

A case report of PVOD patient combined with pulmonary embolism

Anticoagulation or not?

Xiaoling Yuan, MD^a, Xianghe Hou, MD^b, Weihong Guo, MD^a, Haiming Jiang, MD^c, Junmeng Zheng, PhD^c, Stuti Paudyal, BS^d, Yanhua Lyu, PhD^{a,*}

Abstract

Rationale: Pulmonary veno-occlusive disease (PVOD) is a rare form of pulmonary arterial hypertension (PAH). Oral anticoagulation is confined to patients with idiopathic PAH (IPAH), but no oral anticoagulation has been recommended for PVOD, because occult pulmonary hemorrhage was a common finding in PVOD.

Patient concerns: We report a case of PVOD, who was misdiagnosed as IPAH for 5 years with worsening dyspnea and two episodes of pulmonary embolism (PE).

Diagnoses: He was confirmed as PVOD combined with PE by biopsy of the explanted lung specimen.

Interventions: He took oral anticoagulation, warfarin, to treat his first-time PE in July 2010, and his disease was kept stable for about 4 years, until he discontinued the anticoagulation therapy by himself sometime in 2014. Later on, a life-threatening PE recurred in January 2015, so he resumed the anticoagulation therapy.

Outcomes: Fortunately, the bilateral sequential lung transplantation that was performed in July 2015 in time saved his life. He has been living well without dyspnea and the echocardiography showed the normalizations of the once increased pulmonary arterial pressure and the once enlarged right ventricle of his heart. In addition, to the best of my knowledge, he was the first PVOD patient receiving lung transplantation in China.

Lessons: We recommend that PVOD patients combined with PE should be treated with anticoagulation therapy indefinitely to prevent the recurrence of life-threatening PE until they get a chance for lung transplantation.

Abbreviations: CTPA = computed tomography pulmonary angiography, DLCO = diffusing capacity of the lungs for carbon monoxide, FEV₁ = forced expiratory volume in 1 second, FVC = forced vital capacity, HRCT = high-resolution computed tomography, INR = international normalized ratio, PAH = pulmonary arterial hypertension, PAP = pulmonary arterial pressure, PCWP = pulmonary capillary wedge pressure, PE = pulmonary embolism, PH = pulmonary hypertension, PVOD = pulmonary veno-occlusive disease.

Keywords: anticoagulation, case report, lung transplantation, pulmonary arterial hypertension, pulmonary embolism, pulmonary hypertension, pulmonary veno-occlusive disease

1. Introduction

Pulmonary veno-occlusive disease (PVOD) is a rare form of pulmonary arterial hypertension (PAH),^[1] characterized by extensive and diffuse intimal fibrotic narrowing or occlusion of the small pulmonary veins or venules.^[2] About 5% to 10% of

cases were initially misdiagnosed as idiopathic PAH (IPAH),^[3] because they share broadly the similar clinical manifestations and features with the severe precapillary PAH. Oral anticoagulation is routinely used to treat patients with IPAH, but anticoagulation therapy is controversial in patients with PVOD. Most clinicians avoid using anticoagulation therapy for patients with PVOD, because occult alveolar hemorrhage was a common finding in PVOD.^[4] In contrast, some clinicians use anticoagulant to treat PVOD patients indefinitely, as long as these patients do not have an increased risk of bleeding and can continuously monitor their anticoagulation therapy.^[2] However, should anticoagulation therapy be given to a PVOD patient without or with combined pulmonary embolism (PE) indefinitely?

We report a case of 69-year-old man misdiagnosed as IPAH for 5 years with worsening dyspnea, and concomitantly with 2 episodes of PE. He was treated with warfarin as anticoagulation therapy for the first-time PE occurred in July 2010. Warfarin treatment kept his disease stable for about 4 years, until he discontinued the anticoagulation therapy by himself sometime in 2014. Later on, he developed a life-threatening, recurring PE in January 2015, so he resumed the anticoagulation therapy. Fortunately, his life was saved because a bilateral sequential lung

Editor: Shizhang Ling.

The authors report no conflicts of interest.

^aRespiratory Department, ^bPathology Department, ^cCardiothoracic Surgery, People's Hospital of Zhongshan City, Zhongshan City, ^dMedical Intern, Sun Yat-Sen University, China.

* Correspondence: Yanhua Lyu, Respiratory Department, People's Hospital of Zhongshan City, Guangdong Province, China (e-mail: lyhzhongshan@163.com).

Copyright © 2017 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the Creative Commons Attribution-NoDerivatives License 4.0, which allows for redistribution, commercial and non-commercial, as long as it is passed along unchanged and in whole, with credit to the author.

Medicine (2017) 96:13(e6507)

Received: 7 November 2016 / Received in final form: 8 March 2017 / Accepted: 8 March 2017

<http://dx.doi.org/10.1097/MD.00000000000006507>

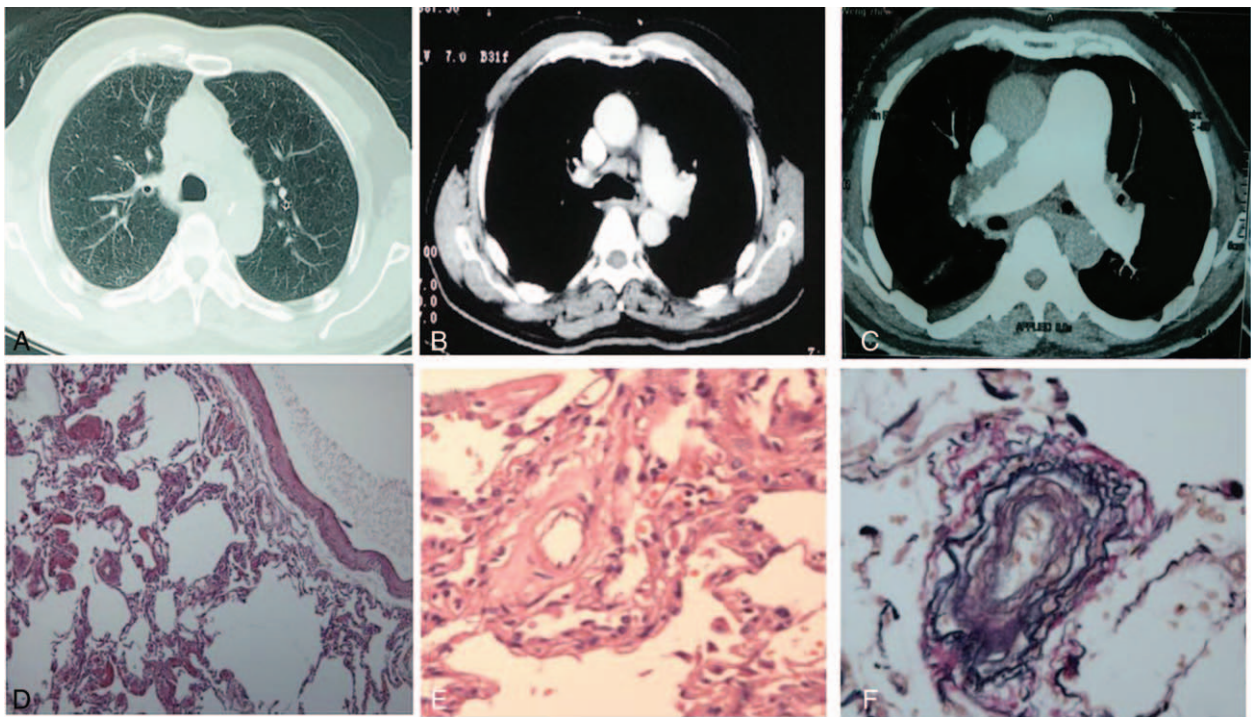


Figure 1. CT scans and histopathology of PVOD. Chest HRCT in September 2011 shows smooth thickening of the interlobular septa and the diffuse centrilobular nodules (A) and the enlargement of the mediastinal lymph node (B). CTPA in January 2015 shows the right main pulmonary artery thrombosis (C). Histopathology of the explanted lung tissue shows the narrowing or occlusive septal and preseptal venules (D), the thickening of alveolar capillary wall (D), the narrowing intimal fibrosis of small preseptal venules (E), and increased hemosiderin-laden macrophages (E). The elastic fiber staining shows the narrowed venules (F). CT=computed tomography; CTPA=computed tomography pulmonary angiography; HRCT=high-resolution computed tomography; PVOD=pulmonary veno-occlusive disease.

transplantation was performed in time in July 2015. His PVOD was confirmed by histopathology of the explanted lung specimen. He has been living very well ever since.

2. Details of the clinical case

A 69-year-old man became aware of the onset of exertional dyspnea in July 2010. He had a history of smoking for more than 40 years, 20 cigarettes per day. His parents and 1 brother had lung cancer. His past medical history was unremarkable. He had no occupational exposure. Due to the exertional dyspnea, he was admitted to the People's Hospital of Shunde District for echocardiography and computed tomography pulmonary angiography (CTPA). Echocardiography indicated that he had severe PAH, because his pulmonary arterial pressure (PAP) was 104 mmHg, and his right heart was enlarged (the right ventricle diameter: 57 mm). CTPA showed that he had not only PAH, but also a thrombus in the upper lobe artery of the right lung. However, the region in the lung affected by this PE was considered too small to induce such a severe PAH. In addition, he did not have connective tissue disease, drug use, history of chemotherapy, or HIV test (+), so he was diagnosed as IPAH combined with PE. He was treated with warfarin (2.5 mg per day with a target of the international normalized ratio [INR] between 1.5 and 2.5) and sildenafil targeted PAH therapy (20 mg twice per day). The patient's dyspnea was relieved slightly after the use of these medications for 1 month and the retested PAP by echocardiography was decreased to 72 mmHg, but all the other symptoms and signs failed to further improve after taking these medications for 6 months.

In March 2011, he went to the Kyorin University affiliated hospital in Japan for further treatment. Right heart catheterization revealed PAP 72/34/47 mmHg, pulmonary capillary wedge pressure (PCWP) 17/5/10 mmHg, cardiac output 4.3 L/min, cardiac ejection index 2.36 L/min/m², and pulmonary vascular resistance 7.3 Wood units. He was retested for CTPA that showed that the thrombus in the upper lobe artery of the right lung disappeared. He was still diagnosed as having IPAH, so treated with sildenafil (20 mg 3 times a day) and sorafenib (400 mg once a day) targeted PAH therapy and oral warfarin anticoagulation therapy (2.5–3.75 mg per day, but the daily dose was adjusted by INR that was between 2 and 3). Disappointingly, his dyspnea was not relieved and the PAP tested by the echocardiography was around 95 mmHg.

In September 2011, he visited the Shanghai Pulmonary hospital in China because of no relief of dyspnea. Arterial blood gas analysis showed that PaO₂ was 63 mmHg with oxygen saturation 93%; lung function test revealed a mild obstructive dysfunction of the pulmonary ventilation (FEV₁/FVC 62.06%, FEV₁% Prediction 80.9%) and a severe reduction in the diffusing capacity of the lungs for carbon monoxide (DLCO 42%); 6-minute walk test was 385 m. Chest high-resolution computed tomography (HRCT) (Fig. 1A and B) showed smooth thickening of interlobular septa, diffuse centrilobular nodules, and the enlargement of mediastinal lymph nodes. The right heart catheterization revealed that PAP was 83/34/53 mmHg and PCWP was 14/6/11 mmHg. Acute vasodilator testing was negative. Coronary angiography and CTPA were both normal; pulmonary ventilation/perfusion (V/Q) lung scan showed a matched ventilation and perfusion defects. Bronchoalveolar

lavage showed an elevated percentage (65%) of hemosiderin-laden macrophages with the Golde score 80 (the normal range: 0–20). He was still diagnosed as having IPAH, but he was suspected as actually having PVOD. He was continuously treated with the targeted PAH therapy, and he was asked to continue his anticoagulation treatment, but he stopped warfarin anticoagulation treatment by himself sometime in 2014 (he failed to recall the exact date.) because he felt that it was too cumbersome to frequently test the INR for blood coagulation monitoring. Furthermore, after he discontinued his warfarin therapy, he also failed to monitor D-Dimer to prevent PE recurrence. His dyspnea was relatively stable, but he developed many, but not fatal, episodes of pulmonary edema during the therapy. In January 2015, he was rushed to hospital because his dyspnea was suddenly exacerbated. CTPA showed a thrombus in the right main pulmonary artery (Fig. 1C). Rivaroxaban was administered for anticoagulation treatment, but this medication did not relieve his dyspnea, therefore, he was too ill to walk. Instead, he was bound to his wheelchair for half a year. The severe PAH (suspected as PVOD) combined with a life-threatening PE mandates a lung transplantation for his survival. Six months later, he was undergone a bilateral sequential allogenic lung transplantation assisted by veno-arterial extra-corporeal membrane oxygenation (VA-ECMO) after he signed the written consent on July 29, 2015. Histology of the explanted lung specimen showed pulmonary vein occlusion (Fig. 1D–F) and the pulmonary embolism in the right pulmonary artery. Until then, he was confirmed as having PVOD combined with PE, instead of IPAH.

He has been living well without dyspnea for more than 1 year after the lung transplantation and the echocardiography showed the normalizations of PAP and the once enlarged right ventricle of his heart.

This study was approved by the Ethics Committee of The People's Hospital of Zhongshan City. The written informed consent was obtained from the patient.

3. Discussion

Pulmonary hypertension (PH) is abnormally elevated pressure in the pulmonary circulation, including both of pulmonary artery and vein. The current classification system divides PH into 5 main groups according to the shared pathophysiology, clinical features, and therapeutic approaches reported in the 2015 European Respiratory Society (ERS) guidelines.^[1] Group 1—PAH; Group 2—PH due to left heart disease; Group 3—PH due to chronic lung disease and/or hypoxemia; Group 4—chronic thromboembolic pulmonary hypertension; Group 5—PH due to unclear and/or multifactorial mechanisms such as hematologic disorders or systemic diseases other than connective tissue disease, metabolic disorders, or miscellaneous disorders.

PVOD is a rare type of malignant PH diseases, together with IPAH, belonging to Group 1 PAH. According to France national PAH registered data, the annual incidence rate of PVOD is 0.1 to 0.2 per million people.^[5] Hora reported the first case of PVOD in detail in 1934.^[6] Since then, nearly 200 cases of PVOD have been reported in the literature, covering all age groups from pediatric to elderly population and having no sex differences. In China, only 10 cases have been reported so far.^[7] The first case was reported in 2005.^[8] Seven cases were clinically diagnosed, 2 cases were confirmed histologically by biopsy, and 1 case was diagnosed by gene test.^[9] Our case is the oldest PVOD patient and the only PVOD patient who had lung transplantation in

China. PVOD shares similar clinical manifestations with IPAH, making the diagnosis much more challenging. In contrast with IPAH, patients with PVOD carry a worse prognosis with an estimated 1-year mortality rate of 74% and are at risk of developing life-threatening pulmonary edema with targeted PAH therapy.^[10] In fact, our case was initially also misdiagnosed as IPAH, but fortunately not fatal. Therefore, it is important to distinguish these 2 diseases.

Lung histology remains the gold standard for a definitive diagnosis of PVOD. The defining pathological feature of PVOD is the diffuse intimal fibrotic narrowing or occlusion of the small pulmonary veins or venules. In fact, our case was confirmed as PVOD by histology of the explanted lung specimen, which showed the typical pathological changes as shown in Fig. 1D–F. However, surgical lung biopsy is too invasive for these frail patients and maybe even fatal, so it is not recommended in clinical practice.^[11] The following noninvasive approaches are useful to help distinguish PVOD from IPAH^[12,13]: the combination of very low DLCO, resting hypoxemia, severe oxygen desaturation on exercise, 2 or more characteristic radiological signs on chest HRCT (such as centrilobular ground-glass opacity, line thickening of interlobular septa, and mediastinal lymphadenopathy), and occult alveolar hemorrhage on bronchoalveolar lavage. Furthermore, genetic mutation-EIF2AK4 gene was reported to be associated with PVOD, so gene test may also be helpful to diagnose PVOD, but our case has not been tested for EIF2AK4 mutation.^[14] Of course, a careful history taking and appropriate examinations must be done to differentiate PVOD from other type of PH.^[1] This case was combined with 2 episodes of PE, but we did not think that he was Group 4 PH caused by chronic thromboembolism. The region affected by the first PE episode was too small to induce such a severe PH and the PAP was not decreased after the thrombus in the upper lobe artery of the right lung disappeared, and the recurrence of PE occurred 5 years after he was found having PH. In addition, we did not think that his PH was Group 2, 3, or 5 PH, because he has no history of left heart disease, hematologic disorders, or systemic disease. Although he has smoking history and can be diagnosed as having a mild chronic obstructive pulmonary disease according to his lung function test, FEV₁/FVC <70%, but his FEV₁% prediction (80.9%) was too good to cause PH.

The options to treat PVOD are limited. General and supportive measures are needed, including oxygen administration to prevent further aggravation of PAH from hypoxic pulmonary vasoconstriction. Lung transplantation remains the only definitive therapy that may offer PVOD patients the potential for long-term survival. The cautious use of PAH-targeted medications in selected patients may allow patients to have more waiting time for a lung transplantation.^[15] The use of anticoagulation has been extrapolated from the recommendations made for PAH,^[11] however, no outcome data on anticoagulation in PVOD exist and the studies have shown that occult pulmonary hemorrhage is a common finding in PVOD,^[4] so many doctors fear to use anticoagulation therapy to treat PVOD patients. However, some doctors use anticoagulation therapy to treat PVOD patients indefinitely who do not have an increased risk of bleeding and can continuously monitor their anticoagulation therapy.^[2] Therefore, the use of anticoagulation therapy for PVOD patients is still controversial. Our case had PVOD combined with 2 episodes of PE. He was treated with oral anticoagulation for the first episode of PE in July 2010. His dyspnea was relieved a little and the retested CTPA in March 2011 showed the disappearance of thrombus, but he stopped the anticoagulation therapy by himself

since 2014 until PE recurred in January 2015. The recurrent PE was life-threatening and forced him to live in a wheelchair. In a cohort of 1626 patients with proximal deep venous thrombosis or PE, the recurrence rate of venous thrombo-embolism after the discontinuation of anticoagulation was 11% after 1 year, 20% after 3 years, and 29% after 5 years, which are surprisingly high.^[16] So, it is important to evaluate the high risk factors for PE recurrence and decide an optimal duration of anticoagulation for the frail PVOD patients. According to the current guideline,^[17] 4 years of oral anticoagulation therapy is enough for low risk PE patients, but may be not enough for PVOD patients. Similar to PAH, PVOD has in situ thrombi in the pulmonary microcirculation and the right heart failure, which are maybe the high risk factors for PE recurrence, so we think that as soon as PE occurs in PVOD patients, anticoagulation therapy should be initiated and continued for the rest of their life to prevent a recurrence of life-threatening PE until they have a chance for lung transplantation. Of course, they should keep monitoring the INR to prevent potential severe hemorrhage.

4. Conclusion

PVOD is still a rare type of malignant pulmonary vascular and heart disease, which is difficult to diagnose correctly and treat effectively. This case we reported was initially misdiagnosed as IPAH for 5 years, but eventually confirmed as PVOD by histology of the explanted lung specimen. He was the first PVOD patient receiving lung transplantation in China. He suffered with life-threatening PE recurrence after discontinuation of his oral anticoagulation therapy for about 1 year. So, we think PVOD patient combined with PE may need a life-long anticoagulation therapy until they get a chance for lung transplantation.

References

- [1] Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2015;46:903–75.

- [2] Montani D, Price LC, Dorfmuller P, et al. Pulmonary veno-occlusive disease. *Eur Respir J* 2009;33:189–200.
- [3] Mandel J, Mark EJ, Hales CA. Pulmonary veno-occlusive disease. *Am J Respir Crit Care Med* 2000;162:1964–73.
- [4] Rabiller A, Jais X, Hamid A, et al. Occult alveolar haemorrhage in pulmonary veno-occlusive disease. *Eur Respir J* 2006;27:108–13.
- [5] Humbert M, Sitbon O, Chaouat A, et al. Pulmonary arterial hypertension in France: Results from a national registry. *Am J Respir Crit Care Med* 2006;173:1023–30.
- [6] Hora. Zur histologie der klinischen “primären pulmonalsklerose”. [On the histology of clinical primary pulmonarysclerosis]. *Frankf Z Pathol* 1934;47:100–18.
- [7] Jiang X, Chen FD, He J, et al. Clinical characteristics and survival of patients with pulmonary veno-occlusive disease. *Chin J Cardiol* 2011;39:896–900.
- [8] Li R, Wang JW, Yao JG. One case report about PVOD by forensic identification. *Acta Univer Medicinalis Nanjing* 2005;5:117–8.
- [9] Li Liang, Guofeng Ma, Kai Chen, et al. EIF2AK4 mutation in pulmonary veno-occlusive disease: A case report and review of the literature. *Medicine (Baltimore)* 2016;95:e5030.
- [10] Holcomb BJ, Loyd JE, Ely EW, et al. Pulmonary veno-occlusive disease: a case series and new observations. *Chest* 2000;118:1671–9.
- [11] Montani D, Lau EM, Dorfmuller P, et al. Pulmonary veno-occlusive disease. *Eur Respir J* 2016;47:1518–34.
- [12] Montani D, Kemp K, Dorfmuller P, et al. Idiopathic pulmonary arterial hypertension and pulmonary veno-occlusive disease: similarities and differences. *Semin Respir Crit Care Med* 2009;30:411–20.
- [13] Montani D, Achouh L, Dorfmuller P, et al. Pulmonary veno-occlusive disease: clinical, functional, radiologic, and hemodynamic characteristics and outcome of 24 cases confirmed by histology. *Medicine (Baltimore)* 2008;87:220–33.
- [14] Eyries M, Montani D, Girerd B, et al. EIF2AK4 mutations cause pulmonary venoocclusive disease, a recessive form of pulmonary hypertension. *Nat Genet* 2014;46:65.
- [15] Montani D, Jais X, Price LC, et al. Cautious epoprostenol therapy is a safe bridge to lung transplantation in pulmonary veno-occlusive disease. *Eur Respir J* 2009;34:1348–56.
- [16] Prandoni P, Noventa F, Ghirarduzzi A, et al. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1626 patients. *Haematologica* 2007;92:199–205.
- [17] Konstantinides S, Goldhaber SZ. Pulmonary embolism: risk assessment and management [J]. *Eur Heart J* 2012;33:3014–22.