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Fatal diffuse alveolar haemorrhage mimicking acute exacerbation in idiopathic pulmonary fibrosis treated with nintedanib

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Acute exacerbation, diffuse alveolar haemorrhage, idiopathic pulmonary fibrosis, nintedanib, recombinant human soluble thrombomodulin.

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Abstract

A 75-year-old man was referred to our hospital with a 1-year history of persistent dry cough and progressive dyspnoea on exertion. He was treated with aspirin due to thrombosis of internal carotid artery. He was diagnosed with idiopathic pulmonary fibrosis (IPF)/usual interstitial pneumonia (UIP), and started on inhaled *N*-acetylcysteine therapy and pirfenidone. Since his clinical condition progressively deteriorated after 6 months, he was switched from pirfenidone to nintedanib. As a result, his general condition worsened rapidly. He was diagnosed with acute exacerbation (AE) of IPF, and was treated with methylprednisolone pulse and recombinant human soluble thrombomodulin. Despite the administration of these treatments, he died of severe haemoptysis four days after the onset of AE. Autopsied lungs revealed significantly dark red-brown appearance corresponding to diffuse alveolar haemorrhage (DAH) histopathogically with a background pattern of UIP with fibrotic change. Notably, there was no evidence of diffuse alveolar damage suggesting IPF-AE.

Introduction

Idiopathic pulmonary fibrosis (IPF) is variable and unpredictable, and occasionally includes periods of acute deterioration in respiratory function, which are termed acute exacerbation of IPF (IPF-AE) when a cause cannot be identified. Recombinant human soluble thrombomodulin (rhTM) directly binds and sequesters high-mobility group box 1 (HMGB-1), leading to suppression of inflammation [1]. Recently, we reported that adding rhTM to conventional treatments may improve survival in IPF-AE [2]. Nintedanib is expected to become a potential treatment option for IPF patients. On the other hand, its adverse events include not only diarrhoea and elevated transaminases but also bleeding. Herein, we describe a case of fatal diffuse alveolar haemorrhage (DAH) in IPF treated with nintedanib, to help clinicians distinguish this condition from IPF-AE.

Case Report

A 75-year-old man was referred to our hospital complaining of a 1-year history of persistent dry cough and progressive dyspnoea on exertion (DOE). He was treated with aspirin due to thrombosis of internal carotid artery. Chest high-resolution computed tomography (HRCT) images revealed subpleural reticular opacities predominantly in the bilateral lower lobes (Fig. 1A, B). Pulmonary function test (PFT) revealed forced vital capacity (FVC) of 2.36 L (78.9% of predicted) with decreased diffusion for carbon monoxide (DLco) of 70.7% of predicted. Surgical lung biopsy specimens showed typical usual interstitial pneumonia (UIP) pattern (Fig. 1C). Furthermore, fibroblastic foci were sporadically present in dense collagen fibrosis and lymphocytes and plasma cells infiltration was mainly observed (Fig. 1D). Finally, he was diagnosed with IPF, and treated by inhaled *N*-acetylcysteine (NAC)

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monotherapy. However, after an 8-month clinical course, pirfenidone with home oxygen therapy was added. Since his clinical condition progressively deteriorated after 6 months of the start of pirfenidone treatment, the patient was switched from pirfenidone to nintedanib. As a result, his general condition worsened rapidly in just a month. We then made a diagnosis based on clinical findings of IPF-acute exacerbation (AE), and he was treated with methylprednisolone (1000 mg/day) intravenously for three days, followed by a tapered dose of prednisolone. Simultaneously, he received synthetic neutrophil elastase (NE) inhibitor, and rhTM. Despite the administration of these treatments, his general condition rapidly worsened with decreased PaO_2/FiO_2 ratio from 231 to 88. Additionally, chest HRCT images at three days after the onset of IPF-AE showed more extensive diffuse ground glass opacities in the bilateral lungs compared to that at admission. The value of serum inflammatory parameters (KL-6 and SP-D) remained unchanged. Results of coagulation studies showed a normal time for activated partial prothrombin time (APPT), but the serum haemoglobin value decreased from 13.0 to 10.8 g/dL. Four days after the onset of AE, he died of severe respiratory failure (Fig. 1E, F). Macroscopic appearance of the bilateral lungs at autopsy revealed significantly dark red-brown in addition to subpleural greyish-white zonal lesions with respiratory tract haemorrhage (Fig. 2A, B). Histopathological findings of autopsied lungs showed extensive DAH and a background pattern of UIP. Notably, there was no evidence of diffuse alveolar damage (DAD) suggesting IPF-AE (Figs. 1E, 2D).

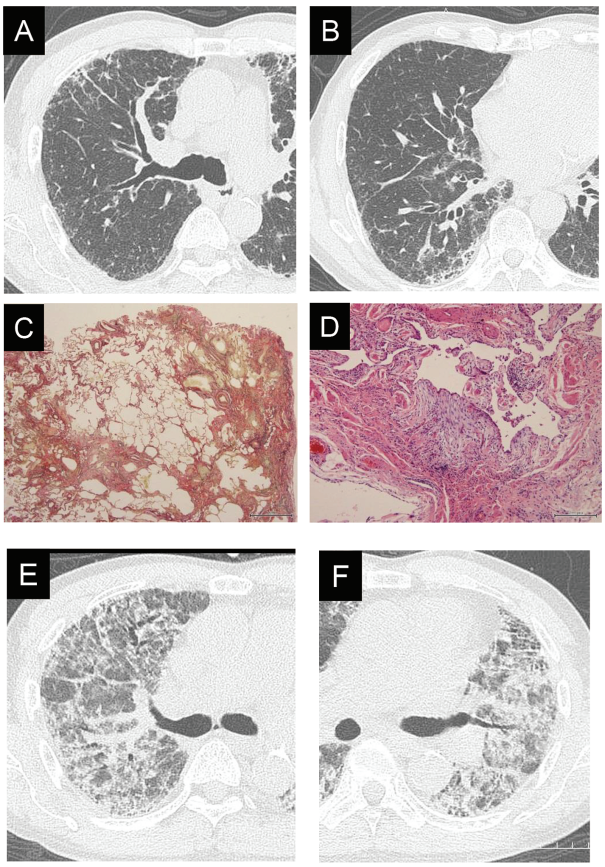

Figure 1. Chest high-resolution computed tomography (HRCT) images on initial visiting: (A) Right upper lobe. (B) Right lower lobe. Chest HRCT images reveal subpleural reticular opacities predominantly in the bilateral lower lobes. Microscopic appearances of lung specimens obtained by surgical lung biopsy: (C) There is heterogeneous interstitial fibrosis with honeycombing in subpleural and perilobular distribution, alternating with areas of normal lung (Elastic van Gieson stain) (1 scale bar = 1 mm); (D) Fibroblastic foci are sporadically present in dense collagen fibrosis and lymphocytes and plasma cells infiltration is mainly observed (haematoxylin–eosin stain) (scale bar = 200 μm). Chest HRCT images after the onset of IPF-AE: (E, F) Chest HRCT images at three days after the onset of IPF-AE show more extensive diffuse ground glass opacity (GGO) in the bilateral lungs.

Discussion

To our knowledge, few reports are available on clinicopathological characteristics of nintedanib-induced DAH mimicking AE in IPF. IPF-AE is characterized by severe worsening dyspnoea and high mortality, histologically manifests as acute or organizing DAD and less commonly as profuse organizing pneumonia superimposed on underlying UIP. Although this patient was diagnosed as having IPF-AE at first, there was no evidence of DAD suggesting IPF-AE at autopsy. It was difficult to differentiate IPF-AE from DAH because he had no symptom such as haemosputum and/or haemoptysis. The rhTM is composed of the active extracellular domain of thrombomodulin. Moreover, rhTM directly binds and sequesters HMGB-1, leading to suppression of inflammation [1]. Recently, Collard et al. [3] studied the plasma biomarker profile of IPF-AE, and found that mechanical ventilation and log change in thrombomodulin were significant predictors of survival at IPF-AE. Actually, we reported that adding rhTM to conventional treatments improves survival in IPF-AE [2]. Therefore, this patient was treated with rhTM and added on methylprednisolone and synthetic NE inhibitor. Nintedanib is a multi-target receptor tyrosine kinase inhibitor of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF), targeting several molecular pathways involved in the pathogenesis of IPF. The adverse events include not only diarrhoea and elevated transaminases but also bleeding and thrombocytopenia. VEGF protects endothelial cells via pathways that inhibit apoptosis and inflammation [4]. In contrast, there is a fine balance of pro- and anticoagulant proteins, platelet activating and inhibiting molecules, and pro- and antifibrinolytic products to maintain vessel

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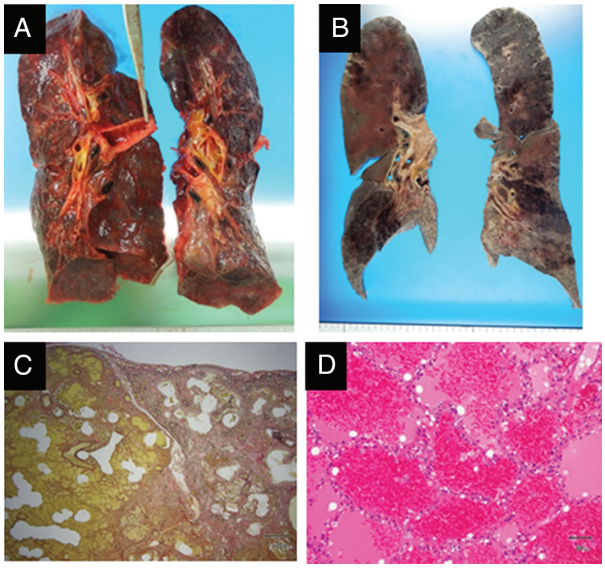

Figure 2. Macroscopic appearance of the bilateral lungs at autopsy: (A) Whole lungs before formalin fixation. (B) Coronal section of formalin-fixed lungs. There is significant dark red-brown in addition to subpleural greyish-white zonal lesions with respiratory tract haemorrhage (1 scale bar = 1 cm). Microscopic appearances of autopsied lungs: (C) Low magnified microscopic appearance of autopsied lungs shows extensive diffuse alveolar haemorrhage (DAH) and a background pattern of usual interstitial pneumonia (UIP) with fibrotic change predominantly distributed in the subpleural and perilobular areas, and an abrupt transition between almost-normal alveolar septum and dense fibrosis with architectural disruption (haematoxylin–eosin stain) (scale bar = 1 mm). (D) High-magnified microscopic appearance of DAH. Note no evidence of diffuse alveolar damage suggesting IPF-AE (haematoxylin–eosin stain) (scale bar = 50 μm).

integrity and intravascular flow [5]. Bleeding complication can probably be caused by disturbance of the tight endothelial cell–platelet interaction. Since there are several confounding variables (the patient was treated with aspirin and rhTM, and the clinical history was worsening before nintedanib was started) that provide alternative explanations for DAH, the direct relationship of DAH to nintedanib therapy is uncertain. However, there was no evidence of DAD suggesting IPF-AE at autopsy in the present case. Thus, we consider that this patient had pulmonary haemorrhage before he was treated with rhTM. Moreover, after this patient was started on rhTM, his pulmonary haemorrhage was rapidly exacerbated. Therefore, rhTM therapy should probably be avoided when a patient with IPF-AE has risk factors for bleeding. In conclusion, fatal DAH in this patient could have been induced by use of aspirin and rhTM in addition to nintedanib.

Disclosure Statements

No conflict of interest declared.
Appropriate written informed consent was obtained for publication of this case report and accompanying images.

Acknowledgments

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