reduced in the left groin lymph nodes, which indicated delayed radiotracer transport in the left lower limb as well as mild lymphatic reflux in the left thigh (Fig 6). The findings in the lower extremities indicated lymphedema. After the findings of T2-weighted MRI of the vaginal wall were combined with the lymphatic leakage in the vagina on lymphoscintigraphy, the association between the vaginal discharge and lymphatic malformation was established.

Moreover, the girl's hypoproteinemia and anemia were thought to be caused by both intestinal lymphangiectasia with protein-losing enteropathy and chronic chylous vaginal discharge. The patient underwent hyperalimentation treatment and was discharged from the hospital.

The importance of lymphoscintigraphy in differentiating lymphatic malformation from venous malformation is highlighted, especially in identifying lymphatic leakage.

DISCUSSION

Clinical analysis. The chief complaint of the patient was intermittent vaginal discharge for 10 years. The chemical tests found a high level of triglycerides in the patient's vaginal secretion, which implied lymphatic lesions in the vagina. T2-weighted MRI showed a bright signal on the rectovaginal septum (Fig 5), which implied a venous or lymphatic malformation. Notably, the lesion on the

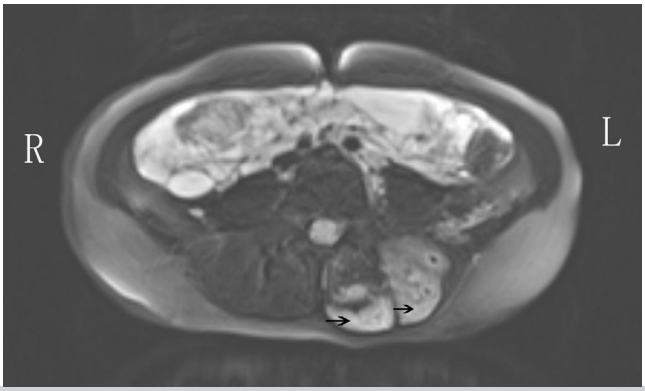

Fig 4. Transverse pelvic T2-weighted magnetic resonance image. Hyperintensity (*arrows*) is seen in the gluteus maximus and the fat layer, which indicated the generalized lymphatic anomaly (GLA).

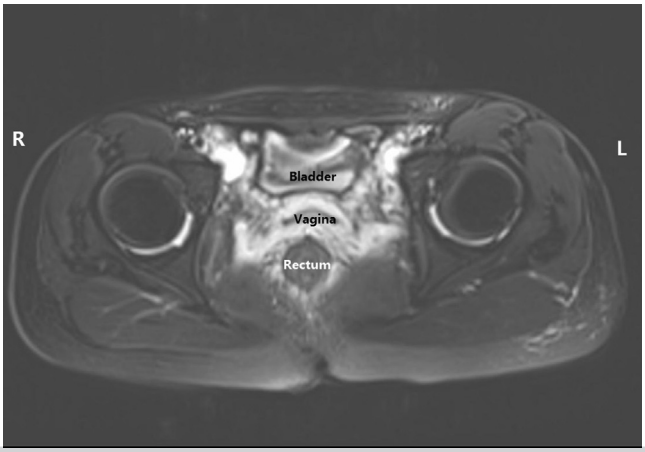

Fig 5. Transverse pelvic T2-weighted magnetic resonance image across vagina. Bright vaginal wall indicated possible lymphatic extravasation, which is the reason for chylous vaginal discharge.

vaginal wall implied the location of the possible lymphatic extravasation. Lymphoscintigraphy showed lymphatic extravasation in the vagina (Fig 6), which was the direct evidence of lymphatic leakage. When these findings were combined, the final diagnosis of chylous vaginal discharge caused by lymphatic malformation was established. This girl had a GLA, a subtype of lymphatic malformation.

A GLA is a multifocal lymphatic malformation. It may affect the skin, superficial soft tissue (Fig 4), and abdominal and thoracic viscera (Figs 1 and 3); it often involves bone, with bone disease that is generally nonprogressive and spares the bone cortical boundaries. Chylous effusions (pericardial, pleural, or peritoneal) can be present. Sclerotherapy with alcohol or Onyx (ev3, Covidien, Plymouth, Minn) is the primary treatment.[4] The disease affected this patient's vaginal wall, leading to chylous vaginal discharge; it affected her intestines, leading to hypoproteinemia and protein-losing enteropathy (Fig 2); and her retroperitoneal tissue was also affected by an asymptomatic macrocystic lymphatic malformation (Fig 1). Except for the chylous discharge, congenital chylorrhea (eg, GLA) can occur anywhere in the body and may be manifested as scrotal chylorrhea,[9,10] lymphedema of external genitalia,[11] chylothorax,[12,13] chylous ascites,[14,15] or chylopericardium.[16]

T2-weighted MRI showed diffuse intestinal lesions (Fig 2), and the blood tests found hypoproteinemia, which indicated intestinal lymphangiectasia and protein-losing enteropathy in this patient. Hypoproteinemia may be caused by protein loss from the intestine as well as by chylous vaginal discharge in this patient (Fig 6). Anemia in this girl may be associated with protein-losing enteropathy.

Vascular anomalies. According to the 2014 International Society for the Study of Vascular Anomalies classification, vascular anomalies are classified as vascular tumors and vascular malformations. Vascular malformations are classified as capillary malformation, venous malformation, lymphatic malformation, AVM, and AVF. Simple lymphatic malformations are further classified as common (cystic) lymphatic malformation (ie, macrocystic, microcystic, mixed cystic), GLA, lymphatic malformation in Gorham-Stout disease, channel-type lymphatic malformation, primary lymphedema, and others.

Clinicohistologic and genetic framework of lymphatic malformations. Mutations in phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) have been found in 16 of 17 specimens (mutant allele fraction, 0.8%-10%) of patients with lymphatic malformation.[17] PIK3CA is a catalytic subunit of PI3 kinases, resulting in the phosphorylation and thus activation of downstream phosphoinositides. This action results in the activation of many cellular responses, including proliferation, angiogenesis, and survival.[18] Through the study of global and endothelial cell-specific PIK3CA knockout mice, Yoshioka et al[19] demonstrated attenuated formation of the vascular network in vivo.

In addition to lymphatic malformations, PIK3CA mutations have also been identified in venous malformation, fibroadipose vascular anomaly, isolated facial infiltrating lipomatosis, and overgrowth syndromes (eg, CLOVES [congenital lipomatous overgrowth, vascular malformations, epidermal nevus, and skeletal deformities syndrome], Klippel-Trénaunay syndrome, megalencephaly-capillary malformation). Vascular anomalies with a PIK3CA mutation were defined as PIK3CA-related overgrowth spectrum. A drug targeted to PIK3CA is in development.[20] If this patient has a PIK3CA mutation, a drug targeted to PIK3CA may be useful in the future. This patient has not yet undergone genetic testing.

Clinicohistologic and genetic framework of vascular malformations. Venous malformations are classified as common venous malformation, familial venous

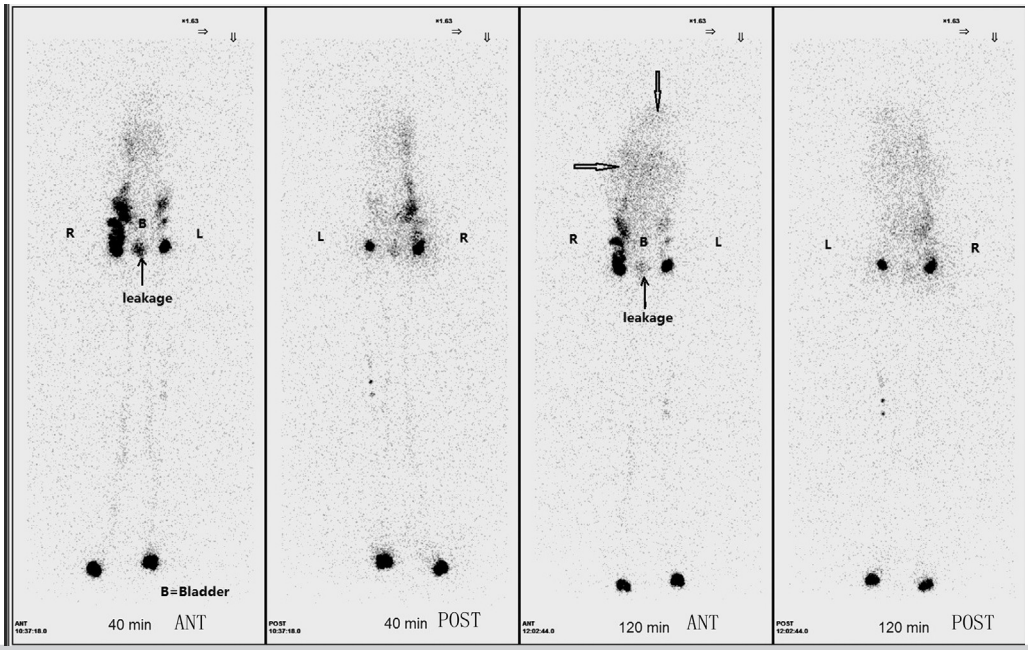

Fig 6. Whole-body lymphoscintigraphy was performed at 40 minutes and 120 minutes after radionuclide injection subcutaneously in the toe webs. Lymphatic leakage was seen in the vagina, which is below the bladder (*B*). Diffuse radioactivity was seen in the abdomen (*arrow*), which is correlated with the multiple macrocystic lesions on T2-weighted magnetic resonance imaging (MRI).

malformation cutaneomucosal, blue rubber bleb nevus (Bean) syndrome, glomuvenous malformation, cerebral cavernous malformation (different types), and others. Venous malformations could be caused by mutations in eight different genes, including tyrosine kinase receptors TIE2, PDGF, ENG, PIK3CA, MAP3K3, Glomulin, and CCM1/KRIT1 (12/20 samples),[21] CCM2/malcavernin (29/35 samples),[22] or CCM3/PDCD10 (8/20 samples).[23]

Imaging analysis. Standard MRI showed retroperitoneal septate lobulated cystic lesions with low signal intensity on T1-weighted imaging and high signal intensity on T2-weighted imaging in this patient (Fig 1). These findings indicated the highest probability to be a lymphatic or venous malformation. The lesions were not enlarged and had no feeding arteries and draining veins; they also had no flow voids on spin echo images, implying a low probability of AVM.

To differentiate venous malformation from lymphatic malformation, DC-MRA (eg, time-resolved angiography with interleaved stochastic trajectories) is the first-line modality in many institutes. On DC-MRA, lymphatic malformation has no enhancement in the lesions and rim and septal enhancement; in contrast, venous malformation has slow gradual enhancement and diffuse enhancement on delayed images with some late enhancement. Furthermore, DC-MRA facilitates differentiation of high-flow AVM and AVF, which have early venous filling and an enlarged feeding artery and draining vein, from low-flow vascular malformations (venous and lymphatic malformations).[6] However, gadolinium may be deposited in the brain and may lead to renal fibrosis.

Non-contrast-enhanced magnetic resonance lymphangiography, a noninvasive imaging technique based on heavily T2-weighted sequences, could display the lymphatic vessels, but it cannot differentiate lymphatic malformation from venous malformation.[24]

Lymphoscintigraphy, notwithstanding its poor anatomic resolution, provides direct evidence of where the lymphatic flow is. This patient presented with diffuse lymphatic abdominal-pelvic and thoracic distribution of cystic lymphatic malformations and intestinal lymphatic anomalies (Fig 6). Lymphoscintigraphy showed lymphatic leakage in the vagina, which identified the cause of the patient's vaginal discharge in this study (Fig 6).

Whole-body blood pool scan has been used to evaluate the slow blood flow of the lesions. The venous malformation has blood in its lesions, whereas the lymphatic malformation does not. This girl did not undergo a whole-body blood pool scan because the physicians thought that the patient's diagnosis, lymphatic malformation, had been confirmed.

Concerning the treatment of lymphatic malformations, sclerotherapy is not applicable in this patient because the lymphatic extravasation is on the vaginal wall. Sclerotherapy is also not applicable in the intestine. The patient underwent hyperalimentation before she visited our institute and again during her stay in our hospital.

Limitations. We did not use single-photon emission computed tomography/computed tomography hybrid

imaging to precisely localize the site of the lymphatic leakage.

CONCLUSIONS

Chylous prepubertal vaginal discharge caused by vaginal lymphatic malformation is a rare entity. T2-weighted MRI showed the high signal on the vaginal wall, whereas lymphoscintigraphy showed vaginal lymphatic leakage, which is the reason for the patient's vaginal discharge. In addition, the patient's hypoproteinemia and anemia were thought to be caused by intestinal lymphorrhagia with protein-losing enteropathy as well as chylous vaginal discharge.

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