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CASE REPORT

Pulmonary capillary hemangiomatosis diagnosed by pathology of explanted lungs: a unique etiology serves as a key of clinical diagnosis

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Abstract
A 27-year-old female patient had presented progressing exertional dyspnea due to pulmonary hypertension. Chest CT revealed diffusely spread patchy ground-glass opacities sparing subpleural parenchymal areas suggesting the diagnosis of pulmonary veno-occlusive disease (PVOD). Despite the diagnosis of PVOD, she was somehow managed by a repetitive escalation of the epoprostenol dose and oxygen supply during the 12-month waiting period until successful bilateral lung transplantation was performed. Pathology demonstrated capillary proliferation in alveolar septae with scarce lesions of narrowed and/or occluded postcapillary small veins, leading to the final diagnosis of pulmonary capillary hemangiomatosis (PCH), not PVOD. We herein present a case of PCH diagnosed after lung transplantation with a focus on its etiology and a key to clinical diagnosis.

Keywords Pulmonary capillary hemangiomatosis · Pulmonary veno-occlusive disease · Lung transplantation

Introduction

Pulmonary capillary hemangiomatosis (PCH) is a rare and refractory disease characterized by a massive proliferation of pulmonary capillaries within the alveolar septae. It is categorized into WHO Group 1′ alongside pulmonary veno-occlusive disease (PVOD). PCH and PVOD are difficult to differentiate preoperatively due to their common clinical features. Since histologic confirmation is essential to diagnosis of PCH and PVOD, they are often discovered after death or following lung transplantation. We experienced a case of pulmonary hypertension (PH) that was successfully treated by bilateral lung transplantation, who had initially been diagnosed as PVOD clinically, and was finally diagnosed as PCH by pathology of the explanted lungs. This case report presents the unique clinicopathologic characteristics and discusses the etiology of PCH that can serve as a means of clinical diagnosis.

Case report

A 27-year-old female patient presented with exertional dyspnea due to PH. A chest X-ray showed bilateral hilar reticular shadows and a chest CT revealed central-dominant diffusely spread patchy ground-glass opacities (GGOs) sparing subpleural parenchyma with some enlarged mediastinum and hilar lymph nodes (Fig. 1a, b). Right heart catheterization demonstrated a mean pulmonary artery pressure of 45 mmHg and a pulmonary capillary wedge pressure of 9 mmHg. Diffusion capacity was severely impaired at 25% of the predicted DLCO. A ventilation–perfusion scan showed normal ventilation with bilateral subsegmental defects in perfusion. Broncho-alveolar lavage demonstrated hemosiderin-laden macrophages indicating alveolar hemorrhage. The initial clinical diagnosis was PVOD with secondary pulmonary hemosiderosis, and the patient was listed for lung transplantation. Although medical treatments for PAH including epoprostenol had been administered, PH persisted. Steroid pulse therapy was introduced for interstitial changes

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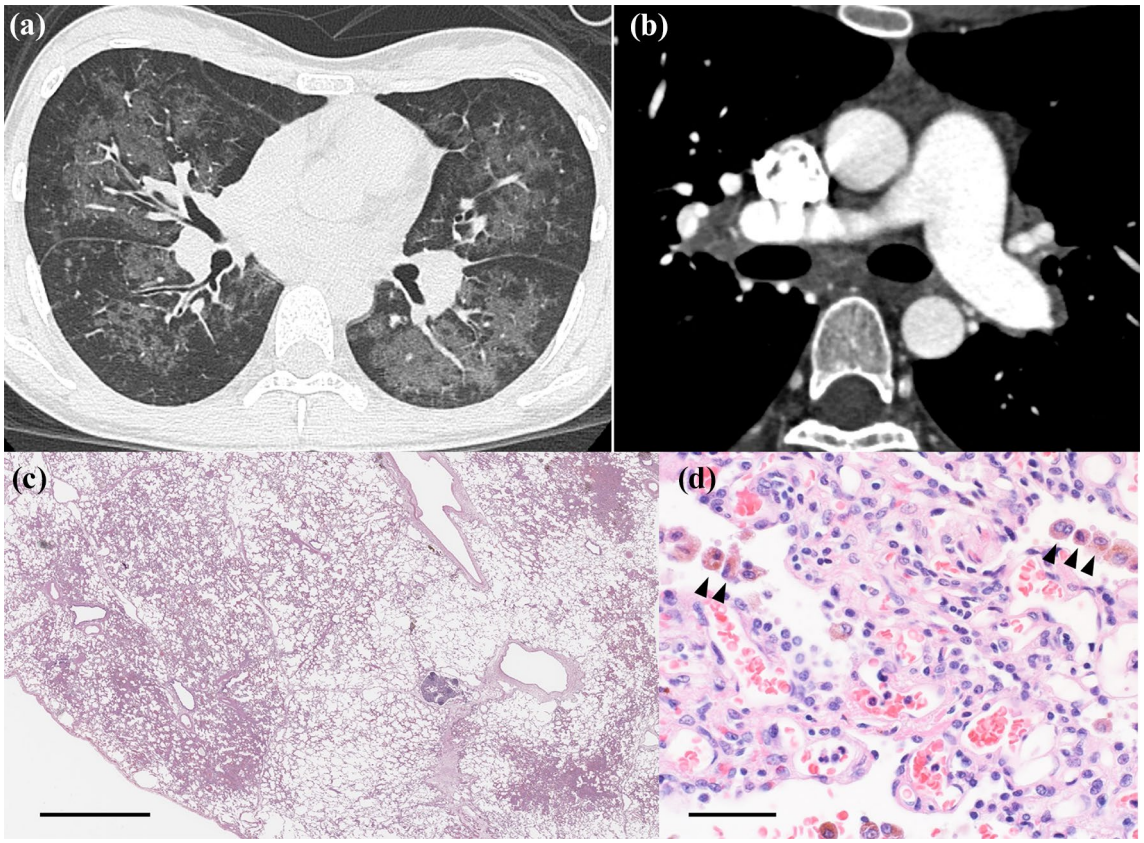

Fig. 1 Radiological and pathological findings. **a** Chest CT shows bilateral central-dominant patchy ground-glass opacities in all lobes sparing the periphery. **b** The mediastinum and hilar lymph nodes are slightly enlarged. **c** Patchy lesions are scattered at low magnification, similar to the distribution of GGOs in high-resolution CT. A scale bar shows 5 mm. **d** Thickened and cellular alveolar septae due to capillary proliferation are demonstrated at high magnification. Hemosiderin-laden macrophages are detected in the alveolar space (arrow heads). A scale bar shows 50 μm

or hemosiderosis, but the bilateral diffuse GGOs did not improve. However, despite the clinical diagnosis of PVOD, the patient's condition was well managed through a repetitive escalation of the epoprostenol dose and oxygen supply during the 12-month waiting period until a successful lung transplantation was performed. The post-operative management was conducted as is done for PAH patients, resulting in uneventful post-operative course. The patient remains stable without oxygen and there is no relapse of pulmonary hypertension for 15 months after lung transplantation.

The gross findings of the explanted lungs presented multiple, red-brown, ill-defined nodular lesions throughout the parenchyma due to alveolar hemorrhage. Capillary proliferation in the alveolar septae was demonstrated in all lobes sparing the periphery, which destroyed alveolar architecture in some parts and remained normal architecture in other parts (Fig. 1c, d). Plexiform lesions were not present. CD31 was immunohistochemically positive, suggesting the existence of proliferative capillary endothelial cells. Precapillary small pulmonary arteries were narrowed with intimal fibrosis adjacent to the lesions of capillary proliferation; however, narrowed and/or occluded postcapillary small veins were not obvious, leading to the final diagnosis of PCH rather than PVOD.

Discussion

Since PCH and PVOD are rare diseases, especially PCH is less frequent than PVOD, clinical features and etiologies of PCH remain still unclear. Differential clinical and pathological characteristics between PCH and PVOD are shown in Table 1. There have been only fewer than 100 cases of PCH reported to date [1], while PVOD accounts for 5–10% of cases initially considered as idiopathic PAH [2]. The prognosis of both diseases is reported to be poor, 3 years after initial symptoms in PCH, and 2 years after clinical diagnosis in PVOD [3], respectively. Radiologic features of PCH include centrilobular nodular GGOs and main pulmonary arterial dilatation. The longest diameter of GGOs is reported to be significantly larger than that of PVOD (mean size: 5.60 ± 1.43 vs 2.51 ± 0.79 mm) [4]. On the contrary, PVOD

Table 1 Differential clinical and pathological characteristics between pulmonary capillary hemangiomatosis (PCH) and pulmonary veno-occlusive disease (PVOD)

	Pulmonary capillary hemangiomatosis (PCH)	Pulmonary veno-occlusive disease (PVOD)
Frequency	Less frequent than PVOD No sexual differences	Accounts for 5–10% of case initially considered as idiopathic PAH [2] Men are affected twice as frequently as women, when considered patients over 20 years old [3]
Prognosis	Better than that of PVOD, 3 years after initial clinical symptoms [3]	Twenty-four months after initial clinical symptoms [3]
Clinical symptoms	Hemoptysis is not reported	Hemoptysis is accompanied with 30% of patients [3]
Radiological findings	Centrilobular nodules of GGOs and main pulmonary arterial dilatation Septal thickening, lymphadenopathy, and pleural effusions, are sporadically reported [3] The longest diameter is described significantly larger than that of PVOD (mean size; 5.60 ± 1.43 mm) [4]	Multi-formed ground-glass opacities (GGOs), subpleural interlobular septal thickenings, lymphadenopathy, and dilated main pulmonary artery GGOs can present various forms, including diffuse, geographic, mosaic, perihilar, patchy, or centrilobular patterns [3] The distribution of GGOs tends to be random or central-dominant sparing the periphery [6] The longest diameter is reported significantly smaller than that of PCH (mean size; 2.51 ± 0.79 mm) [4]
Pathological findings	Capillary proliferation within alveolar walls that can infiltrate adjacent structures, including bronchioles, vessels, and visceral pleura Immunohistochemical CD31 and CD34 are positively stained [1]	Intimal fibrosis leading to the stenosis and occlusion of small pulmonary veins The venous lesions are located in edematous interlobular septae
	Accompanied by secondary arteriopathy with intimal fibrosis and/or medial hypertrophy [7] Hemosiderin-laden macrophages are often present in alveolar space	

presents various unique radiologic manifestations of GGOs, such as diffuse, geographic, mosaic, perihilar, patchy, or centrilobular patterns. Subpleural interlobular septal thickening, centrilobular GGOs, and lymphadenopathy are demonstrated to be more frequently detected in PVOD than in PAH patients with a statistical significance [5].

When PCH and PVOD are considered as clinical diagnosis, patients should be put on the list for lung transplantation as promptly as possible because the prognosis of both diseases is very poor and lung transplantation is the only effective fundamental treatment. These patients often present severely impaired respiratory function in addition to pulmonary hypertension which makes surgical biopsy difficult before lung transplantation as in our case. Therefore, it is vital to differentiate PCH and PVOD from PAH based on clinical findings such as clinical courses and radiological features, without pathological confirmation. On the other hand, as the clinical course and management of PCH and PVOD before and after lung transplantation are similar to each other, the advantages of differentiating these diseases before lung transplantation remains unclear.

PVOD is known to be associated with collagen disease (scleroderma), cytotoxic drugs, and bone marrow transplantation; however, the association of PCH is unknown due to a scarce opportunity of the diagnosis. Two different hypotheses exist with regard to the etiology of PCH. The one is a neoplastic process, and the other is a secondary change due to other diseases [3]. PCH can be present in the absence of significant PAH and of causative background diseases, which supports the idea of the neoplastic theory, expressed as 'primary PCH' [7]. Secondary PCH can develop in the lungs with PVOD, connective tissue diseases, and chronic passive congestion based on a few previously published case reports.

In radiology, the present case demonstrated patchy as well as nodular GGOs that were relatively representative for PVOD. Furthermore, there was no clinical evidence of secondary PCH. As to pathology, our case predominantly presented capillary proliferation within the alveolar septae which corresponded to radiological GGOs, and the stenosis and occlusion of small pulmonary veins were noted only in very limited areas of the lung, thereby suggesting PCH rather than PVOD since PVOD is mainly located in post-capillary small pulmonary veins. Such mosaic radiological and pathological manifestations suggest that both PCH and PVOD may be on the same spectrum of disease, manifesting in different clinicopathologic features. Interestingly, recessive EIF2AK4 mutations were identified in familial cases with these diseases [8], which may provide a critical clue to understand the etiologies.

Epoprostenol, the mainstay of the medical treatment for PAH, has been historically reported to negatively affect patients with PCH or PVOD via sudden onset pulmonary edema. Meanwhile, other groups during the last decade

asserted that cautious application of epoprostenol can be considered as a therapeutic option to bridge lung transplantation in these patients [9]. In our case, the patient could be somehow managed with the escalation dose of epoprostenol. The reason of this would be that the relatively healthy area of pulmonary vasculature could be observed in the parenchyma and the remaining healthy parenchyma may have responded to an escalation of epoprostenol dose.

Conclusion

We experienced a case with PCH who manifested similar radiological features to those of PVOD in which the GGOs lesions were finally revealed as proliferative postcapillary proliferation as PCH in the pathology of the explanted lungs. Progressive hypoxia, the diffuse distribution of patchy GGOs, and the existence of PAH responding to epoprostenol could be clues to the clinical diagnosis of PCH. Since PCH and PVOD are rare forms of PAH, the accumulation of case reports with these diseases is fundamental to recognize their etiology and develop further treatment strategy for these diseases.

Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

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