INTERNAL MEDICINE

□ CASE REPORT □

An Autopsy Case of Hermansky-Pudlak Syndrome: A Case Report and Review of the Literature on Treatment

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Abstract

Hermansky-Pudlak syndrome (HPS) is a rare genetic disorder, the most common complication of which influencing the prognosis is pulmonary fibrosis. In the present report, we describe an autopsy case of a Japanese woman with HPS. The patient was diagnosed at 50 years of age based on the presence of oculocutaneous albinism, hemorrhagic diathesis, ceroid-lipofuscin accumulation and pulmonary fibrosis. Although systemic steroids, immunosuppressants and pirfenidone were administered for pulmonary involvement, she died from respiratory failure two years later. Obtaining an early diagnosis and taking into consideration the need for lung transplantation is necessary in order to improve the prognosis of HPS. We herein report this very rare Japanese case of HPS with a review of the treatment approaches for HPS complicated with pulmonary fibrosis.

Key words: Hermansky-Pudlak syndrome, pulmonary fibrosis, autopsy, pirfenidone, lung transplantation

(Intern Med 53: 2705-2709, 2014)
(DOI: 10.2169/internalmedicine.53.2239)

Introduction

Hermansky-Pudlak syndrome (HPS) was first described in 1959 by two Czechoslovakian physicians, Hermansky F. and Pudlak P., as a rare group of genetic disorders consisting of oculocutaneous albinism (OCA), hemorrhagic diathesis and ceroid-lipofuscin accumulation (1). HPS is recognized to constitute a genetically heterogeneous set of related autosomal recessive conditions resulting from mutations in genes that affect the function of intracellular organelles. The most common complication of HPS is pulmonary fibrosis, which is directly associated with a poor prognosis. Currently, nine types of HPS-causing gene mutations (*HPS1-HPS9*) have been reported in humans (2-9), among which *HPS1*, *HPS2*, and *HPS4* are recognized to be associated with pulmonary fibrosis (10, 11). In the present report, we describe an autopsy case of HPS complicated with pulmonary fibrosis in a patient waiting for lung transplantation.

Case Report

The patient was a 50-year-old Japanese woman who reported having had OCA and amblyopia since childhood. Her family history was unremarkable, except for the fact that her parents were consanguineous. Although she began experiencing exertional dyspnea and a productive cough around 45 years of age, she had experienced no episodes suggestive of hemorrhagic diathesis. She had been referred to a hospital for progressive exertional dyspnea, and a lung biopsy performed via video-assisted thoracic surgery had been conducted at 46 years of age. Although a definitive diagnosis had not been made, prednisolone (30 mg/day) and immunosuppressants (cyclophosphamide and cyclosporin) were ad-

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Received for publication December 2, 2013; Accepted for publication May 21, 2014
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Table 1. Laboratory Data on Admission

Peripheral blood		
WBC	5,200	/μL
Ne	62	%
Mo	4	%
Eo	9	%
Ly	25	%
RBC	384×10^4	/μL
Hb	11.9	g/dL
Ht	36.8	%
Plt	31.1×10^4	/μL

Coagulation test		
Bleeding time	9	min
PT(INR)	0.99	
APTT	24.3	sec
Fibrinogen	393	mg/dL

Blood chemistry		
TP	7.1	g/dL
Alb	3.8	g/dL
T-Bil	0.5	mg/dL
Cho	240	mg/dL
AST	21	IU/L
ALT	15	IU/L
LDH	203	IU/L
CK	38	IU/mL
γ-GTP	15	IU/L
CRP	0.16	mg/dL
Na	137	mEq/L
K	4.0	mEq/L
Cl	102	mEq/L

Tumor marker		
CEA	5.7	ng/mL
sIL-2R	469	U/mL

Serology		
RA	25.9	IU/mL
ANA	(-)	
KL-6	764	U/mL
SP-D	187	ng/mL
SP-A	132	ng/mL

Arterial blood gas analysis		
pH	7.411	
PaO_2	93.9	torr
$PaCO_2$	43.7	torr
HCO_3^-	27.2	mmol/L
BE	2.7	mmol/L
(2.5 litter of oxygen)		

Pulmonary function test		
VC	1.06	L
%VC	39.7	%
$FEV_{1.0}$	1.07	L
$FEV_{1.0}$%	95.5	%
%DLCO	10.0	%

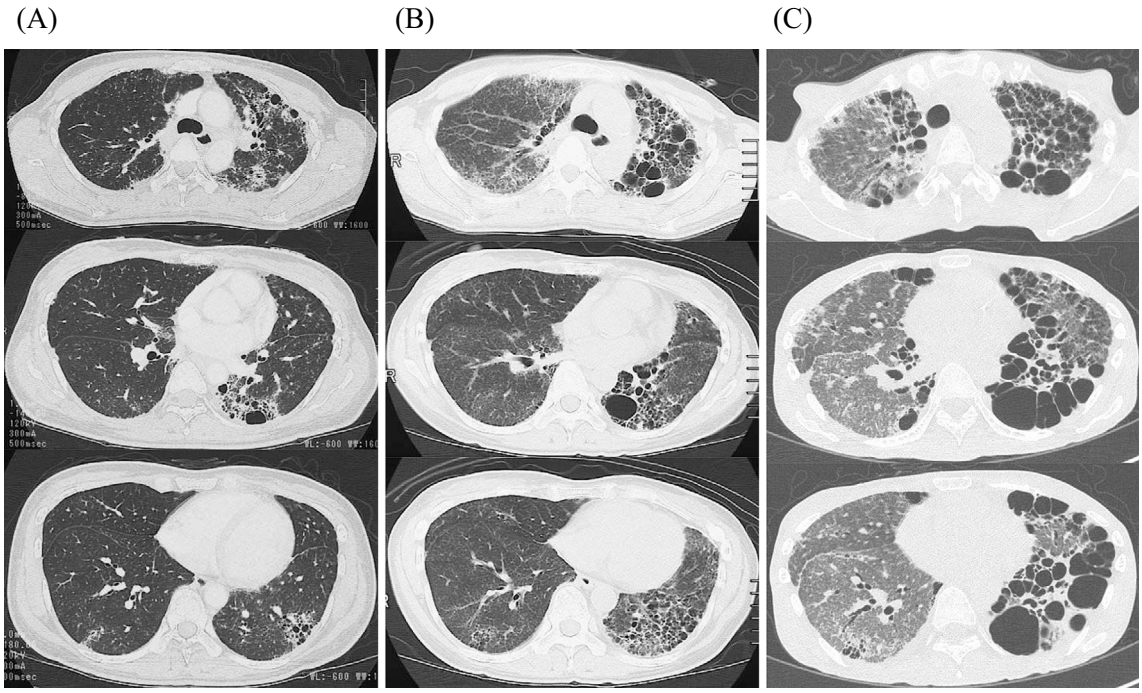

Figure 1. High-resolution computed tomography. (A) At the first hospital visit (four years before visiting our hospital). (B) At the beginning of pirfenidone therapy (six months before visiting our hospital). (C) At the last admission (nine months after visiting our hospital).

ministered. The immunosuppressants were discontinued two years later, and treatment with pirfenidone (1,200 mg/day) and long-term oxygen therapy was initiated due to disease progression. The patient was subsequently referred to our hospital for a further examination and assessment regarding lung transplantation.

The laboratory findings on admission are shown in Table 1. The oxygen partial pressure of arterial blood while breathing 2.5 L of oxygen was 93.9 torr. A pulmonary function test revealed a severe restrictive ventilatory defect and diffusion disorder [% vital capacity (VC): 39.7%, % diffusing capacity for carbon monoxide (DLco): 10.0%]. High-resolution computed tomography demonstrated a subpleural reticular shadow, traction bronchiectasis and honeycombing with volume loss (Fig. 1A, B). The suspected diagnosis was HPS due to the patient's congenital OCA and amblyopia in addition to lung disease. A blood test showed a prolonged bleeding time without a low platelet count or prolonged prothrombin or activated partial thromboplastin time (Table 1). We reexamined the surgical lung biopsy specimen re-

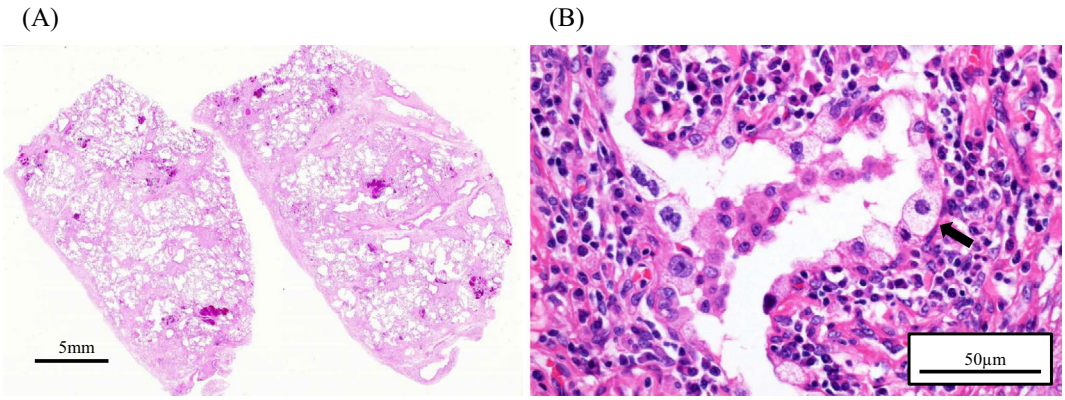

Figure 2. **Surgical lung biopsy specimen. (A) A panoramic view showed usual interstitial pneumonia-type fibrosis. (B) A high-power view showed foamy swelling of type-2 cells (arrow) and interstitial inflammatory cell infiltration. Hematoxylin and Eosin staining.**

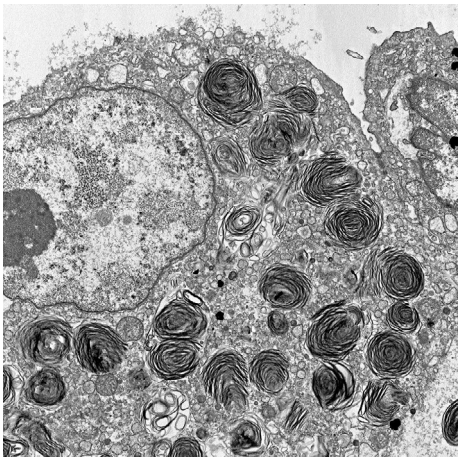

Figure 3. **Type-2 pneumocyte electron micrograph of the autopsied lung. Numerous giant lamellar bodies are observed in the cytoplasm.**

sected at the previous hospital, the results of which showed usual interstitial pneumonia-type fibrosis (Fig. 2A) and foamy swelling of type-2 pneumocytes in the non-fibrous inflammatory area (Fig. 2B). The secondary aggregation activity of platelets was reduced, and an electron micrograph showed a partial defect of the dense bodies. Although a gene analysis performed with informed consent revealed no *HPS1* or *HPS4* gene mutations, we diagnosed the patient with HPS, as the clinical and histopathological findings were compatible with this condition. We registered the patient as a recipient for lung transplantation with the Japan Organ Transplantation Network; however, she died 12 months after her first visit, at 51 years of age, due to rapid disease progression with refractory pneumothorax and infection (Fig. 1C). The autopsied lungs showed bullous changes and abscesses in the left-upper, left-lower and right-lower lobes. Diffuse interstitial fibrosis with decreased inflammatory cells and florid, foamy swelling of type-2 pneumocytes was observed histopathologically. An electron micrograph revealed that the florid, foamy swelling corresponded to the presence of giant lamellar bodies (Fig. 3). In addition, the accumulation of ceroid-like pigments was observed in the large intestine, liver, spleen and bone marrow. These findings were compatible with a diagnosis of HPS.

Discussion

In Japan, only 120 cases of HPS have been reported since 1980, almost half of which (59 cases) involved pulmonary fibrosis. The prognosis of HPS complicated with pulmonary fibrosis is very poor. Most HPS patients tend to be diagnosed with simple OCA due to the appearance of the disease in childhood. However, these patients may be diagnosed with HPS in their later years, as characteristic symptoms, such as hemorrhagic diathesis, melena and bruising, subsequently develop. Therefore, long-term observation after diagnosis is necessary in cases of OCA or HPS, as pulmonary fibrosis may occur after 40 years of age in some patients. Suzuki et al. reported that 10% of OCA patients have HPS (12). Currently, nine types of HPS-causing gene mutations have been reported in humans, among which *HPS*1, *HPS2* and *HPS4* are known to be associated with pulmonary fibrosis (10, 11). However, the most important diagnostic finding is to confirm the presence of the HPS triad (OCA, hemorrhagic diathesis and ceroid-lipofuscin accumulation), rather than identify gene mutations, as such symptoms are essentially the result of intracellular organelle dysfunction, and mutations other than the nine currently identified mutations may also be related to the intracellular organelle function.

While it is possible to estimate the likelihood of the occurrence of pulmonary fibrosis, the utility of performing gene analyses in all children affected by OCA is limited because HPS with pulmonary fibrosis is extremely rare and the only established curative therapy for pulmonary fibrosis is lung transplantation. Furthermore, the patient may lack gene mutations, as was the case with our patient.

Several reports have described treatments for fibrosis associated with HPS (13-17) (Table 2), and many case reports

Table 2. Review of Theatment for HPS Complicated with Pulmonary Fibrosis

Reference	Year	Article type	Treatment	Result
13	2000	Original article	Corticosteroid	No improvement of the respiratory function was achieved, and all patients died of respiratory failure 2-7 years after the onset of respiratory symptoms.
14	2005	Case report	Corticosteroid	Clinical symptoms slightly improved. The lung lesion did not improve on chest roentgenograms and chest CT.
15	2002	RCT	Pirfenidone	Pirfenidone group lost FVC at a rate 5% of predicted per year slower than placebo group.
16	2011	RCT	Pirfenidone	No significant difference between the placebo and pirfenidone group in the loss of FVC.
17	2005	Case report	Lung transplantation	Marked improvement of the pulmonary function and the limitations in daily activities.

RCT : Randomized controlled trial

have also described diagnostic methods and the roles of various gene mutations. In the present case, corticosteroids and immunosuppressants were initially administered because the surgical lung biopsy specimens showed interstitial inflammation. However, no previous reports have indicated whether corticosteroids have favorable effects in such cases (13, 14). Corticosteroids and immunosuppressants should be administered cautiously, especially in candidates for lung transplantation, as these drugs can result in infectious disease. Several recent reports have suggested that pirfenidone can be used to treat pulmonary fibrosis in patients with HPS (15, 18). Gahl et al. reported that, in their study, pirfenidone therapy, when restricted to patients with an initial forced vital capacity (FVC) of >50% predicted, decreased the loss of FVC, forced expiratory volume in one second, total lung capacity and DLco at rates 8%/year slower than those observed in the placebo group (15). However, O'Brien et al. reported no statistical differences between the placebo and pirfenidone groups in their series (16). Meanwhile, Lederer et al. reported a case of successful bilateral lung transplantation in an HPS patient with pulmonary fibrosis (17). Although it is possible that pirfenidone has a favorable effect, lung transplantation is currently accepted as the only curative treatment. In the present case, therapy with corticosteroids and pirfenidone was not effective in treating the patient's pulmonary fibrosis. In addition, we registered the patient as an immediate lung transplantation recipient due to her poor prognosis; however, she succumbed to her disease before undergoing transplantation. She died five years after developing dyspnea on exertion. Therefore, providing an early diagnosis and taking into consideration the need for lung transplantation is important for prolonging survival, as HPS may be complicated by progressive pulmonary fibrosis, even in patients without *HPS1* or *HPS4* mutations.

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

Acknowledgement

We greatly acknowledge the assistance of T. Suzuki at the Second Department of Dermatology of Yamagata University for conducting the HPS gene analysis and K. Nagai at the Transfusion and Cell Therapy Unit, Nagasaki University Hospital for performing the platelet secondary aggregation activity analysis and providing assistance with the electron micrographs.

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