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Case report

Pulmonary capillary hemangiomatosis-predominant vasculopathy in a patient with rheumatoid arthritis-associated interstitial lung disease: An autopsy report

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ABSTRACT

Pulmonary capillary hemangiomatosis (PCH) is a rare cause of pulmonary hypertension (PH) associated with poor prognosis. Clinically, it is characterized by severe hypoxemia, centrilobular ground-glass opacities on computed tomography, and pulmonary congestion triggered by pulmonary vasodilating therapy. In some cases, PCH has been reported to develop with other disorders including connective tissue disease; however, to date, no reports have described PCH in a patient with rheumatoid arthritis. We report a case of a 59-year-old male PCH patient with rheumatoid arthritis and associated pulmonary fibrosis. He was initially diagnosed with severe group 3 PH and received sildenafil, which generated a favorable hemodynamic response. However, 5 years later, his pulmonary hemodynamics deteriorated, and he died at the age of 67. An autopsy was performed, and thickening of alveolar septa and capillary proliferation, pathological features of PCH, were extensively observed in both lungs. We discuss when PCH developed, how sildenafil improved his hemodynamics, and how PCH could be clinically detected by noninvasive evaluations.

1. Introduction

Pulmonary capillary hemangiomatosis (PCH) is a rare cause of pulmonary hypertension (PH), which typically coexists with pulmonary veno-occlusive disease (PVOD). Clinically, PCH is characterized by severe hypoxemia, centrilobular ground-glass opacities on high resolution computed tomography (HRCT), and pulmonary congestion triggered by an administration of pulmonary vasodilator(s) [1–3]. PCH may develop without any comorbid diseases; however, in some cases, it occurs in association with conditions such as connective tissue disease (CTD) and the use of anticancer agents [3–5]. Among CTDs, systemic sclerosis is the most well-known underlying disease for PCH. Conversely, rheumatoid arthritis (RA) often is a common autoimmune disease that is not considered to be an underlying condition for PCH. In the present report, we describe a 59-year-old man with RA and PH, who exhibited a favorable response to sildenafil. Five years later, however, pulmonary hemodynamics worsened, and he eventually died of right heart failure. In the autopsy, we unexpectedly found extensive PCH-like changes in both lungs. Here, we report the histopathological details of the pulmonary vasculopathy and discuss when PCH might have developed in this patient and how it could have been clinically recognized at an early stage.

2. Materials and methods

In 2009, a 59-year-old man with RA was referred to our department for evaluation of interstitial infiltrates on chest X-ray. He was on prednisolone (5 mg daily), etanercept (25 mg weekly), and salazosulfapyridine (1000 mg daily) for RA. His anti-cyclic citrullinated peptide antibody level was elevated to >100 U/ml (normal range: <4.5 U/ml). His antinuclear antibody titer was also elevated at 1:160, but specific autoantibodies of autoimmune diseases other than RA were negative. His arterial gas analysis indicated that PaO2 was 69.8 mmHg and PaCO2 was 40.1 mmHg on room air. His chest high resolution computed tomography (HRCT) indicated honeycomb changes extensively in both

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Abbreviations

CTD	connective tissue disease
DOE	dyspnea on exertion
HRCT	high resolution computed tomography
PAH	pulmonary arterial hypertension
PAP	pulmonary arterial pressure
PCH	pulmonary capillary hemangiomatosis
PDE	phosphodiesterase
PH	pulmonary hypertension
PVOD	pulmonary veno-occlusive disease
RA	rheumatoid arthritis
RHC	right heart catheterization

lower lobes along with subpleural fibrosis in upper and middle lobes. On pulmonary function test, forced vital capacity (FVC) was 1.91 L (56% of predicted), forced expiratory volume in 1 second ($FEV_{1.0}$) was 1.65 L (61% of predicted), and the diffusing capacity of the lungs for carbon monoxide (DLco) was 4.76 mL/min/mmHg (24.9% of predicted).

Regarding his pulmonary hemodynamics, his electrocardiogram did not indicate right atrial/ventricular hypertrophy, and serum brain-type natriuretic peptide (BNP) concentration was slightly elevated at 22.7 pg/mL (normal range: 0–18.4 pg/mL). On echocardiography, there were no right atrial/ventricular dilatation and transtricuspid pressure gradient (TRPG) was unmeasureable since there was no detectable tricuspid regurgitation. These suggested no or negligible PH at this time and, thus, right heart catheterization (RHC) was not conducted. This comprehensive work-up led to the diagnosis of interstitial pneumonia associated with RA, or RA-lung, without PH. He was prescribed supplemental oxygen therapy and his medical treatment was unchanged.

Two years later, however, he reported a worsening of dyspnea and hypoxemia. His chest X-ray exhibited a slight cardiomegaly (cardiothoracic ratio of 54%), but no noticeable changes in the interstitial infiltrates **(Fig. 1)**.

His electrocardiogram showed a high R wave in lead V1, a deep S wave in lead V5, and a rightward shift of the QRS axis, indicative of right ventricular hypertrophy (Fig. 2).

On blood examination, serum BNP concentration had increased to 843.3 pg/mL. Arterial blood gas analysis indicated reduced PaO2 (61.9 mmHg) and slightly low PaCO2 (33.7 mmHg) on 7 L/min of oxygen via oxygen mask. HRCT showed a honeycomb pattern in both lower lobes and subpleural reticular shadows in upper and middles lobes **(Fig. 3)**, with no significant disease progression compared to the CT images taken 2 years ago. At this time, no findings suggestive of PCH, such as centrilobular ground-glass opacities or mediastinal lymphadenopathy, were present.

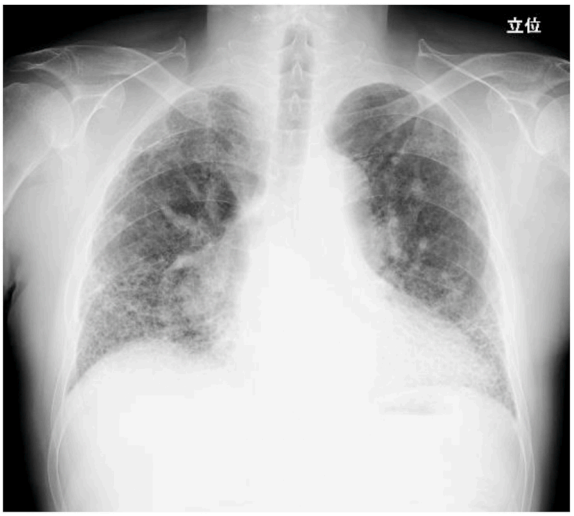

Fig. 1. Chest X-ray taken two years after the initial assessment.

On pulmonary function test, FVC was 2.06 L (60% of predicted), and $FEV_{1.0}$ was 1.78 L (68% of predicted), both of which were largely stable as compared with the previous data. In contrast, DLco had decreased to 1.59 mL/min/mmHg (8.8% of predicted). Echocardiography showed an enlarged right ventricle, the interventricular septum bowing toward the left ventricle, and an increased TRPG (117 mmHg), which indicated a significant increase in pulmonary arterial pressure (PAP) during the preceding 2 years. The patient underwent first RHC, which showed an elevation of PAP (systolic/diastolic/mean, 85/43/52 mmHg, respectively) with normal pulmonary arterial wedge pressure (2 mmHg) and right atrial pressure (5 mmHg). Cardiac output and cardiac index were 4.14 L/min and 2.46 L/min/m^2, respectively, and pulmonary vascular resistance was 12.1 Wood units, indicative of severe precapillary PH. The pulmonary ventilation-perfusion scan was negative for pulmonary embolism. During the disease course, there was no serological or new clinical data to suggest a cause of his PH.

Regarding the classification of PH, the results of systematic work-up lead to the diagnosis of PH due to lung disease, i.e., RA-lung in this case. We did not conduct acute vasoreactivity test. Notably, however, we suspected a development/progression of PAH-like vasculopathy rather than the progress of ILD-associated PH, because spirometry and HRCT findings were stable, whereas BNP, echocardiography, and RHC indicated a noticeable elevation of PAP. Thus, considering the condition of "PAH phenotype" introduced in the latest guidelines [3], we cautiously started sildenafil (20 mg t.i.d.). The patient did not experience any adverse events such as worsening of hypoxemia, and during the following five months, his shortness of breath significantly improved. Additionally, DLco increased to 3.04 mL/min/mmHg (17% of predicted), and RHC showed an improvement in pulmonary hemodynamics (mean PAP, 35 mmHg; CO, 4.59 mL/min; PVR, 5.9 Wood units). A follow-up RHC performed 2 years later also revealed well controlled pulmonary hemodynamics (mean PAP, 28 mmHg; CO, 4.59 mL/min; PVR, 4.7 Wood units). The patient's clinical condition remained stable for the next 2 years. However, at the age of 66 years, dyspnea on exertion (DOE) and hypoxemia worsened, without a progression of RA-lung evaluated by spirometry and HRCT, but with a deterioration of pulmonary hemodynamics (mean PAP, 50 mmHg; CO, 4.09 mL/min; PVR, 11.7 Wood units). We added 10 mg of macitentan, which did not induce pulmonary edema or worsening of oxygen saturation; however, it did not improve his DOE and pulmonary hemodynamics. His general condition and hypoxemia gradually worsened, and he died of respiratory and right heart failure at the age of 67. During his clinical course, he experienced several episodes of pneumonia whereas respiratory infection was relatively controlled at the time of death. With written permission from his family, an autopsy was performed under an ethical approval by Graduate School of Medicine, Hokkaido University.

3. Autopsy

Upon gross observation, there were honeycomb-like changes in both lower lobes at low magnification **(Fig. 4A)**. In low magnification microscopic observation, obvious honeycomb-like changes were observed in both lungs **(Fig. 4B)**. Fibrotic changes were noted in the subpleural regions in the upper and middle lobes of the right lung and in the upper lobe of the left lung **(Fig. 4C)**. Fibroblastic foci were also noted **(Fig. 4D)**. These findings were consistent with interstitial pneumonia associated with RA (RA-lung). Of note, in most of the areas without honeycomb changes, the alveolar septa were thickened with capillary proliferation in two or more layers of endothelial cells **(Fig. 4E)**. The capillaries were immunohistochemically confirmed by highlighting the endothelial cells with the anti-CD34 antibody. Capillary proliferation

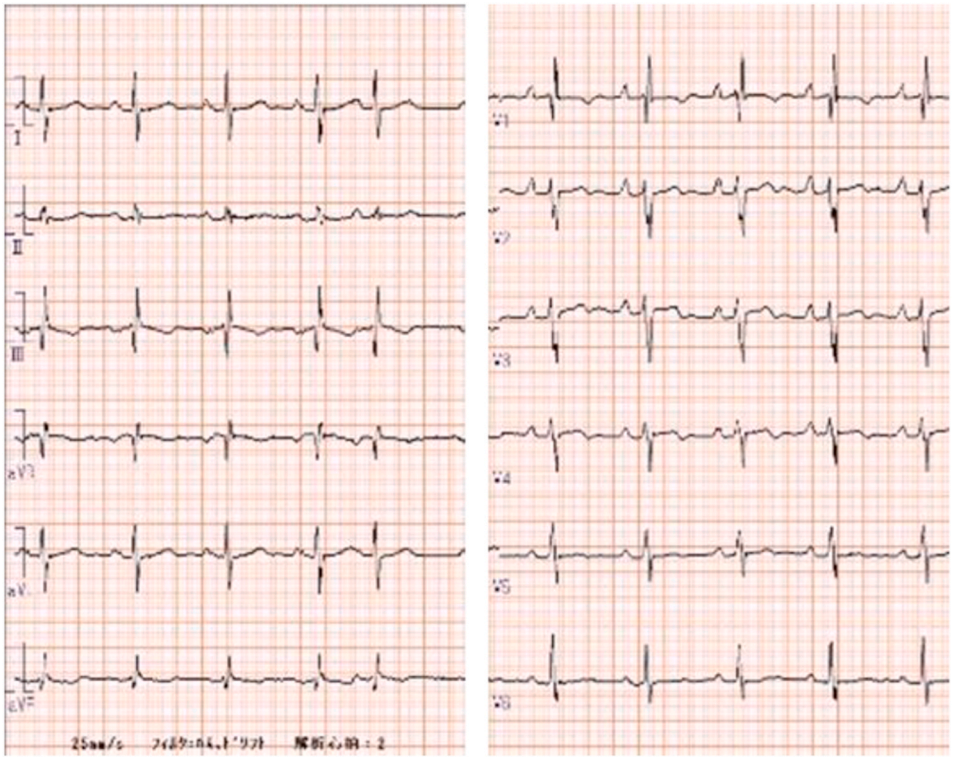

Fig. 2. Electrocardiogram two years after the initial assessment.

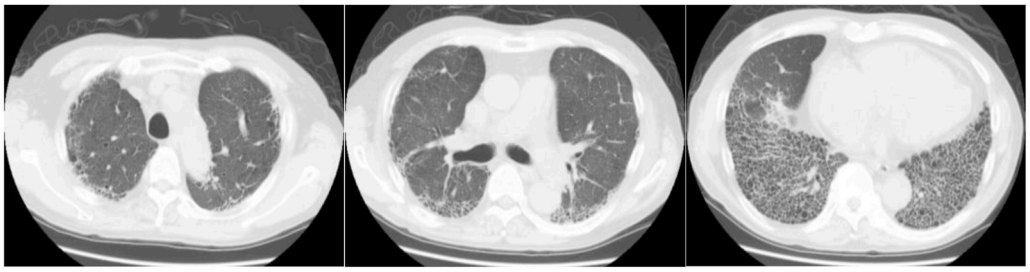

Fig. 3. High resolution computed tomography of the lungs.

was also observed surrounding the bronchial walls in some lesions (Fig. 4F). Hemosiderin-phagocytic macrophages were observed in the alveolar spaces (Fig. 4G). These findings were compatible with the findings of PCH [2,4], while there were a few areas with narrowed and/or occluded pulmonary veins, indicating PVOD. Arterial/arteriolar changes characteristic to PAH were minimally observed. Immunohistochemical study using anti-PDE5 receptor antagonist (ab64179, 1:200, Abcam, MA) exhibited an expression of PDE5 on the arterial/arteriolar walls, but not on the PCH/PVOD-like lesions (Fig. 4H).

A, Gross images of the lungs show honeycomb-like changes in both lower lobes. B, Honeycomb-like changes in the low-power view. C, Fibrotic changes in the subpleural regions. D, Fibroblastic foci. E, Capillary proliferation in the thickened alveolar walls in two or more layers of endothelial cells. F, Proliferative capillaries (CD34 positive) surrounding bronchial walls. G, Hemosiderin-phagocytic macrophages in the alveolar space. H, Immunohistochemical study using anti-PDE5 receptor antagonist exhibited an expression of PDE5 on the arterial/arteriolar walls (upper left inset), but no such expression was observed on proliferated capillary cells (lower right inset).

4. Discussion

The pathological hallmark of PCH is an abnormal proliferation of microvessels in the alveolar septa. There should be at least two layers of aberrant microvessels, by which PCH can be distinguished from mere capillary congestion. The microvessels often infiltrate into the adjacent bronchial and/or vascular walls. In addition, hemosiderin-laden macrophages are often observed in the alveolar spaces [6–8]. In the present case, these findings indicative of PCH were extensively observed in both lungs post-mortem. However, slight yet significant arterial/arteriolar and venous/venular changes were noted. Accordingly, we regarded the present case as PCH-predominant pulmonary vasculopathy that developed in a patient with RA-associated interstitial lung disease.

Prior studies have reported that PCH develops in patients with connective tissue disease(s) such as scleroderma and systemic lupus erythematosus [4,9]. To the best of our knowledge, this is the first report of PCH in a patient with RA.

In our case, it is uncertain whether PCH developed in association or independent of RA. Several recent reports have also documented PCH-like changes in cases with interstitial lung disease (ILD) [10–12]. This also raises the possibility that PCH might have developed in association with the interstitial lung disease process rather than with RA. However,

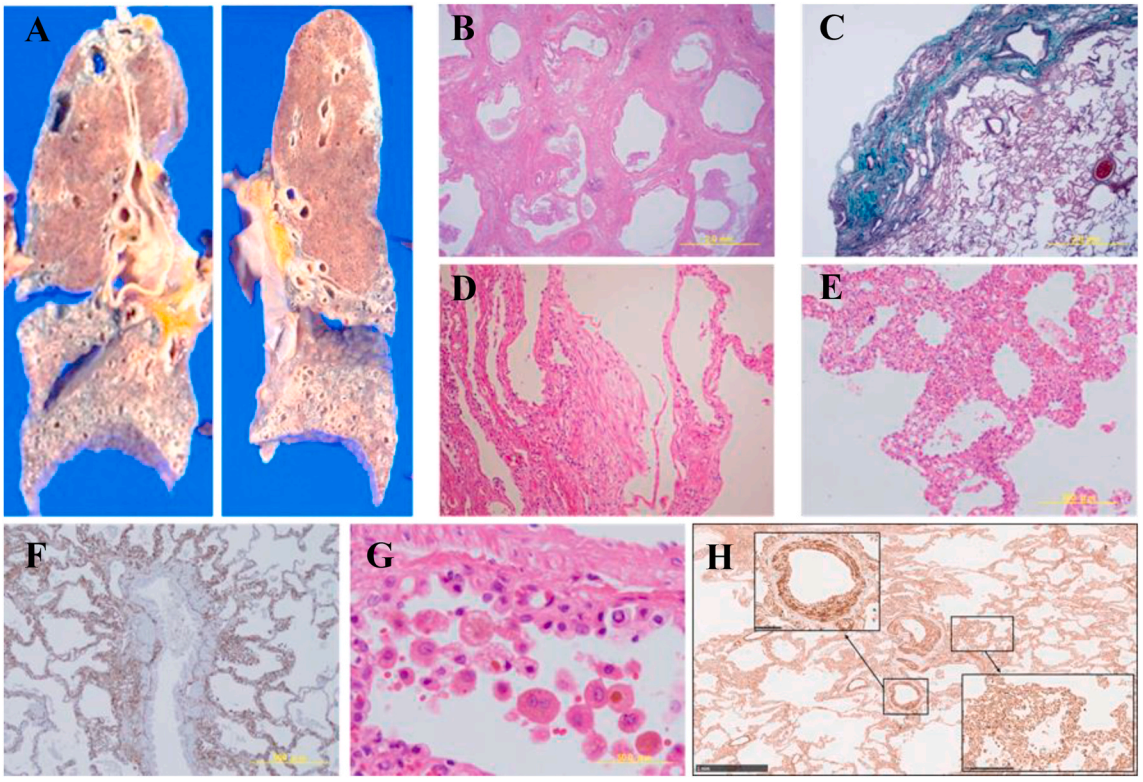

Fig. 4. Gross and microscopic images of the lungs.

PCH changes dominated in both upper lobes where minimal interstitial changes were present. Thus, the pathogenesis of PCH in association with RA and/or interstitial lung disease is still obscure and needs further exploration.

At the age of 66, our patient exhibited significant elevation of PAP and PVR confirmed by RHC. Retrospectively, this worsening of pulmonary hemodynamics might have reflected the development of PCH. We carefully reviewed the HRCT images, but were unable to notice any changes indicative of PCH. This is clinically important because HRCT is considered as a sensitive modality to detect PCH [13,14]. Thus, the present case suggested that the sensitivity of HRCT for the diagnosis of PCH is not necessarily high. Alternatively, a significant decrease in DLco was documented in our case, simultaneous with the worsening of dyspnea, hypoxemia, and hemodynamics. This indicates that a decrease in DLco, not accompanied either by a parallel decrease in lung volumes or noticeable changes in HRCT, should raise suspicion for the development of pulmonary vascular disease(s).

In some reports on PCH/PVOD, severe pulmonary edema developed following the introduction of pulmonary vasodilators [15,16]. In contrast, there have been some reports in which intravenous epoprostenol was useful as bridging therapy to lung transplantation [17]. In the present case, we used sildenafil (phosphodiesterase (PDE)-5 inhibitor), considering that he had a component of PAH. Prior reports, including ours, have indicated a favorable effect of PDE5 inhibitor(s) in severe Group 3 PH patients [18–20]. Regarding the use of pulmonary vasodilators to PH patients with ILD, current guidelines for PH recommend the use of such drugs only when the degree of PH is disproportionately high ("PAH phenotype") in patients with ILD [3]. Based on these recommendations, in our institution, we use pulmonary vasodilator(s) to Group 3 PH patients exclusively when they meet the following criteria: 1. PH being classified as "severe" (mean PAP ≧35 mmHg and/or CI < 2.5 L/min/㎡) [1–3], 2. Signs/symptoms and RHC results indicative of a progression of PH, and 3. Background lung disease considered to be stable by spirometry (except DLco) and CT. Our case met these three criterion.

Fortunately, in the present case, the patient showed an improvement in pulmonary hemodynamics following the start of sildenafil. This might be due to the vasodilatory effect of sildenafil on the arteries where PDE-5 was noted in the immunohistochemical study (Fig. 4H). However, after the worsening of hypoxemia and an increase in PAP 5 years after the introduction of sildenafil, he did not show any favorable response to an addition of macitentan. This might be a reflection of the transition of the patient's predominant vasculopathy from arteriopathy to PCH. Indeed, no prior reports have demonstrated any beneficial effects of endothelin receptor antagonists including macitentan on PCH despite its proven efficacy in PAH [21].

There is a widespread perception that PCH and PVOD are the same disease. In our case, however, the autopsy study exhibited extensive PCH-like changes in both lungs whereas there were only minor changes indicative of PVOD. This suggests that, at least in some cases, PCH and PVOD may not develop in parallel. Indeed, recent reports have focused small but significant differences between PCH and PVOD in physiological and radiological findings [22–24]. In these reports, relatively larger ground glass opacities with a poorly defined nodular pattern, and a lack of septal lines and lymph node enlargement, are suggestive of PCH rather than PVOD. In our case, however, none of these features were noted and thus, neither PCH nor PVOD was suspected. Similarities and differences between PCH and PVOD need to be further investigated in future pathological and clinical studies. From a clinical viewpoint, our case suggests that development of PCH-like changes also should be kept in mind when PH with extremely low values of DLco is observed.

In conclusion, we have documented a 59 year old man with RA and PH who initially exhibited a favorable response to sildenafil, but eventually died of right heart failure. An autopsy revealed broad capillary proliferation in the alveolar septa consistent with PCH, indicating that PCH-predominant vasculopathy can occur in patients with RA. From a clinical viewpoint, our case suggested that development of PCH-like change also should be kept in mind when PH with extremely low value of DLCO was observed.

CRediT authorship contribution statement

Junichi Nakamura: Conceptualization, Data curation, Visualization, Writing - original draft. **Ichizo Tsujino:** Conceptualization, Investigation, Writing - review & editing, Supervision. **Gaku Yamamoto:** Data curation. **Toshitaka Nakaya:** Data curation. **Kei Takahashi:** Data curation, Writing - original draft. **Hirokazu Kimura:** Data curation. **Takahiro Sato:** Conceptualization, Data curation. **Taku Watanabe:** Data curation. **Shimpei Nakagawa:** Visualization, Writing - original draft. **Noriyuki Otsuka:** Methodology, Formal analysis, Investigation. **Hiroshi Ohira:** Conceptualization, Investigation, Writing - review & editing. **Satoshi Konno:** Writing - review & editing, Supervision.

Declarations of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2020.101215.

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