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An Autopsy Case of Pulmonary Capillary Hemangiomatosis with an Electron Microscopy Study

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Male, >60
Final Diagnosis: Pulmonary capillary hemangiomatosis
Symptoms: Dynpnea • general fatigue
Medication: —
Clinical Procedure: —
Specialty: Pulmonology

Objective: Rare disease

Background: Pulmonary capillary hemangiomatosis (PCH) and pulmonary veno-occlusive disease (PVOD) are rare diseases that share clinical, X-ray, and histological features. Most patients have poor prognosis due to severe respiratory impairment. Recently, *EIF2AK4* mutations were found in some patients with PCH and PVOD, but the role of this mutation is still unknown. We report an autopsy case of PCH and discuss a mechanism of respiratory dysfunction based on an electron microscopy study.

Case Report: The patient was a Japanese man in his sixties. He suffered from acute exacerbation of dyspnea during treatment of COPD. Respiratory function testing revealed DLCO' 32.1% and DLCO'/VA 23.6%. Echocardiography demonstrated findings consistent with pulmonary hypertension. A CT scan showed mild emphysema and small ground-glass opacity in the lungs. However, we could not find the exact cause of his respiratory failure and he died 28 days after admission. At autopsy, the histology showed multilayering capillary proliferation within the alveolar walls. Electron microscopy examination revealed prominent widening of the air–blood barrier, scarce fusion of the epithelial and capillary basement membranes, and frequent narrowing of the capillary lumen.

Conclusions: We reported an autopsy case with PCH with no histological findings of PVOD. Whether PCH and PVOD are 2 different histological patterns of the same disease remains to be verified. The changes in the air–blood barrier detected by electron microscopy may explain the respiratory impairment and pulmonary arterial hypertension.

MeSH Keywords: Blood–Air Barrier • Hypertension, Pulmonary • Microscopy, Energy-Filtering Transmission Electron • Pulmonary Veno-Occlusive Disease

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Background

Pulmonary capillary hemangiomatosis (PCH) is a rare disease with an estimated incidence of less than 1 per million population [1]. Most patients complain of progressive dyspnea on exertion, and fatigue [2,3]. They are often misdiagnosed as having pulmonary arterial hypertension (PAH) [4]. Radiologic features typically show changes associated with pulmonary hypertension [1,2]. High-resolution CT scans often reveal centrilobular ground-glass opacity and sometimes mediastinal lymph node enlargement, but thickened septal line and pleural effusions are unusual [1,2]. Histologically, they are characterized by abnormal proliferation of pulmonary capillaries within alveolar walls [1,2]. The prognosis is poor and PCH is frequently confirmed after lung transplantation or post-mortem [3,5]. PCH and pulmonary veno-occlusive disease (PVOD) have been included together in the same subgroup within the group of PAH in the Dana Point classification in 2008 and 2015 ESC/ERS Guidelines because of clinical, X-ray imaging, and histopathological similarities between PCH and PVOD [4,5]. Recently, eukaryotic translation initiation factor 2 alpha kinase 4 gene (*EIF2AK4*) mutations have been identified in the heritable patients and some of the sporadic patients with PCH and PVOD [3,6]. However, the role of this mutation in vascular remodeling of the lung remains to be elucidated [7]. We report an autopsy case of PCH with no veno-occlusive changes and discuss the mechanism of respiratory dysfunction and PAH based on an electron microscopy study.

Case Report

The patient was a Japanese man in his sixties. His smoking history was 80 pack-year. He had been treated against asthma-COPD overlap with home oxygen therapy, long-acting muscarinic antagonist, and inhaled corticosteroid beginning 1 year before. However, he was taken by ambulance to our hospital due to acute exacerbation of dyspnea. The severity of cardiac function failure was classified as NYHA III. His pulse rate was 117/min, respiratory rate was 36/min, and SpO_2 was 75% with 5 L/min oxygen by mask. Blood gas testing under the respirator mask showed pH 7.505, pCO_2 19.3 mmHg, pO_2 49.0 mmHg, ABE –4.7 mmol/l, HCO_3 –15.1 mmol/l, AG 15.3 mmol/l, and A-aDO_2 212 Torr. Respiratory function testing revealed forced expiratory volume 1 sec (FEV1)/forced vital capacity (FVC) 71.05%, DLCO' 32.1%, and DLCO'/VA 23.6%. Echocardiography demonstrated findings compatible with pulmonary hypertension (tricuspid regurgitation pressure gradient 41 mmHg and right ventricular systolic pressure 56 mmHg). Invasive pulmonary artery pressure measurement was not done due to his worsening condition. High-resolution CT did not show any signs of interstitial pneumonia/fibrosis, or thickening of the interlobular septa and pleural effusion except for mild-to-moderate emphysema predominantly in the upper lobes, and patchy, very faint ground-glass opacification in the lower lobes (Figure 1A). Contrast-enhanced CT showed an enlarged right ventricle with septal thickening that mildly bulged to the left ventricle, which is in keeping with right ventricular overload (Figure 1B). The central pulmonary artery was not enlarged and no pulmonary emboli were identified. He was considered to have severe type-1 respiratory failure. However, we could not perform a histological examination due to his serious condition, and exact cause of the failure was unknown. His condition gradually

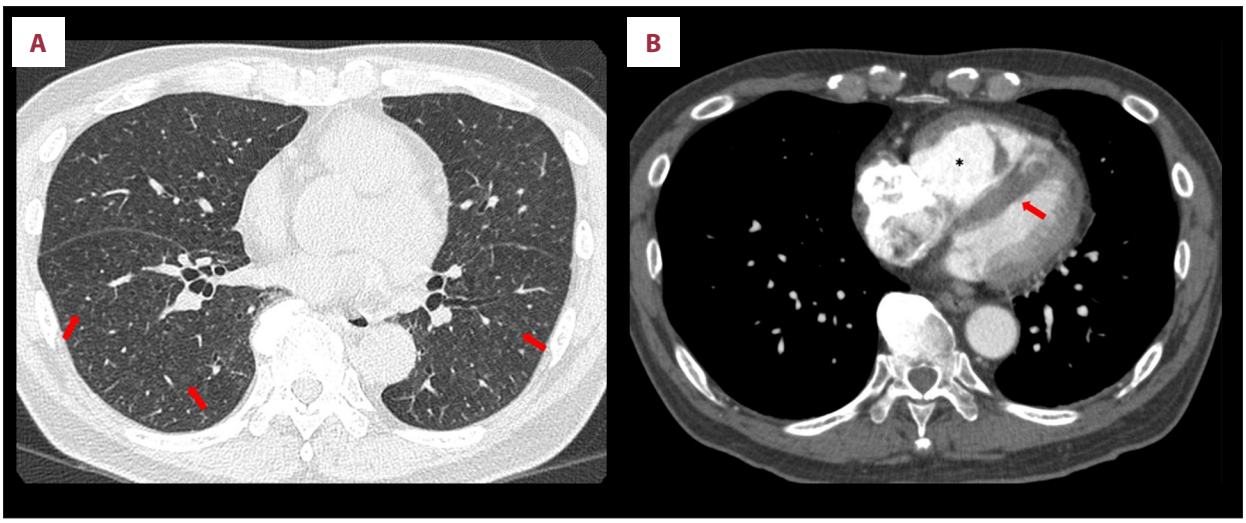

Figure 1. (**A**) High-resolution CT at the level of the right inferior pulmonary vein showing very faint ground-glass nodules scattered in both lower lobes (arrows). (**B**) Contrast-enhanced CT shows enlarged RV (asterisk) with septal thickening that mildly bulges to the LV (arrow), representing RV pressure load.

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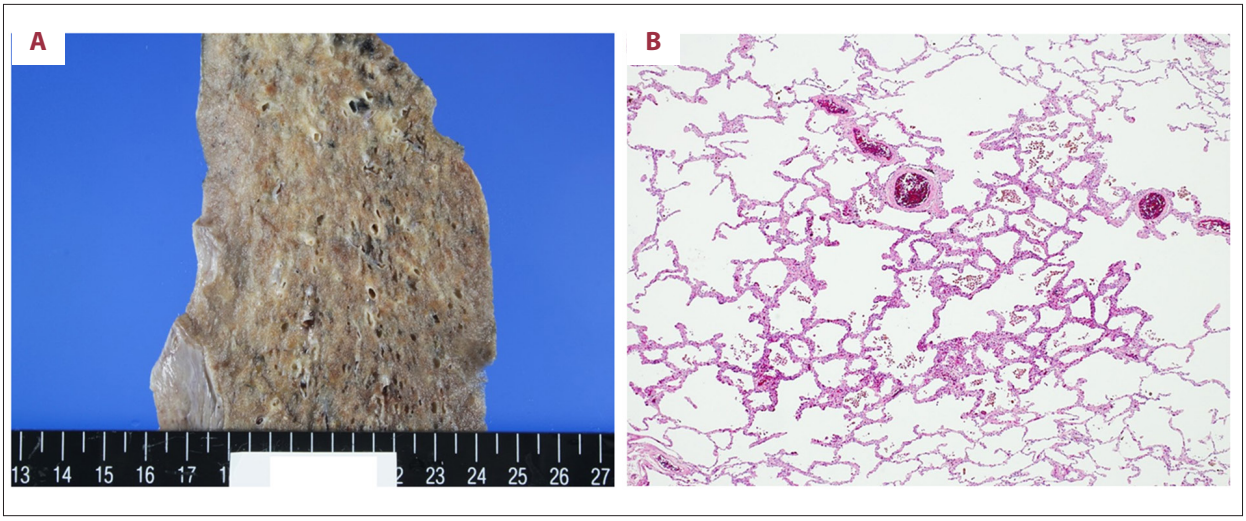

Figure 2. (**A**) A macroscopic view of the right lower lobe showing many tiny brownish nodules with poor delineation. (**B**) A low-power microscopic field of the 2.5-mm nodule demonstrates moderate thickening of alveolar walls with well-preserved alveolar structures. H&E, ×40.

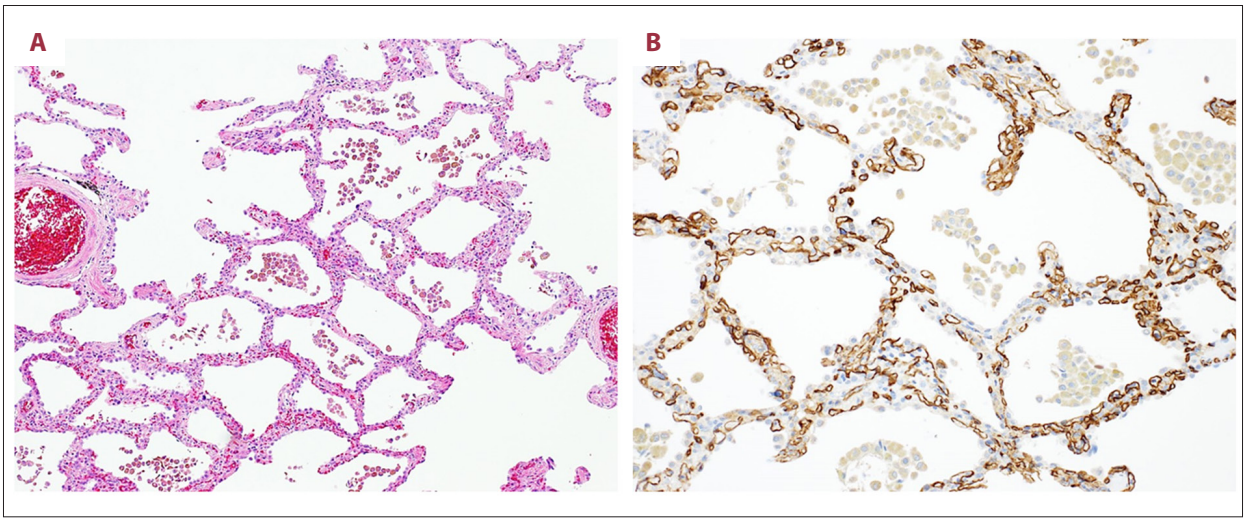

Figure 3. (**A**) A moderately magnified view of Figure 2B reveals thickened alveolar walls consisting of numerous capillaries and scattered microhemorrhages, and a moderate number of hemosiderin-laden macrophages in the alveolar spaces. H&E, ×100. (**B**) Immunohistochemical staining of the alveolar wall with CD 34 clearly shows multilayering proliferation of capillaries with back-to-back appearance, with frequent narrowing of the lumina. ×200.

deteriorated despite administration of nasal high-flow cannula therapy, and he died 28 days after admission.

An autopsy was performed to examine the pulmonary lesions that caused the severe respiratory failure. Gross examination did not disclose any apparent lesions, including pleural effusion and widening of the interlobular septa, except for mild emphysema in the upper lobes of both lungs. There were neither thrombi in the large pulmonary vessels nor hemorrhagic lesions. However, closer inspection identified many tiny, pale brown nodules approximately 1 mm to 5 mm in size, with poor delineation, being scattered especially in the lower lobes (Figure 2A).

The heart weighed 447 g and showed severe dilatation with mild hypertrophy (the wall thickness was 6 mm) of the right ventricle. However, the left ventricle did not reveal hypertrophy or infarcts and all 4 valves had no abnormal changes. The other organs did not show any specific changes except for marked acute congestion of the liver and mild degeneration of the renal tubules.

Histology of the pulmonary nodules showed a moderately thickened alveolar wall with overall preservation of the alveolar structure (Figure 2B). The moderately magnified microscopic views revealed an abnormal increase of capillary

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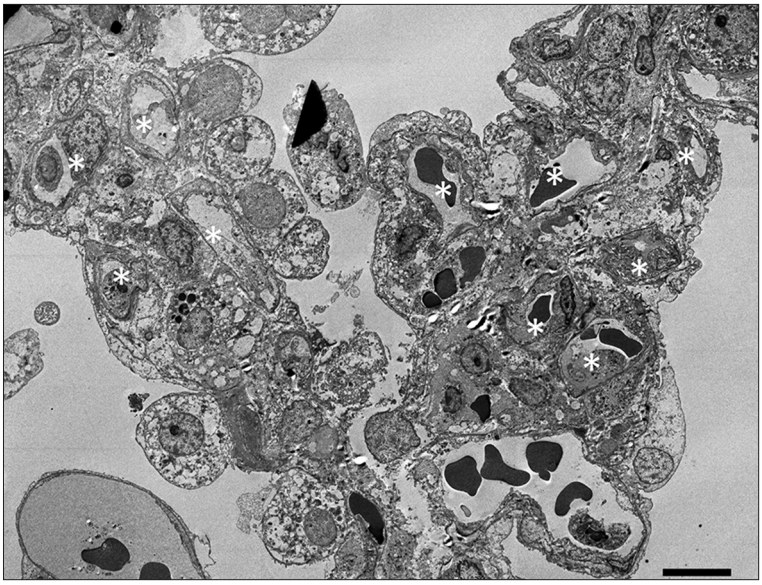

Figure 4. An electron microscopic view of the nodule reveals multilayering proliferation of capillaries with narrowed lumina (asterisk). Only a few dilated capillaries are seen. The bar is 10 µm long. ×1500.

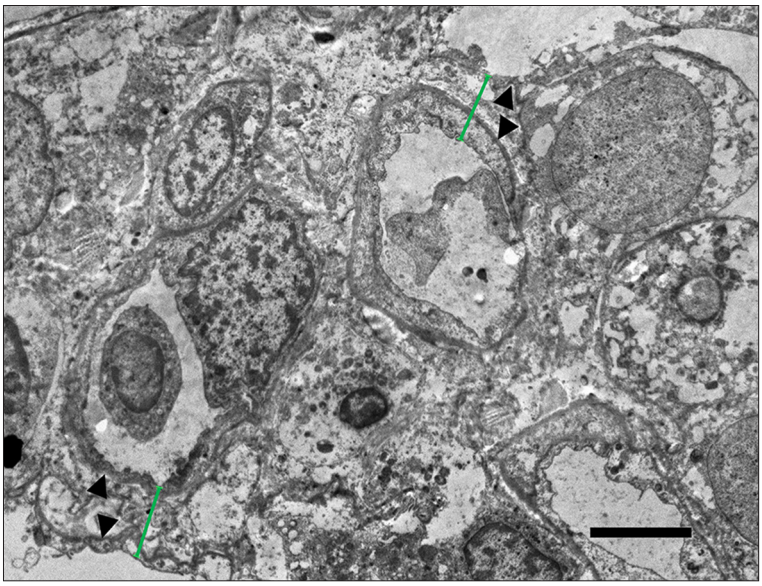

Figure 5. A magnified view of the left alveolar wall at Figure 4. The capillary and epithelial basement membranes (arrowheads) are not fused. The thickness of the air–blood barrier (upper green line) is 3.39 µm and that of the other barrier (lower green line) is 3.53 µm. The bar is 5 µm long. ×4500.

and scattered microhemorrhages within the alveolar walls (Figure 3A). Mild-to-moderate hemosiderin deposition in the walls and spaces was also observed. Capillary invasion to the venous or bronchiolar wall was not evident. Silver staining revealed that argyrophilic fibers were moderately increased, and Azan staining showed barely detectable collagen fibers in the alveolar wall. We observed focal and mild hypertensive changes of pulmonary arteries of small-to-medium-sized caliber. We did not find any occlusive lesions, thrombi, intimal fibrosis, or mural thickening of the veins. The interlobular septa were not thickened. Immunohistochemically, endothelial cells positive for CD31, CD34, and ERG lined the proliferating capillary, with frequent narrowing of the lumen. A multilayered capillary structure with back-to-back appearance was clearly observed in most of the thickened alveolar walls (Figure 3B). We identified a small number of CD3-positive lymphocytes and CD68-positive macrophages. In consideration of all these findings, we decided that the histological diagnosis was PCH rather than PVOD because of the capillary proliferation within the alveolar wall with no veno-occlusive changes.

We sampled electron microscopic specimens from the formalin-fixed small brown nodules. Electron microscopy showed multilayering proliferation of capillaries with back-to-back appearance. Many capillary lumina were narrow (Figure 4). We measured the shortest distance between the alveolar epithelial surface and the endothelial surface of the proliferative capillary closest to the alveolar epithelium. We considered this distance as the thickness of the air–blood barrier. There was prominent widening of the air–blood barrier, with its

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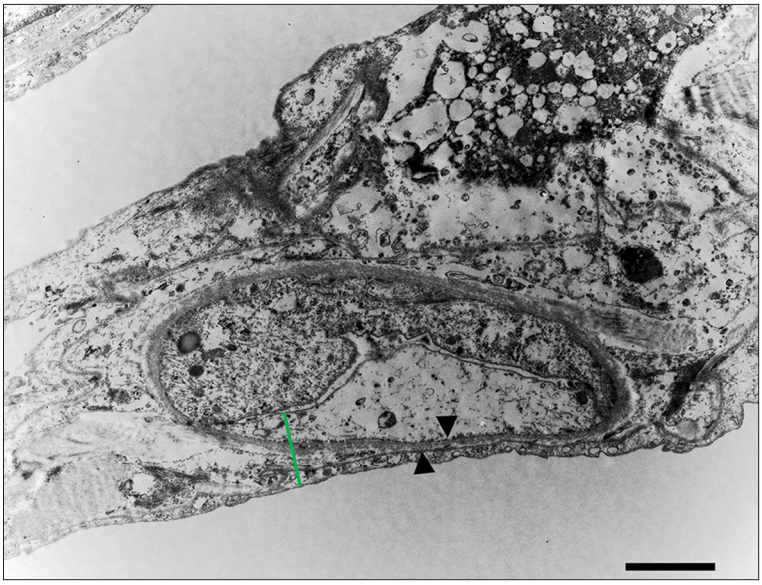

Figure 6. A capillary closely adjacent to the alveolar space has basement membrane separated from that of the alveolar epithelium (arrow heads) and the lumen is narrow because of the swollen cytoplasm. The thickness of the air–blood barrier (green line) is 1.68 µm. The bar is 2 µm long. ×10000.

thickness being usually more than 2 µm, which was 10 times wider than the thinnest part of the normal air–blood barrier (Figure 5) [8]. There was scant fusion of epithelial and endothelial basement membranes (BM) at the barrier, which was involved in the angioproliferative area (Figure 5). Separation between the BMs was also observed even in non-angioproliferative areas. Endothelial cells were swollen and the lumen was narrow (Figure 6). The capillary BM was thickened focally and mildly, but there was no duplication or multilayering of the BM. Electron-dense deposits were not found. Some pericytes were found around the capillary, surrounded by the basement membrane. There were small amounts of collagen and elastic fibers, and a few mesenchymal cells and inflammatory cells were found in the interstitial tissue and the space between the separated membranes.

Discussion

PCH and PVOD are uncommon diseases and their true incidences remain unknown mainly because many cases are still classified as PAH [4]. The annual incidence of PVOD is estimated at 0.1–0.2 per million population, and PCH is reported to be much less frequent than PVOD [1]. Some cases are finally recognized at lung transplantation and post-mortem [3,5]. PCH was first reported in 1978, more than 4 decades after the first report of PVOD [9,10]. Since then, there has been debate as to whether PCH and PVOD are 2 distinct diseases or rather are varied expressions of a single disease [1]. In the 1998 Evian classification of pulmonary hypertension, the 2 entities were included in separate groups, both distinct from the PAH category [11]. However, in the 2003Venice classification, they were included in the same group and placed in 2 different subgroups within the category of PAH [12], and in the 2008 Dana Point classification and the 2015 ESC/ERS Guidelines, it was finally decided to place them in a separate group – PVOD and/or PCH [4,5]. A dominant contemporary conception of PVOD and PCH is that they are 2 different histological patterns of the same disease with a common genetic risk factor [6].

One reason for classifying PVOD and PCH together in a specific subgroup is the clinical and radiological differences between PVOD/PCH and the other forms of PAH [4]. The clinical difference is that PVOD/PCH shows much more severe hypoxemia and lower DLco than the other forms of PAH [4,5,13]. The respiratory impairment often leads to worse prognosis of PVOD/PCH [4,5,13]. PVOD/PCH has a high risk of developing severe pulmonary edema with PAH-specific therapy [4,12]. The typical radiographic findings suggestive of PVOD/PCH are presence of thickened subpleural septal line, centrilobular ground-glass opacities, mild pleural effusion, and mediastinal lymphadenopathy [4,5,13,14]. However, it was reported that there are more numerous septal lines in PVOD than in PCH, while there are more well-circumscribed ground-glass nodules in PCH than in PVOD [1]. Moreover, a genetic study of PAH indicated that subtle or gross centrilobular ground-glass opacity was found in 36% of patients clinically diagnosed with PAH and carrying no mutations, and in 67% of patients with PAH, and the bone morphogenetic protein receptor type 2 (*BMPR2)* mutations that are the commonest genetic cause of PAH [15]. The same study also demonstrated that gross interlobular septal thickening and mediastinal lymphadenopathy were significantly more common among patients with PAH and biallelic *EI2AK4* mutations and in those with PVOD compared with patients with PAH and no mutations or *BMPR2* mutations [15].

A histopathological study of PVOD and PCH indicated that PCH could be a secondary angioproliferative process frequently

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associated with PVOD [16]. Nonetheless, venous intraluminal septa and/or recanalization were found in only 1 of the 5 cases with PCH, compared with 91% in PVOD [16]. We believe that the total number of cases with PCH was too small to draw a clear conclusion. Another study suggested that the most distinctive histologic feature of PCH was proliferation of capillary channels within alveolar walls, which led to the histologic appearance of densely cellular alveolar walls, in contrast to the distended capillary loops seen in PVOD [1,2,14]. In our case, we observed capillary proliferation with back-to-back appearance within the alveolar walls, and did not find any venous changes that were histologically typical of PVOD. We believe the histological diagnosis should be PCH rather than PVOD. Although a histologic diagnosis was the criterion standard to confirm a diagnosis of PVOD/PCH, it is no longer recommended in most cases because of the hazards involved in lung biopsy [4,17]. However, diagnosis of PVOD/PCH was only definitely confirmed in 30% of the mutations in non-carriers [18]. With cases in which definitive diagnosis is difficult, we believe that histological examination should whenever feasible be used to confirm the diagnosis of PVOD and/or PCH.

In 2014, *EIF2AK4* mutations was discovered in patients with PCH and PVOD [3,6]. Pathologic biallelic *EIF2AK4* mutations are rarely identified in patients diagnosed with heritable PAH. Therefore, identification of pathogenic biallelic *EIF2AK4* mutations can aid clinicians in differentiating heritable PAH from heritable PVOD or PCH [17]. The largest cohort study, which enrolled 94 patients with PVOD/PCH, defined important clinical features of the mutation carriers and non-carriers [18]. The mutation carriers were much younger at presentation of disease than were the non-carriers. It is also important to note that the both groups had similarly severe pulmonary precapillary hypertension, severe functional impairment, almost the same frequency of drug-induced pulmonary edema, and no significant difference in event-free survival. Nevertheless, the mutation rate is not high (9–25%) in sporadic cases with PVOD/PCH [18]. The absence of *EIF2AK4* mutations does not exclude PVOD or PCH [17]. Definite diagnosis in non-carriers may require pathological examination of the lung, in the context of either lung transplantation, post-mortem examination, or lung biopsy [18].

There have been only a few electron microscopy studies of PCH and PVOD. A transmission electron microscopic (TEM) study of PVOD showed focal or diffuse thickening of the alveolar capillary BM [19]. Another study of PVOD found pronounced thickening and multilayering of the endothelial BM, separation of BMs by cell processes of pericytes or proliferating endothelial cells, and electron-dense deposits within the BM [20]. Although we could not find any TEM studies of PCH through online searching, there have been a few scanning electron microscopic studies of PCH. One study of PCH showed tumor-like outgrowth of capillary vessels, and another demonstrated multifocal intussusceptive micro-angiogenesis and vascular sprouting [21,22]. In our TEM study of PCH, we identified pronounced proliferation of capillary with frequent narrowing of the lumen. We found prominent widening of the air–blood barrier, with the thickness often being more than 2 μm in width. Typically, the thinnest part of the normal barrier was reported to be about 0.2 μm in width [8,23], and we rarely observed fused BM, which is normally present in nearly half of the contact surface between the alveolar epithelium and capillary endothelium [23]. We believed that the widened air–blood barrier might be the mechanism by which severe hypoxemia and low DLco occur, and we suggest that frequent narrowing of the capillary lumen leads to severe PAH. We thus hypothesize that these changes represent a remodeling failure of the normal air–blood barrier caused by abnormal angiogenesis.

Conclusions

We report an autopsy case with PCH, which showed no histological findings of PVOD. Whether PCH and PVOD are 2 different histological patterns of the same disease remains to be verified. Therefore, a histological examination should be performed whenever feasible to confirm the diagnosis of PVOD and/or PCH, as well as the other forms of PAH. We believe that the described electron microscopic changes are the cause of the respiratory impairment and PAH. We hypothesize that PCH represents a remodeling failure of the normal air–blood barrier caused by abnormal angiogenesis, but further study is needed to test this hypothesis.

Department and Institution where work was done

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Conflict of interest

None.

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