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【 CASE REPORT 】

# Interstitial Pneumonia Secondary to Hermansky-Pudlak Syndrome Type 4 Treated with Different Antifibrotic Agents

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**Abstract:**

Hermansky-Pudlak syndrome (HPS) is an autosomal recessive hereditary disease that may be complicated by progressive and potentially fatal interstitial pneumonia. We herein report a 64-year-old woman with interstitial pneumonia associated with HPS type 4 whom we treated with nintedanib after pirfenidone proved ineffective. To our knowledge, there have been no previous reports of nintedanib being used to treat a patient with HPS type 4. There is a need for clinical trials of antifibrotic agents, including nintedanib, pirfenidone, and new therapeutic agents with different mechanisms of action in these patients.

**Key words:** interstitial pneumonia, Hermansky-Pudlak syndrome type 4, idiopathic pulmonary fibrosis, antifibrotic agents, nintedanib, pirfenidone

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## Introduction

The first report of Hermansky-Pudlak syndrome (HPS) came from Czechoslovakia in 1959 and described albinism with a bleeding tendency involving the eyes and skin (1).

HPS is an autosomal recessive hereditary disease, and interstitial pneumonia develops as a complication in 70-80% of affected individuals, typically in their early 30s and 40s; the respiratory function progressively worsens, and most patients eventually succumb to respiratory failure (2, 3). There are 10 subtypes of HPS linked to 10 different genes, among which *HPS-1*, *HPS-2*, and *HPS-4* mutations are considered to be associated with severe interstitial pneumonia (3).

There is no effective treatment for interstitial pneumonia as a complication of HPS. However, it has been reported that pirfenidone, an antifibrotic drug for the treatment of idiopathic pulmonary fibrosis (IPF), suppressed the progression of HPS-associated interstitial pneumonia (HPS-IP) (4).

Two antifibrotic agents, pirfenidone and nintedanib, are available for the treatment of IPF (5). Furthermore, nintedanib has demonstrated efficacy in patients with progressive fibrosing interstitial lung disease (6).

We herein report a patient with interstitial pneumonia associated with HPS type 4 treated with nintedanib after pirfenidone proved ineffective. After the failure of treatment with pirfenidone, we started this patient on nintedanib in the hope of suppressing the progression of HPS-IP. Nintedanib suppressed the further decline of the lung function in this patient for at least six months. To our knowledge, there have

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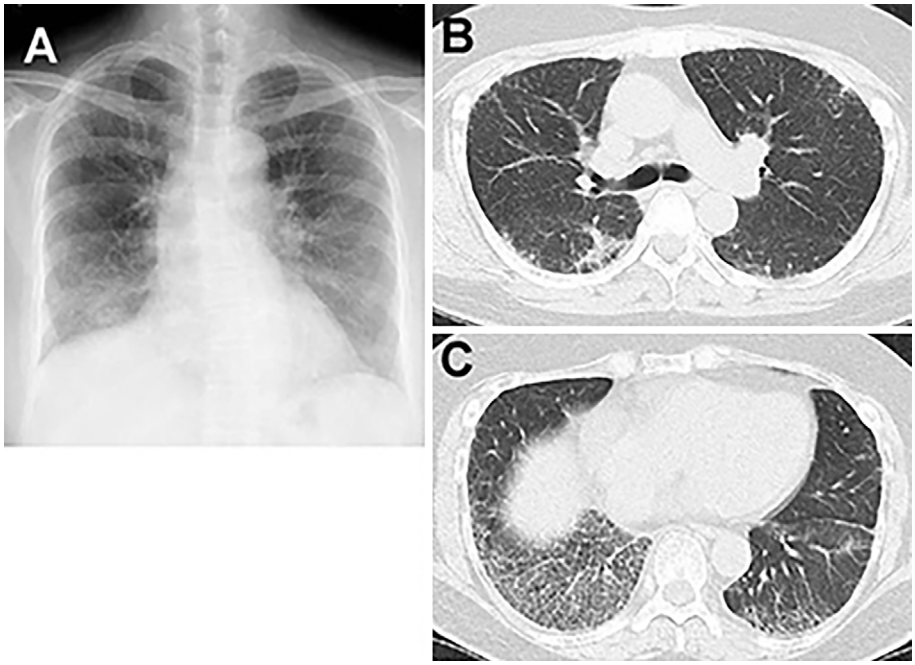


**Figure 1. Imaging findings at the time of the initial diagnosis at another hospital. (A) Chest radiography showing ground-glass opacities and reticular shadows on both sides, indicating a loss of lung volume. (B, C) Computed tomography showing reticular shadows and ground-glass opacities in the peripheral regions of the upper and lower lobes of both lungs and especially in the lower lobes.**

been no other reports of HPS type 4 treated with nintedanib.

This investigation was approved by the institutional ethics committee at Minami-Okayama Medical Center and Kurashiki Central Hospital. The patient agreed ante mortem and her family post mortem to the publication of this report. This case report follows the CARE guidelines (7).

## Case Report

A 64-year-old woman presented to our hospital with a cough and dyspnea. She had had skin albinism and amblyopia since childhood. There was no obvious bleeding tendency or history of smoking, dust exposure, pet breeding, or allergies. There was also no family history of consanguineous marriage, leukoderma, or low vision. She had developed a cough and dyspnea at about 50 years old but had not sought medical treatment. About four years later, her cough and dyspnea worsened.

She had first consulted a doctor at another hospital at approximately 60 years old. Chest radiography had shown areas of reticular shadow and ground-glass opacity in the middle and lower lung fields and a loss of lung volume (Fig. 1A). Computed tomography (CT) had revealed reticular shadows and ground-glass opacities in the lower lobes on both sides (Fig. 1B, C). Blood tests had shown elevation of markers associated with interstitial pneumonia, with Krebs von den Lungen-6 (KL-6) elevated to 937 U/mL (reference range, 0.0-500 U/mL). Pulmonary function tests had shown marked restrictive disorder [vital capacity (VC) 1.02 L; percentage of predicted vital capacity (%VC) 45.1%; forced vital capacity (FVC) 0.72 L; and percentage of predicted forced vital capacity (%FVC) of 31.9%]. The previous doctor could not rule out the possibility of interstitial pneumonia secondary to underlying disease. At that time, the patient did not wish to undergo a more detailed examination, including bronchoscopy. Instead, she and her family requested pharmacotherapy. She was diagnosed with idiopathic interstitial pneumonia and started on pirfenidone 1,200 mg/day orally, which had been reported to be effective in this indication in a Japanese study (8).

After 7 months of starting pirfenidone, her KL-6 level decreased to 894 U/mL, and pulmonary function tests showed an FVC of 0.82 L and a %FVC of 36.3%. Pirfenidone suppressed the decline in FVC and %FVC.

After 15 months of pirfenidone administration, her KL-6 level was 876 U/mL and remained around 700 U/mL 6 months later. Time-sequence CT images are shown in Fig. 2. No further deterioration was observed on imaging after 15 months of treatment with pirfenidone (Fig. 2A-D). However, at this time, there was a decline in the FVC and %FVC. Her pulmonary function tests showed an FVC of 0.62 L and a % FVC of 25.0%. Therefore, she was started on home oxygen therapy. Her dyspnea continued to worsen, as did her CT findings (Fig. 2E, F). Because of disease progression, she first visited our hospital approximately two years after beginning treatment with pirfenidone.

When she first visited our hospital, at presentation, she had blue pupils, bilateral strabismus and amblyopia, and was blind in the left eye. All her body hair was white, and her scalp hair was a mixture of white and brown (Fig. 3).

She had a body temperature of 35.7°C, a pulse rate of 110/min, a blood pressure of 131/94 mmHg, and an oxygen

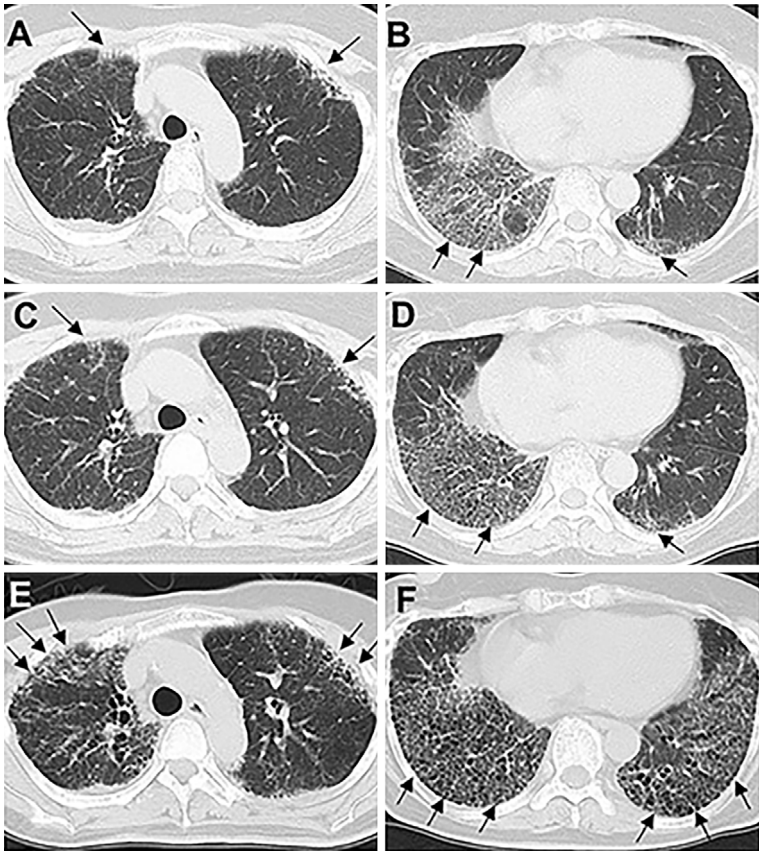


**Figure 2.** **Changes in computed tomography (CT) findings after administration of pirfenidone. (A, B) CT images acquired at the start of treatment with pirfenidone show ground-glass opacities and reticular shadows in the peripheral regions of both lungs (arrows). (C, D) After 15 months of treatment with pirfenidone, the CT images indicate no further deterioration (arrows). (E, F) CT images obtained after 24 months of treatment with pirfenidone reveal progressive structural destruction and development of a honeycomb pattern in the peripheral regions of the upper and lower lobes in both lungs (arrows).**

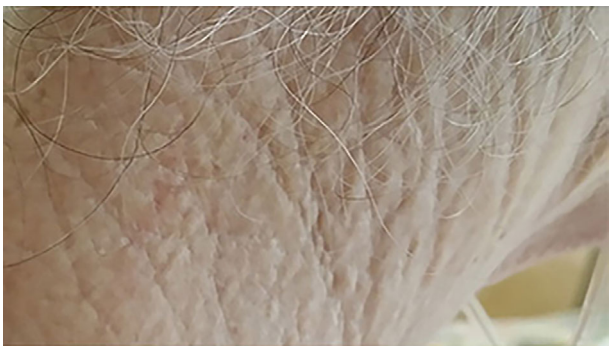

**Figure 3.** **The skin on the dorsal side of the neck in this patient. All her body hair was white, and her scalp hair was a mixture of white and brown.**

saturation of 92% while receiving oxygen via a nasal cannula at a flow rate of 2 L/min. There were no abnormal heart sounds on chest auscultation. Fine crackles were heard around both lungs during inspiration. Her abdomen was soft and flat. The liver was not palpable.

Her laboratory investigations showed no abnormal findings in the blood count, and her coagulation profile was within the normal range. All autoantibodies for the autoimmune disease were negative, and her inflammatory marker levels were not elevated. Serum levels of markers associated with interstitial pneumonia, i.e., KL-6, surfactant protein-D, and surfactant protein-A, were elevated to 952 U/mL (reference range, 0.0-500 U/mL), 271.8 ng/mL (reference range, 0.0-110 ng/mL), and 101.7 ng/mL (reference range, 0.0-43.8 ng/mL), respectively. An arterial blood gas analysis revealed a partial pressure of oxygen in arterial blood of 78.9 mmHg, a partial pressure of carbon dioxide in arterial blood of 35.6 mmHg, and an alveolar-arterial oxygen difference of 47.7 mmHg on inhaled oxygen at a flow rate of 2 L/min.

Pulmonary function tests showed a marked restrictive disorder (VC of 0.56 L, %VC of 24.2%, FVC of 0.51 L, and %FVC of 23.5%). Her diffusing capacity of the lung for carbon monoxide was not measurable. Chest radiography showed areas of reticular shadow and ground-glass opacity in the upper and lower lung and a loss of lung volume (Fig. 4A). CT revealed worsening of the ground-glass opacities and reticular shadows in the peripheral regions of the upper and lower lobes with honeycombing in both lungs. Traction bronchiectasis was noted, particularly in the right

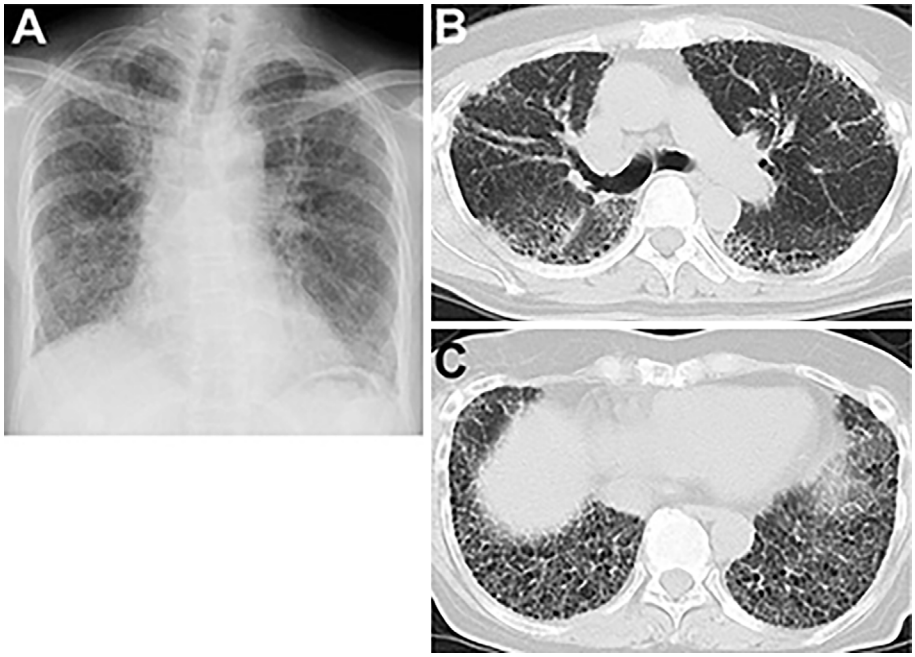


**Figure 4. Imaging findings at the time of the patient's first visit to our hospital. (A) Chest radiography showed areas of reticular shadow and ground-glass opacity in the upper and lower lung fields, indicating a marked loss of lung volume (A). (B, C) Computed tomography revealed worsening of the ground-glass opacities and reticular shadows in the peripheral regions of the upper and lower lobes in both lungs. Traction bronchiectasis was noted, particularly in the right upper lobe, and honeycombing was noted in both lower lobes.**

upper lobe (Fig. 4B, C). The radiologic appearance was suggestive of IPF.

We suspected that the albinism, ocular symptoms, and pulmonary fibrosis in this patient were secondary to HPS. There had been a previous report of bleeding diathesis in HPS (9). However, our patient's blood cell count, including the platelet count and coagulation status, were normal, and she had no bleeding tendency. The platelet aggregation capacity was not measurable at our institution. Based on her signs and symptoms, our diagnosis was HPS-associated interstitial pneumonia (HPS-IP).

We carefully counseled the patient and her family about the diagnosis and potential treatment. The patient and her family requested a change in antifibrotic therapy from pirfenidone to nintedanib to prevent further progression of her disease. We agreed to the switch to nintedanib after counseling the patient and her family on the potential risks, including bleeding, and the benefits of nintedanib and obtaining adequate informed consent. Because of the patient's chronic anorexia and the potential for side effects, we started oral nintedanib at a dose of 200 mg/day. She was started on nintedanib while hospitalized for one month, during which she was monitored very carefully for side effects.

The patient and her family requested diagnostic genetic testing. They were referred for genetic counseling by a multidisciplinary team of pulmonologists and a dermatologist. Genetic testing was approved by the institutional ethics committee of Minami-Okayama Medical Center and Kurashiki Central Hospital. Testing of *HPS-4* revealed compound heterozygous mutations consisting of a frameshift mutation of c.57dup (p. Leu20Serfs*3) and a nonsense mutation of c.649C>T (p. Arg217*). In a previous study, *HPS-4* was identified as a nonsense mutation of c.649C>T (p. Arg217*) and found to be associated with IP (10).

In accordance with the clinical course, imaging, and genetic findings, the diagnosis was HPS-IP with HPS type 4. The patient's clinical course is shown in Fig. 5. At three months after starting nintedanib therapy, there was no radiologic evidence of deterioration in her CT findings (Fig. 5A-C). After six months of treatment, the serum KL-6 level decreased, and the FVC and %FVC values slightly increased. However, nine months later, her cough and dyspnea gradually worsened. After 10 months of treatment with nintedanib, she developed anorexia and could not take any medications, including nintedanib. Furthermore, she was unable to visit our hospital because of dyspnea and respiratory failure. At 14 months after starting nintedanib, the patient died at another hospital due to respiratory failure.

## Discussion

A previous report showed the efficacy of lung transplantation for HPS-IP (11); however, no effective treatment for HPS-IP has yet been established. Treatment with corticosteroids is not adequate for this disease (12). In one placebo-controlled study, pirfenidone suppressed the annual rate of decrease in FVC by 8% in patients with an initial %FVC >50% (4). The study showed that, if the %FVC was <50%

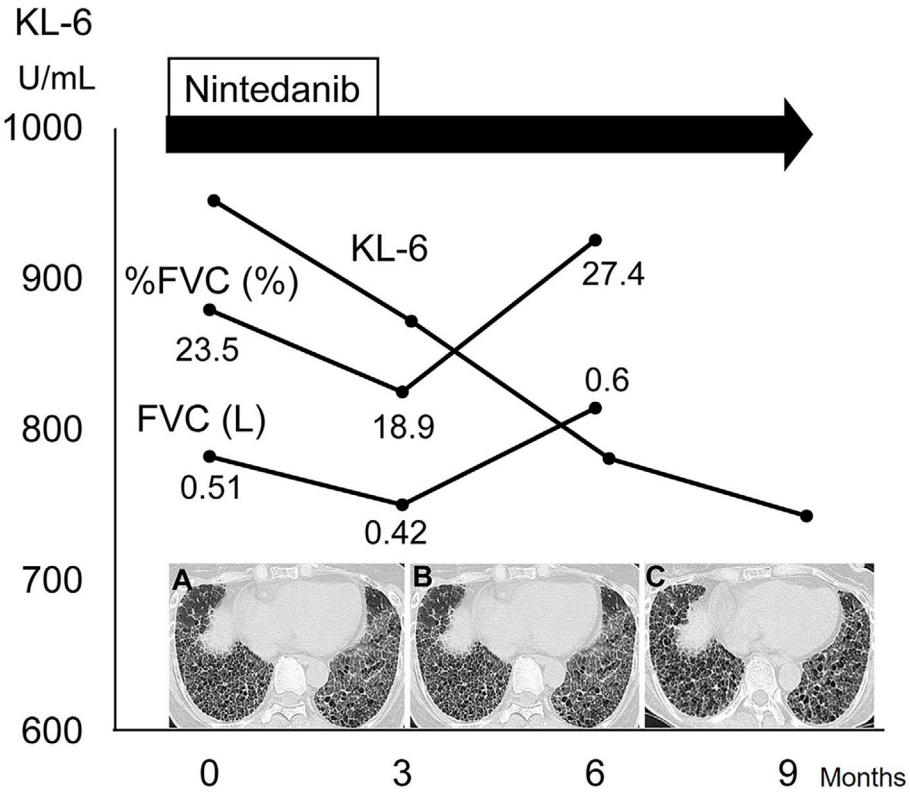


**Figure 5.** **The patient's clinical course. After the initiation of nintedanib, computed tomography images (A-C) obtained at three-month intervals showed no further radiologic evidence of exacerbation of interstitial pneumonia. There was a slight improvement in the forced vital capacity (FVC) and the percentage of predicted forced vital capacity (%FVC) as well as a decreased serum KL-6 level. FVC: forced vital capacity, %FVC: percentage of predicted forced vital capacity, KL-6: Krebs von den Lungen-6, VC: vital capacity**

of the predicted value, the subsequent progression of respiratory failure and decline in the lung function would be very rapid, with a survival time of about 2 years. One patient with HPS type 1 in the placebo group had an initial %FVC <50% and died 16 months later (4).

The evidence concerning the use of pirfenidone is conflicting, and there is a report suggesting that pirfenidone is not an effective treatment for HPS-IP (13). In our case, the %FVC was 31.9% before starting pirfenidone, and there was no further deterioration of her respiratory failure during the first 7 months after starting this treatment. Pirfenidone might have therefore inhibited the disease progression in our patient.

The pathogenesis of fibrosis in HPS-IP is similar to that in IPF, involving the activation of fibroblasts in response to inflammation of alveolar macrophages and cytokines. However, HPS-IP is attributable to lysosomal dysfunction because of the genetic abnormalities encoding HPS proteins. When there is a mutation of *HPS-4*, the intracytoplasmic vesicle transport is disrupted, causing lysosomal dysfunction (14, 15). The lysosome dysfunction leads to the accumulation of the abnormal surfactant and induces the apoptosis of type II alveolar epithelium, resulting in persistent inflammation and lung fibrosis (16).

There are still no large clinical trials of pirfenidone in patients with HPS type 4. Treatment for HPS-IP with HPS type 4 has not yet been established. High-dose corticosteroids and pirfenidone were reportedly effective in patients with HPS type 4 (17). In our case, pirfenidone might have reduced the chronic inflammation and fibrosis during the first few months of treatment. However, its efficacy could not be maintained, probably because of the persistent inflammation caused by her *HPS-4* mutation.

Nintedanib inhibits several intracellular kinases, including the respective receptor tyrosine kinases of platelet-derived growth factor, fibroblast growth factor, and vascular endothelial growth factor. By inhibiting such growth factor signaling, nintedanib inhibits processes involved in lung fibrosis progression in IPF (18). Furthermore, nintedanib also has simultaneous antifibrotic and anti-inflammatory effects (19). Indeed, it was recently shown to attenuate the annual rate of reduction in FVC to a greater extent than placebo in patients with systemic sclerosis-associated interstitial lung disease (20) and those with progressive fibrosing interstitial lung disease (6).

In the present case, switching to nintedanib appeared to delay the disease progression for about six months despite her pulmonary function worsening on pirfenidone (Fig. 5). Nintedanib has both an anti-inflammatory effect and an antifibrotic effect via a cascade that is different from pirfeni-

done. The patient survived for 14 months after starting treatment with nintedanib and for more than 3 years after starting pirfenidone. Pirfenidone and nintedanib might have suppressed disease progression even in the presence of a poor lung function with a %FVC <50%. However, there have been no other reports of nintedanib being used for HPS-IP, so it is difficult to assess the efficacy of nintedanib in suppressing disease progression.

Of note, nintedanib has several side effects, including bleeding. Although the platelet function could not be evaluated, the patient and her family had a strong preference for being treated with nintedanib. We therefore admitted her for one month and administered nintedanib while monitoring her closely for side effects. No bleeding was observed during her clinical course. When starting nintedanib therapy for patients with HPS-IP, the platelet function should be evaluated if possible, and treatment should be started while the patient is admitted to the hospital in order to strictly monitor side effects.

An effective treatment for HPS-IP has yet to be identified. Antifibrotic drugs are of limited benefit. The further elucidation of the pathogenesis of HPS-IP is necessary.

## Conclusion

We encountered a case of HPS-IP that was treated with nintedanib. The pathophysiology of HPS-IP remains unknown, and the effect of nintedanib on HPS-IP is not well understood. The further elucidation of the pathogenesis of HPS-IP and the development of therapeutic methods are required.

**The authors state that they have no Conflict of Interest (COI).**

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