Case Report

Hermansky-Pudlak syndrome with interstitial lung disease: A holistically worked up couplet

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ABSTRACT

Hermansky-Pudlak syndrome (HPS) is an extremely subtile autosomal recessive disorder characterized by tyrosinase-positive oculocutaneous albinism (Ty-pos OCA), bleeding tendencies, and systemic complications associated to lysosomal dysfunction. The most grave complication of disease is interstitial lung disease (ILD) leading to irrevocable pulmonary fibrosis. Patients with HPS-1, HPS-2, and HPS-4 variants have a penchant to develop pulmonary fibrosis. The pulmonary involvement is characterised by progressive dyspnea hypoxemia respiratory failure and corpulmonale. The disease has an unfortunate prognosis with a high mortality rate and a poor quality of life. The options currently available in the therapeutic armamentarium are dismal with a dire need for opportune research. We hereby narrate an intriguing case scenario of a pair of siblings affected with this rare disorder with its associated ILD.

KEY WORDS: Hermansky–Pudlak syndrome, lysosomal dysfunction, occulo-cutaneous albinism, pulmonary fibrosis

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INTRODUCTION

Hermansky–Pudlak syndrome (HPS) was first described in 1959 by Dr. Frantisek Hermansky and Dr. Paulus Pudlak, who pinpointed two patients with oculocutaneous albinism and bleeding diathesis in Czechoslovakia.[1] Subsequently, nine classic forms of the disorder, based on the genetic mutation,[2] have been described and distinguished by their signs, symptoms, and genetic traits. In most cases, each subtype has more than one genetic variant. Of these nine variants, HPS-1 is the most fatal form while HPS-2 and HPS-4 also have solemn manifestations. The precise etiopathogenesis remains obscure; however, it seems to be interplay of various genetic and environmental influences. The biogenesis of lysosome-related organelles complexes (BLOCs)[3] are the fundamental elements in the pathogenesis, which are HPS gene encoded HPS protein complex. HPS is relatively common in Puerto Rico, where the prevalence of HPS-1 is estimated to be about 1 in 1,800 people in the northwest region of the island, accounting for approximately 50% of all cases globally;[4] however, the data pertaining to its incidence from the other parts of the globe are sporadic. Pulmonary involvement in HPS is known in the form of interstitial lung disease (ILD). Accumulation of amorphous lipid–protein complexes called ceroids, which increase with age in patients with HPS, has been speculated to be a potential trigger for the development of pulmonary fibrosis in these patients with ILD. We hereby report a couplet of a sister who was suspected and diagnosed with HPS and the latter unearthing of her brother harboring the same disease.

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CASE REPORTS

Case 1

A 36-year-old woman, farmer by occupation nonaddict, followed up to our outpatient department for management

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of her cough and dyspnea. She was a diagnosed case of albinism since childhood. From respiratory point of view, she was symptomatic for 5–6 years with complaints of cough and predominantly dry and progressive dyspnea. For these symptoms, the patient was previously treated with empirical antituberculosis therapy at a peripheral hospital with no relief of her symptoms. In view of the increase in her symptoms, the patient followed up to our side. On inquiry, she also gave a history of bleeding tending since childhood along with a family history of albinism and bleeding tendency in brother too. On examination, her pulse rate was 110 beats/min, respiratory rate: 24 cycles/min, blood pressure: 110/70 mm of mercury, and saturation of 90% on pulse oximeter at room air. Respiratory system examination revealed bilateral crackles. Cardiovascular system examination was unremarkable except for a loud pulmonary component of the second heart sound. Rest systemic examination was within normal limits. She was evaluated with a complete blood count which showed hemoglobin of 8.5 g/dl, which later on was labeled as iron deficiency anemia after an iron profile study. All the other serum biochemical values were within normal limit except for Vitamin D_3 level which was low. Her chest X-ray (CXR) was suggestive of bilateral fibrocystic opacities along with reticulonodular opacities with a shift of trachea toward the right [Figure 1]. High-resolution computed tomography (HRCT) scan of the thorax was suggestive of atypical usual interstitial pneumonia (UIP) pattern seen as a part of HPS [Figure 2]. Her arterial blood gas (ABG) analysis showed Type 1 respiratory failure. Spirometry was restrictive abnormality with forced expiratory volume at 1^{st} s by forced vital capacity (FVC) ratio of 100 and FVC of 0.5 l (18% predicted). Six-minute walk distance (6MWD) was 110 m with desaturation from 90% to 78%. Further, she underwent a fiber-optic bronchoscopy along with transbronchial lung biopsy (TBLB), where histopathology was consistent with the diagnosis of UIP pattern seen in association with HPS. Genetic mutation for HPS was performed, where HPS-4 gene mutation was detected. Electron microscopy (EM) for platelet dysfunction showed marked deficient granules [Figure 3]. Hence, diagnosis of HPS-related ILD was confirmed on clinical, radiological, histopathology, genetic, and microscopic background. Two-dimensional echocardiography showed pulmonary artery systolic pressure by tricuspid regurgitation jet of 60 mm of mercury with right atrial and ventricle dilatation. Dual-energy X-ray absorptiometry (DEXA) scan showed T-score of 3.8. On ophthalmological examination, her retina showed albinotic changes. The patient was managed with cough suppressant, supplemental oxygen, Vitamin D_3 supplement, calcium, antacids, and iron–folate supplements. Pulmonary rehabilitation with chest physiotherapy and vaccination with influenza and pneumococcal vaccine was also done. The patient showed subjective improvement in ward and was discharge on long-term oxygen therapy along with above medications.

Case 2

A 20-year-old man, student by occupation, brother of our index patient was screened for similar findings of HPS

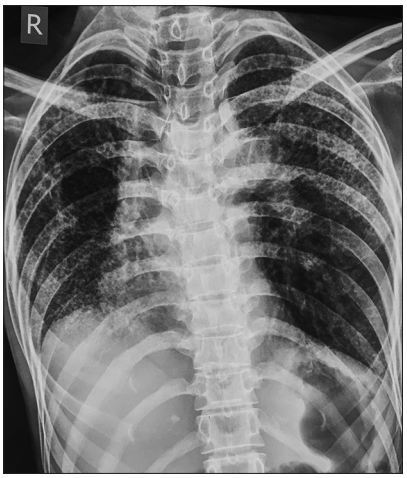

Figure 1: Bilateral fibrocystic opacities along with reticulonodular opacities with shift of trachea toward the right

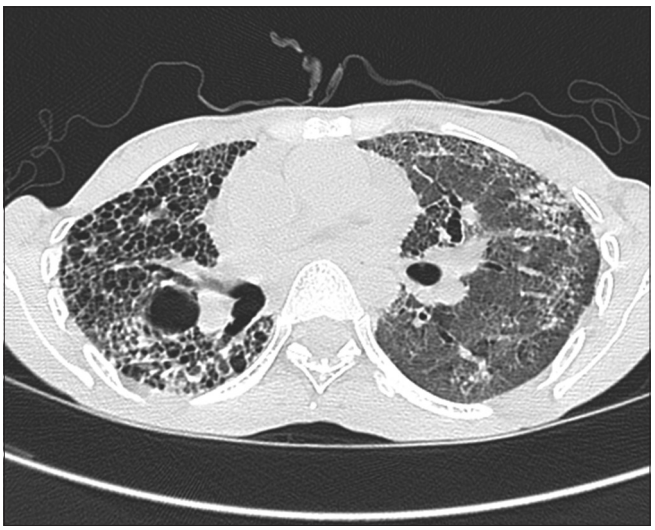

Figure 2: Ill-defined areas of intralobular, interstitial septal thickening bilaterally with peripheral distribution and upper zone predominance. Extensive honeycombing bilaterally. Large cyst in posterior segment of the right upper lobe

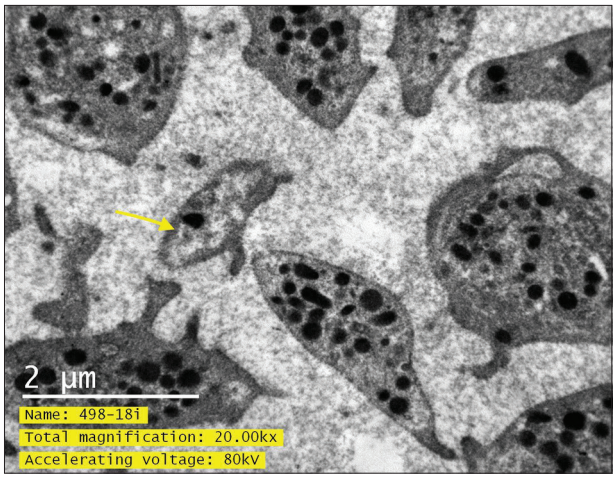

Figure 3: The buffy coat showing reduction in number of dense granules along with distorted alpha granules

clinicoradiologically. The patient was asymptomatic from respiratory point of view. Local and systemic examination was normal. All serum biochemical markers are within normal limits. CXR was normal. However, his HRCT thorax showed subtle changes suggestive of atypical UIP pattern seen as a part of HPS. His ABG and two-dimensional echocardiography were normal, with spirometry suggestive of restrictive abnormality with FVC 66% predicted. 6MWD was 400 m without desaturation. He too had albinotic retina, hypopigmentation of skin, and hair along with bleeding tendency. His EM for platelet dysfunction also showed marked deficient granules. His DEXA scan showed osteoporosis. The patient was kept under observation and follow-up planned every 3 months for clinical assessment, spirometry, and 6MWD and a HRCT assessment planned yearly.

Both cases were diagnosed as case of HPS-associated ILD with osteoporosis

DISCUSSION

HPS is a rarefied malady characterized by multisystemic involvement of oculocutaneous albinism (decreased pigmentation), bleeding problems due to a platelet abnormality (platelet storage pool defect), and respiratory involvement in the form of ILD. HPS Type 1 is the most common single gene disorder in Puerto Rico. It is most prevalent in the northwestern quadrant of the island. Epidemiologic studies report that in this region, 1 out of 1,800 persons has the syndrome. In this area, approximately 1 out of 21 persons carries the gene encoding for HPS Type 1. On the other hand, HPS Type 3 is more prevalent in the central mountainous region of the Caribbean island.[5] Systemic complications in HPS are associated with accumulation of a ceroid-like substance in lysosomes of a variety of tissues. Ceroid deposition in patients with HPS has been associated with pulmonary fibrosis, granulomatous enteropathic disease, and renal failure.[6] The BLOC Types 1 and 3 are required for normal biogenesis of specialized organelles of the endosomal–lysosomal system, such as melanosomes and platelet dense granules. This lysosomal defect has been reported in reticuloendothelial cells, bone marrow, and lung macrophages. This forms the basis for the multisystem involvement in this syndrome. Ophthalmological manifestations occur in the form of nystagmus, strabismus, iris transillumination, foveal hypoplasia, albinotic retinal mid-periphery, and infrequently legal blindness. Our patients had an albinotic retina on eye examination. Skin affliction is present in the form of the evident skin depigmentation. Skin biopsies may reveal normal number of melanocytes; however, melanosomes are reduced in both melanocytes and keratinocytes. Patients with HPS also tend to exhibit peculiar abnormalities in their platelets. The platelets in affected individuals accumulate abnormal volumes of thrombin, epinephrine, and adenosine diphosphate. Furthermore, platelets in these individuals have a lower amount of dense bodies. This phenomenon is classically reflected in whole-mount EM appearance as the absence of dense bodies intriguingly described as "butter cookie" instead of a "chocolate chip cookie"(filled with the stored chemicals they look like "chips" and the platelets appear to look like a "chocolate chip cookie" under an electron microscope. These chemical substances are destined to be released to assist in clotting).[7] In HPS, these dense granules are missing. This unique phenomenon was seen on EM examination of platelets in our index patient too. The "gold standard" test for the platelet abnormality in HPS is analysis by for the testing of platelet aggregation after platelet stimulation with adenosine diphosphate or epinephrine (using a platelet aggregometer) provides a less specific alternative. Murine models of HPS reliably share many aspects of the human disease including hypopigmentation, deficiency of platelet dense granules, and abnormalities of Type 2 alveolar epithelial cells and alveolar macrophages.[8]

Pulmonary involvement in the disorder is in the form of an ILD with a UIP pattern. HPS-1, HPS-2, and HPS-4 are associated with the development of pulmonary fibrosis. The origins of these fibroblasts are unclear, but combinations of mechanisms are hypothesized, including the transdifferentiation of epithelial cells (epithelial–mesenchymal transformation), the differentiation of fibrocytes and stem cells, and the proliferation of resident fibroblasts.[9] In a joint statement of the American Thoracic Society and European Respiratory Society, HPS-related pulmonary fibrosis (HPS-PF) and idiopathic pulmonary fibrosis (IPF) are considered similar entities (albeit with distinct causes) because both can show similar histological patterns. Both HPS-PF and IPF are characterized by irreversible and progressive fibrosis of the lung parenchyma and interalveolar septa ultimately leading to permanent remodeling and irreversible lung function damage with resultant respiratory failure. The clinical presentation of HPS-PF and IPF is identical including progressive dyspnea initially manifested as exercise intolerance that progresses to dyspnea at rest with the need for supplemental oxygen over time. Our index patient had presented at an advanced stage of her disease when she was already a candidate for long-term oxygen therapy. Her brother was diagnosed at a preliminary stage when significant fibrosis had not set it. This explains his mild restrictive lung functions. A high index of suspicion is required to identify pulmonary fibrosis at an early age in patients with HPS. Chest radiograph may be normal in the early stages of the disease. Hence, HRCT chest is pivotal in patients suspected to have HPS to pick up subtle lung changes like our index patients' brother. The most common abnormalities seen are interlobular septal thickening, reticular opacities, ground-glass opacities, and subpleural honeycombing. The radiological pattern fits into the UIP picture. Bronchoscopy and TBLB have been performed in a handful of cases but do not have proven benefits for the diagnosis of HPS-PF. In contrast to IPF, an open or a thoracoscopy-guided lung biopsy can be done for patients with suspected HPS-PF to see for histopathological changes

and the presence of ceroid bodies.[10] In our patient, we were successful in establishing a pathological diagnosis of UIP on a TBLB itself, and hence, further invasive modalities for lung biopsy could be avoided. Spirometry generally shows 18 a restrictive abnormality with low FVC. The clinical progression of HPS-PF is rapid and is characterized by the development of increasingly debilitating dyspnea and progressive hypoxemia. Thus, it is recommended that all patients with HPS be evaluated for lung function during adolescence and yearly thereafter by pulmonary function tests, including diffusing capacity of the lung for carbon monoxide, and a HRCT chest.[11] This helped us in cataloging the pulmonary involvement in our second patient too.

The diagnosis of HPS is established by amalgamation of clinical findings of hypopigmentation of the skin and hair, characteristic eye findings, and demonstration of absent dense bodies on whole-mount EM of platelets. Our patient satisfied all these criteria. Genetic testing by sequence analysis method is available for mutations in HPS-1, HPS-2, and HPS-4 of which HPS-1 and HPS-4 are the commonly encountered mutations and are more feasible, readily available, and economical. Hence, we performed these mutations on our index patient only due to financial constraints. However, we intriguingly detected HPS-4 mutation positive in our patient which ascertained our diagnosis. The treatment options available for the pulmonary manifestations of the disease are scarce. The approval of two new antifibrotic drugs, pirfenidone and nintedanib, for the treatment of IPF has prompted new interest in identifying drugs capable of reversing or, at the very least, halting the progression of HPS-PF. It should, however, be emphasized that these drugs are not curative but instead aid in decelerating the decline of lung fibrosis in IPF. Pirfenidone, a small molecule capable of inhibiting transforming growth factor-β, showed success in slowing pulmonary dysfunction in clinical trials with patients with IPF.[12] As is the case for IPF, treatment relies heavily on pulmonary rehabilitation with chest physiotherapy for graded exercised, nutritional support management of osteoporosis, and psychiatric components secondary to chronic disease. Patients with hypoxemia should be provided supplemental oxygen. Infection prophylaxis is important; thus, influenza and 13-valent and 23-valent pneumococcal vaccinations are recommended and administered with caution to avoid intramuscular bleeding. In addition, a 5-year polysaccharide booster vaccine may be beneficial.[13] Treatment for chronic hemorrhages associated with the disorder includes therapy with Vitamin E and the antidiuretic desmopressin 1-deamino-8-D-arginine vasopressin (dDAVP).[14] The course of the disease is mercurial and prognosis is generally oppressive with the need for fertile research to add promising options in the therapeutic basket.

A systematic search of the PubMed database (from inception till May 1, 2018) with the following search terms was undertaken: ("Hermansky–Pudlak syndrome" or "HPS" or "interstitial fibrosis" or "ILD"). The search yielded 46 citations, of HPS which were identified to be associated with ILD. Most of the search laid emphasis on genetic mutation involved in disease and recent advances in the treatment of disease.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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