



## Diffuse alveolar hemorrhage complicating acute exacerbation of IPF

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### ABSTRACT

An 83-year-old man with a history of interstitial lung disease (ILD) presented with a 1-week history of progressive dyspnea. Computed tomography of the chest revealed right lung-predominant, diffuse, ground glass opacities superimposed upon reticular opacities. Despite methylprednisolone pulse therapy under a diagnosis of acute exacerbation (AE) of ILD, lung involvement and renal dysfunction worsened and disseminated intravascular coagulation developed. The patient died on day 5 of hospitalization. Pathological examination at autopsy revealed diffuse alveolar hemorrhage (DAH) superimposed upon organizing diffuse alveolar damage and usual interstitial pneumonia. We reached a final diagnosis of DAH-predominant AE of idiopathic pulmonary fibrosis (IPF). Abundant expression of the oxidative stress marker hemeoxygenase-1 (HO-1) was observed in alveolar macrophages. These suggest that HO-1 expression in the lungs may offer a useful biomarker for this atypical histological subtype of AE of IPF.

### 1. Introduction

The prognosis of acute exacerbation (AE) of idiopathic pulmonary fibrosis (IPF) is poor, and the histological pattern typically involves diffuse alveolar damage (DAD) superimposed upon usual interstitial pneumonia (UIP) [1]. However, the histological findings of AE of IPF include not only DAD, but also other atypical subtypes including diffuse alveolar hemorrhage (DAH), organizing pneumonia (OP), pulmonary thromboembolism, lung cancer and bronchopneumonia. As a result, definitive diagnosis of AE and the selection of treatment options are expected to be very difficult [2].

Hemeoxygenase-1 (HO-1) converts heme to carbon monoxide, iron, and bilirubin, leading to pulmonary cellular protection upon exposure to various stimuli, including cytokines, hypoxia, and diesel exhaust particles [3]. As a result, this enzyme is used as a marker of oxidative stress. HO-1 is reportedly upregulated in the lungs of patients with various interstitial lung diseases (ILDs), including pulmonary sarcoidosis, desquamative interstitial pneumonia, acute respiratory distress syndrome

(ARDS), and silica-induced lung injury [4–6]. Serum HO-1 has also been reported to serve as a useful biomarker in patients with ARDS or AE of ILD [7,8].

We encountered a case of DAH-predominant AE of IPF, in which abundant HO-1 expression in the lungs was considered useful for reaching the diagnosis of AE.

This research was approved by the Institutional Review Board of Yokohama City University Medical Center (approval number D1303019).

### 2. Case presentation

An 83-year-old man with a several-year history of stable ILD (Fig. 1A) was admitted with a 1-week history of progressive dyspnea. He had been suffering from membranous nephropathy without specific treatment since 2009, and had received steroid pulse therapy in April 2009, then prednisolone until April 2010. The patient had also been diagnosed with ILD since October 2015 (Fig. 1A) and had been taking

*Abbreviations:* AE, acute exacerbation; CO, carbon monoxide; DAD, diffuse alveolar damage; DAH, diffuse alveolar hemorrhage; DIC, disseminated intravascular coagulation; HO-1, hemeoxygenase-1; ILD, interstitial lung disease; IP, interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia.

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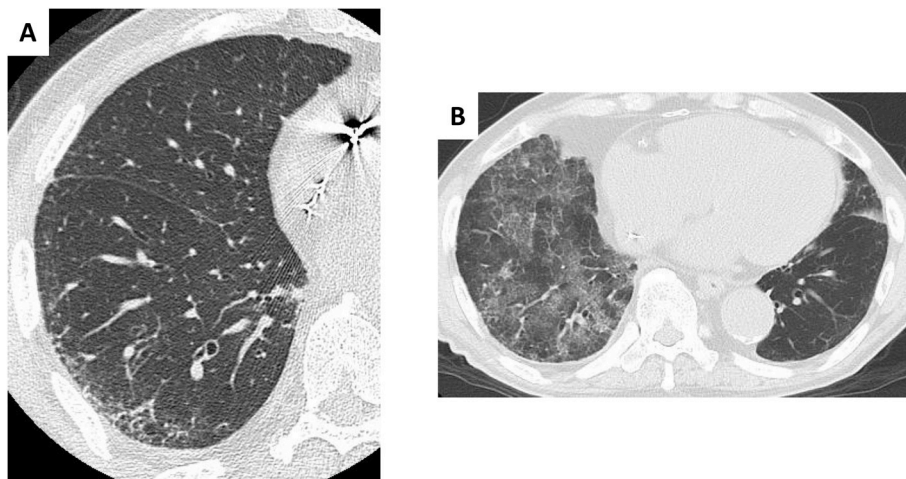
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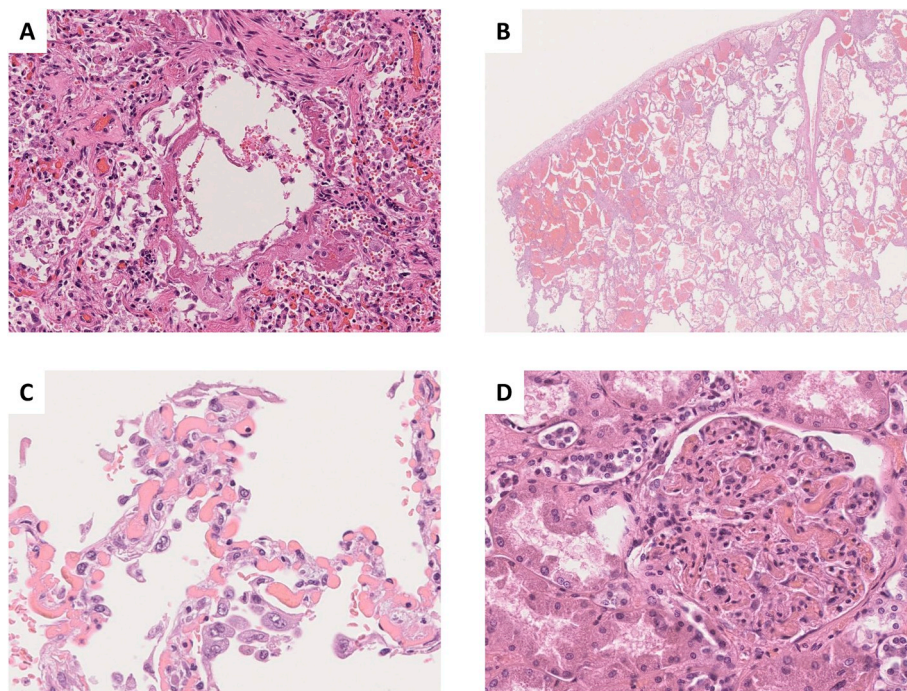
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**Fig. 1. Computed tomography findings of the chest.**

High-resolution computed tomography of chest shows bilateral reticular and ground glass opacities with subpleural distribution in lower lobes which is indeterminate for usual interstitial pneumonia [9] at 1 year before admission to hospital with progressive dyspnea (A). New ground glass opacity appeared mainly in right lung when interstitial lung disease became acutely exacerbated (B).

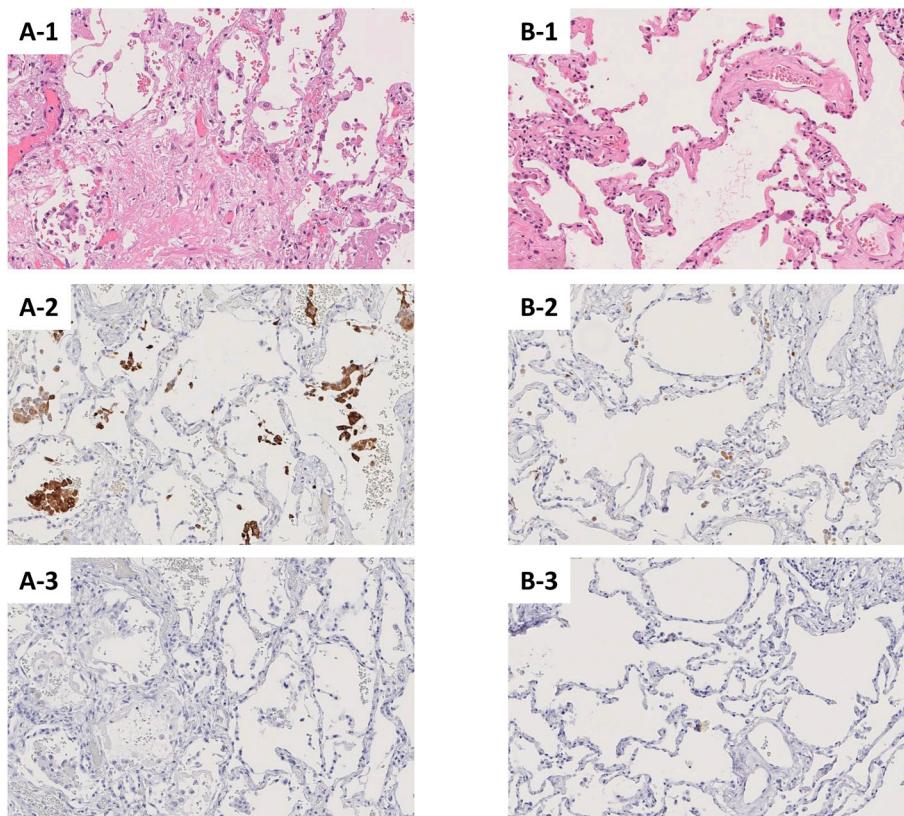


**Fig. 2. Pathological findings of hematoxylin-eosin staining at autopsy.**

Organizing diffuse alveolar damage and alveolar hemorrhage are superimposed upon usual interstitial pneumonia (A and B: original magnification,  $\times 100$  and  $\times 5$ , respectively). Pulmonary (C) and renal vascular (D) thrombosis is also evident (original magnification, both  $\times 200$ ).

clarithromycin until hospitalization. Chronic atrial fibrillation had been diagnosed in 2009 and he had therefore also been taking warfarin until this hospitalization. Computed tomography of the chest revealed new right lung-predominant and diffuse ground glass opacities superimposed on reticular opacities (Fig. 1B) compared to an image from 1 year previously (Fig. 1A). Arterial blood gas analysis indicated severe hypoxemia, with pH 7.412, PaCO<sub>2</sub> 26.9 mmHg, and PaO<sub>2</sub> 65.5 mmHg on ambient air. Peripheral blood levels of lactate dehydrogenase (290 IU/L; normal, <225 U/L), creatinine (4.01 mg/dL; normal, <1.2 mg/dL), surfactant protein-D (412 ng/mL; normal, <110 ng/mL), and D-dimer (7.75  $\mu$ g/dL; normal, <0.5 ng/dL) were high, but no increases were seen in levels of blood Krebs von den Lungen-6, antinuclear antibodies, antineutrophil cytoplasmic antibody, or anti-glomerular basement membrane antibody. Although methylprednisolone pulse therapy was initiated under a diagnosis of AE of ILD, and warfarin administration was also discontinued due to chronic atrial fibrillation, the involvement

in the left lung field spread. The decreases in blood platelet count and hemoglobin level and the increased blood D-dimer level indicated a diagnosis of disseminated intravascular coagulation (DIC). Despite intensive treatment with sivelestat sodium hydrate and intravenous recombinant human thrombomodulin, he died on day 5 of hospitalization due to severe hypoxemia with progressive lung involvements. Histological findings at autopsy revealed DAH superimposed upon mild organizing DAD and UIP, as well as pulmonary and renal vascular thrombosis (Fig. 2). This suggested that progression of anemia was caused by DAH. After multidisciplinary discussion between pathologists and pulmonologists, we concluded that the appropriate clinical diagnosis for the previous lung involvement was early IPF [9], based on the combination of findings from HRCT (Fig. 1) and histopathology (Fig. 2). The cause of death was thus considered to be DAH-predominant AE of IPF.



**Fig. 3.** Immunohistochemical staining for hemoxygenase (HO)-1 expression in lung specimens.

**A-1.** The present case (original magnification, HE staining  $\times 20$ ).

**A-2.** The present case (original magnification, HO-1 immunostaining  $\times 20$ ).

**A-3.** The present case (original magnification, negative control (without primary antibody)  $\times 20$ ).

**B-1.** Stable idiopathic pulmonary fibrosis (IPF) (original magnification, HE staining  $\times 20$ ).

**B-2.** Stable idiopathic pulmonary fibrosis (IPF) (original magnification, HO-1 immunostaining  $\times 20$ ).

**B-3.** Stable idiopathic pulmonary fibrosis (IPF) (original magnification, negative control (without primary antibody)  $\times 20$ ).

In a patient with acute exacerbation of IPF (A: original magnification  $\times 20$ ), high expression of HO-1 is observed mainly in alveolar macrophages, while expression of HO-1 in fibrotic lesions or alveolar macrophages is not conspicuous in stable IPF (B: original magnification  $\times 20$ ).

### 3. Discussion

The histological profile of AE of IPF is typically that of DAD superimposed upon UIP. Oda et al. reported that pathological findings for patients with AE of IPF include the characteristics not only of DAD, but also of other atypical pathological conditions including DAH, organizing pneumonia, pulmonary thromboembolism, lung cancer, and bronchopneumonia [2]. The pathological findings for our patient at autopsy were organizing DAD, pulmonary thromboembolism, and marked alveolar hemorrhage superimposed upon UIP. The pathological status of AE of IPF is apparently diverse, and this might result in high variability in treatment responses. Due to the histological diversity, the diagnosis of AE and prediction of prognosis are very difficult. The present case showed atypical histological findings mainly comprising DAH rather than DAD, leading to DIC via activation of the coagulation system and thrombus formation in the lungs and glomeruli, with a predictably fatal outcome. Also, we speculate that although warfarin administration may have partially influenced the disease progression, DAH was mainly attributed to AE of IPF because the clinical condition progressively worsened after warfarin discontinuation. In the further research, it will be necessary to clarify the clinical features by evaluating the patients' backgrounds of this similar cases.

HO-1 is a 32-kDa heat shock protein that converts heme to CO, iron, and bilirubin and is released from alveolar macrophages and bronchial epithelial cells under conditions of oxidant stress [3]. We have also previously reported that alveolar macrophages from a patient with AE of IPF appeared to possess higher HO-1 expression than macrophages from a patient with stable IPF, and suggested that serum HO-1 may serve as a useful biomarker for detecting AE and predicting hospital mortality among patients with IP [7]. In the present case, we performed HO-1 immunostaining of lung tissue and revealed high expression of HO-1 mainly in alveolar macrophages, while expression of HO-1 in fibrotic lesions and alveolar macrophages was not conspicuous in stable IPF (Fig. 3). This result suggests that evaluation of HO-1 expression in the

lungs may be useful in diagnosing AE of IPF, even in atypical histological subtypes of this pathology.

### 4. Conclusion

We encountered a case of DAH-predominant AE of IPF. HO-1 expression in the lungs might be useful as a biomarker for AE of IPF, even in atypical histological subtypes of this pathology. Further research is needed to evaluate the clinical utility of HO-1 expression in patients with AE of IPF.

#### Statement confirming consent

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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None.

#### Declaration of competing interest

None of the authors have any conflicts of interest to declare.

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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.2020.101022>.

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