Case Report

Hermansky-Pudlak Syndrome with Nonspecific Interstitial Pneumonia

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Abstract

We herein report a case of Hermansky-Pudlak syndrome (HPS) with nonspecific interstitial pneumonia (NSIP). A 58-year-old Japanese woman presented with oculocutaneous albinism and dyspnea on exertion. A high resolution computed tomography scan showed areas of reticular and ground glass opacity in the lungs, and a surgical lung biopsy revealed fibrotic NSIP. Foamy type 2 pneumocytes and the absence of dense granules in platelets were also observed, consistent with a diagnosis of HPS. Ultimately, a genetic analysis revealed a mutation in the HPS1 gene. The interstitial pneumonia progressed despite treatment with prednisolone, cyclosporine A and pirfenidone. In this report, we discuss the pathological lung features and treatment of HPS associated with interstitial pneumonia.

Key words: Hermansky-Pudlak syndrome, nonspecific interstitial pneumonia, HPS1

(DOI: 10.2169/internalmedicine.53.1311)

Introduction

Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive disease characterized by oculocutaneous albinism (OCA) and platelet dysfunction due to lysosomal ceroid accumulation. HPS is more common in Puerto Rico and is relatively rare in areas such as Japan and Europe (1). There are eight known human HPS genes causing different subtypes of HPS (HPS1-8) (2). In particular, patients with HPS1 and HPS4 gene mutations frequently develop interstitial pneumonia, the most serious complication of HPS (3-5). The pathological features and patterns of interstitial pneumonia in patients with HPS (HPS-IP) have not been fully elucidated, and no effective treatments have been reported (6-8), except for lung transplantation (9). We herein report a case of HPS with nonspecific interstitial pneumonia (NSIP) and discuss the pathological lung features and treatment of HPS-IP.

Case Report

A 58-year-old Japanese woman was admitted to our hospital with dyspnea on exertion and a dry cough in 2006. She had blonde hair and naturally pale, white skin, consistent with the findings of oculocutaneous albinism. In addition, she had slight bruising, strabismus, horizontal nystagmus and decreased visual acuity. She was a nonsmoker and had no history of fever, weight loss or hemoptysis. She safely underwent cholecystectomy due to cholelithiasis before admission.

Her elder brother also had albinism and had died of a cerebral hemorrhage at 47 years of age, although he had not been diagnosed with HPS. The patient was childless. A physical examination revealed bilateral chest fine crackles and skin hypopigmentation. No finger clubbing was found. The patient’s blood pressure was 118/70 mmHg, her pulse was 90 beats/min and her respiratory rate was 20 breaths/min. An arterial blood gas analysis showed a PaO2 of 92.4 Torr and a PaCO2 of 30.0 Torr on room air. Her oxygen saturation level was 97% on room air at rest; however, it decreased to 87% during a 6-minute walk test. Laboratory studies showed a normal complete blood count and immunoglobulins, with no autoantibodies. The prothrombin, partial thromboplastin and bleeding times were within the normal ranges. Serum biochemistry showed an increased level...
the right B5. Although the total cell count and cell fractions of pleural lung, and no honeycombing was found. Lower lobes (Fig. 2). There was relative sparing of the sub- traction bronchiectasis predominantly in the middle and phy scan of the chest revealed extensive ground glass and lung volume (Fig. 1). A high resolution computed tomogra- daphy in the middle and lower lung fields and a decreased pgraph showed areas of reticulonodular and ground glass reactivity in the lungs for carbon monoxide of 11.65 mL/min/mmHg (63.1%). A chest radio- pany showed diffuse interstitial collagen deposition (Fig. 3b), and Sudan staining (Fig. 3c). Based on these results, the granules were considered to be ceroid-like mate-xins. Subsequently, a surgical lung biopsy of right S3 and S9 was performed. Hematoxylin and Eosin staining of the lung specimens showed diffuse interstitial collagen depo-xion with mild mononuclear cell infiltration (Fig. 3d). The lung lesion was temporally uniform, consistent with fibrotic NSIP. Foamy and brown-pigmented macrophages were fo-xentially aggregated in the alveolar air space despite the pa-xin’s lack of smoking history (Fig. 3e), and there were en-xlarged foamy type 2 alveolar epithelial cells on the alveolar wall (Fig. 3f). Both the macrophages and type 2 alveolar epithelial cells were positive for PAS staining, consistent with the features of HPS (Fig. 3g).

In order to make a definitive diagnosis of HPS, electron microscopy of platelets and a genetic analysis were per-xormed. The absence of dense platelet granules was seen on whole mount electron microscopy compared with that ob-xerved in healthy controls (Fig. 4). Regarding the genetic an-xalysis, an IVS5+5 G>A homozygous pattern mutation was found in the HPS1 gene in the patient’s peripheral blood cells.

Treatment with 40 mg/day of oral prednisolone and 100 mg/day of cyclosporine A was initially commenced. How-xever, the patient’s vital capacity decreased and the areas of lung opacity deteriorated by degrees. Therefore, pirfenidone, an antifibrotic agent, was added to the immunosuppressive regi-xmen after three years. The maintenance dose was limited to 1,200 mg/day due to the adverse effect of anorexia. Al-though the patient’s respiratory symptoms became stable and the serum KL-6 level decreased for a few months, the treatment was unable to prevent the progression of interstitial pneumonia. The areas of diffuse lung opacity grew, and the patient’s lung volume gradually decreased. Home oxy-xgen therapy was administered due to progressive hypoxemia. The patient died of an acute exacerbation of interstitial pneumonia 54 months after the initiation of treatment.

Discussion

HPS was first described in 1959, when Hermansky and Pudlak reported two unrelated patients with albinism, hem-orrhagic diathesis, unusual pigmented reticular cells in the bone marrow and pulmonary disease (10). This syndrome is currently recognized to constitute a rare, heterogeneously in-herited autosomal recessive group of disorders that manifest as OCA, platelet storage pool deficiency and the lysosomal accumulation of ceroid lipofuscin in the reticuloendothelial system. In the present patient, a definitive diagnosis of HPS was apparent from the physical findings, several staining re-sults of alveolar macrophages, the electron microscopic find-ings of platelets and based on the presence of a mutation in the HPS1 gene.

HPS1 is the most common subtype and can cause severe comorbidities such as interstitial pneumonia or inflammatory bowel disease (2-5, 11). In addition, HPS4 patients charac-teristically develop severe interstitial pneumonia as well as HPS1 (2, 5). The prevalence of HPS1 was shown to be 9.6% among 125 Japanese patients with OCA (12). Fur-thermore, in the HPS1 gene, an IVS5+5 G > A splice consensus mutation is most frequently observed in Japanese pa-xients (13). In this case, an IVS5+5 G > A homozygous pat-xern mutation was found in the patient’s peripheral blood cells, and the existence of severe interstitial pneumonia was consistent with the findings of previous reports.

Interstitial pneumonia is the most serious complication and primary cause of death in patients with HPS. It usually presents in the third or fourth decade of life, accounting for premature death in 50% of HPS patients, generally by the fifth decade (8, 11). The underlying pathogenesis of HPS-IP is unclear. Nakatani et al. reported that foamy degeneration of type 2 alveolar epithelial cells (AEC2) is the most impor-tant histopathological feature of HPS and that a basic defect.
Figure 2. High-resolution computed tomography scan of the chest showing extensive ground glass and reticular opacity along the bronchovascular bundle and traction bronchiectasis predominantly in the middle and lower lobes (a, b). There was relative sparing of the subpleural lung. No honeycombing was found.

Figure 3. The first row (a-c) shows the bronchoalveolar lavage fluid (BALF) cytology obtained from the right B5. Alveolar macrophages with granules were stained with Periodic-acid Schiff (PAS) staining (a), Schmorl’s staining (b) and Sudan staining (c). The arrows indicate positive macrophages for each staining. The second and third rows (d-g) show the surgical lung biopsy specimens obtained from the right S3 and S9. Diffuse interstitial collagen deposition with mild mononuclear cell infiltration was found (d, Hematoxylin and Eosin (HE) staining, ×12.5). The lung lesion was temporally uniform, consistent with the findings of fibrotic nonspecific interstitial pneumonia (NSIP). Foamy and brown-pigmented macrophages were focally aggregated in the alveolar air space (e, HE staining, ×400). There were foamy type 2 alveolar epithelial cells (arrows) on the alveolar wall (f, HE staining, ×400). The foamy macrophages and foamy type 2 alveolar epithelial cells were positive for PAS staining (arrows) (g, ×400).
in the formation/secreton of surfactant by AEC2 may be the triggering factor for the development of HPS-IP (14). Extensive surfactant abnormalities cause severe lysosomal and endoplasmic reticulum stress with apoptosis of AEC2 in patients with HPS-IP (15). Moreover, it has been reported that dysfunction of alveolar epithelial cells and activation of macrophages via S-nitrosylated surfactant protein D initiates the development of lung inflammation in the early stage of HPS-IP (16). In the present case, we also found enlarged foamy AEC2 on the alveolar wall in the surgical lung biopsy specimens, and this pathological finding is the most important difference between HPS-IP and other types of interstitial pneumonia, such as idiopathic interstitial pneumonia (IIP).

The histopathological pattern of HPS-IP is unclear, although there are several patterns, including usual interstitial pneumonia (UIP), NSIP and so forth, in IIP. Peribronchiolar patchy fibrosis is frequently reported in HPS-IP patients (14). Additionally, HPS-IP is a differential diagnosis of idiopathic UIP (i.e., idiopathic pulmonary fibrosis) (17). Meanwhile, in our patient, the pathological findings of the surgical lung biopsy specimens were consistent with an NSIP pattern, which exhibits uniformity in the distribution and phase of interstitial pneumonia. Case reports in which an NSIP pattern was confirmed in patients with HPS are quite rare (18). It is unclear whether the pathological patterns of interstitial pneumonia are important with respect to the therapeutic response and prognosis of patients with HPS-IP. Therefore, further studies are needed to clarify this question. However, attention must also be paid to the safety of surgical lung biopsies, due to the bleeding tendency observed in patients with HPS.

Regarding the treatment of HPS-IP, there is no effective therapy, except for lung transplantation (9). Treatment with corticosteroids and immunosuppressive agents is not effective for HPS-IP (4, 8). Pirfenidone, a pyridine molecule with anti-inflammatory and antifibrotic activities, has been administered in HPS-IP patients in previous studies (6, 7). However, the latest trial conducted in patients with mild to moderate HPS1 and HPS4 pulmonary fibrosis showed no statistical differences in the change in forced vital capacity at 12 months between the placebo and pirfenidone groups (7). In the present case, pirfenidone was added to prednisolone and cyclosporine A. The addition of pirfenidone improved the patient’s respiratory symptoms for a few months, although it did not alter the natural course of HPS-IP. Azuma et al. reported that treatment with pirfenidone ameliorated coughing and dyspnea in patients with idiopathic pulmonary fibrosis (19). The mechanisms by which pirfenidone improves respiratory symptoms have not been fully elucidated. However, the suppression of Substance P, a sensory neuropeptide that stimulates the cough reflex, and alleviation of decreases in the neutral endopeptidase (NEP) activity, which improves coughing via the suppression of submucosal gland secretion, smooth muscle contractions and vascular permeability, have been observed following treatment with pirfenidone (20). Therefore, there is a possibility that pirfenidone improves the quality of life in patients with HPS-IP by suppressing the cough reflex. Furthermore, in this case, the addition of pirfenidone temporarily decreased the serum KL-6 level. An additive or synergistic effect of pirfenidone and cyclosporine A may exist in the treatment of HPS-IP.

In conclusion, we herein described a case of HPS with NSIP. The absence of dense granules in platelets and a mutation in the HPS1 gene were found in the patient. The surgical lung biopsy specimens showed a fibrotic NSIP pattern in addition to foamy AEC2. The interstitial pneumonia progressed despite treatment with multiple drugs, including pirfenidone. The exact mechanisms and significance of the pathological patterns observed in patients with HPS-IP remain unknown. Therefore, future studies are needed to clarify the pathogenesis and develop a novel treatment for HPS-IP.

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

We would like to thank Dr. Hidenori Suzuki (Laboratory of Electron Microscopy, Tokyo Metropolitan Institute of Medical Science) for performing the electron microscopic examination and Prof. Tamio Suzuki (Department of Dermatology, Yamagata University School of Medicine) for performing the genetic analysis.

References