Primary Pulmonary Lymphatic Flow Disorder Associated Plastic Bronchitis

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Abstract

Background: Lymphatic plastic bronchitis (PB) most commonly occurs in children with congenital heart disease as a result of secondary pulmonary lymphatic flow disorder (PLFD). However, PB caused by primary PLFD is rare. We made a retrospective analysis of two children diagnosed with PB due to primary PLFD, in order to contribute to further understanding of these disorders. Results: Patient 1, an eight-year-old boy, presented with chronic productive cough and expectorated milky-white mucous plugs accompanied by intermitted wheezing for one year. Patient 2, a nine-month-old girl, presented with episodes of acute respiratory distress with expectoration of milky-white bronchial casts for four months. There was no obvious evidence of infection in either child. Bronchoscopy showed massive milky-white casts blocking the airway in patient 2; no casts were observed in patient 1. Bilateral thickening of bronchovascular bundles and interlobular septal, as well as multiple patchy ground-glass opacities were seen on chest computed tomography (CT) in both patients. Lymphangioscintigraphy demonstrated pulmonary lymph reflux in both patients and slowed lymphatic drainage of the lower limbs in patient 1. Primary PLFD was considered for both patients, and a diagnosis of yellow nail syndrome was made in patient 1. Both patients received lymphatic interventional treatment, but all experienced recurrence following the procedure. Conclusions: Primary PLFD is a rare but significant cause of PB in children. Chest CT findings have highly suggestive significance for the diagnosis. The lymphatic interventional procedure may be effective for short-term resolution of symptoms, but prone to recurrence.

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evidence of infection in either child. Bronchoscopy showed massive milky-white casts blocking the airway in patient 2; no casts were observed in patient 1. Bilateral thickening of bronchovascular bundles and interlobular septal, as well as multiple patchy ground-glass opacities were seen on chest computed tomography (CT) in both patients. Lymphangioscintigraphy demonstrated pulmonary lymph reflux in both patients and slowed lymphatic drainage of the lower limbs in patient 1. Primary PLFD was considered for both patients, and a diagnosis of yellow nail syndrome was made in patient 1. Both patients received lymphatic interventional treatment, but all experienced recurrence following the procedure.**Conclusions:** Primary PLFD is a rare but significant cause of PB in children. Chest CT findings have highly suggestive significance for the diagnosis. The lymphatic interventional procedure may be effective for short-term resolution of symptoms, but prone to recurrence.

Key words

pulmonary lymphatic flow disorder, plastic bronchitis, children

Background

Plastic bronchitis (PB) is a rare disease characterized by the expectoration of rubbery, cohesive, and branched bronchial casts that obstruct the airway partially or totally. BP is associated with respiratory disorders such as bronchopulmonary infection, asthma, allergic bronchopulmonary aspergillosis (ABPA), and cystic fibrosis. However, it most commonly occurs in children with congenital heart disease, especially those with single ventricle physiology following the Fontan procedure. Elevation of central venous pressure after the procedure and secondary pulmonary lymphatic flow disorder (PLFD), leading to abnormal perfusion of the bronchial submucosa with lymph and formation of the airway cast [1-2]. 'Lymphatic PB' is used to differentiate it from PB related to other causes[3]. However, PB caused by primary PLFD is rare and the clinical manifestation and severity vary among patients; thus, the diagnosis can be challenging, especially in the absence of chylothorax. In this paper, we report two cases of primary PLFD presenting primarily as PB, in order to contribute to further understanding of these disorders.

Results and Case Presentation

patient 1 An eight-year-old boy presented to our department with a complian of chronic productive cough, expectorated milky-white mucous plugs, resembling bronchial casts every 4-5 days (Figure. 1A), accompanied by intermitted wheezing for 1 year. Treatment of antibiotics, inhaled corticosteroids and brinchoidilaters fail to control the symptoms. His medical history revealed recurrent pneumonia as well as intermitted wheezing from two years of age, and he was diagnosed with asthma. His mother noticed the slow yellowing and thickening of the first toenail on his right foot about three years ago. The nail changes had been interpreted as onychomycosis. He had no history of trauma or surgery. On physical examination, he was normally developed; slight shortness of breath was noticed with a respiratory rate of 28 breaths/min and oxygen saturation of 97% on room air. Chest auscultation showed decreased air entry at the left lung base. The first toenail on his right foot had been removed before presentation to the hospital and a small and yellowish new toenail was observed (Figure. 1B). There was no peripheral edema, and the remainder of his examination was unremarkable.

The patient's white blood cell (WBC) count, eosinophil count, and C-reactive protein (CRP) were normal. The serum levels of aspergillus specific IgE, 1,3-β-glucan, and galactomannan were normal. Antineutrophil cytoplasmic antibodies, antinuclear antibodies, and rheumatoid factor were all negative. Sputum cultures were positive for*Candida albicans* , while bacterial and mycobacterium cultures were negative. Fungal microscopic examination and culture of the first toenail were negative. Serial chest computed tomography (CT) revealed migratory patchy ground-glass opacities and focal mild bronchiectasis with mucus impactions. Bronchoscopy showed that the airway mucosa was rough and swollen, with thin white secretions attached; however, no casts were observed. The bronchial lavage fluid (BALF) was slightly milky-white and turbid; fluid cultures showed no pathogens. BALF cell composition analysis was as follows: small lymphocytes 60%, macrophages 20%, exfoliated epithelial cells 20%. The pulmonary function test showed mild obstructive

ventilatory disturbance and the bronchodilation test was negative. An echocardiogram showed no abnormalities.

Suspicion of allergic bronchopulmonary mycosis (ABPM) was arised after the patient's admission. He was treated with fluconazole (8 mg/kg.d) and prednisone (1 mg/kg.d, gradually decreased to 0.5 mg/kg.d) for three weeks. However, his cough and expectoration of mucous plugs worsened. Repeated chest CT showed the progression of lung lesions with bilateral thickening of bronchovascular bundles, multiple patchy ground-glass opacities, and interlobular septal thickening, mainly in the middle-inferior lung, indicating pulmonary lymphatic stasis (Figure. 1C). Evaluation of the lymphatic system by lymphangioscintigray was performed subsequently and the results demonstrated slow lymphatic drainage in both lower limbs, abnormal distribution of the radiotracer in the bilateral hilar and lungs, suggesting pulmonary chylous reflux. Moreover, continuous widening of the left venous angle and the radiotracer was retained in the proximal end of the thoracic duct were observed, suggesting thoracic duct obstruction (Fig. 1D).

Based on the patient's clinical picture, medical history, chest CT and lymphangioscintigraphy findings, in addition to the yellow toenail on his right foot, the patient was finally diagnosed with yellow nail syndrome (YNS) and lymphatic PB. He was treated with a low-fat diet and percutaneous embolization of the thoracic duct was performed three weeks later. His respiratory symptoms were relieved. However, three months after the surgery, he experienced recurrence of bronchial cast expectoration. His parents refused further evaluation and treatment as he had developed no other symptoms.

Patient 2 A nine-month-old girl was referred to our department for episodes of acute respiratory distress with cough and expectoration of milky-white bronchial casts requiring bronchoscopy treatment for 4 months. During the course of the disease, there was no obvious fever. She had been admitted to the local intensive care unit and required mechanical ventilation two times because of severe bouts of dyspnea. Bronchoscopy demonstrated many milky-white casts blocking the airway (Figure. 2A); these were extracted by aspiration and her dyspnea and hypoxemia can be temporarily relieved. Chest CT demonstrated diffuse thickening of the interlobular septa and bronchovascular bundles, left partial atelectasis and consolidations, as well as enlargement of the mediastinum and hilar lymph nodes (Figure. 2B). Diagnoses of severe pneumonia and PB were made. However, despite vigorous therapy with antimicrobials (including antifungal drugs), intermittent systemic and inhaled glucocorticoids, and intravenous immunoglobulin, she continued to exhibit chronic expectoration of bronchial casts and episodes of acute respiratory distress requiring bronchoscopy to clear the airways about every two weeks. Her birth history was normal. She had normal development and no history of trauma or surgery. Physical examination revealed tachypnea, a respiratory rate of 42 breaths/min, and oxygen saturation of 90% on room air. Chest auscultation showed bilateral moist rales and wheezing. Heart auscultation and the remainder of her examination was unremarkable.

The patient's WBC count, eosinophil count, hemoglobin, and CRP were normal. Sputum and BALF cultures showed a small amount of*Klebsiella pneumoniae.* Serum and nasopharyngeal aspiration for influenza virus, adenovirus, and mycoplasma detection were all negative. The echocardiogram showed no abnormalities. Abdominal ultrasound showed multiple cysts of the spleen. Lymphangioscintigraphy was performed subsequently and revealed thoracic duct obstruction, abnormal distribution of the radiotracer in the bilateral hilar and lungs, suggesting pulmonary chylous reflux (Figure. 2C).

Given her early age of onset, congenital lymphatic dysplasia was considered. Splenic cystic lesions were observed on abdominal ultrasound, suggesting extrathoracic involvement. The child was treated with high medium-chain triglycerides (MCT) milk powder, and oral rapamycin was administered (0.8-1 mg/m^2.d). Her symptoms had gradually improved and there were no further episodes of acute dyspnea for one month. Serum sirolimus levels were maintained at 8-13 ng/mL without any adverse reactions. Because the patient was still coughing up casts intermittently, percutaneous lymphatic intervention was performed (thoracic duct and right lymph duct outlet compression band loosening and stenotic adventitia stripping). Unfortunately, on postoperative day ten, she was readmitted with acute respiratory distress requiring emergent intubation. Bronchoscopy demonstrated that tenacious bronchial casts were obstructing the airways. After a series of bronchoscopies, her acute respiratory distress could not be alleviated, and thus, surgical ligation of the

thoracic duct was performed. Her respiratory symptoms gradually improved. Currently, four months post-surgery, she is asymptomatic.

Discussion

PLFD involves abnormal lymphatic flow via the lymphatic channels to the lungs and pleural space; this disorder has been described as pulmonary lymphatic perfusion syndrome (PLPS) [4]. PLFD commonly occurs in children with congenital heart disease and primary lymphatic dysplasia, including diffuse pulmonary lymphangiomatosis, primary pulmonary lymphangiectasis, and lymphatic dysplasia syndrome (i.e., YNS, Noonan syndrome). The main complication of PLFD is chylothorax; more rarely, accompanied by lymphatic PB. This study describes two cases of primary PLFD presenting as PB in the absence of chylothorax.

YNS is a rare disorder characterized by thickened yellow nails, primary lymphedema, and respiratory manifestations. The etiology of YNS remains unclear; however, a unifying lymphatic mechanism characterized by anatomical and/or functional lymphatic drainage abnormalities has been proposed [5-6]. The main respiratory system manifestations are bronchiectasis and pleural effusion, and about 20% of the pleural effusion cases are chylothorax [7-8]. In the current study, patient 1 presented with a chronic cough and expectoration of milky-white mucous plugs resembling bronchial casts, but without pleural effusion and lymphedema. The nail changes on the first toe had been interpreted as onychomycosis and had been removed before admission. Thus, the consideration of chyloptysis and YNS are challenging, resulting in a long diagnosis delay. To our knowledge, this is the first report of YNS presenting as lymphatic PB which further supports a lymphatic mechanism of YNS. The age at onset of patient 2 was early infancy; she had normal development and no history of other diseases, suggesting congenital lymphatic dysplasia. Diagnostic pulmonary biopsy was not performed because of the risk of massive chyloptysis or refractory chylothorax [9-10].

The clinical symptoms of lymphocytic PB are nonspecific and vary from case to case. Productive cough, wheezing, shortness of breath, and dyspnea are the most common manifestations and may be misdiagnosed as asthma, recurrent pneumonia, or other respiratory diseases. In the current study, patient 1 has been diagnosed with asthma and recurrent pneumonia, but inhaled corticosteroids and bronchodilators, as well as anti-infection therapy, failed to control the symptoms. ABPM was aslo suspected in patient 1; however, oral corticosteroids combined with antifungal treatment were ineffective. Patient 2 had been misdiagnosed as severe pneumonia. The casts produced by patient 1 and patient 2 were large, highly branched, and had multi-antennary structures; while the smaller and simpler structures with fewer branches are always seen in nonlymphocytic casts[3].

The chest CT findings, even if non-specific, were highly suggestive of PLFD. The typical findings include smooth thickening of the interlobular septa and bronchovascular bundles, patchy ground-glass opacities, mediastinal and hilar masses, as well as pleural effusions[11-12]. Our two cases both had features suggestive of PLFD. Pulmonary lymphatic flow disorder was demonstrated by lymphoscintigraphy in both children. Lymphoscintigraphy has been widely considered as the main investigation to establish a diagnosis of lymphatic flow disorder; it has a high sensitivity of about 95%, a specificity of 100%, and can be used to visualize the functional status of the lymphatic system [13-14].

Due to the rarity of PLFD, there are no standardized treatment protocols. Dietary treatments, such as total low-fat and high MCT diets, have generally proven to be minimally effective. Systemic glucocorticoids, recombinant interferon, and chemotherapeutic agents have been tried with variable outcomes; these treatments are largely limited by their toxicity [15]. Recently, treatments with the mTOR inhibitor sirolimus have been shown to be effective in patients with lymphatic malformations and those with vascular malformations with a lymphatic component, with good tolerability and few side effects[16-17]. In the current study, patient 2 received diet and sirolimus treatment only for one month and exhibited gradual improvement in her symptoms, thus the efficacy of these treatments could not be fully evaluated. It has been reported that percutaneous embolization of abnormal pulmonary lymphatic vessels in pediatric patients with a single-ventricle and in adult patients with PB results in alleviation of the symptoms [3, 18]. However, the two children in the current study both had recurrence of casts after the lymphatic interventional procedure. Reasons for the recurrence

might be associated with congenital lymphodysplasia, abnormal generation and proliferation of lymphatic vessels, and collateral development.

In conclusion, primary PLFD is a rare but important cause of PB in children. The clinical symptoms of lymphocytic PB are nonspecific; thus, the diagnosis may be long delayed, especially in the absence of chylothorax. Chest CT findings have highly suggestive significance for the diagnosis. Lymphatic interventional procedure may be effective for short-term resolution of the symptoms, but prone to recurrence.

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Conflicts of interest

All authors declare that there are no conflicts of interests.

Ethics statement

The patients' parents gave their informed consent for the publication of this

case report.

Authors' contributions

XYZ was involved in diagnosis and treatment of both patients and drafted the initial manuscript. HX and HMY were involved in the diagnostic process of the patients. JRL and SYZ were responsible for the diagnosis and treatment of both patients, and revised the manuscript. All authors read and approved the final manuscript.

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Figure legends

Figure 1. Patient 1. A, Expectorated large mucous plugs. B, Yellow toenail on the right foot. C, Chest CT showing interlobular septal thickening and multiple patchy ground-glass opacities. D, Lymphoscintigraphy obtained 3 hours after injection reveals excessive accumulation of the radiotracer in the bilateral hilar and lungs.

Figure 2. Patient 2. A, Extracted bronchial cast with preservation of subsegmental airway divisions. B, Chest CT demonstrates diffuse thickening of the interlobular septa and bronchovascular bundles, left partial atelectasis and consolidations, enlargement of the mediastinum and hilar lymph nodes. C, Lymphoscintigraphy obtained 3 hours after injection reveals excessive accumulation of the radiotracer in the bilateral hilar and lungs.