Hermansky-Pudlak Syndrome with Interstitial Pneumonia without Mutation of HSP1 Gene

Yoshihiro KOBASHI, Kouichiro YOSHIDA, Naoyuki MIYASHITA, Yoshihito NIKI and Toshiharu MATSUSHIMA

Abstract

A 57-year-old man with oculocutaneous albinism was admitted to our hospital because of exertional dyspnea and an abnormal shadow on chest roentgenogram. Chest CT revealed diffuse interstitial shadows with reticular nodular opacities in the bilateral whole lung fields and his pulmonary function test was consistent with a restrictive finding. Histologically, intraluminal diffuse fibrosis and interstitial fibrosis existed and ceroid-like materials within alveolar macrophages were demonstrated in a transbronchial lung biopsy specimen. In addition, because platelet dysfunction and ceroid-like materials within the reticuloendothelial cells of urine and bone marrow aspiration were recognized, we made a diagnosis of Hermansky-Pudlak syndrome (HPS). Gene analysis of the patient's peripheral blood cells did not reveal that he was a compound homogeneity for HPS1 gene mutations. Concerning treatment, although corticosteroid therapy was administered, his clinical symptoms and abnormal chest shadow have not changed.

Key words: Hermansky-Pudlak syndrome, ceroid-like materials, corticosteroid therapy

Introduction

In 1959 Hermansky and Pudlak first described an autosomal recessive, multisystem disorder characterized by tyrosinase-positive oculocutaneous albinism, a bleeding tendency secondary to platelet dysfunction, and a ceroid-lipofuscin lysosomal storage disease (1). Life-threatening manifestations are frequent, including progressive pulmonary fibrosis, granulomatous colitis, renal failure and cardiomyopathy. Death usually results from restrictive lung disease, hemorrhage or colitis at age 30 to 50 years (2).

To date, some genes causing Hermansky-Pudlak syndrome (HPS) such as HPS1 (3), AP3B1 (4), HPS3 (5), HPS4 (6) have been reported and HPS caused by an individual gene was differentiated into HPS1, HPS2, HPS3, HPS4. Among them, the HPS1 gene is the most frequently detected and only HPS1 mutations have been reported in patients with HPS in Japan (7–9). The HPS1 gene is located on chromosome 10q23 (10) and consists of 20 exons that encode a 700 amino acid, 30.5-kb protein that contains two putative transmembrane domains (11). Although the prognosis of HPS with interstitial pneumonia is poor in Japan or Puerto Rico and corticosteroid or other immunosuppressive drugs have been ineffective (12–14), HPS with interstitial pneumonia caused by the same HPS1 gene mutations in the Swiss Alps has generally been less clinically severe than in other populations. This is because the difference in prognosis among races has been suspected to relate to the difference in the abnormal portion of HPS1 gene (15). We report a rare case of HPS with interstitial pneumonia to further add to the molecular analysis data of HPS1 gene.

Case Report

A 57-year-old man visited a regional hospital on January 15, 2003 because of exertional dyspnea and an abnormal shadow recognized on a chest roentgenogram. Although the abnormal finding on his chest X-ray had been noted two years earlier, he had been taking no medications. Subsequently, he was referred to our hospital and admitted for diagnosis and treatment on January 29, 2003. He had an occupational history of working with magnesium chloride in the chemical industry for 30 years. As to his smoking his-
tory, he had smoked 30 cigarettes per day for 20 years. His family history was not remarkable and his patients had no consanguinity. He had had pneumonia at the age of 20 years old.

His height and body weight were 160cm and 50 kg, respectively. He was afebrile, and his pulse rate was 92/min with a blood pressure of 124/70 mmHg. His respiratory rate was 20/min and regular. His skin color was milk-like whitish, but there were no petechia or purpura. His hair color was reddish-brown. Ophthalmologically, he had amblyopia, strabism and horizontal nystagmus. Fine crackles were audible in the bilateral lower lung fields, but his heart sounds were normal. The results of abdominal and neurological examinations were normal.

Regarding laboratory data on admission (Table 1), although his total white blood cell count was normal, his erythrocyte sedimentation rate and C-reactive protein were slightly increased. TP, albumin, and albumin were decreased. Total globulin and all fractions of globulin were increased. Serological data, including tumor markers, were increased in SP-D, KL-6, CEA, CYFRA, and SLX. Results of an arterial blood gas analysis in room air showed mild hypoxia. A pulmonary function test revealed a marked reduction of % vital capacity and % diffusing capacity for carbon monoxide. A tuberculin skin test was negative. In coagulation tests, only fibrinogen was slightly increased. As for renal function, though serum creatinine or urea nitrogen and urine β2-microglobulin or NAG were normal, creatinine clearance and β2-microglobulin were slightly abnormal. Urinalysis disclosed both macrohematuria and microproteinuria. The level of hyaline and granular casts was marked in the urinary sedimentation test. A platelet function test revealed a lack of secondary wave aggregation to only collagen, and normal aggregation to ADP and epinephrine (Table 2).

A chest roentgenogram disclosed the presence of diffuse reticulonodular infiltrates and the distribution of infiltrates and the distribution of infiltrates was homogeneous in both upper and lower lung fields (Fig. 1) and chest CT demonstrated reticulonodular opacity with a honeycomb pattern and ground glass opacity in the bilateral whole lung fields (Fig. 1).
A gallium scintigram showed diffuse uptake in both lungs. Bronchoscopy with bronchoalveolar lavage (BAL) was performed seven days after admission. BAL fluid examination showed an increase in alveolar macrophages and a decrease in the OKT 4/8 ratio in T cell subsets. Cultures of BAL fluid for common bacteria and mycobacteria proved negative. Cytology was also negative for malignant cells (Table 3). Transbronchial lung biopsy (TBLB) specimens obtained from the right S' lung revealed intraluminal diffuse fibrosis and interstitial fibrosis in addition to lymphocyte infiltration of the alveolar septa dominant in the perivascular region (Fig. 3). Alveolar macrophages with a fine granular pigment proved positive with PAS and Sudan staining, consistent with ceroid-like materials observed in the reticuloendothelial cells of urine and bone marrow aspiration. He also had ocular albinism on ophthalmoscopy.

Based on these features; i.e., oculocutaneous albinism, ophthalmoscopy, transbronchial lung biopsy, and histopathological examination, the diagnosis of albinism-associated pulmonary alveolar proteinosis was made.

### Table 2. BALF Analysis

<table>
<thead>
<tr>
<th>Total cell</th>
<th>6 × 10^5/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell count</td>
<td></td>
</tr>
<tr>
<td>Alveolar macrophage</td>
<td>64.6%</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>28.8%</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>6.2%</td>
</tr>
<tr>
<td>Eosinophil</td>
<td>0.4%</td>
</tr>
<tr>
<td>T cell subsets</td>
<td></td>
</tr>
<tr>
<td>OKT 3</td>
<td>77.6%</td>
</tr>
<tr>
<td>OKT 4</td>
<td>25.2%</td>
</tr>
<tr>
<td>OKT 8</td>
<td>53.5%</td>
</tr>
<tr>
<td>OKT 4/8</td>
<td>0.47</td>
</tr>
<tr>
<td>Bacteria</td>
<td>Normal flora</td>
</tr>
<tr>
<td>Tbc</td>
<td>Smear (–), Culture (–)</td>
</tr>
<tr>
<td>Cytology</td>
<td>Class 1</td>
</tr>
</tbody>
</table>

### Table 3. Platelet Aggregation Test

<table>
<thead>
<tr>
<th></th>
<th>(10 μM)</th>
<th>61%</th>
<th>(2.0 μg/ml)</th>
<th>39%</th>
<th>(2.0 μg/ml)</th>
<th>57%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collagen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Figure 1. Chest radiograph taken at admission showing a diffuse reticulonodular shadow in the bilateral whole lung fields.

### Figure 2. Chest CT scan taken at admission showing reticulonodular opacity with a honeycomb pattern and ground glass opacity in the bilateral whole lung fields.

### Figure 3. Transbronchial lung biopsy specimen obtained from the right S' lung. Intraluminal diffuse fibrosis and interstitial fibrosis were noted in addition to lymphocyte infiltration of the alveolar septa and perivascular region (HE stain, ×100).
platelet dysfunction and ceroid-like materials in the reticuloendothelial cells within various organs, the final diagnosis was considered to be HPS. The clinical course is shown in Fig. 4. The patient was treated with intraoral prednisolone from the time of diagnosis was HPS (40 mg/day). However, despite treatment using corticosteroid drugs, his clinical symptoms and signs only slightly improved, and the lung lesion did not improve on chest roentgenograms and chest CT. Compared with the laboratory data on admission, LDH was slightly increased. PaO₂, PaCO₂, %VC and %DLco was also unchanged as of April 28. Regarding the gene analysis, no mutation was found in the HPS1 gene in the peripheral blood cells of this patient.

**Discussion**

Hermansky-pudlak syndrome, which is characterized by oculocutaneous albinism, platelet dysfunction, and accumulation of ceroid-like materials, is associated with interstitial pneumonia (8–10). Although there was evidence of interstitial pneumonia in one of the original cases described by Hermansky and Pudlak (1), Davis and Tuddenham (10) were the first to suggest that this syndrome is associated with pulmonary fibrosis. Three of their four patients had TBLB evidence of interstitial pneumonia have been rare. The complication rate of HPS with interstitial pneumonia is an important factor which influences the prognosis of HPS.

Interstitial pneumonia due to HPS differs from idiopathic interstitial pneumonia (IIP) in the distribution of abnormal shadows as a radiological finding and fibrosis as a pathological finding (6, 12). Namely, the distribution of abnormal shadows is dominant in subpleural zones in the bilateral lower lung fields in cases with IIP. With HPS, abnormal shadows are present in all lung fields but not in the subpleural zones. Furthermore, progression usually occurs in diffuse interstitial fibrosis, but there is little decrease in lung volume, as was true in the present case (13). It was suggested that the reason why interstitial pneumonia in the perivascular area was dominant was that microbleeding in the lung accompanying the platelet dysfunction occurred and the surrounding secondary change was severe pathologically. Supporting this theory, interstitial pneumonia around the perivascular area was dominant in our case (Fig. 3).

The origin of ceroid-like materials is unknown, but it has been suggested that the accumulation of lipopigment in various tissues reflects a problem with the catabolism of lipids,
and a specific defect in glutathione peroxidase has been proposed to explain this problem (14). The ceroid-like materials seen in the alveolar macrophages may be a passive products or they could play a role in inducing fibrosis (8). When activated, macrophages undergo an increase in oxygen consumption and in the secretion of superoxide anions and hydrogen peroxide. These oxygen metabolites have been implicated in the cause of a variety of cellular and tissue injuries (15). Because phagocytosis is one process known to be accompanied by the production of superoxide anions (16), it is possible that the phagocytosis of ceroid-like materials by macrophages leads to increased superoxide production and release, and these active substances may contribute to subsequent parenchymal damage.

Clinically, pulmonary disease typically presents with insidious onset of dyspnea. A diffuse interstitial pneumonia is seen on chest roentgenogram and a pulmonary function test may show a restrictive ventilatory pattern similar to the finding in the present case. Some patients have progressed to respiratory failure. The response to corticosteroids or other immunosuppressive drugs has been poor in Japanese HPS patients (4–6). Corticosteroid therapy was also ineffective in the present patients. Although new anti-fibrotic drugs (for example: interferon-γ which induces resolution by reducing extracellular matrix production and by increasing matrix metalloprotease and hepatocyte growth factor which has an inhibitory effect of TGF-β, and pirfenidone which has an inhibitory effect of apoptosis or TGF-β, or PDGF), were recently developed for idiopathic interstitial pneumonia (17), they have not yet become widely used in patients with interstitial fibrosis of HPS.

HPS is an autosomal recessive hereditary disease and has often occurred in patients with a familial history of HPS, but in the present patient there were no apparent hereditary history. Concerning the gene analysis, although some genes causing HPS such as HPS1, HPS2, HPS3, HPS4 have been reported, the HPS1 gene is most frequently detected and only HPS1 mutations have been reported in patients with HPS in Japan (7–9). Various mutations in the HPS1 gene of HPS patients have been found (18, 19). Unfortunately, no mutation was found in the HPS1 gene of our patient. Later, we considered that it may have been recommended to perform gene mutation analysis of not only HPS1, but also HPS2, HPS3, HPS4. One mutation in the splice-donor site of IVS 5 (IVS 5+5 G→A) is identical to our recently described in a Japanese HPS patient in Kyushu, who is a homozygote (18).

Finally, we found it comparatively easily to be suspected HPS in this case because co-author Matsushima et al had already encountered and reported another case (20). Final diagnosis was obtained after autopsy in the previous report and was confirmed by cereoid-like materials in reticuloendothelial cells of the liver, spleen, bone marrow, and tubular and intestinal epithelium. Because apparent cutaneous albinism and atypical radiological findings of diffuse interstitial pneumonia were recognized in the present case, we suspected HPS and performed TBLB positively being aware of the bleeding tendency because the platelet aggregation test to only collagen was abnormal but the bleeding time was within the normal limit. Then we could obtain an early diagnosis of HPS. White et al (21) reported that BAL was effective in patients with HPS because the recovered alveolar macrophages were shown to contain characteristic ceroid-like material, especially in HPS patients with a remarkable bleeding tendency. Therefore, the diagnostic method should be determined with consideration of the patient’s condition.

We gratefully acknowledge the assistance of Y. Ikegami and M. Nakajima in the Second Department of Internal Medicine of Hiroshima University in the gene analysis of HPS.

References


