Case Report

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Dyspnoea and diffuse pulmonary nodules in a patient with pulmonary veno-occlusive disease: a case report and literature review

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Abstract

Pulmonary veno-occlusive disease (PVOD) is a rare type of pulmonary hypertension characterized by capillary damage or arterial pulmonary hypertension. Early lung transplantation is the only effective treatment for PVOD because of the lack of specificity in its clinical manifestations and its rapid progression and poor prognosis. A 28-year-old woman presented with exertional dyspnoea. A chest computed tomography scan revealed diffuse centrilobular ground glass opacities in both lungs, a ratio of the transverse diameter of the main pulmonary trunk to the ascending aorta of >1, and enlargement of the right ventricle and right atrium. A right atrial floating catheter test showed right ventricular pressure of 82/0/4 mmHg, mean pulmonary artery pressure of 83/34/53 mmHg, and pulmonary artery wedge pressure of 15/8/12 mmHg. A mutation was found in the eukaryotic translation initiation factor 2 alpha kinase 4 (*EIF2AK4*) gene. Thus, the patient was diagnosed with PVOD and subsequently given standard bosentan treatment (62.5 mg twice a day). However, after 6 months of follow-up, there was no significant improvement in the pulmonary artery pressure or activity tolerance (6-minute walking test). Therefore, cardiopulmonary transplantation was performed. Early diagnosis and timely treatment of PVOD may improve the patient's prognosis.

Keywords

Pulmonary veno-occlusive disease, dyspnoea, diffuse pulmonary nodules, case report, computed tomography, genetic mutation

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Introduction

Pulmonary veno-occlusive disease (PVOD) is a rare type of pulmonary hypertension (PH) (a subgroup of arterial PH) characterized by specific damage to the pulmonary capillaries and venous system.[1,2] The pathology is typically characterized by diffuse vasculopathy of venules as well as dilatation and angioproliferation of alveolar capillaries. This leads to occlusion of small pulmonary capillaries and pulmonary veins, a gradual increase in pulmonary vascular resistance and PH, and finally right heart failure and death.[3]

PVOD is classified as a subgroup of Group 1 PH. It has an extremely low incidence and is considered to constitute only 5% to 10% of the histological subtypes of PH.[4] Although cases of PVOD were well documented 80 years ago, and despite great progress having been made in gene, cell, and molecular biology in recent years, most doctors still do not fully understand the pathophysiological changes and clinical features of PVOD. Despite discrepancies in its anatomical and histological patterns as well as its rapid progression and poor prognosis, PVOD has clinical manifestations very similar to those of other types of PH.[5] Moreover, there is currently no effective drug therapy for PVOD, and early lung transplantation is still the only effective treatment. Therefore, early diagnosis and timely treatment are particularly important.

A patient with PVOD was admitted to our hospital in February 2019. We herein report this case in combination with a review of the recent literature to improve the understanding of this disease among clinicians.

Case presentation

Chief complaints

A 28–year–old woman was admitted to the Affiliated Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology in 2019 (Wuhan, China) for further evaluation of dyspnoea. Her chief complaint was a 6-month history of exertional dyspnoea and a 1-week history of aggravation with coughing and expectoration. She had no fever, haemoptysis, wheezing, or other abnormalities.

Medical history

The patient had no history of hypertension, diabetes, or heart disease; however, she had a history of a pregnancy complicated with hypertension in 2011.

Personal and family history

The patient had no family history suggestive of a genetic syndrome, no history of exposure to toxic chemical products, and no current employment.

Physical examination

The patient's vital signs upon presentation were as follows: body temperature, 36°C; respiratory rate, 25 breaths/minute; pulse, 98 beats/minute; and blood pressure, 100/70 mmHg. No obvious cyanosis of the lips or obvious jugular vein filling was present. Low respiratory sounds were present in both lungs, and no dry or wet rales were present. The patient had no obvious heart arrhythmia, but accentuation of the second heart sound present; no murmurs in the auscultation area of the heart valves; and no oedema in the lower limbs. The result of the 6-minute walking test was 160 m.

Laboratory examinations

A routine blood examination produced the following results: haemoglobin concentration, 98 g/L; leucocyte count, 8.53×10^9/L; and neutrophil count, 6.34×10^9/L. A complete coagulation panel showed the following: prothrombin time, 16.2 s; international

standardized ratio, 1.31; D-dimer concentration, 0.57 μg/mL; erythrocyte sedimentation rate, 10 mm/h; C-reactive protein concentration, 4.8 mg/L; N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration, 2050 ng/L; immunoglobulin E concentration, 11.38 IU/mL; and thrombotic disease screening, negative. The test results for troponin, liver and kidney function, electrolyte, rheumatism, human immunodeficiency virus, rheumatoid, anti-condensate antibody, antineutrophil cytoplasmic antibodies, and immunity were normal, and a T-SPOT.TB test was not reactive. Arterial blood gas analysis indicated hypoxaemia.

Imaging and other examinations

Echocardiography showed that the right ventricle and right atrium were enlarged and that the pulmonary artery pressure was increased (75 mmHg). Lung function testing revealed that the end-stage expiratory flow rate was mildly decreased. The pulmonary dispersion was moderately decreased (diffusing capacity of the lungs for carbon monoxide, 54%; forced vital capacity (FVC), 3.05 L; forced expiratory volume in 1 s (FEV1), 2.47 L; and FEV1/FVC ratio, 81%). Pulmonary computed tomography (CT) showed diffuse centrilobular ground glass opacities in both lungs and thickened septa of both lower lobes. The ratio of the transverse diameter of the main pulmonary trunk to the ascending aorta was >1, and the right ventricle and right atrium were enlarged. Contrast-enhanced CT confirmed no pulmonary embolism (Figure 1).

A bronchial lung specimen was obtained by transbronchial lung biopsy (TBLB). The results showed diffuse vasculopathy of venules and dilatation and angioproliferation of alveolar capillaries (Figure 2). A right atrial floating catheter test showed the following results: right atrial pressure, 6/−1/2 mmHg; right ventricular pressure, 82/0/4 mmHg; mean pulmonary artery pressure, 83/34/53 mmHg; pulmonary artery wedge pressure (PAWP), 15/8/12 mmHg; cardiac output, 5.87 L/min; cardiac index, 3.89 L/min/m^2; and pulmonary vascular resistance, 6.92 Wood units. We considered a diagnosis of isolated pre-capillary PH. Eukaryotic translation initiation factor 2 alpha kinase 4 (*EIF2AK4*) gene mutation detection was performed, and a mutation was found in the 7th base site of *EIF2AK4* exon 11.

Final diagnosis

Based on the combination of the above-described laboratory findings and typical CT imaging findings, the patient was diagnosed with PVOD.

Treatment

The patient was given standard bosentan treatment (62.5 mg twice a day). However, after 6 months of follow-up, no significant improvement was found in her pulmonary artery pressure or activity tolerance (6-minute walking test, 150 m; NT-proBNP, 2187 ng/L). Therefore, we recommended consultation with the transplantation surgery department for lung transplantation.

Outcome and follow-up

The patient underwent cardiopulmonary transplantation. She recovered with no complications. At the 1-month follow up, the patient was clinically well. Echocardiography showed that her pulmonary artery pressure was 35 mmHg, and her NT-proBNP concentration had decreased to 843 ng/L.

Discussion

PVOD is a rare subgroup of Group 1 PH that is difficult to diagnose. The prevalence of PVOD is difficult to objectively evaluate

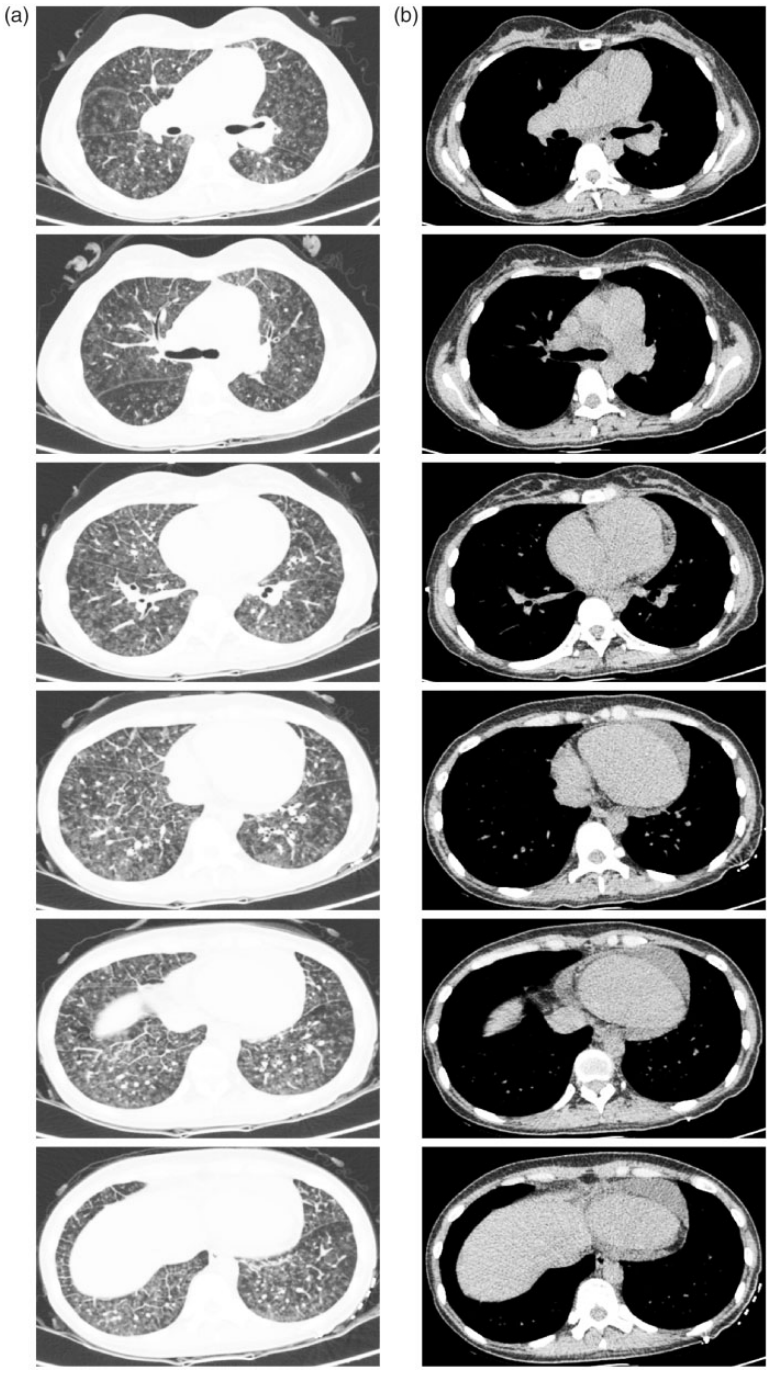

Figure 1. Imaging findings. (a) A chest computed tomography scan revealed diffuse grated hyaline nodules in both lungs with thickened septa of both lower lobes, a ratio of the transverse diameter of the main pulmonary trunk to the ascending aorta of >1, and enlargement of the right ventricle and right atrium. (b) Mediastinal window of (a).

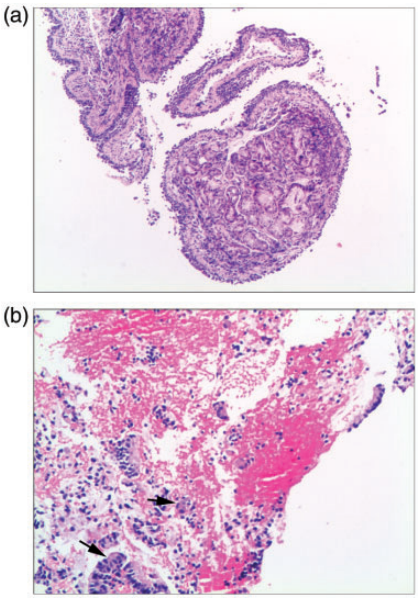

Figure 2. Histological findings of lung biopsy. Haematoxylin and eosin-stained samples of the transbronchial lung biopsy specimen are shown. (a) 100×. (b) 200×.

because of the low incidence, nonspecific clinical manifestations, and high rates of misdiagnosis and missed diagnosis of this disease.[6] In a previous study of PVOD, the patients' age at onset showed a relatively wide range, and the disease was reported from birth to the age of 70 years.[7] PVOD affects both sexes, but the incidence of genetically related PVOD is slightly higher in young women. Most patients with sporadic PVOD are older men at the time of diagnosis.[8]

The aetiology of PVOD is unclear. Previous reports have suggested that although PVOD has no obvious genetic tendency, it has a significant genetic background. Troussard et al.[9] found a double-allele, autosomal recessive mutation in the eukaryotic translation promoter *EIF2AK4* in a family with PVOD. *EIF2AK4* mutations cause a large number of protein-coding mutations or nonsense mutations, leading to widespread loss of protein function that promotes the development of PVOD. Many studies have confirmed that *EIF2AK4* mutations are the main cause of hereditary PVOD.[10] Studies have also shown that environmental exposure is closely related to the disease, and PVOD has been reported after the application of multiple chemotherapy regimens, including bleomycin, cyclophosphamide, and mitomycin.[11] French PH researchers recently found PVOD in patients with anal squamous cell carcinoma treated with mitomycin C alone or with 5-fluorouracil.[12] Moreover, the authors successfully used mitomycin to induce PVOD in animal models,[12] but the mechanism is not yet clear. The same study also showed that trichloroethylene was closely related to the onset of PVOD and that patients with a positive history of exposure had an older age at onset and no mutations in the *EIF2AK4* gene.[12] Smoking has also been found to aggravate PVOD, possibly because of injury to the pulmonary venule endothelium.[13]

Increasing numbers of studies are showing that connective tissue disease and inflammation-related diseases are also closely related to PVOD. In patients with PH associated with connective tissue disease (especially systemic sclerosis), significant venous involvement can lead to the occurrence of PVOD. PVOD is also reportedly associated with other inflammatory diseases, such as sarcoidosis, Langerhans cell histiocytosis, and Hashimoto thyroiditis.[14] However, the exact cause of PVOD has not yet been determined.

The present case involved a young woman with no history of exposure to the above-mentioned chemical drugs, no tobacco exposure, no connective tissue disease, and no inflammatory disease. However, she had a mutation in the *EIF2AK4* gene, which may have been the main cause of her condition.

The typical pathological features of PVOD are diffuse vasculopathy of venules along with dilatation and angioproliferation of alveolar capillaries.[15] With the development of PVOD-related vascular lesions, the extent of intimal remodelling of the venules varies. In the early stage, the intima is loose and giant cells gather. Calcified plaques may appear in the elastic fibres of the venous wall, presenting as dark pigmented deposits with severe lumen obstruction in the later stages. The alveolar capillaries dilate and fill because of downstream obstruction. Vascular hyperplasia is prominent. The lymphatics of the lung and pleura are dilated. The interstitium is characterized by oedema, some occult lung haemorrhage, and infiltration of alveolar macrophages and type II lung cells with deposition of large amounts of haemosiderin. The interstitial oedema and haemosiderin deposition along the interlobular septa and its distribution in the interstitium eventually progresses to fibrosis.[16]

In the present case, the patient showed widened alveolar septa, interstitial oedema, fibrous connective tissue hyperplasia, granulomatous changes, and focal cellulose necrosis and haemorrhage, all of which are consistent with the pathological manifestations of PVOD. Because of the small amount of tissue sampled, no lumen stenosis or occlusion caused by typical pulmonary venule intimal fibrosis were observed by microscopic examination.

Although the pathological changes of typical PVOD are easy to understand theoretically, lung biopsies are not common in practical clinical work, and sampling the lung tissues is extremely high-risk when the pulmonary artery pressure is significantly increased and combined with haemorrhage. Thus, few lung biopsy specimens are available in such patients, and the pathological changes associated with PVOD have no gold standard for pathological confirmation. Therefore, it is difficult to carry out objective clinical practice based on the lung pathology. TBLB is contraindicated in patients with PVOD because of the high risk of bleeding.

In the present case, the patient had obvious PH; thus, we considered this a cardinal manifestation. Based on the combination of the auxiliary examination results and her clinical manifestations, we excluded left heart disease and PH caused by chronic thromboembolism. Moreover, the patient had no history of drug or toxicant exposure, no evidence of connective tissue disease, no human immunodeficiency viral infection, and no objective evidence of portal hypertension, congenital heart disease, schistosomiasis, chronic haemolytic anaemia, or other common causes of PH. The differential diagnoses of her PH that we considered after admission included idiopathic PH, lung disease, and cancer. Thus, TBLB was performed.

PVOD has the same clinical symptoms and signs as other types of PH, which cannot be identified clinically simply from the symptoms and signs. As with other types of PH, typical symptoms of PVOD include exercise-induced dyspnoea, chest pain, dizziness or syncope, and haemoptysis in some patients.[17] Other symptoms include coughing, expectoration, palpitations, and fatigue. Patients and physicians often ignore the lack of symptom specificity, frequently leading to diagnostic delays. As the disease progresses, the right heart function becomes involved. The common signs of decompensated PVOD are a right ventricular bulge, hyperactivity of the second heart sound, systolic tricuspid regurgitation, and obvious right heart failure.

Clinically, PVOD should be distinguished from other types of pulmonary artery hypertension (PAH), especially idiopathic PAH. Both idiopathic PAH and PVOD are characterized by elevated pulmonary artery pressure, but the pulmonary capillary wedge pressure is normal. In

PVOD, however, the capillary pressure increases; in both cases, the dispersion capacity decreases, but PVOD is worse and more serious. In addition, idiopathic PAH is strongly correlated with mutations of *BMPR2*, but this mutation rarely occurs in patients with PVOD.[18] In the present case, the patient had shortness of breath after activity in the early stages, followed by coughing and expectoration of phlegm. Among the physical signs, only the second heart sound was found to be hyperactive; additionally, the patient had visited the outpatient clinic several times, which did not attract enough attention.

The patient underwent cardiac ultrasound in our hospital, and we found that the pulmonary artery pressure was abnormally elevated. However, what truly attracted our attention and vigilance were the changes in the pulmonary high-resolution CT (HRCT) imaging, which showed thickened interlobular septa, diffuse central lobular nodules in both lungs, and enlarged mediastinal lymph nodes with rapid progression. Our first consideration was that underlying pulmonary disease was causing increased pulmonary artery pressure. The imaging results showed that the patient had a long disease course that manifested only by PH in the clinical setting, and the laboratory auxiliary examinations did not support a diagnosis of infection, connective tissue disease, a tumour, idiopathic interstitial pneumonia, or other common non-infectious diseases. In the absence of cardiac, pulmonary, and systemic diseases, her condition was difficult to explain because most interstitial lung lesions rarely cause severe PH in such a short time.

What exactly caused the PH? Were the pulmonary imaging changes and increased pulmonary artery pressure two manifestations of the same disease? Some studies have shown that typical HRCT signs in patients with PH include a ground glass shadow in the centre of the lobules, smooth thickening of the interlobular septa, and mediastinal lymph node enlargement. When these three signs exist simultaneously, the specificity of a PVOD diagnosis is 100% and the sensitivity is 66%.[19] Our patient had PH, and her HRCT imaging findings were consistent with the above three changes; therefore, we considered the possibility of PVOD.

Haemodynamic measurement of the pulmonary circulation is also very important in the diagnosis of PVOD. Combined with the patient's clinical manifestations and imaging changes, the results of pulmonary circulation haemodynamic testing can support the diagnosis of PVOD. The differences in the haemodynamic characteristics between PVOD and other types of PH include a mean pulmonary artery pressure of >20 mmHg and a PAWP of ≤ 15 mmHg.[19] Although the anatomical site of the main lesion of PVOD is located in the posterior capillary venules, PAWP is usually normal. The haemodynamic measurements of the pulmonary circulation in this patient supported the diagnosis of PVOD. Of course, lung function testing, the 6-minute walking test, and other examinations are helpful for the assessment of patients' function and the monitoring of disease progression or remission.

The diagnosis and treatment of PVOD remain extremely challenging. At present, it is believed that on the basis of excluding parenchymal lung diseases (e.g., interstitial pneumonia, sarcoidosis, pneumoconiosis, congestive heart failure, and chronic thromboembolic PH), HRCT imaging of patients with PH suggests pulmonary oedema, a central ground glass blur, thickened lobular septa, and enlarged mediastinal lymph nodes. The PCWP is normal. The diagnosis of PVOD should be considered in such cases.[19]

No effective drugs are currently available for the treatment of PVOD. It is generally

believed that targeted drugs for the treatment of Group 1 PH are not suitable for use, especially the intravenous use of epoprostenol, because it will aggravate the pulmonary oedema and lead to deterioration of the condition. Nevertheless, few reports have shown that drugs can improve the symptoms of PVOD. Although PAH-targeted therapy may not improve PVOD-related haemodynamics and may actually worsen the PVOD-related haemodynamics caused by pulmonary oedema, several studies have revealed that treatment with bosentan can improve the patient's exercise capacity, haemodynamics, and quality of life.[8] Moreover, in the present case, there was no suitable organ donor at the time of the initial treatment. Thus, bosentan was given with the consent of the patient and her family.

Routine treatment for PVOD includes rest, avoidance of heavy physical activity, warmth, infection prevention, oxygen therapy, and other supportive measures. Warfarin is not recommended in patients with PVOD according to recent guidelines. Lung transplantation is the only effective treatment. Because of the rapid progression and poor prognosis of PVOD, many patients have lost the chance for lung transplantation by the time a definitive diagnosis is reached. Therefore, after correct recognition of the disease, patients with PVOD should be referred to a transplant centre for evaluation as soon as possible.

Conclusion

PVOD is a rare type of PH. Because of its nonspecific clinical manifestations, rapid progression, and poor prognosis, early lung transplantation is the only effective treatment. Therefore, early clinical identification is crucial. In clinical practice, specific HRCT changes in patients with PH should raise the suspicion for PVOD and are helpful for diagnosis of the disease. Further testing for *EIF2AK4* di-allele mutations and haemodynamic changes can also help to achieve earlier diagnosis of the disease. Early lung transplantation may improve the outcomes of patients with PVOD.

Acknowledgement

We thank the patient, who requested anonymity, for agreeing to our report and providing a detailed medical history.

Ethics

The patient and her guardian provided informed consent for publication of this case report. This research was conducted in accordance with the provisions of the Declaration of Helsinki. The Huazhong University of Science and Technology Committee and the Tongji Medical College Ethics Committee at Tongji Hospital approved the study.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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