【 CASE REPORT 】

Pulmonary Veno-occlusive Disease: A Surgical Lung Biopsy-proven and Autopsied Case Radiologically Mimicking Hypersensitivity Pneumonitis at the Time of a Transbronchial Lung Biopsy

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Abstract:

Pulmonary veno-occlusive disease (PVOD) is a rare disease in the subgroup of conditions known as pulmonary arterial hypertension. Although a histological examination is needed for a definitive diagnosis, a non-invasive diagnosis is required for patients with pulmonary hypertension because a lung biopsy is deemed risky. We herein report a 32-year-old woman diagnosed with PVOD via a surgical lung biopsy and autopsy whose disease showed radiological findings mimicking those of hypersensitivity pneumonitis (pneumonia) at the time of the transbronchial lung biopsy, without obvious pulmonary hypertension on admission. When clinicians encounter patients with interstitial lung disease, they should not forget the possibility of PVOD and should be alert for emerging pulmonary hypertension.

Key words: pulmonary veno-occlusive disease (PVOD), pulmonary hypertension, hypersensitivity pneumonitis (pneumonia), transbronchial lung biopsy, surgical lung biopsy, autopsy

Introduction

Pulmonary veno-occlusive disease (PVOD) is a rare form of pulmonary hypertension (PH) characterized by the preferential involvement of the pulmonary venous system (1, 2). Although histology remains the gold standard for a definitive diagnosis of PVOD, a lung biopsy is contraindicated in the setting of clinically significant PH (2). Thus, in previous studies, the diagnosis of PVOD was based on histology from an explanted lung or an autopsy (3, 4).

We herein report a rare case of PVOD diagnosed via a surgical lung biopsy (SLB) and autopsy, exhibiting radiological findings mimicking those of hypersensitivity pneumonitis (pneumonia) at the time of the transbronchial lung biopsy.

Case Report

A 32-year-old woman who had never smoked was referred to Kinki-Chuo Chest Medical Center with a 2-month history of exertional dyspnea, desaturation, and bilateral lung ground-glass opacity (GGO) on chest computed tomography (CT) in November 2010. She had had pneumonia and bronchial asthma when she was 14 years of age. She was not taking any medications, had no pets, and reported no excessive exposure to dust. She had worked in food processing jobs in supermarkets since the 19 years of age. Her mother had Basedow's disease and epilepsy, and her younger brother had congenital deafness while the patient had no hearing loss.

A physical examination on admission revealed the following: body height, 157 cm; body weight, 99 kg; body mass

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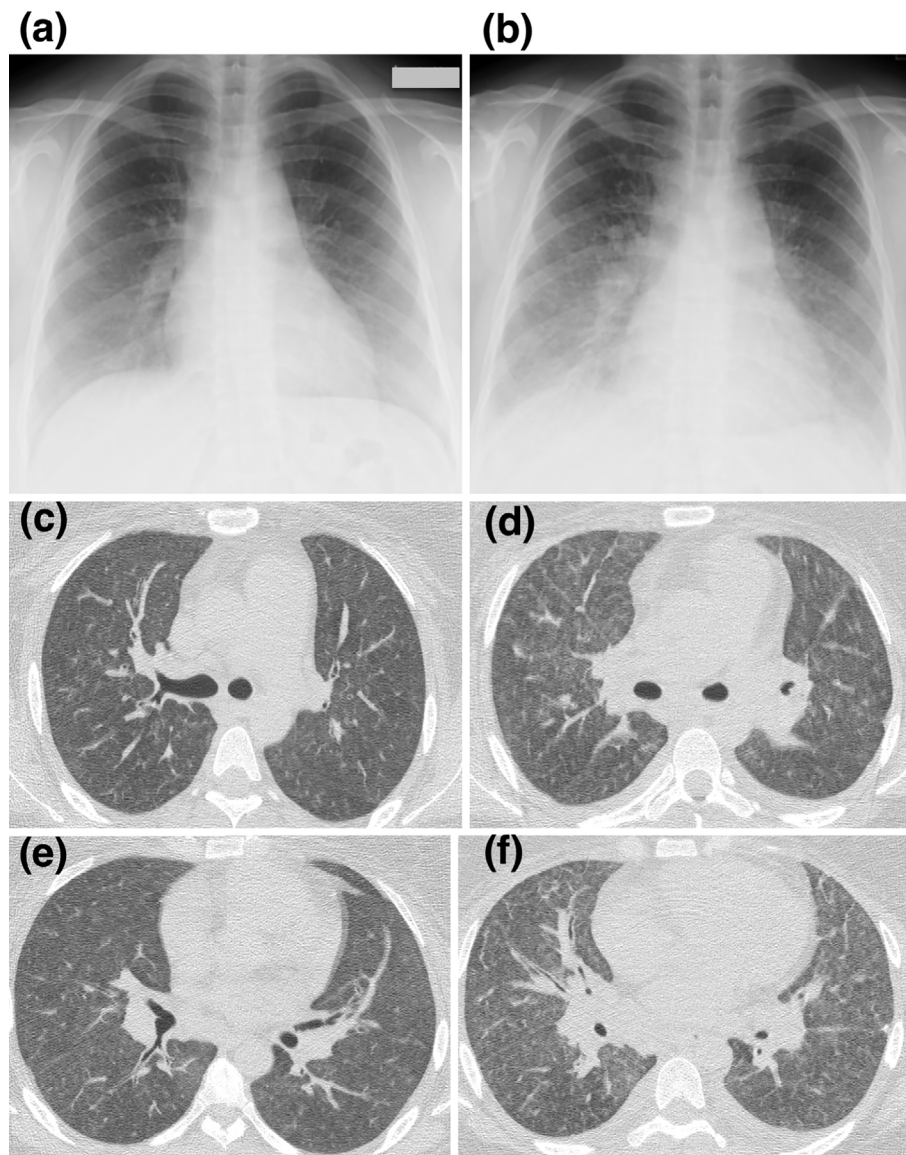
Figure 1.   Chest radiography and high-resolution chest computed tomography. (a) Chest radiography on admission showed bilateral GGO in November 2010 and (b) increased GGO and enlargement of pulmonary artery in January 2012. (c, e) High-resolution chest computed tomography showed GGO with centrilobular accentuation in the bilateral lung fields in November 2010 and (d, f) revealed increased GGO, interlobular septal thickening, peribronchovascular interstitial thickening, and a mild degree of bilateral pleural effusion in January 2012. In addition, bronchial stenosis was suspected. GGO: ground-glass opacity

index (BMI), 40.2 (normal range: 20-24); no palpable surface lymph nodes; no fine crackles heard on chest auscultation; no clubbing of the fingers; and no skin rashes. The laboratory findings of peripheral blood on admission were as follows: white blood count, 5,200/μL; lactate dehydrogenase, 253 IU/L; C-reactive protein, 0.09 mg/dL; Krebs von den Lungen-6 (KL-6), 317 U/mL (normal, <500); surfactant protein (SP)-D, 171 ng/mL (normal, <110); SP-A, 74.7 ng/mL (normal, <43.8); angiotensin converting enzyme, 10.3 U/L (normal range, 8.3-21.4); and brain natriuretic peptide (BNP), 10.3 pg/mL (normal, <43.0). A tuberculin skin reaction test was negative. Chest radiography revealed bilateral GGO (Fig. 1a), and chest high-resolution CT (HRCT) re-

vealed GGO with a centrilobular pattern in all lung fields (Fig. 1c, e). Pulmonary function tests revealed almost normal values with the exception of a reduced percentage of predicted lung diffusion capacity for carbon monoxide (%DL_{CO}) of 46.5%. An arterial blood gas analysis revealed a reduced partial pressure of oxygen in the arterial blood of 53.1 Torr and an increased alveolar-arterial oxygen difference of 56.2 Torr. Her walking distance in the 6-minute walk test (6MWT) was 54 m with a decrease in saturation of arterial percutaneous blood oxygen (SpO_2) to 85%. Ultrasound cardiography (UCG) showed nearly normal left ventricular wall motion and a tricuspid regurgitation pressure gradient (TRPG) of 33 mmHg. Ventilation perfusion scintig-
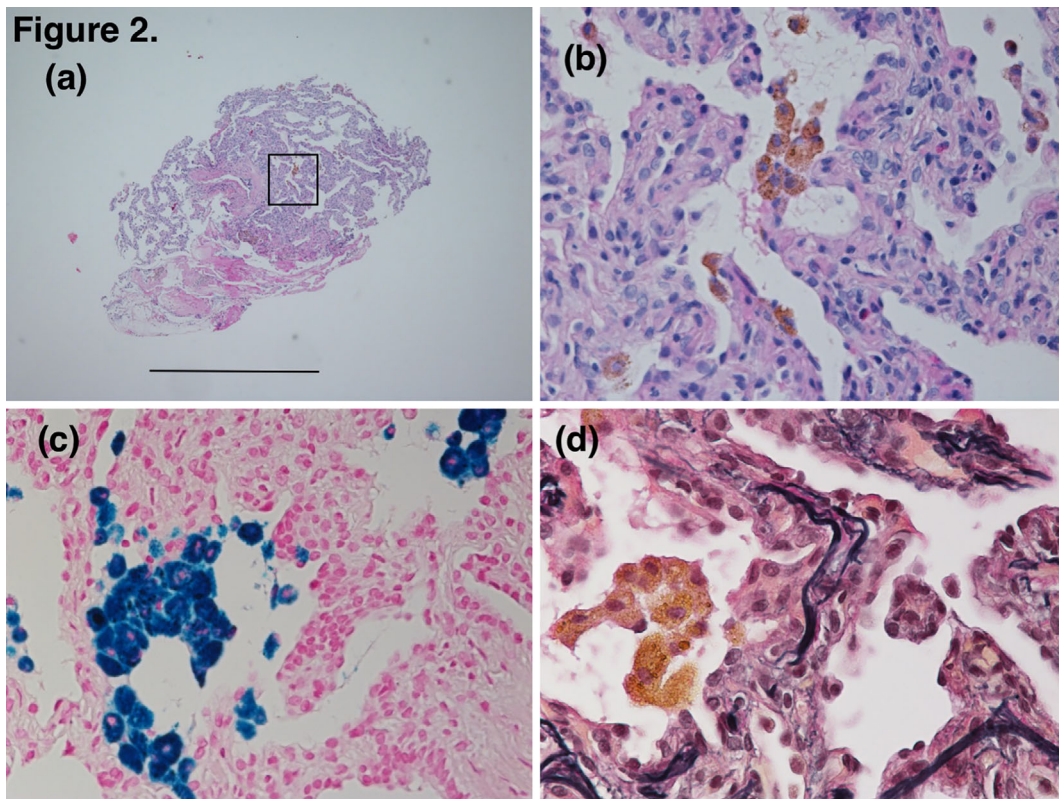
Figure 2.   **Histopathologic findings of the transbronchial lung biopsy specimens performed in November 2010. (a) A lung specimen measuring 1.2×2 mm biopsied from S^8 of the right lung showed diffuse alveolar wall thickening measuring 12.5-50 μm in thickness (normally 1.0-5.0 μm in thickness, including pneumocytes) with alveolar septal fibrosis, mild infiltration of lymphoid cells and eosinophils, and hyperplasia of the pneumocytes. The alveolar macrophages were filled with brown (hemosiderin) pigments in the cytoplasm measuring 0.1-2.5 μm [Hematoxylin and Eosin (H&E) staining, ×4, scale bar=1 mm]. (b) Higher magnification of the area shown in panel (a) (H&E staining, ×60). (c) The adjacent section of lung specimen measuring 1.1×2.1 mm stained with the Berlin blue method showed more blue-stained hemosiderin-laden macrophages in the terminal air spaces than was expected by H&E staining findings (Berlin blue stain, ×60). (d) Weigert's elastic tissue stain of the lung tissue showed elastic fibers and small blood vessels in the alveolar walls. However, the authors could find no occlusive features of the pulmonary veins (Weigert's elastic tissue stain, ×60).**

raphy showed no mismatch and no defect. A bronchoscopic examination revealed normal bronchial mucosa. Bronchoalveolar lavage (BAL) was performed in the right B^{5}a. The recovery rate of BAL fluid (BALF) was 72%, and the total cell count in BALF was 7.09×10^5/mL with subset counts of 96.5% macrophages, 3.0% lymphocytes, and 0.5% neutrophils. The CD4/CD8 ratio of the lymphocytes was 1.13, and no pathogens were detected. Hemosiderin-laden macrophages were observed in the BALF. The Golde score to assess alveolar hemorrhaging was 93 (normal 0-20, medium 20-70, high >70) (5).

A transbronchial lung biopsy (TBLB) was obtained from B^{8}a and B^{3}a of the right lung. The two lung specimens from the right B^{8}a showed mural alveolitis with fibrotic thickening and mild infiltration of lymphoid cells and a few eosinophils in the alveolar walls. Macrophages in the terminal air spaces showed brown pigments in the cytoplasm, suggesting hemosiderin. Occlusion/stenosis of the pulmonary veins was

not evident in the TBLB specimens (Fig. 2). The two lung specimens from the right B^{3}a showed mucin and fragmented ciliated epithelium without alveolar structures (not shown). No malignant cells or granulomas were detected. An SLB was not conducted at the time due to the patient's obesity. Approximately 1 year after the TBLB, the patient's body weight had decreased to 86 kg (BMI=34.9), and a surgical biopsy was performed on the left lung (S^4 and S^8) in November 2011. Pulmonary hypertension was not examined precisely before the lung biopsy, with increased titers of amino-terminal pro-BNP 481 ng/mL (normal, <125). After the lung biopsy, she required continuous positive airway pressure (CPAP) therapy for two days due to severe respiratory failure. The SLB specimens showed multifocal centrilobular accentuation with fibrotic lesions of the alveolar walls and luminal stenosis and occlusion of the small pulmonary veins. Hemosiderin-laden macrophages were confirmed in the alveolar airspaces via Berlin blue staining,
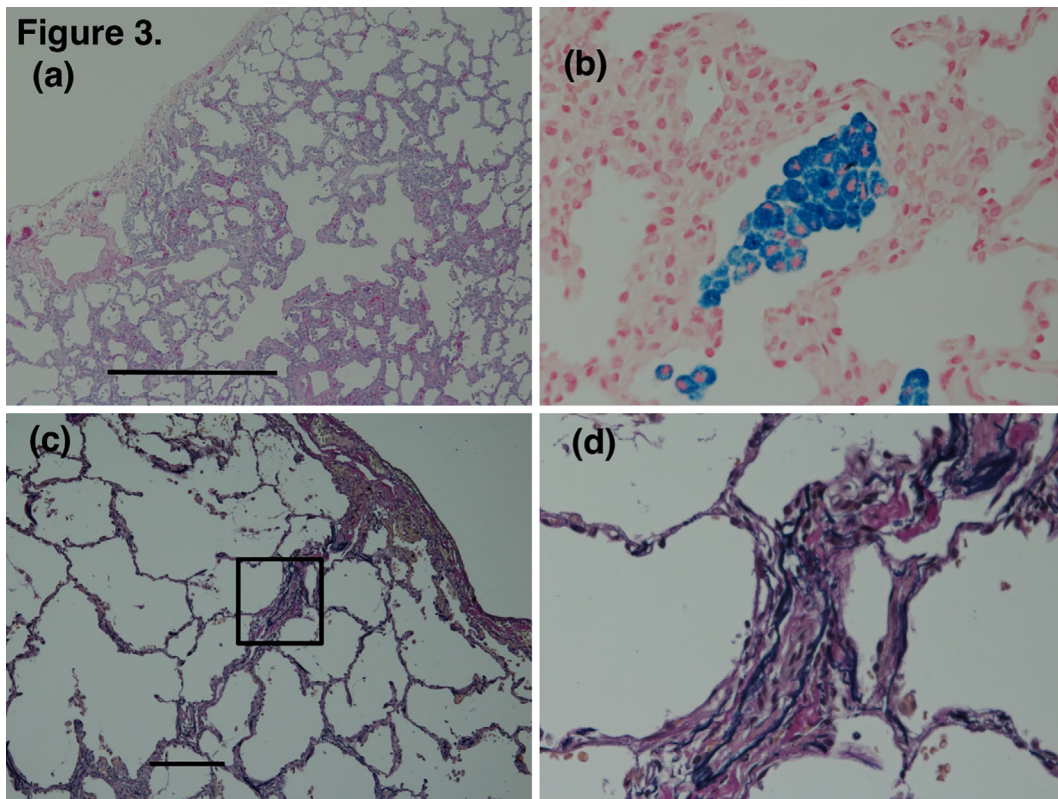
Figure 3. Video-assisted surgical lung biopsy findings in November 2011. Lung tissues were biopsied from the left lung (S^4 and S^8). (a) Lung tissue from the left lower lobe (S^8). The lung tissue showed centrilobular accentuation of alveolar septal thickening with infiltration of lymphoid cells and fibrotic lesions, findings suggestive of PVOD (Hematoxylin and Eosin staining, ×4, scale bar=1 mm). (b) Intra-alveolar macrophages showed marked hemosiderosis in the cytoplasm (Berlin blue stain, ×40). (c) Lung tissue from the left upper lobe (S^4). Medium-power magnification showed luminal occlusion of a small pulmonary vein in a lobule with intimal fibrosis (Weigert's elastic van Gieson stain, ×10, scale bar=200 μm). (d) Higher-magnification image of the same area shown in panel (c). The small pulmonary vein was occluded by intimal fibrosis, a diagnostic finding of PVOD (Weigert's elastic van Gieson stain, ×40). PVOD: pulmonary veno-occlusive disease

suggesting chronic hemorrhaging in the alveolar areas (6). Based on these histopathologic findings, we made a diagnosis of PVOD in November 2011 (Fig. 3). The alveolar walls involved in the pathologic spectrum of PVOD showed thickening with capillary proliferation [so-called pulmonary capillary hemangiomatosis (PCH)-like lesions]. Many muscular pulmonary arteries showed medial thickening. Intimal thickening was observed in a small number of muscular pulmonary arteries. PCH-like lesions were not observed in the bronchiolovascular sheath, interlolular septae or visceral pleura (Fig. 4).

The patient was treated with oxygen therapy with no specific medication. She was hospitalized again to prepare for lung transplantation in January 2012. At that time (January 2012), chest radiography showed increased GGO and enlargement of the pulmonary artery (Fig. 1b). HRCT revealed increased GGO, interlobular septal thickening, peribronchovascular interstitial thickening, and a mild degree of bilateral pleural effusion. In addition, bronchial stenosis was suspected. (Fig. 1d and f). UCG revealed that the TRPG had increased to 76 mmHg, and the left ventricle was com-

pressed by the right one. Right heart cardiac catheterization revealed a mean pulmonary artery pressure, 45 mmHg; pulmonary capillary wedge pressure, 14 mmHg; cardiac output, 4.14 L/m; cardiac index, 2.17 L/min/m²; and pulmonary vascular resistance, 738.5 dyne·sec·cm⁻⁵. She was registered as a lung transplant recipient in the same month. As her condition, including right heart failure and respiratory failure, was worsening, invasive positive pressure ventilation was initiated in the respiratory care unit in February 2012. However, her cardiopulmonary function continued to worsen, and she ultimately passed away on the day ventilator management was initiated in February 2012, one month after being registered for a lung transplant (Fig. 5).

Before her death, no drugs, including steroids, immunosuppressive agents, or specific agents, were administered for pulmonary hypertension. A systematic autopsy was performed. Her body weight was approximately 80 kg. Essential abnormalities were almost entirely restricted to the lungs and heart, except for two uterine leiomyomas. The pleural fluid volume was 645 mL in the right pleural cavity and 295 mL in the left pleural cavity. The pericardial fluid was 50
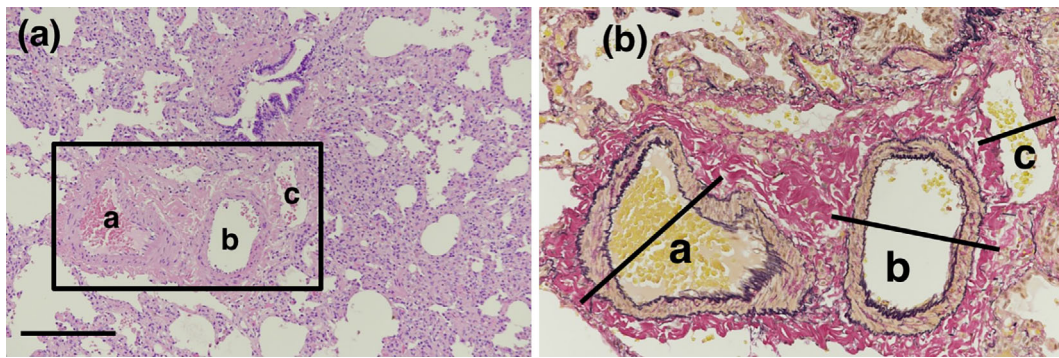
Figure 4. **Vascular lesions of the surgical lung biopsy specimens (left S4). (a) Muscular pulmonary arteries accompanying terminal bronchiole and a lymphatic vessel were observed. They were surrounded by pulmonary capillary hemangiomatosis (PCH) -like lesions on the alveolar walls (Hematoxylin and Eosin staining, ×10, scale bar=200 μm). (b) Higher-magnification image of the rectangular area of (a). A muscular pulmonary artery (a) measuring 205 μm between the external elastic layers (external vessel diameter, ED), showed a medial thickness (%MT) of 27.3%. The percentage of intimal thickness (%IT) was 0%. Another muscular artery (b) with an ED of 175 μm showed a %MT of 22.4% and %IT of 7.3%. Both muscular arteries had a %MT exceeding 7%. A dilated lymphatic vessel measuring 55 μm in diameter was observed. These measurements were made along the axes of the vessels shown in the figure. PCH-like lesions were not observed in the bronchiolovascular sheath (11, 12). PCH: pulmonary capillary hemangiomatosis**
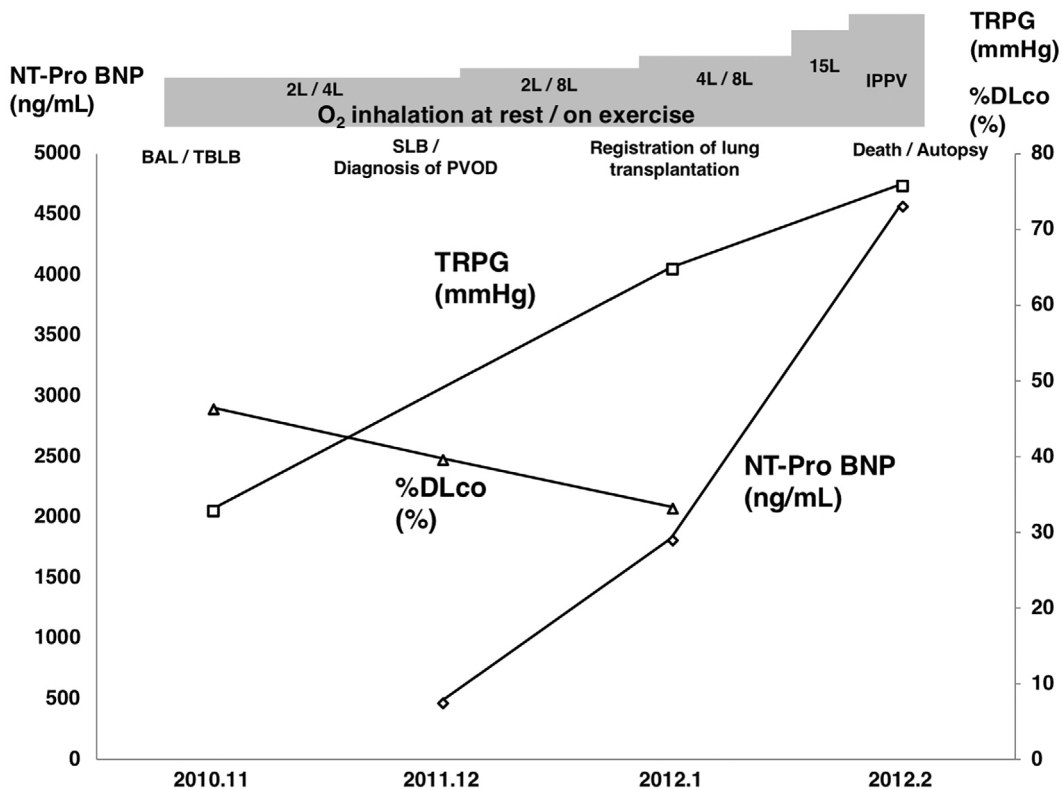
Figure 5. **Clinical course from November 2010 through February 2012. The cardio-pulmonary function worsened, and the patient died about 14 months after the first admission. NT-pro BNP: amino-terminal pro-brain natriuretic peptide, TRPG: tricuspid regurgitation pressure gradient, %DL$_{CO}$: percentage of predicted lung diffusion capacity for carbon monoxide, BAL: bronchoalveolar lavage, TBLB: transbronchial lung biopsy, SLB: surgical lung biopsy, PVOD: pulmonary veno-occlusive disease**

mL, while the peritoneal fluid was 38 mL. The lungs weighed 1,505 g, and the heart weighed 340 g and exhibited thickness of the right ventricle (2 mm) and left ventricle (12 mm) (Fig. 6). The myocardial cells in the right ventricle
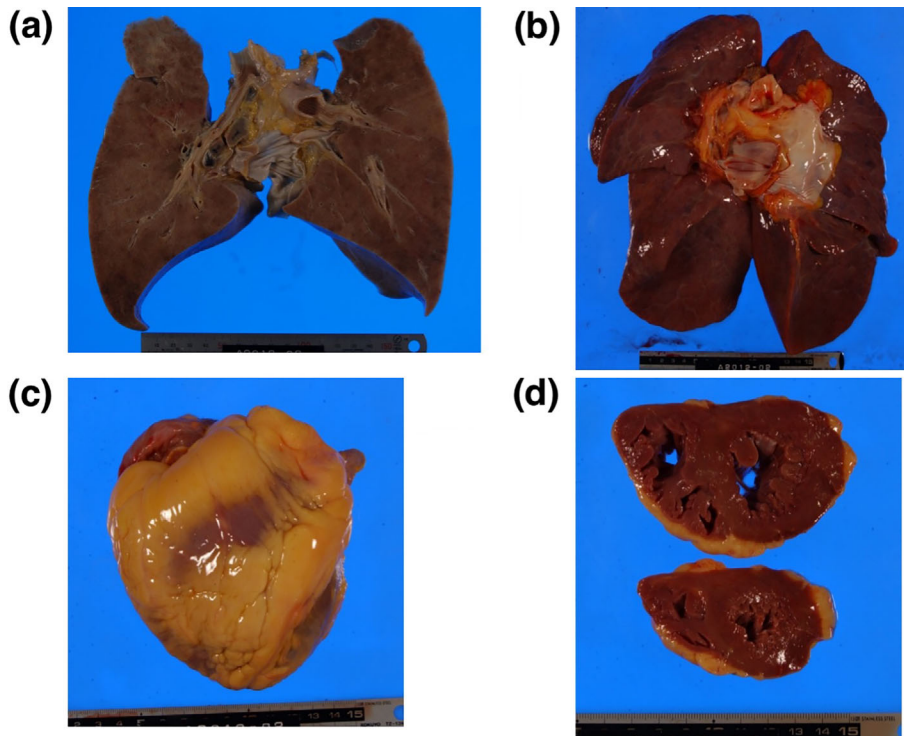
Figure 6. Macroscopic findings of the autopsied lungs and heart in February 2012. (a, b) The lungs weighed 1,505 g. On the cut surfaces of the lungs, there were reddish lesions measuring 1×1 mm to 3×1 mm in the central portion of almost all secondary lobules. There were no findings of mass lesions, pulmonary emphysema, bullae, honeycombing of the lung, bronchiectasis, mucoid impaction of the bronchi, or thrombosis of the major pulmonary blood vessels. (c, d) The heart weighed 340 g. The thickness of the myocardium was 2 mm in the right ventricle and 12 mm in the left ventricle. The right ventricle showed an enlarging tendency.

were hypertrophic compared to those in the left ventricle (Fig. 7).

No malignant neoplasms or granulomas were noted in the 85 paraffin blocks taken from the thoracic and abdominal organs. The 36 autopsy specimens of the lungs were taken from all lobes. The lung tissue findings confirmed PVOD histologically, with a progressive form of fibrotic lesions along the alveolar walls and centrilobular accentuation, as well as occlusion of the small pulmonary veins with intimal fibrosis and hemosiderin-laden macrophages in the pulmonary alveoli (Fig. 8). Many muscular pulmonary arteries showed increased thickness of the medial layer, as in Fig. 4. Several muscular arteries showed a marked increase in the thickness of the medial and intimal layers. Alveolar walls with centrilobular accentuation showed thickening with PCH-like lesions. However, the PCH-like lesions were not observed in the bronchiolovascular sheaths, interlobular septae, or visceral pleura (Fig. 9). The major pulmonary artery trunk showed mild atherosclerotic lesions (not shown). The bronchial structures of the lungs showed mild-to-moderate luminal stenosis due to the edematous lesions, dilation of lymphatic vessels, and engorgement of small blood vessels in the subepithelial layers with preservation of the ciliated epithelial layers (Fig. 10). The direct cause of death was considered to be a marked increase in the resistance of the pulmonary circulation due to luminal occlusion of numerous small pulmonary veins and secondary right-sided cardiac failure.

Discussion

We herein report a rare case of PVOD diagnosed via an SLB. Clinically, this was thought to be a case of idiopathic PVOD at the time of the SLB (November 2011) without a specific trigger factor (2), although her younger brother was later diagnosed with PVOD at another hospital a few years later. The PVOD in the present case might have been hereditary, although there was no genetic examination performed. To our knowledge, this is the first report of the histological characteristics of PVOD based on three successive histological examinations (TBLB, SLB, and postmortem autopsy findings). It took time to make a definitive diagnosis of the disease because the HRCT findings were similar to those associated with subacute hypersensitivity pneumonitis, and the pulmonary hypertension in this patient was not obvious on admission. It took approximately one year for the patient to receive an SLB after her initial admission and TBLB, primarily due to her obesity.

Although a histological analysis of a lung sample is still considered the gold standard for obtaining a definitive diag-
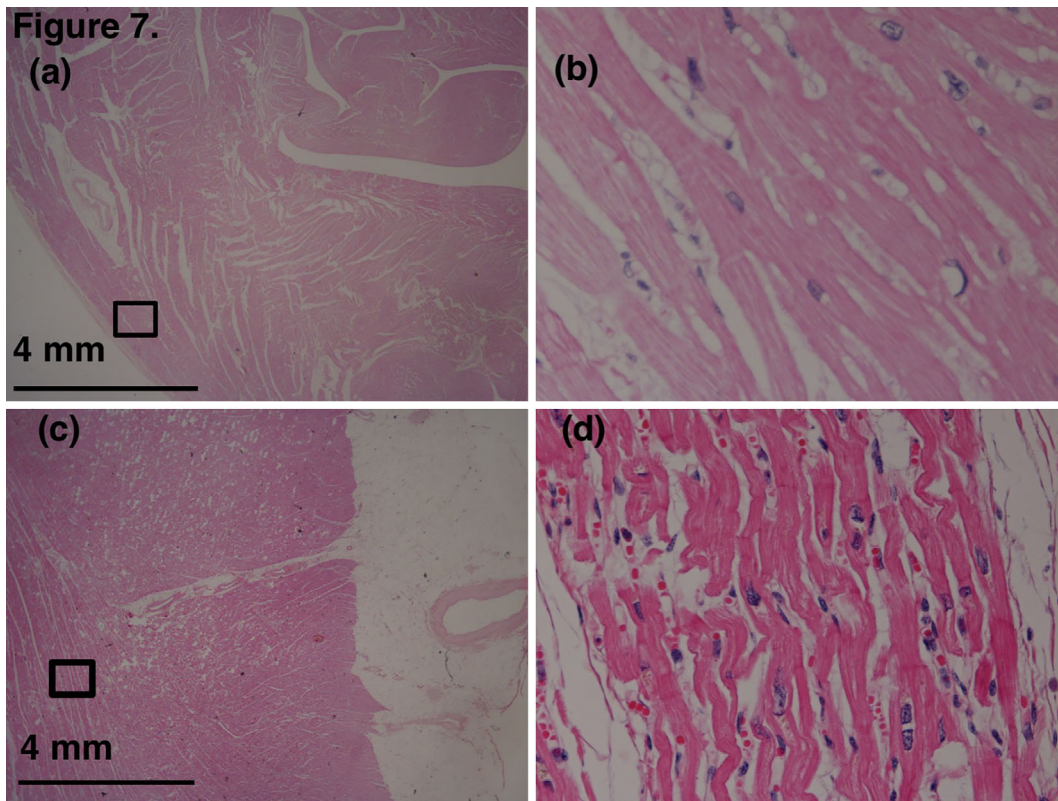
Figure 7. Microscopic findings of the right and left ventricles of the heart. (a, b) Lateral wall of the right ventricle. (a) The thickness of the myocardium was 1.2 mm in the thinnest area (not shown in the a) [Hematoxylin and Eosin (H&E) staining, ×1, scale bar=4 mm]. (b) Higher-magnification image of the rectangular area of (a) (H&E staining, ×40). The mean of the top 5 thickness of myocardial cells was 32.3 μm (range: 30-35 μm). (c, d) Lateral wall of the left ventricle. (c) The thickness of the myocardium was 9.0 mm (H&E staining, ×1, scale bar=4 mm). (d) Higher-magnification image of the rectangular area of (c) (H&E staining, ×40). The mean of the top five thicknesses of the myocardial cells was 18.6 μm (range: 13.75-25 μm).

nosis of PVOD, an SLB is too invasive for these frail patients (2). The histopathologic diagnosis of PVOD is therefore rarely made via an SLB. The authors were unable to make a diagnosis of PVOD using TBLB specimens, although unexplained hemosiderosis of the alveolar macrophages was noted in the setting of diffuse alveolar septal fibrosis and inflammation in our non-smoker patient. In most cases reported in the literature, the diagnosis of PVOD is based on autopsy specimens (3, 4). Thus, this was a rare case of PVOD diagnosed via an SLB and autopsy in addition to the TBLB findings.

The American Thoracic Society/European Respiratory Society guidelines recommend that multidisciplinary discussions including SLB findings be held in order to diagnose idiopathic interstitial pneumonias (7); however, SLBs are associated with a risk of morbidity and mortality in patients with pulmonary hypertension (8). Indeed, the current patient developed severe respiratory failure after the SLB, requiring immediate CPAP for two days in the respiratory care unit.

The Japan Intractable Diseases Information Center suggests the following clinical diagnostic criteria for PVOD (9): 1) pulmonary artery hypertension including a mean pulmonary artery pressure at rest ≥25 mmHg, pulmonary vascular resistance ≥3 Wood Units, and pulmonary wedge pressure ≤ 15 mmHg from right heart catheterization; 2) HRCT findings of thickness of the interlobular septa, small nodules, reticular opacities, GGOs and swelling of the mediastinal lymph nodes, and exclusion of other interstitial lung diseases; and 3) induction of pulmonary edema by specific pulmonary artery dilator agents, such as endothelin receptor antagonists, phosphodiesterase 5 inhibitors, and prostacyclin. A reduced %DL$_{CO}$, reduced arterial partial pressure of oxygen and reduced peripheral capillary oxygen saturation in the 6MWT (2), and occult alveolar hemorrhaging observed in the BAL (2, 6) also suggest a diagnosis of PVOD. In the current patient, PVOD was not suspected during the first admission because pulmonary hypertension was not obvious and the chest CT findings were similar to those associated with other interstitial lung diseases complicated by obesity. Subacute hypersensitivity pneumonitis was considered at the time of the TBLB due to the two-month history of exertional dyspnea, centrilobular GGO found on HRCT, and TBLB findings of mural alveolitis with infiltration of lymphoid cells in the alveolar walls. However, her condition was atypical of subacute hypersensitivity pneumonitis because there was 1) no increase in numbers of lymphocytes
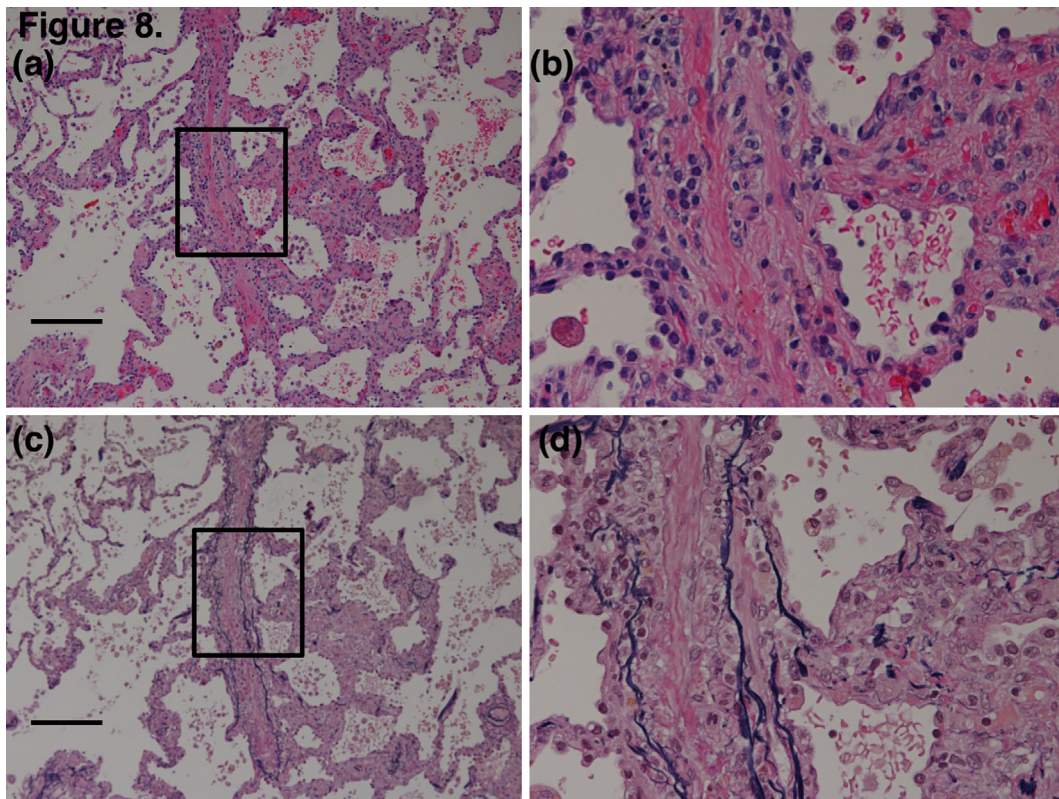
Figure 8. Veno-occlusive lesions in the interlobular septum of the autopsied lungs (left S^{1+2}). (a, c) A small vein was almost occluded. The small vein with a diameter of 40-60 μm between the elastic fibers showed increased stroma and nucleated cells between the endothelial cells and elastic fibers [a: Hematoxylin and Eosin (H&E) staining ×10, c: Weigert's elastic van Gieson stain ×10, scale bar=200 μm]. (b, d) Higher-magnification image of the area shown in panels (a) and (c). Veno-occlusive lesions or marked stenosis of the pulmonary veins with more than 85% stenosis of the venous lumens were observed in the interlobular septae and in the intra-lobular pulmonary veins in the present case (b: H&E staining ×40, d: Weigert's elastic van Gieson stain ×40).
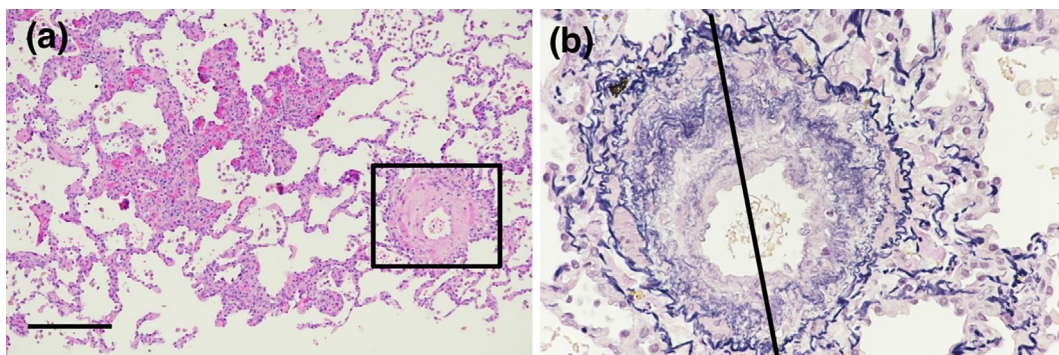
Figure 9. Alveolar septal capillary and muscular pulmonary artery lesions of the autopsied lungs (left S1+2). (a) Alveolar septae showed marked thickening with proliferated capillaries and fibrotic changes [so-called pulmonary capillary hemangiomatosis (PCH)-like lesions], while several alveolar walls were normal in thickness. A muscular pulmonary artery showed medial and intimal thickening with moderate luminal stenosis. PCH-like lesions were not observed in the adventitial layer of the muscular pulmonary artery (Hematoxylin and Eosin staining, ×10, scale bar=200 μm). (b) Higher-magnification image of the rectangular area of (a). The external vessel diameter (ED) was 210 μm, while the internal vessel diameter (ID) was 75 μm along the axis in the figure. The percentage medial thickness (%MT) was 35.3%, which was greater than 7%, while the percentage intimal thickness (%IT) was 49% along the axis in the figure. The muscular pulmonary artery showed medial hypertrophy and intimal fibrosis, a finding considered to be consistent with pulmonary hypertension (Weigent's elastic tissue stain, ×40) (2, 11, 12). PCH: pulmonary capillary hemangiomatosis
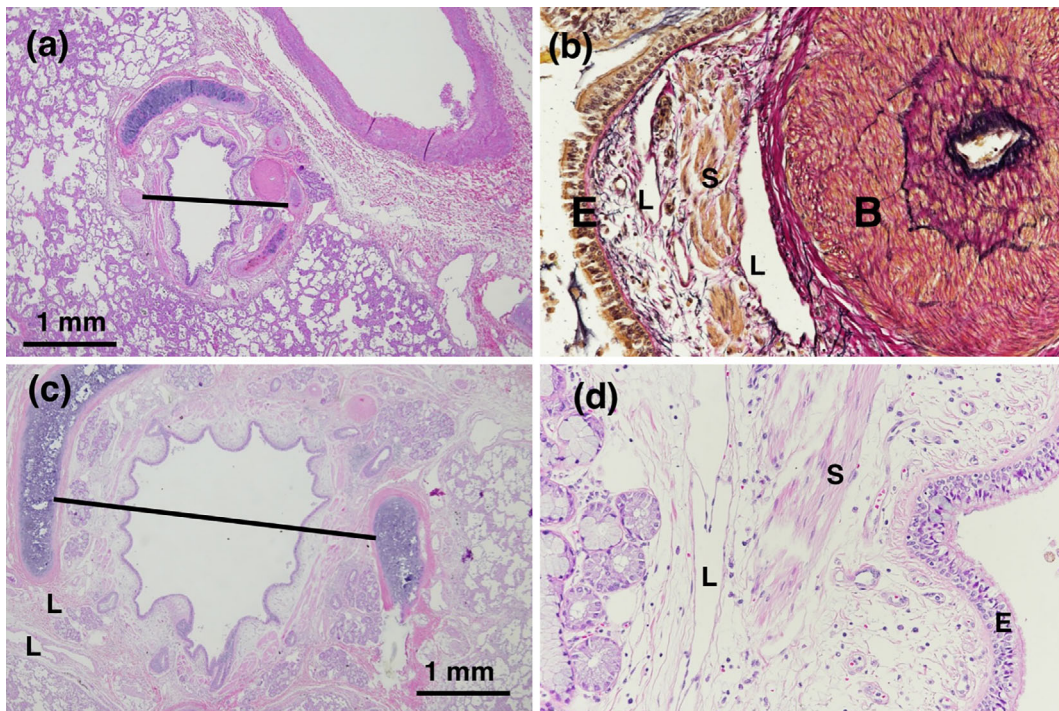
Figure 10. Luminal stenosis of the bronchial structures. (a-d) Bronchial structures with cartilaginous tissues in the bronchial wall were observed in 4 places among the 19 paraffin blocks of the right lung and in 3 places among the 17 paraffin blocks of the left lung. The bronchial luminal diameter (BLD) and the inter-cartilage diameter (ICD) of each bronchial structures were measured along the axis, as shown in (a, c). The ratio of BLD per ICD (BLD/ILD ratio) was calculated as a parameter of bronchial stenosis. (a, b) A bronchial structure observed at the right lower lobe (segment 10). The BLD/ICD ratio was 56.86%. (c, d) Only in one section of the bronchial structures among the seven places where the round slices of the bronchial structure were observed as in (a) and (c), the marked hypertrophy of the medial layer of a muscular type bronchial artery (B) was noted. A bronchial structure observed in the upper lobe (segment 3) of the left lung. The BLD/ICD ratio was 56.86%. Lymphatic vessels (Ls) around the bronchial structure were dilated, as noted in (c). The causes of bronchial luminal stenosis were edematous lesions, dilation of Ls with a valvular structure, and engorgement of small blood vessels in the subepithelial layers of the bronchial structures. These changes were considered to have been caused by secondary effects from the occlusion and marked stenosis of multiple pulmonary veins in the parenchyma of the bilateral lungs. The ciliated bronchial epithelial layer (E) was preserved without goblet cell hyperplasia or significant infiltration of eosinophils, as observed in (a, b) and (c, d). The BLD/ICD ratios of the 4 bronchial structures observed in the right lung ranged from 38.61% to 50.00% (mean, 43.09%). The BLD/ICD ratios of the 3 bronchial structures observed in the left lung ranged from 37.76% to 56.86% (mean, 45.93%). In contrast, the BLD/ICD ratios of the 5 normal bronchial structures of 4 non-smoking women (age: 53-79 years old, mean age: 65.5 years old) who underwent lobectomy (n=3) or segmentectomy (n=1) for primary pulmonary adenocarcinoma [pathologic stage IA (n=3) and stage IB (n=1)] at the National Hospital Organization Minami Wakayama Medical Center from April 2015 ranged from 65.77% to 91.49% (mean, 75.15%) (unpublished data). Therefore, all seven bronchial structures of the present case of PVOD were confirmed histologically to reveal bronchial stenosis at the time of autopsy. [a, c: Hematoxylin and Eosin (H&E) staining, ×1, scale bar=1 mm, b: Weigert's elastic van Gieson stain, ×20, d: H&E staining, ×20]. S: smooth muscle layer between the epithelial layer and the cartilage in the bronchial structure, BLD: bronchial luminal diameter, ICD: inter-cartilage diameter, BLD/ICD ratio: bronchial luminal diameter per inter-cartilage diameter ratio (%) of a bronchial structure

in the BALF, 2) no increase in serum levels of KL-6, 3) no improvement even after hospitalization that included environmental isolation during treatment, and 4) observations of hemosiderosis in the alveolar macrophages in the TBLB specimens despite no history of smoking (10). Although it was a relatively obscure possibility, in retrospect, we should have investigated the possibility of PVOD by performing non-invasive examinations before the SLB and started preparations for a lung transplant as soon as possible.

In conclusion, we encountered a rare case of PVOD diag-

nosed via an SLB and autopsy with histologic findings of TBLB specimens that were obtained one year before the SLB. When clinicians encounter patients with interstitial lung disease, they should not forget the possibility of PVOD and be alert for emerging pulmonary hypertension. When pathologists observe unexplained pulmonary hemosiderosis of alveolar macrophages in the TBLB specimens, as shown in Fig. 2, in the clinical setting of bilateral diffuse infiltrative lung disease, especially in non-smokers, they also should consider the possibility of PVOD in order to improve the prognosis.

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