Hermansky-Pudlak Syndrome with a Novel Mutation

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Abstract

We report a case of Hermansky-Pudlak syndrome (HPS) with a novel mutation in the \textit{HPS1} gene. This case showed oculocutaneous albinism and lysosomal ceroid accumulation, however platelet dysfunction was not observed. Histopathological findings of the biopsied lung tissue were compatible with HPS. Sequencing analysis showed the insertion of C in the codon 178 (739 bp) of the \textit{HPS1} gene forming a stop codon at codon 181. To the best of our knowledge, this is a novel \textit{HPS1} gene mutation.

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Key words: HPS1, mutation, codon178, exon20

Introduction

Hermansky-Pudlak syndrome (HPS) is a relatively rare autosomal recessive disorder; its manifestations include oculocutaneous albinism, platelet dysfunction and lysosomal ceroid accumulation (1). After the discovery of the location of the \textit{HPS1} gene on band 10q23, the other five subtypes [HPS2 (AP3B1), HPS3, HPS4, HPS5 and HPS6 (2–5)] have been reported. The incidence of HPS is frequent in Puerto Rico, however it is relatively rare in non-Puerto Rican countries (6). Patients with the \textit{HPS1} gene disorder frequently present with pulmonary fibrosis (7). Here, we report a case of HPS who presented with interstitial pneumonia and had a novel \textit{HPS1} gene mutation.

Case Report

This study was reviewed and approved by the Kagoshima University Faculty of Medicine Committee on Human Research. Written informed consent was obtained from the present case investigated in this study.

A 46-year-old woman was admitted to our hospital because of dry cough and dyspnea on effort. She showed congenital albinism. The patient’s family history revealed that her parents were cousins, and her sibling also had congenital albinism. She had a history of recurrent bacterial infection in her lungs during childhood. Twenty-two months prior to admission, she developed a non-productive cough and 6 months prior to admission, she developed dyspnea on effort.

Physical examination on admission revealed brown hair, brown eyebrows, pale white skin, and ecchymosis on the upper and lower extremities (Fig. 1). Auscultation of her lungs revealed fine crackles in the lower regions bilaterally. The results of the laboratory studies on admission are shown in Table 1. White blood cell and platelet counts were elevated. Bleeding time was slightly extended however, platelet aggregation was normal. Blood chemistry showed elevation of LDH, KL-6, and SP-D. Arterial blood gas analysis indicated hypoxemia, and pulmonary function test disclosed restrictive pattern and reduced diffusion capacity. Chest radiography revealed reticulonodular pattern in the upper and lower right lobes and in all the left lobes and chest computed tomography (CT) showed bilateral diffuse scattered reticulonodular pattern with slightly increased density (Fig. 2).

For histopathological diagnosis, lung biopsy under video-assisted thoracic surgery (VATS) was performed. The biopsied specimen showed thickening of the alveolar septal wall along with fibrosis and infiltration of lymphocytes. Alveolar macrophages revealed ceroid substance that was positive for periodic acid Schiff (PAS) staining (Fig. 3). On electronmicroscopy, not only alveolar macrophages but also alveolar epithelial cells were observed to contain ceroids in their cytoplasm (Fig. 3E, F).

Genetic studies

The sequence of genomic DNA and cDNA of the \textit{HPS1}}
of C was detected in the codon 178 (739 bp) forming a stop codon at codon 181. Further, the insertion of C was detected at the same site on one side of the base pair in the sample of patient’s mother (Fig. 4). Considering the histopathological findings and genetic findings together, Hermansky-Pudlak syndrome with a novel HPS1 gene frame shift was diagnosed.

**Discussion**

Here, we report a HPS case with a novel mutation that causes a frameshift in the HPS1 gene. HPS is an autosomal recessive disorder characterized by oculocutaneous albinism, a tendency to bleed, and a ceroid-lipofuscin lysosomal storage disease (1). Life-threatening manifestations are frequent, and death typically results from restrictive lung disease (68%), hemorrhage (17%), or granulomatous colitis (15%), in patients aged 30–50 years (8). There is no specific therapy for HPS, and treatment is usually limited to supportive care.

HPS is rare in most populations however, it is a frequent single-gene disorder found in Puerto Rico, where it occurs with an estimated frequency of 1/1,800 persons (8). HPS is also frequent in a long-isolated village in the Swiss Alps (9). The human HPS gene consists of 20 exons that span 30.5 kb (10), and it encodes a 700 amino acid polypeptide that contains two apparent transmembrane domains but that has no evident homology to any other known proteins (5). Codon 491–496 frameshift is common in the HPS cases found in Puerto Rico, and codon 322–324 frameshift is common in European HPS patients (6). In Japan, four mutation patterns have been reported (Table 3) (6, 11–13). All cases showed typical HPS symptoms that include albinism, bleeding diathesis and abnormal ceroid-lipofuscin lysosomal storage. One of them showed heterozygous HPS1 gene mutations with a typical HPS phenotype (11) and one case with 1bp duplication in codon 441 developed systemic lupus erythematosus and pulmonary fibrosis (12). The present case showed albinism, abnormal ceroid-lipofuscin lysosomal storage and pulmonary fibrosis however, the platelet function was almost normal. Thus, the present case has a novel mutation pattern and a unique phenotype.

Pulmonary fibrosis is a typical clinical feature of HPS1 (1), and HPS1 gene mutations in general, rather than homozygosity for the 16-bp duplication in exon15 specifically, constitute the risk factor for pulmonary fibrosis (7). Patients with HPS2 have mild pulmonary fibrosis and suffer from recurrent childhood infections due to neutropenia (14, 15). The clinical features of HPS4 disease resemble those of HPS1, and include granulomatous colitis and pulmonary fibrosis (2, 16). Pulmonary fibrosis is not seen in HPS3 (17), HPS5 (18) and HPS6 (19). Bleeding diathesis is a common feature of HPS1 (1), HPS2 (14) and HPS6 (19). In HPS4 and HPS5, platelet count is almost normal, however, platelet aggregation is reduced, and bleeding time is moderately prolonged (18, 19). In HPS3, bleeding diathesis is very mild (4). Thus, the pulmonary fibrosis seen in the present case is
compatible with the clinical features of HPS1 however, results regarding platelets are similar with those of HPS3, HPS4 and HPS5.

At the cellular level, HPS is associated with defects of multiple cytoplasmic organelles, including melanosomes, platelet-dense granules, and lysosomes (1, 5). It possibly results from a defect in a protein required for the biogenesis, structure, or function of these various membrane-bound organelles. Idiopathic pulmonary fibrosis-like interstitial pneumonia has been known to be the most serious complication of HPS (7), and possible association of pulmonary inflammatory cell dysfunction, including alveolar macrophage, with

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**Table 1. Laboratory Findings on Admission**

<table>
<thead>
<tr>
<th>Blood analysis</th>
<th>LDH</th>
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<tbody>
<tr>
<td>WBC 12,700 (×10^9/μl)</td>
<td>1,025 IU/</td>
</tr>
<tr>
<td>Neu 72%</td>
<td>CRP 0.86 mg/dl</td>
</tr>
<tr>
<td>Lym 23%</td>
<td>KL-6 6,066 U/ml</td>
</tr>
<tr>
<td>Eo 1%</td>
<td>SP-D 260 ng/ml</td>
</tr>
<tr>
<td>RBC 421 (×10^12/μl)</td>
<td>Blood gas analysis</td>
</tr>
<tr>
<td>Ht 42.1%</td>
<td>(room air)</td>
</tr>
<tr>
<td>Hb 13.9 g/dl</td>
<td>pH 7.406</td>
</tr>
<tr>
<td>Plt 35.3 (×10^12/μl)</td>
<td>PaO2 61.9 mmHg</td>
</tr>
<tr>
<td>PT 99%</td>
<td>PaCO2 42.5 mmHg</td>
</tr>
<tr>
<td>APTT 30.2 s</td>
<td>Pulmonary function test</td>
</tr>
<tr>
<td>Fibrinogen 461 mg/dl</td>
<td>VC 1.51 l</td>
</tr>
<tr>
<td>bleeding time: 10 min</td>
<td>%VC 57.6%</td>
</tr>
<tr>
<td>platelet aggregation: normal</td>
<td>FEV1 1.33 l</td>
</tr>
<tr>
<td>AST 18 IU/l</td>
<td>FEV1/VC 85.8%</td>
</tr>
<tr>
<td>ALT 14 IU/l</td>
<td>DLco 6.11 ml/min/mmHg</td>
</tr>
<tr>
<td></td>
<td>%DLco 34.3%</td>
</tr>
</tbody>
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**Figure 2.** A. The chest radiography showing reticulonodular pattern in the upper and lower right lobes and in all left lobes. B. Chest computed tomography (CT) scan demonstrating bilateral diffusely scattered reticulonodular pattern with inner zone predominance and peripheral infiltrative shadows in both lungs.
Figure 3. A to D: Biopsied tissue specimens of the lung showing septal fibrotic thickening and infiltration of lymphocytes. The lesions were found with irregular patchy patterns within normal original structures (A. HE stain, B. staining for elastic tissue ×80 original manifestation). Tissue staining with periodic acid Schiff (PAS) (C. ×200, D. ×1,000 original magnification) showed phagocytes including ceroid substance that are PAS-positive (arrows). E and F: Electron microscopy (×9,000) showing linear granules in alveolar macrophages (E) and in alveolar epithelial cell (F).
the pathogenesis of interstitial pneumonia in HPS has been suggested (20, 21). However, its detailed molecular pathogenesis remains unknown. According to a previous report, fibroblasts derived from a HPS1 gene-deficient patient did not change the expression pattern of lysosome-associated membrane protein (LAMP)-1 and LAMP-3 which are important for antigen presenting cell functions (22). Furthermore, in culture cells derived from patients with HPS2 gene mutation, CD1b failed to efficiently gain access to lysosomes, resulting in a profound defect in antigen presentation (23) while another human fibroblast with HPS2 mutation caused complete deficiency of adaptor complex-3 protein and increased protein trafficking through LAMP-3 with up-regulation of antigen-presenting capacity (14, 22). Thus, the HPS gene is likely to affect immunological mechanisms.

The present case had a new pattern of HPS1 mutation and the pathogenesis of interstitial pneumonia in HPS has been suggested (20, 21). However, its detailed molecular pathogenesis remains unknown. According to a previous report, fibroblasts derived from a HPS1 gene-deficient patient did not change the expression pattern of lysosome-associated membrane protein (LAMP)-1 and LAMP-3 which are important for antigen presenting cell functions (22). Furthermore, in culture cells derived from patients with HPS2 gene mutation, CD1b failed to efficiently gain access to lysosomes, resulting in a profound defect in antigen presentation (23) while another human fibroblast with HPS2 mutation caused complete deficiency of adaptor complex-3 protein and increased protein trafficking through LAMP-3 with up-regulation of antigen-presenting capacity (14, 22). Thus, the HPS gene is likely to affect immunological mechanisms.

The present case had a new pattern of HPS1 mutation and
had a history of recurrent bacterial infection in the lungs. It is apparent that the proteins encoded by the HPS gene have multiple effects on the immune system (14, 22, 24). Harmon et al reported that macrophage-derived peptides are important candidate molecules in the initiation of alveolar remodeling in fibrotic lung disorders (25). Our next aim is to clarify the immunological aspects of the present case.

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References