

# Acute exacerbation of combined pulmonary fibrosis and emphysema associated with Hermansky–Pudlak syndrome

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## Keywords

Acute exacerbation, combined pulmonary fibrosis and emphysema, Hermansky–Pudlak syndrome.

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## Introduction

Hermansky–Pudlak syndrome (HPS) is an extremely rare autosomal recessive disorder that is characterized by systemic albinism, hemorrhagic diathesis, and generalized ceroid lipofuscinosis [1]. Although some researchers have reported HPS associated with pulmonary fibrosis, little information is available on the clinicopathological characteristics of HPS associated with combined pulmonary fibrosis and emphysema (CPFE). Moreover, to our knowledge, this is the first report on acute exacerbation (AE) of CPFE in a patient with HPS.

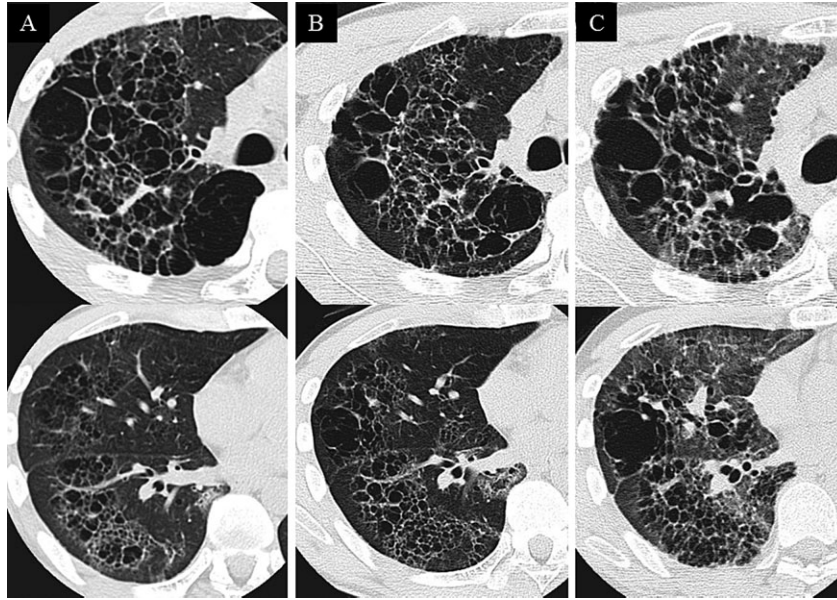
## Case Report

A 30-year-old male with brown-colored hair and white skin, consistent with oculocutaneous albinism including congenital amblyopia and nystagmus, was admitted to Toho University Omori medical center with complaints of persistent dry cough and progressive dyspnea on exertion (DOE).

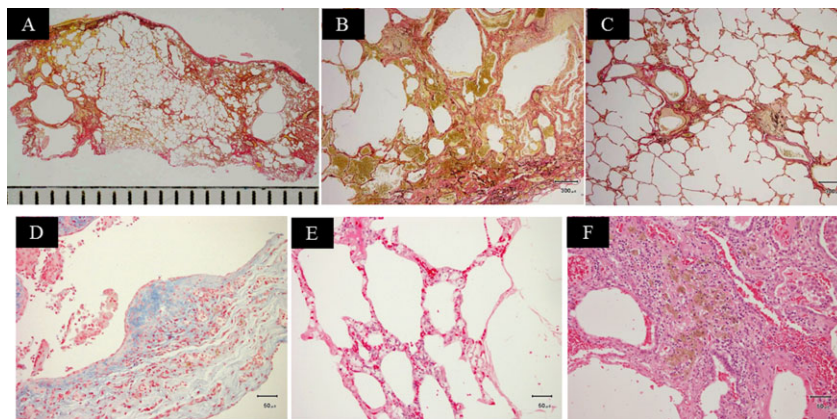
## Abstract

A 30-year-old male smoker with congenital amblyopia and oculocutaneous albinism was admitted to our hospital complaining of progressive dyspnea on exertion. Chest computed tomography images revealed diffuse reticular opacities and honeycombing in the bilateral lower lobes with sparing of the subpleural region along with emphysema predominantly in the upper lobes. Lung biopsy specimens showed a mixture of usual interstitial pneumonia and a non-specific interstitial pneumonia pattern with emphysema. Of note, cuboidal epithelial cells with foamy cytoplasm on the alveolar walls and phagocytic macrophages with ceroid pigments in the fibrotic lesions were observed. The patient was diagnosed with Hermansky–Pudlak syndrome (HPS) associated with combined pulmonary fibrosis and emphysema (CPFE). Six years following the patient's initial admission to our hospital, he died from acute exacerbation (AE) of CPFE associated with HPS. This is one of only few reports available on the clinicopathological characteristics of AE in CPFE associated with HPS.

He had a 30 pack-year history of smoking with no exposure to dust. High-resolution computed tomography (CT) images of the chest revealed diffuse reticular opacities and a mixture of cystic lesions and honeycombing mainly in the mid-zone of the bilateral lower lobes with sparing of the subpleural region and emphysema predominantly in the upper lobes (Fig. 1A). Laboratory data revealed a white blood cell count of 11,700/ $\mu$ L, platelet count of  $28.3 \times 10^4$ / $\mu$ L, and Krebs von den Lungen-6 level of 887 U/mL with no autoantibodies. The prothrombin and partial thromboplastin times were within the normal ranges, but the bleeding time was prolonged. Platelet secondary aggregation activity was reduced. The results of arterial blood gas analysis included pH of 7.41, PaCO<sub>2</sub> of 40.8 Torr, and PaO<sub>2</sub> of 97.4 Torr on room air. The pulmonary function test revealed decreased vital capacity, corresponding to 1.9 L (45.7% of the predicted value), and a diffusing capacity of 38.5% of the predicted value. Lung biopsy analysis revealed subpleural and patchy interstitial fibrosis with chronic inflammatory cell infiltration in addition to



**Figure 1.** Chest high-resolution computed tomography (HRCT) images. (A) Initial admission: Chest HRCT images reveals diffuse reticular opacities and mixture of cystic lesions and honeycombing in the mainly mid-zone of bilateral lower lobes with sparing of the subpleural region and emphysema predominantly in the upper lobes. (B) Three years after the initial admission: Chest HRCT images reveal apparent mixture of multiple cystic lesions and honeycombing in the bilateral lobes with sparing of the periphery, as well as prominent traction bronchiectasis in the bilateral lobes. (C) Six years after the initial admission: Chest HRCT images reveal diffuse interstitial fibrosis admixed with ground-glass opacity in both lungs.



**Figure 2.** Surgical lung biopsy specimens. (A) Low magnified microscopic appearance of the right upper lobe shows that subpleural and patchy interstitial fibrosis with chronic inflammatory cell infiltration in addition to emphysematous changes (elastic van Gieson stain) (1 scale bar = 1 mm). (B) Air space enlargement of varying size with thick walls, the so-called honeycombing is evident (elastic van Gieson stain) (1 scale bar = 300 µm). (C) Patchy centrilobular fibrosis is centered along the respiratory bronchioles (Elastic van Gieson stain) (1 scale bar = 300 µm). (D) High magnified microscopic appearance of fibrotic alveolar lumens. Note fibroblastic foci adjacent to fibrotic alveolar lumens (arrows) (Alcian blue stain) (1 scale bar = 50 µm). (E) High magnified microscopic appearance of alveolar walls. Note cuboidal type II alveolar epithelial cells with foamy cytoplasm (arrows) (hematoxylin–eosin stain) (1 scale bar = 50 µm). (F) High magnified microscopic appearance of areas in the fibrotic lesions. Note brown-pigmented macrophages phagocytizing ceroid pigments (hematoxylin–eosin stain) (scale bar = 50 µm).

emphysematous changes (Fig. 2A). In particular, air space enlargement of varying size with thick walls, the so-called honeycombing, was evident (Fig. 2B). Patchy centrilobular fibrosis was centered along the respiratory bronchioles (Fig. 2C), and fibroblastic foci (FF) were observed adjacent

to the fibrotic alveolar lumens (Fig. 2D). Of note, cuboidal type II alveolar epithelial cells with foamy cytoplasm were found on the alveolar walls (Fig. 2E). Brown-pigmented macrophages phagocytizing ceroid pigments were focally aggregated within the fibrotic lesions (Fig. 2F).

The patient was diagnosed with HPS associated with CPFE. Over the 3-year clinical course without treatment, his symptoms, pulmonary function test findings, and fibrosis on chest CT images gradually deteriorated (Fig. 1B). Genetic analysis for HPS was not performed. We registered the patient as a recipient for lung transplantation at Tohoku University Hospital. However, 6 years after initial admission to our hospital, the patient started complaining of progressive dyspnea developing over 3 weeks along with a slight fever (38°C). A chest CT scan revealed diffuse ground-glass opacities in both lung fields (Fig. 1C). In addition, there was no evidence of pulmonary infection as evidenced by the analysis of bronchoalveolar lavage and sputum culture, in combination with negative blood tests for other potentially infectious pathogens (e.g., *Pneumocystis jiroveci* and cytomegalovirus). Moreover, left heart failure, pulmonary embolism, and alternative causes of acute lung injury were excluded. As a result, the patient was diagnosed with AE of CPFE associated with HPS and was treated with methylprednisolone (1000 mg/day) intravenously for 3 days, followed by a tapered dose of 60 mg/day. At the same time, a synthetic neutrophil elastase inhibitor and antibiotics were administered. Despite the administration of these treatments and mechanical ventilation under intubation, his general condition progressively deteriorated. Twenty-two days after the onset of AE, he died of respiratory failure due to refractory AE.

## Discussion

HPS is an autosomal recessive disorder characterized by systemic albinism, hemorrhagic diathesis, and generalized ceroid lipofuscinosis frequently complicated by interstitial pneumonia (IP) [1]. In the present case, the patient died of respiratory failure due to AE after developing persistent dry cough and progressive DOE at the age of 30.

Although it is unclear whether emphysema was induced by HPS itself or cigarette smoking in the present case, we speculate that exposure to exogenous inducers such as silica, bleomycin, and cigarette smoking induces lung fibrosis and emphysema (i.e., CPFE) in patients with HPS [2, 3].

In the present case, subpleural predominance of cystic lesions extending to the inner zones of the entire lungs with sparing of the periphery was found, unlike the case of the patient with idiopathic pulmonary fibrosis reported by Avila et al. [4]. Furthermore, histological findings were compatible with the diagnosis of HPS-IP, including several

typical patterns such as usual IP (UIP) with scattered FF and patchy centrilobular fibrosis. Thus, we suppose that the patient in our case developed AE under UIP with FF triggered by some sort of respiratory infection.

Except for lung transplantation, no effective therapy including corticosteroids is available for HPS-IP; therefore, HPS-IP is known as an extremely refractory disease. Recently, O'Brien et al. [5] reported that pirfenidone administration resulted in no beneficial change in forced vital capacity at 12 months between placebo and pirfenidone groups.

In conclusion, patients with HPS-IP should be monitored and treated according to their disease behavior. Further studies are needed on the treatment of HPS-IP using novel drugs or multidrug regimens.

## 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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## References

- Pierson DM, Ionescu D, Qing G, et al. 2006. Pulmonary fibrosis in Hermansky-Pudlak syndrome. *Respiration* 73:382–395.
- Young LR, Pasula R, Gulleman PM, et al. 2007. Susceptibility of Hermansky-Pudlak mice to bleomycin-induced type II cell apoptosis and fibrosis. *Am. J. Respir. Cell Mol. Biol.* 37:67–74.
- Yoshioka Y, Kumasaka T, Ishidoh K, et al. 2004. Inflammatory response and cathepsins in silica-exposed Hermansky-Pudlak syndrome model pale ear mice. *Pathol. Int.* 54:322–331.
- Avila NA, Brantly M, Premkumar A, et al. 2002. Hermansky-Pudlak syndrome: Radiography and CT of the chest compared with pulmonary function tests and genetic studies. *Am. J. Roentgenol.* 179:887–892.
- O'Brien K, Troendle J, Gochuico BR, et al. 2011. Pirfenidone for the treatment of Hermansky-Pudlak syndrome pulmonary fibrosis. *Mol. Genet. Metab.* 103:128–134.