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A case report of PVOD in a young woman with pulmonary hypertension

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ABSTRACT

Pulmonary veno-occlusive disease (PVOD) is a rare and fatal disease with non-specific clinical presentation often misdiagnosed as group 1 pulmonary arterial hypertension (PAH). The rate of occurrence per one million people is reported to be one-tenth to two-tenths of cases, annually. Our case was a 25-year-old young woman who complained of aggravation of dyspnea during exertion and slight chest pain for two months. Her work-up included pulmonary function test (PFT), an echocardiogram, body box plethysmograph test, diffusing capacity of the lungs for carbon monoxide (DLCO) test, positive ventilation/perfusion (V/Q) scan, computed tomography (CT) scan of chest, cardiac catheterization, and video-assisted thoracopic surgery (VATS). Echocardiography showed high pulmonary artery systolic pressure (PASP). The particular aspect of the present case was that due to the V/Q scan, the patient was diagnosed with chronic thromboembolic PH (CTEPH) and treated with anticoagulant, which did not have a good response. The crucial point is that in PVOD patients, V/Q scan can report segmental and subsegmental defects similar to CTEPH patients that creates a diagnostic challenge in patients. Definitive diagnosis of PVOD was based on VATS. Hypoxia, decreased DLCO, normal V/Q scan, and chest CT findings were used to diagnose PVOD. The patient's treatment with diuretics, bosentan, and tadalafil led to the recovery of the patient's hypoxia, saving her life for further treatment. With respect to the heterogeneous nature of the clinical presentation in PVOD patients, high clinical suspicion and appropriate diagnostic measures are required for diagnosis. The present study showed that PAH specific drugs in addition to diuretics can be used cautiously to control disease progression and save patients for lung transplantation.

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Introduction

Pulmonary veno-occlusive disease (PVOD) is a rare form of fatal pulmonary arterial hypertension (PAH) (1,2) that has clinical and hemodynamic similarities to group 1 PAH (3). PVOD and PAH both show evidence of pulmonary hypertension, characterized by elevated pulmonary artery pressure (equal to or greater than 25 mm Hg at rest) that eventually leads to right heart failure and death (4).

PVOD prevalence is estimated at 0.1 to 0.2 per million people annually (2,5). This disease was first described by Dr. Julius Hora in 1934 by diffuse obstruction of the pulmonary veins by fibrous tissue, pulmonary venous congestion, and associated complications including severe pulmonary hypertension (pHTN), non-cardiogenic pulmonary edema, hypoxia and right ventricular failure (5,6).

In terms of etiology, occupational exposure

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to organic solvents such as trichloroethylene and various chemotherapy agents, especially alkylating agents, bone marrow transplantation, and radiotherapy have been related to PVOD (7).

Biallelic mutations in the eukaryotic translation initiation factor 2 alpha kinase 4 (EIF2AK4) gene are pathogenic and lead to hereditary PVOD (3). The clinical manifestations of patients are usually nonspecific and include shortness of breath that worsens during exertion, fatigue, chest pain, dizziness, cough, and hemoptysis (6). Diagnosis of PVOD is based on clinical presentation and tissue confirmation (2). Although the gold standard for confirming the diagnosis is lung biopsy, due to the risk of bleeding posed by fragile pulmonary veins, biopsy is unsafe in most patients with PAH and is not performed (1,5). Usually, the initial clue to the diagnosis of PVOD is a combined imagine of PAH with concomitant pulmonary edema findings on diagnostic imaging (2,5).

The preferred diagnostic method is non-invasive cross-sectional imaging, e.g., CT (1). The diagnostic process typically includes a high-resolution CT scan of the chest, a pulmonary function test with diffusion capacity, a V/Q scan, an echocardiogram, and cardiac catheterization. The use of PAH-specific therapy for PVOD, which is often misdiagnosed as idiopathic pulmonary arterial hypertension (categorized as PAH class I by WHO) (6), precipitates life-threatening pulmonary edema (3). Unfortunately, PVOD is usually diagnosed late in its clinical course, and has a very poor prognosis (4).

Currently there is no medical treatment to prevent disease progression and lung transplant is the best and final treatment available (6). In the present study, a case of PVOD in a young woman with pulmonary hypertension who finally became a lung transplant candidate is described. The aim of the present study was to provide valuable information regarding the diagnosis of PVOD, its clinical symptoms, and its management. The diagnostic challenge created at the beginning of the patient's treatment and promptly changing the treatment approach was the unique aspect of this study.

Case report

The case subject was a 25-year-old woman who visited the lung clinic due to shortness of breath and a frequent cough. She complained of aggravation of dyspnea during exertion and mild chest pain. SpO2 was 88% at the time of admission, which decreased after brief activity. Cyanosis and clubbing were not identified in the clinical examination. The patient had slight tachycardia and tachypnea. Lung auscultation showed bilateral crackle, particularly in the right lung. The patient complained of worsening symptoms in the last two months. After visiting the doctor, the patient was treated with azithromycin and a respiratory inhaler for about 10 days, but her symptoms did not improve significantly. In the first visit of the patient in our center, the pulmonary function test (PFT) was requested for her, and due to the patient's shortness of breath during exertion, she was referred to a cardiologist for cardiac examination and echocardiography. The spirometry test showed restrictive composition: FEV1: 58%, FVC: 56%, FEV/FVC: 85.

Echocardiography results indicated moderate RV enlargement with mild systolic dysfunction, mild RVH (FAC: 31%), and severe pulmonary hypertension (PASP≥85-90 mmHg). According to the restrictive pattern of lung involvement in PFT, the patient was a candidate for the body box plethysmograph test and diffusing capacity for carbon monoxide (DLCO) test (Table 1).

Table 1. The results of the body box and DLCO tests

Test	Result	Test	Result
FEV1	58%	TGV	98%
FVC	56%	TLC	78%
FEV1/FVC	82	RV	133%
RAW (tot)	55%	RV/TLC	169%
sRAW (tot)	54%	DLCO	46%

FEV1: Forced expiratory volume in the first second; FVC: Forced vital capacity; RAW: Airway resistance; sRAW: specific airway resistance; TGV: Thoracic gas volume; TLC: Total lung capacity; RV: Residual volume; DLCO: Diffusing capacity for carbon monoxide

Considering the high rate of PASP in echocardiography and the severe decrease of DLCO in the body box test, the V/Q scan was requested for the patient. In the V/Q scan, segmental and sub-segmental defects were observed similar to CTEPH patients. Hence, it showed high probability for pulmonary embolism (PE) according to PIOPED criteria. According to the results of the V/Q scan and high PASP, the patient was diagnosed with CTEPH and treated with anticoagulants, but due to the lack of improvement in symptoms and worsening of dyspnea, she finally became a candidate for right heart catheterization (RHC).

RHC results were as follows: Right atria pressure (RAP):8 mmHg, right ventricular pressure (RVP): 50/0-10 mmHg, pulmonary artery pressure (PAP): 50/30(36) mmHg, pulmonary capillary wedge pressure (PCWP):10 mmHg, cardiac output (CO):7lit/min, and cardiac index (Cl):4.7 lit/min/m2. Pulmonary angiography showed no filling defect. Results of imaging (Fig 1) exhibited ground glass opacity (GGO), septal lines, mediastinal lymphadenopathy, and presence of pleural effusion (PE) (Fig 2). With respect to the appearance of septal thickening and GGO mostly in the upper lobes, the

patient became a candidate for VATS. Pathology results revealed pulmonary veno-occlusive disease (PVOD)/pulmonary capillary hemangiomatosis (PCH).

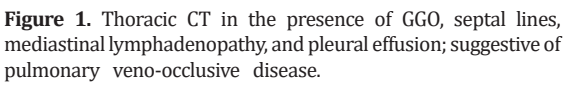

Figure 1. Thoracic CT in the presence of GGO, septal lines, mediastinal lymphadenopathy, and pleural effusion; suggestive of pulmonary veno-occlusive disease.

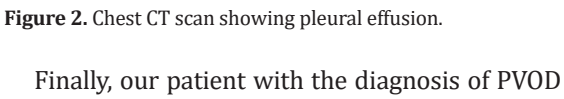

Figure 2. Chest CT scan showing pleural effusion.

Finally, our patient with the diagnosis of PVOD was treated with diuretics, bosentan and tadalafil. At follow-up visits, the patient's hypoxia improved and she was referred to another center for lung transplant evaluation. The measures taken for the patient and the results of the decisions and interventions are shown in Fig 3.

Figure 3. Flow of events with interventions and outcomes

Discussion

PVOD can occur in the first year of life or in the seventh decade, but most cases are reported in children and young adults, with a male to female ratio of 2 to 1 (8). The great similarity in terms of clinical symptoms and hemodynamic characteristics between PVOD and idiopathic PAH can be challenging for the differential diagnosis of PVOD and the possibility of misdiagnosis is high (9). Hence, 5 to 10% of cases initially diagnosed as PAH are actually patients with PVOD (6).

In the present case, the correct and timely diagnosis of PVOD led to partial recovery of the patient and prepared her for the next stage of treatment. A case of PVOD was reported in a 27-year-old woman in Italy, who was misdiagnosed as idiopathic PAH for six months. Like the present report, the case was treated with diuretics and bosentan, leading to the patient's recovery (9).

These two drugs were administered because diuretics are used in the treatment process of RV failure (10) and clinical improvement or stabilization has been reported in a number of patients treated

with oral bosentan (8).

According to a case report from China, two cases of PVOD were misdiagnosed as idiopathic PAH. In these cases, typical findings of PAH were absent and mutation screening revealed the presence of PVOD by identifying the EIF2AK4 gene. These patients had a good response to PAH-targeted therapy (2). However, some PAH-specific drugs may be dangerous in patients with PVOD and can cause fatal pulmonary edema (11).

In fact, treatment guidelines for PVOD are not defined (6) and there are few treatment options other than lung transplant for PVOD (11). Due to the relatively fast progressive nature of the disease and late or misdiagnosis, the prognosis of PVOD is poor and the survival time is short. One-year mortality is estimated at 72% (6).

In our case, GGO, septal lines, and mediastinal lymphadenopathy were seen in the thoracic CT scan images. Bilateral pleural effusions, GGO, hilar and mediastinal lymphadenopathy, and interlobular septal thickening are typically not seen in patients with idiopathic PAH or CTEPH (5).

In the present study, the result of the DLCO test was 46%. In a 57-year-old female of PVOD, RHC showed near normal pulmonary hemodynamics. Lung function was normal, but DLCO was only 42% (12). Similar to our study, Montani et al. also stated that severe hypoxia and severely decreased DLCO, V/Q scan with normal results, severe PH on RHC, and CT scan findings including GGO, lymphadenopathy, and septal thickening along with high clinical suspicion can be extremely effective in the diagnosis of PVOD (9).

Conclusion

In conclusion, regardless of the rarity of PVOD, considering the poor prognosis of the disease and the low chance of survival in case of late or wrong diagnosis, it is necessary to include PVOD in the differential diagnosis of PAH through a comprehensive clinical and diagnostic work-up.

Although the cautious use of PAH-specific treatments along with diuretics to slow down the progression of PVOD and improve the patient's clinical condition is not a definitive treatment for the patient, it can act as a bridge to bring the patient to a lung transplant. This case report can be helpful in future research in the approach of PVOD patients who had a positive ventilation scan in the examinations performed.

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