Hermansky-Pudlak syndrome

Tiyas Sen*, Jai Mullerpattna*, Dipika Agarwala**, Deepak Naphdeb***, Ramesh Deshpande†, Ashok A Mahashur‡

Abstract
We present a rare disease condition Hermansky-Pudlak syndrome in a 33 year old male. He was born of a consanguineous marriage, had occulo-cutaneous albinism, nystagmus, decreased visual acuity, refractory errors, pulmonary fibrosis and granulomatous inflammation of the colon. In spite of all the classical features of this genetic disorder he was labeled to have disseminated tuberculous infection with a drug resistant strain for many years. The actual diagnosis made was based on a strong clinical suspicion. We report this rare condition which might be misdiagnosed as tuberculosis.

Introduction
Hermansky-Pudlak syndrome (HPS) is a rare group of autosomal recessive diseases whose manifestations include occulo-cutaneous albinism, bleeding, and abnormal lysosomal ceroid storage. Its etiology has been related to defects in seven genes: HPS1, HPS2 (AP3 b1), HPS3, HPS4, HSP5, HSP6, and HSP7. The type of albinism associated with HPS is a tyrosinase-positive form. Because patients with HPS can produce some melanin, varying amounts of pigmentation may be present; some patients have blond hair and others have brown hair. Secondary to the albinism that results from HPS, visual defects, including photophobia, strabismus and nystagmus occur. The bleeding problems of HPS result from platelet dysfunction and manifest with easy bruising, nose bleeds, and prolonged bleeding times. Pulmonary fibrosis, inflammatory bowel disease, and kidney disease are all symptoms linked to ceroid accumulation in the cells of these organs. HPS was first noted in 1959 by Hermansky and Pudlak, who described two unrelated persons with albinism with lifelong bleeding tendencies and peculiar pigmented reticular cells in the bone marrow as well as in biopsy samples of the lymph node and the liver.

Our patient was diagnosed to have disseminated tuberculosis with pulmonary and gastrointestinal involvement not responding to antitubercular treatment. A suspicion of drug resistant tuberculosis was thought of. A strong clinical suspicion helped in diagnosing the condition. But unfortunately the survival of patients with this condition per se is only 30 to 50 years and treatment is only symptomatic.

Case Report
A 33 year old male, finance officer, non-smoker presented with breathlessness and dry cough since one year. He was started on antitubercular treatment for the last one year. The treatment was mainly started on the basis of findings on the chest radiograph. No microbiological proof of acid fast bacilli was present in the sputum examination. During the initial phase of treatment he received four drug antitubercular treatment with rifampicin, isoniazid, ethambutol and pyrazinamide. At the end of one year of treatment he received four drug antitubercular treatment for the last one year. The patient remained asymptomatic between 2004 to 2006. From 2006 his symptoms of breathlessness and dry cough had started, and not relieved till date in January 2008 in spite of treatment with the antitubercular treatment.

On examination, he had occulo-cutaneous albinism, nystagmus more in the horizontal axis, decreased visual acuity of 6/12, and refractory error. On respiratory system examination, he was clubbed, no cyanosis, velcro crepts were present on auscultation of the chest, mainly in the bilateral infra-axillary and infra-scapular region. His abdomen was soft with no organomegaly. He had a postoperative scar in the abdomen. His hematological evaluation including the test for platelet aggregation was normal. The renal and hepatic functions were normal. The chest radiograph showed reticulo nodular pattern (Fig 1). The high resolution computed tomography of the chest (HRCT) revealed multiple cystic shadows in bilateral subpleural areas, with interseptal thickening (Fig. 2). The arterial blood gas and the electrocardiogram was normal. The pulmonary function test showed mild restriction with FVC of 60% and decreased diffusión capacity of 40 percent. The serum ACE level was sent, the value of which was within the normal range. His HIV status was negative. A video assisted thoracoscopic biopsy (VATS) of the lung tissue was done and the histopathology was consistent with usual interstitial pattern (UIP) of pulmonary fibrosis with fibroblastic foci and temporal heterogeneity.

Since the lung biopsy confirmed UIP pattern of interstitial
pneumonia, hence the patient was not subjected to any further investigations for sarcoidosis.

The patient was treated with oral steroids, prednisolone with 20 mg per day, and was asked to follow up after 3 months (Fig. 3).

Discussion

Hermansky-Pudlak syndrome (HPS) is a rare group of autosomal recessive diseases whose manifestations include oculocutaneous albinism, bleeding, and lysosomal ceroid storage. HPS was first noted in 1959 by Hermansky and Pudlak. It is of two types, HPS-1, HPS-3. HPS is associated with tyrosinase positive oculocutaneous albinism, and consanguinity increases the risk in offspring by 25%. The gene involved is HPS-1 gene and the chromosome involved is chromosome 10q.

HPS may be the most frequent single-gene disorder in Puerto Rico. Some have estimated a frequency of about 1 case in 2000 population among Puerto Ricans. Others state that, in Puerto Rico, HPS has a frequency of about 1 case in 1800 population, with an estimated carrier frequency of 1 in 21.

Systemic manifestations of HPS involve accumulation of a ceroid-like substance in tissue lysosomes. Ceroid is the name given to the wax-like substance. This lysosomal defect has been reported in reticuloendothelial cells, bone marrow, and lung macrophages. In HPS, particularly the cases in Puerto Rico, ceroid-lipofuscin-like pigment accumulates in lysosomal structures, causing tissue damage. In addition, clinical evidence of storage disease manifesting with restrictive lung disease, granulomatous colitis, kidney failure, and cardiomyopathy is present.

The clinical manifestations include hematological involvement with easy bruisability, defect in the platelet aggregation, pulmonary involvement in the form of interstitial pneumonias, most commonly pulmonary fibrosis, and gastrointestinal involvement with granulomatous inflammation of the colon. It also has ocular manifestations in the form of refractory errors, astigmatism, pale optic nerves, iris transillumination, congenital nystagmus and photophobia. The skin manifestations include albinism, premalignant and malignant skin lesions. There is usually a history of parental consanguinity.

In our patient, the differential diagnosis after the detailed history and clinical presentation was as follows:

1. Systemic syndrome.
2. Pulmonary fibrosis.
3. Pulmonary fibrosis and tuberculosis.
4. Drug resistant tuberculosis.
5. Disseminated tuberculosis.

But after the confirmed histopathology report of UIP pattern with fibroblastic foci and temporal heterogeneity on the lung biopsy the diagnosis was confirmed to be that of a systemic syndrome i.e. "Hermansky-Pudlak syndrome", keeping in mind the other findings of a young male born of a consanguineous marriage, with albinism, nystagmus, decreased visual acuity, HRCT suggestive of ILD, granulomatous inflammation of the intestine, brother has similar oculocutaneous manifestations, no haematological abnormality and no response to antitubercular treatment. However he did not have any hematological involvement.

These patients need a complete workup with hematological evaluation, platelet studies to test for the aggregation of platelets and platelet electron microscopy to see the absence of dense bodies. The chest radiograph and HRCT of the chest will be suggestive of an interstitial pneumonia. The pulmonary function test will reveal restrictive defect with decreased diffusion capacity. Colon biopsy will be consistent with granulomatous inflammation. Genetic analysis will pinpoint the defect but unfortunately it is not done in our subcontinent, so the diagnosis depends mainly on the clinical suspicion and important systemic manifestations.

There is no definitive treatment for this condition. The treatment is mainly symptomatic. For UIP pattern of pulmonary fibrosis, treatment is usually with oral steroids and oxygen supplementation. The treatment for granulomatous colitis is with steroids. The treatment for bleeding diathesis it is with desmopressin injection 0.3 mcg/kg diluted in sterile physiological saline in the form of intravenous infusion over 15 to 30 minutes.

Our patient did not have any response to antitubercular treatment since he never had tuberculosis. There was a significant lag period between the onset of his symptoms and signs and the starting of his definitive treatment for his condition Hermansky-Pudlak syndrome with steroids. Unfortunately he had to take years of antitubercular treatment for a wrong diagnosis of disseminated tuberculosis with a drug resistant strain without any improvement. This was the first time in January 2008, that he...
was given definitive treatment with steroids for his underlying systemic syndrome.

The mortality of HPS is high. The average patient survival is 30 to 50 years. In more than 50% cases death is due to pulmonary fibrosis, in 15% cases death is due to hemorrhagic episodes and in 15% cases death is due to granulomatous colitis.

We report this rare disease entity to make the clinicians aware of the condition, so that early diagnosis and immediate treatment is possible.

References