Lengthy Diagnostic Challenge in a Rare Case of Pulmonary Veno-Occlusive Disease: Case Report and Review of the Literature

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Abstract

Pulmonary veno-occlusive disease (PVOD) is a rare and usually survival poor disorder. We report a patient with a long history of progressive dyspnea of over 8 years, who with a diagnosis of chronic cor pulmonale confirmed elsewhere, was ultimately diagnosed as PVOD via histological analysis of a lung biopsy. After treatment with combined bosentan, diuretics and digoxin, his symptoms and function improved. This case highlights that PVOD is an under-recognised and often misdiagnosed disease, especially in its chronic form. Understanding its pathogenesis, its poor response to medical therapy and its dismal prognosis remain challenges for the treatment of PVOD.

Key words: pulmonary hypertension, pulmonary veno-occlusive disease, lung biopsy, bosentan

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Introduction

Pulmonary veno-occlusive disease (PVOD), also currently classified as a subgroup 1’ of PAH, is a rare cause of pulmonary hypertension. It is a clinicopathologic syndrome characterized by a progressive obstruction of small pulmonary veins that leads to an elevation in pulmonary vascular resistance and right ventricular failure (1). A review of the English literature from 1934 when a well-documented case was first described by Hora et al to 2010 yielded fewer than 200 patients (2). In spite of great advances related to pulmonary hypertension, including pathogenesis, diagnostic approach and treatment strategies during the last thirty years, PVOD survival is still poor with a mean length of 49 months from symptom onset to diagnosis and death within 2 years after diagnosis (3). Here, we report a surgical lung biopsy finding of PVOD in a patient who suffered from progressive dyspnea for 8 years and is still alive now.

Case Report

A 40-year-old male xanthoderm patient was admitted to our hospital in August 2009, because of progressive dyspnea for more than 8 years and worsening symptoms for 6 months. Since April 2002, his symptoms of dyspnea on great exertion began, but they were alleviated with rest. At that time, a chest x-ray revealed signs of pulmonary arterial hypertension (Fig. 1a). Because the patient’s symptoms were mild, further testing and treatment was not performed. Over the next five years, his symptoms of exertional dyspnea progressed and were accompanied by intermittent lower extremity edema, cyanosis and digital clubbing. In March 2007, he was referred to a respiratory medicine department of a hospital, and chronic cor pulmonale was diagnosed and treated with oxygen therapy and diuretics. He was referred to our hospital (August 2009) for respiratory failure which had developed after 6 months of worsening dyspnea. He had a history of smoking 40-50 cigarettes/day for 20 years. He had no other reported respiratory symptoms such as cough, expectoration, fever, hemoptysis, chest pain or syncope, and no history of chemotherapy, bone marrow transplantation or hematopoietic blood stem cell transplantation.

Physical examination revealed a heart rate at 98 bpm, a blood pressure of 100/60 mmHg and a respiratory rate at 22 breaths/min. The patient had some signs of fluid overload,
such as jugular vein distension and lower extremity edema and was in functional New York Heart Association (NYHA) class 4. Upon laboratory testing, arterial blood gases revealed severe hypoxemia (pH 7.41, PaCO₂ 36 mm Hg, PaO₂ 46 mmHg and SO₂ 82% in room air). In late August 2009, pulmonary function testing identified severely restrictive ventilatory defects (MVV 49% of predicted value) and a marked reduction in CO diffusion (DLCO/alveolar volume ratio of 0.41 mmol/min/kPa/L; 25.5% of predicted value). The electrocardiogram revealed a sinus rhythm at 98 bpm, electrical axis at 140°, right atrial and right ventricular hypertrophy and complete right bundle branch block. M-mode, 2D and Doppler echocardiography confirmed dilatation of both the right atrium and right ventricle (diameter of right atrium: 59 mm, ventricular dimensions: 41 mm), thickening of the right ventricular wall (previous wall thickness: 6 mm), widened pulmonary artery (diameter: 29 mm) and normal left ventricular function (left ventricular ejection fraction of 80%). Tests for connective tissue diseases, HIV infection and chronic pulmonary embolism were all negative.

On the first day of the patient in hospital, his posteroanterior chest x-ray (Fig. 1b) demonstrated bilateral hilar enlargement, a prominent medial arch and pulmonary artery trunk and a diffuse micronodular pattern with ground-glass opacities. Same date, a high-resolution computed tomography (HRCT, Fig. 1c) of his chest revealed thickened septal lines, fissural thickening and diffuse mosaic ground-glass opacities. No enlarged hilar lymph node and/or mediastinal lymph node was observed. CT pulmonary angiography (CTPA, Fig. 1d) identified an enlarged pulmonary trunk and no signs of pulmonary embolism.

After admission to our hospital, he was treated with continuous oxygen, diuretics and anticoagulation, but the dyspnea symptoms did not obviously improve. Based on his progressive increasing dyspnea, his physical signs of severe pulmonary hypertension, his CTPA that excluded chronic thromboembolic pulmonary disease and his low DLCO and high-resolution computed tomography findings, we suspected a diagnosis of idiopathic pulmonary arterial hypertension (PAH), pulmonary veno-occlusive disease (PVOD) or
pulmonary capillary hemangiomatosis (PCH). Surgical lung biopsy was required for a definitive diagnosis, but the procedure would have risked worsening his respiratory failure. However, for the purpose of definitive diagnosis and to guide the appropriate treatment, the patient consented to a thoracoscopic lung biopsy after balancing the benefits and risks of a surgical lung biopsy. In late September 2009, after some symptoms improved by medical treatment, a lung biopsy thoracoscopy was performed for histological study.

Histological examination of the lung biopsies (Fig. 2) identified arterial lesions, intimal proliferation, fibrous thickening, obstruction and arterialisation of the septal and pre-septal pulmonary veins. Muscular arteries could also be found with marked intimal fibrosis and adjacent bronchioles. Some lobules presented with an oedematous interlobular septum. In particular, large amounts of alveolar hemorrhage and hemosiderosis were present within the interstitial space. On the basis of these pathological findings and clinic features, the patient was diagnosed as PVOD.

Given that lung transplantation is considered the only possible therapeutic alternative, it was offered to prolong his life, but the patient declined. Therapy was continued with diuretics in addition to bosentan (62.5 mg twice a day). After one additional month of treatment, the patient presented with significant functional improvement and was in NYHA class 3. In late October 2009, blood gas analysis showed pO2 (room air) of 62 mmHg and pCO2 of 38 mmHg. Despite our advice, the patient insisted on being discharged in early November 2009. Although his symptoms of progressive dyspnea have become intermittently aggravated during the follow-up period from April to September 2010, the patient is currently alive.

**Discussion**

PVOD is a usually fatal condition in which there is a gradual obliteration of the pulmonary veins and venules. Clinical manifestations vary according to the size and location of the vascular lesions and the right ventricular dysfunction symptoms resulting from the progressive elevation of pulmonary vascular resistance. Due to its clinical features, laboratory data and the fact that radiologic manifestations are not specific (4), a PVOD misdiagnosis or missed diagnosis frequently occurs, exhibited by the fact that this patient 7 years previously had been misdiagnosed elsewhere as chronic cor pulmonale. Although a definitive diagnosis depends on the histological analysis of a lung sample, a better understanding of different clinical presentations of PVOD patients should increase the clinical suspicion and help reduce the misdiagnosis or missed diagnosis rates.
There are three features of the present case that suggest PAH: 1) marked right heart failure occurring in the late phase of the disease; 2) the progressive dyspnea accompanying intermittent radiological alterations suggestive of pulmonary edema, and 3) normal left heart function. These clinical and imaging results, in our opinion, suggest some form of capillary, venule or small arterial disease. Further non-invasive diagnostic test results for the case, including the marked reduction in CO diffusion on pulmonary function testing and severe hypoxemia without simultaneous CO2 increase in the arterial blood gas, helped to confirm a diagnosis of PVOD from PAH (5-7). Additionally, some other characteristic findings, which were absent in this patient, include septal lines and/or mediastinal lymph node enlargement on the HRCT of the chest; furthermore, the presence of hemosiderin-laden macrophages and a higher Golde score on bronchialveolar lavage was also helpful to diagnose PVOD (7).

Several risk factors for PVOD have been proposed that may be etiologically related, such as HIV infection (8), sarcoidosis and pulmonary Langerhans cell granulomatosis (9, 10), chemotherapy (11), bone marrow transplantation and hematopoietic blood stem cell transplantation (12, 13), collagen vascular disease and genetic factors (14, 15). There was no indication of a possible cause for the present patient based on medical, familial history, clinical and serological findings. In addition, regarding BMPR2, the gene for bone morphogenetic protein receptor type II mutation, it was reported that BMPR2 mutations are present in 50% of familial cases and responsible for dysregulated vascular proliferation and remodeling (16, 17). Although no other similar patient was found in the case family, further analysis for BMPR2 mutation is important to understand their gene phenotype. Interestingly, the association between tobacco exposure and PVOD has also been revealed; Wright et al noted that tobacco exposure may contribute to pulmonary vascular injury, and these injurious effects are likely the result of upregulated gene expression of various vasoactive mediators (18). Thus, the present patient had a long history of smoking that might have contributed to the etiology of his PVOD.

In most cases, the prognosis of PVOD is harrowing despite effective therapeutic interventions. Data show that the one-year mortality rate may be as high as 72% for PVOD (7), and few patients can be expected to survive more than two years from their first symptoms until either death or lung transplantation (3). Surprisingly, this patient’s symptoms of progressive dyspnea existed for more than seven years until a definitive diagnosis. The prognosis is correlated with the degree of narrowed or occluded pulmonary veins and venules that frequently result in right ventricular dysfunction and pulmonary edema. In this case, the histological study showed that the septal and pre-septal pulmonary veins were predominantly significantly narrowed but not so severely narrowed to exhibit complete luminal obliteration. Thus, we speculate that this may have been due to a slowly progressing delayed course of disease; the exact cause is still unclear.

To date, there have not been classic medications to cure PVOD. Lung transplantation or heart and lung transplantation are the only effective ways to treat PVOD. According to some case reports, different specific PAH therapies (i.e., epoprostenol, bosentan and calcium channel blockers) have a risk of pulmonary vasodilator-induced pulmonary edema when taken without precautions (19). However, there have also been isolated instances of cases successfully managed using drug regimens (20, 21). In the present case, we used a drug regimen of bosentan (a non-selective endothelin antagonist) in combination with diuretics and digoxin to treat the patient and relieve his symptoms. The combination seemed to reduce lymphatic and venous congestion, thereby reducing the risk of hemodynamic complications, and it may have contributed to improvements in his clinical status and slowed disease progression (6), as described above (20).

In summary, this case demonstrates that PVOD is a rare disease with a variety of clinical manifestations and misdiagnosis is relatively common. A case history and general tests (i.e., arterial blood gases, chest x-ray, HRCT and pulmonary function tests) can provide clues to suspect PVOD, but a definitive diagnosis still relies on a histological examination. Although some PAH-specific therapies are perhaps harmful for patients with PVOD, if lung transplantation is impossible, bosentan combined with diuretics and digoxin, used cautiously, may be helpful for some patients. Nevertheless, further evaluation is still needed. In addition, this long-term case history highlights the possibility of surviving longer than two years with PVOD.

The authors state that they have no Conflict of Interest (COI).

References


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