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CLINICAL CASE REPORT

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Primary Intestinal Lymphangiectasia Manifested as Unusual Edemas and Effusions

A Case Report

Xuefeng Wang, MD, Hong Jin, MD, PhD, and Weilu Wu, MD

Abstract: Primary intestinal lymphangiectasia (PIL) is a rare disorder of unknown etiology characterized by diffuse or localized dilation and eventual rupture of the enteric lymphatic vessels in mucosa, submucosa, and/or subserosa. Lymph, rich in all kinds of proteins and lymphocytes, leaks into the gastrointestinal tract via the affected lymphatic vessels causing hypoproteinemia and lymphopenia. The main symptom is variable degrees of pitting edemas of bilateral lower limbs. But edemas of any other parts of body, and mild serous effusions may also occur sometimes. PIL occurs in conjunction with a right hemifacial edema, a right upper limb lymphedema, asymmetric bilateral calves edemas, and a unilateral massive pleural effusion seems never to be reported before. In addition, increased enteric protein loss that may cause severe hypoproteinemia usually get overlooked, and the lymphatic system disorders always put the diagnoses in a dilemma.

We described a case of a 17-year-old Chinese girl with a history of gradually progressive swellings of right-sided face, right upper limb, and bilateral calves since 3 to 4 months of age. A right-sided massive pleural effusion, a moderate pericardial effusion, and a mild ascites have been proved unchanged by a series of computerized tomography (CT) scans since 5 years ago. The diagnosis of PIL was finally confirmed by severe hypoproteinemia, endoscopic changes, and histology of jejunum biopsy. Further lymphoscintigraphy and lymphangiography also identified lymph leakage in her bowel and several abnormal lymphatic vessels. A high-protein, low-fat diet supplemented with medium-chain triglycerides (MCT) showed some benefit.

This case suggested that PIL was a rare but important etiology of hypoproteinemia, effusions, and edemas. PIL, effusions, and lymphedema can be the features of multisegmental generalized lymphatic dysplasia. In addition, both lymphoscintigraphy and intranodal lymphangiography could be considered when lymphatic system disorders are suspected.

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Abbreviations: CT = computerized tomography, HIV = human immunodeficiency virus, MCT = medium-chain triglycerides, PIL = primary intestinal lymphangiectasia, TB = tuberculosis.

INTRODUCTION

Primary intestinal lymphangiectasia (PIL) is a rare disorder of unknown etiology characterized by diffuse or localized dilation and eventual rupture of the enteric lymphatic vessels in mucosa, submucosa, and/or subserosa. Lymph, rich in all kinds of proteins and lymphocytes, leaks into the gastrointestinal tract via the affected lymphatic vessels causing hypoproteinemia and lymphopenia. The main symptom is variable degrees of pitting edemas of bilateral lower limbs. But edemas of any other parts of body, and mild serous effusions may also occur sometimes. PIL occurs in conjunction with a right hemifacial edema, a right upper limb lymphedema, asymmetric bilateral calves edemas, and a unilateral massive pleural effusion seems never to be reported before. In addition, increased enteric protein loss that may cause severe hypoproteinemia usually get overlooked, and the lymphatic system disorders always put the diagnoses in a dilemma.

CASE REPORT

A 17-year-old Chinese girl, the daughter of nonconsanguineous healthy parents, presented with a history of gradually progressive swellings of right-sided face, right upper limb, and bilateral calves since 3 to 4 months of age. Edemas firstly occurred on the right-sided face and then expanded to the right upper limb, finally the bilateral calves. She also displayed a discontinuous diarrhea and nausea. A right-sided massive pleural effusion, a moderate pericardial effusion, several hepatic nodules, a mild ascites and many enlarged mesenteric lymph nodes have been proved unchanged by a series of computerized tomography (CT) scans since 5 years ago (Figure 1A). But she denied having cough, dyspnea, fever, chest pain, night sweats or history of tuberculosis (TB), filarial, and surgery. On physical examination, the right hemifacial edema was mild, and the bilateral calves edemas were mild, pitting but asymmetric (the left one was severer than the right one), while the right upper limb edema was severe and woody with a positive Stemmer sign (Figure 1B). A decreased lung sound on the right-sided chest wall was heard. The remainder was unremarkable.

Laboratory tests including stool and urine routine examination, liver, renal and thyroid function, coagulation and blood lipid profiles, electrolytes and assays for human immunodeficiency virus (HIV), hepatitis virus B and C were all unremarkable. Autoantibodies such as antinuclear antibodies, antidouble strand DNA antibodies, antiribonucleoprotein antibodies, anti-Sm antibodies, anti-SSA antibodies, anti-SSB antibodies, anti-SCI-70 antibodies, anti-Jo-1 antibodies, antineutrophilic

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From the Department of Cardiology, Department of Respiratory Medicine, Department of Pathology, West China Hospital, Sichuan University, Chengdu, Sichuan, China.
Correspondence: Hong Jin, Department of Respiratory Medicine, West China Hospital, Sichuan University, No. 37, Guo Xuexiang, Chengdu 610041, Sichuan, China (e-mail: hjin63@163.com).
Because our case report does not refer to the patient's privacy, ethical approval is not necessary. But an oral consent has been obtained from the patient.
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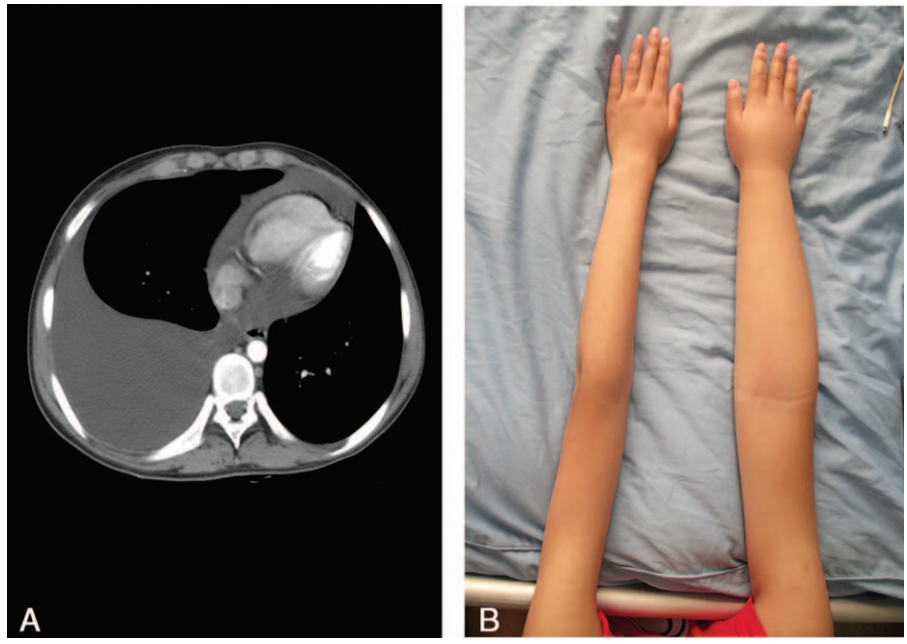

FIGURE 1. (A) The pericardial and pleural effusions. (B) The dramatically swollen right upper limb.

cytoplasmic antibodies, antimitochondrial antibodies type M2, antiliver–kidney microsomal antibodies, antiliver cytosol antibodies type 1, and antisoluble liver antigen antibodies were all negative. No filaria was found in her midnight blood. Fecal occult blood test was positive. Her complete blood count revealed a markedly low total lymphocyte count (560 cells/μL) with a reference range 1100-3200 cells/uL, and the percent distributions of CD3+ T cells and CD4+ T cells were 53% and 22.2%, respectively (reference range is 66.9-83.1% and 33.19-47.85% respectively). Total serum protein was 4.00 g/dL (reference range is 6.50–8.50 g/dL), albumin 2.12 g/dL (reference range is 4.00–5.50 g/dL), globulin 1.88 g/dL (reference range is 2.00–4.00 g/dL), but alpha-1-antitrypsin was within the reference range. Thoracentesis demonstrated a straw yellow transudate effusion with negative culture, cytology findings, and tubercular DNA-PCR. Paracentesis of one hepatic nodule showed a hydropic and a fat degeneration of liver cells with many lymphatic cells and Kupffer cells mingling with them. Ultrasonography of 4 limbs' vessels and heart, gastroscopy, and colonoscopy were all unremarkable. Then a capsule endoscopy was performed and the scattered swollen villi covering on the whole small intestinal mucosa were discovered (Figure 2). Histology of jejunum revealed a series of enlarged lymphatics in mucosa and submucosa (Figure 3) and confirmed the diagnosis of PIL. Further lymphoscintigraphy detected some leakage of radioactivity in her bowel and a poor uptake of ^{99}mTc-human serum albumin in axillary lymph nodes. Intranodal lymphangiography also identified an extremely enlarged left lumbar trunk.

A lifelong, high-protein, low-fat diet supplemented with medium-chain triglycerides (MCT) was prescribed and a tight-fitting stocking was used to control her right upper limb edema. One month later, her total serum protein increased to 5.21 g/dL and albumin 2.97 g/dL. The edemas of lower limbs and right-sided face gradually subsided and the amount of effusions decreased in some degree, while her woody edema remained unchanged.

DISCUSSION

The age of onset of edemas suggests a congenital disorder. The asymmetric edemas (especially the right upper limb lymphedema), unilateral massive pleural effusion, and the severe hypoproteinemia are the most important clinical clues. But the cause of hypoproteinemia is the key to appropriate diagnosis. When the likelihoods of malnutrition, impaired protein synthesis (eg, hepatic dysfunction), chronic wasting diseases

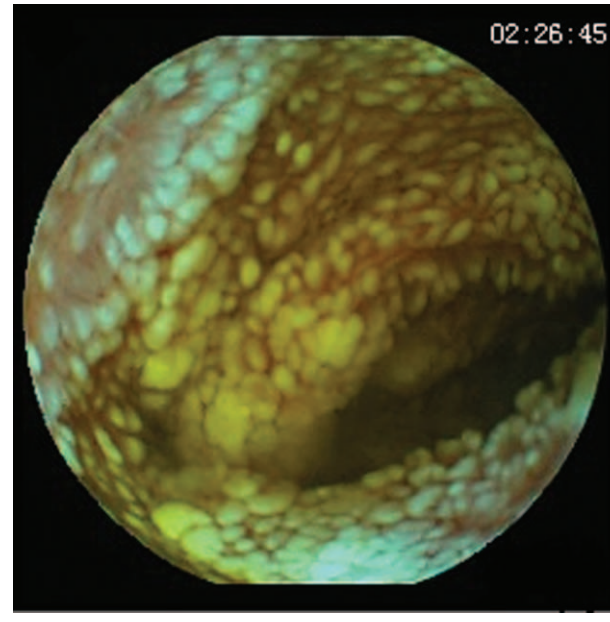

FIGURE 2. Capsule endoscopic findings: the scattered white dots are in fact the swollen villi that make the appearance of cobblestone road.

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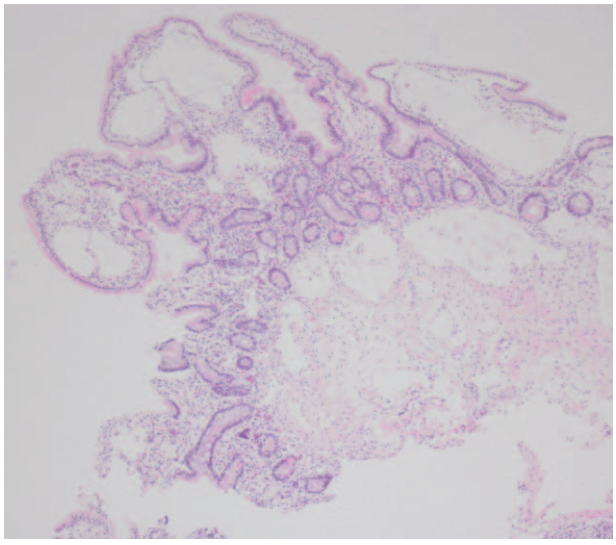

FIGURE 3. Hematoxylin–eosin staining of the jejunum: some extremely enlarged lacteal vessels in mucosa and lymphatic vessels in submucosa (magnification ×100).

(eg, TB or malignancy), and increased protein loss through other organs (ie, liver, kidney, or skin) are low, the increased1 fecal proteins should be considered. This condition is called protein-losing enteropathy and can be confirmed by the elevated 24-hour stool α1-antitrypsin clearance with the exclusion of gastrointestinal bleeding.[1] Because of a positive fecal occult blood test, a test of 24-hour stool α1-antitrypsin clearance was meaningless for our patient.

PIL, a kind of chronic protein-losing enteropathy, is a rare disorder of unknown etiology characterized by diffuse or localized dilation and eventual rupture of the enteric lymphatic vessels in mucosa, submucosa, and/or subserosa. Lymphatic fluid, rich in all kinds of proteins and lymphocytes, leaks into the bowel causing hypoproteinemia and lymphopenia. The main symptom is variable degrees of pitting edemas of bilateral lower limbs. But edemas of any other parts of body, and mild serous effusions may also occur sometimes. Other common features are nausea, vomiting, moderate diarrhea, and failure to thrive. Lymphedema and gastrointestinal bleeding are very rare. Diagnosis relies on characteristic endoscopic changes (diffused swollen villi with appearance of white dots) and is confirmed by corresponding histology of intestinal biopsy.[2,3] Simultaneously, intestinal lymphangiectasia secondary to constrictive pericarditis, intestinal lymphoma, Whipple's disease, Crohn disease, sarcoidosis, intestinal TB, systemic sclerosis, lymphenteric fistula, radiation and/or chemotherapy, HIV-related enteropathy, or Fontan operation should be excluded.[3] A life-long, high-protein, low-fat diet supplemented with medium-chain triglycerides has been proven to be an effective treatment and consists the cornerstone of medical management. Steroids are often prescribed to patients with PIL secondary to inflammatory disease (eg, systemic lupus erythematosus). Ranexamic acid and octreotide have also shown variable benefits in several cases. When medical treatment of PIL has failed and the affected bowl is segmental and localized, small bowel resection remains an option.[1,2,3]

To our knowledge, PIL occurs in conjunction with a hemifacial edema, a unilateral upper limb lymphedema and a unilateral massive pleural effusion seems never to be reported before. Hypoproteinemia-induced effusions and edemas are always bilateral and symmetric. Given that abnormal lymphatics identified by lymphoscintigraphy and lymphangiography, the impaired lymph drainage of right upper limb may be responsible for our patient's right upper limb lymphedema, and the extremely enlarged left lumbar trunk for a severer left calf edema. Pleural, pericardial, and peritoneal effusions may be the result of hypoproteinemia, but the mechanism of unilateral massive pleural effusion remains obscure. Parietal pleural lymphatics play a central role in effusion reabsorption (especially the proteins in effusions). Recently, Luis Valdés et al reviewed nearly 150 patients with yellow nail syndrome (YNS) and found that all patients with pleural effusions had lymphedema. This finding consisted with the theory that recurrent pleural effusion resulted from an impaired lymphatic drainage.[4,5] But unlike YNS, our patient was young, her nails were all normal, and her pleural effusion was transudate with low proteins 1.56 g/dL. So our patient's pleural effusion may be independent of lymphatic abnormality.

Our patient's symptoms affecting different body parts suggested a generalized disorder of lymphatic system. In fact, PIL can be a separate entity or, just a part of a variety of congenital lymphatic system disorders (eg, Hennekam syndrome).[2,3,6] Overall, this disorder can also be termed as type I multisegmental generalized lymphatic dysplasia according to Connell et al's classification system.[7] In 2013, they went further and hypothesized that somatic mosaicism in gene(s) involved in this process based on a low sibling and offspring recurrence risk.[8] But it seems unbelievable that somatic mutation(s) leads to a generalized disorder of the lymphatic system. Maybe multisegmental generalized lymphatic dysplasia is too rare to identify an autosomal recessive family. Other etiologies such as an abnormal embryologic development in its early stage or environmental factors may also be possible.

The FLT4 gene (VEGFR3), one of the most significant genes in lymphangiogenesis, participates in the migration, proliferation, and survival of endothelial cell and its mutations are thought to be responsible for Milroy primary congenital lymphedema.[9] But less than 5% patients with atypical phenotype of Milroy disease (eg, lymphedema in areas other than lower limbs, pleural effusions, or intestinal lymphangiectasia) have mutations in VEGFR3.[10] However, Hokari et al's[11] studies did revealed abnormal expressions of VEGFR3 in the duodenal mucosa from PIL patients. So our patient probably has no mutations in VEGFR3 and this indicates that another mutation in gene(s) may affect the expressions of VEGFR3. Regrettably, genetic analyses were not available.

At last, the diagnoses of lymph system disorders are often in dilemma for normal image checks or serological tests fail to hit the diagnosis. Lymphoscintigraphy can not only identify abnormal lymphatic tree and lymphedemas in limbs but also detect lymph leakage.[3] Intranodal lymphangiography,[12] a technically successful, time-saving, and minimally invasive procedure, seems never to be used among PIL patients, but visualized our patient's lymphatic vessels such as lymphatic trunks and thoracic duct very clearly. Both procedures could be considered when necessary.

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