Title: A Rare Case of Hermansky-Pudlak Syndrome

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Abstract

Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive disorder characterised by oculocutaneous albinism, a bleeding diathesis and platelet storage deficiency. The aim of this paper is to report a case of a patient with HPS who was followed over a decade. A 2-and-a-half-year-old boy presented with recurrent respiratory tract infections and

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Abstract

Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive disorder characterised by oculocutaneous albinism, a bleeding diathesis and platelet storage deficiency.

The aim of this paper is to report a case of a patient with HPS who was followed over a decade. A 2-and-a-half-year-old boy presented with recurrent respiratory tract infections and global developmental delay. On examination, he had light golden hair, grey iris with nystagmus, fundus hypo-pigmented fovea and white macules all over the body. Also found to have neutropenia without granules on peripheral smear. HPS can often be a diagnostic dilemma mimicking disorders like Chediak-Higashi syndrome, in this case diagnosis was made due to characteristic skin and hair hypopigmentation and ocular findings along with bleeding diathesis. Our patient was categorised under the HPS2 subtype which has mild immunodeficiency.

HPS is usually associated with neutropenia and hence pyogenic infections, the present case however was associated with an advanced form of pulmonary Tuberculosis- miliary TB and granulomatous TB lymphadenitis giving rise to the possibility of a T-cell defect.

Key words: Hermansky-pudlak syndrome, oculocutaneous albinism, nystagmus, neutropenia, T-cell defect.

Introduction

Hermansky-Pudlak syndrome (HPS) is hereditary multi-system disorder characterized by oculocutaneous albinism, a bleeding diathesis, platelet storage deficiency. Individuals can also present with pulmonary fibrosis, granulomatous colitis, and/or immunodeficiency. Ocular findings include nystagmus, reduced iris pigment, reduced retinal pigment, foveal hypoplasia with significant reduction in visual acuity (usually in the range of 20/50 to 20/400), and strabismus. Hair colour ranges from white to brown; skin colour ranges from white to olive and is usually at least a shade lighter than that of other family members.(3) The storage-pool defect arises from the absence of platelet dense bodies which normally contain adenosine diphosphate

(ADP), adenosine triphosphate (ATP), calcium and serotonin which are necessary to trigger the secondary aggregation response of platelets(4)

The accumulation of ceroid lipofuscin, an amorphous lipid-protein complex, is associated with the mentioned findings of pulmonary fibrosis(5)(6), and granulomatous colitis(7) which can result in increased morbidity in these individuals. HPS is more prevalent in Puerto Rico, where HPS type 1 has an estimated prevalence of 1:1800(1) and most clinical research studies have been conducted there. Worldwide HPS is rare inherited autosomal recessive disorder, with an estimated prevalence of only 1:500,000 to 1:1,000,000 in non- Puerto Rican populations(2), thus making it's presentation in a South-Asian country such an India extremely rare. In this case report, we discuss a patient with Hermansky Pudlak Type II who was followed over a decade. This case is unique because the patient developed disseminated tuberculosis twice during the course of follow up despite compliance to treatment, implying a possible T cell defect and hence merits publication.

Case

A 2-and-a-half-year-old boy presented with recurrent respiratory tract infections since 7 months of age, poor weight gain and developmental delay. Previously was treated for bronchopneumonia and dysentery. Birth history was normal. Third degree consanguinity was present. There was a sibling death at 2 months of age, possibly due to bronchopneumonia.

Examination findings

On examination, the following findings were noted- light golden hair, grey iris with nystagmus, low set ears, high arched palate, fundus hypopigmented fovea, hyperextension of joints, genu recurvatum, and white macules all over the body. Umbilical hernia also present.

Investigations

Peripheral smear showed neutropenia without granules. Lowest absolute neutrophil count was 51cells/µL. X-ray of the wrist showed bullet shaped phalanges as shown in Figure A (interestingly a finding seen in patients of mucopolysaccharidoses). X-ray of the nasopharynx showed 80% adenoids and X ray lateral spine showed kyphosis.

Course of the illness and treatment

Chediak Higashi syndrome was considered in view of overlapping symptoms of oculocutaneous albinism and neutropenia, hence Vitamin C was given and there was gradual catch up in gross motor milestones, with normal speech and mentation. TSH was raised and hence started on daily thyroid replacement therapy in view of primary hypothyroidism.

He continued to remain neutropenic and had multiple episodes of upper respiratory tract infections.

At 4 years of age he presented with fever and respiratory distress. ANC was 151cells/µL and X-ray showed bilateral diffuse non homogenous opacities suggestive of miliary tuberculosis as seen in Figure B. Patient was started on anti-tubercular treatment - pyrazinamide, rifampicin and isoniazid, which was continued for 2 years and compliance was good.

At follow up diagnosis was revised to be Hermansky-Pudlak syndrome due characteristic skin and hair hypopigmentation with ocular findings and neutropenia with absence of characteristic cytoplasmic granules in neutrophils on peripheral smear along with bleeding diathesis.

At 8 years of age patient presented with multiple firm submandibular, upper deep cervical and submental lymph nodes. FNAC of the cervical lymph nodes showed granulomatous lymphadenitis suggestive of TB— started on anti-tubercular treatment - pyrazinamide, ethambutol, isoniazid and rifampicin. After few months there was increase in size of the swellings, as Hermansky-Pudlak Type 2 is a high-risk condition for lymphoma a LN biopsy was done which showed caseating granulomatous lymphadenitis. Ciprofloxacin was added along with ATT.

ATT given for 18 months, and lymph nodes regressed.

At 10 years of age patient was admitted with Dengue fever, serology was positive for NS1 Dengue. He had hepatosplenomegaly and petechiae over lower limbs and hands, treated with supportive measures. ANC at this time was 70 cells/ µL.

At 12 years the patient was admitted with adenotonsillitis with membranous patch over left tonsil. Lateral X ray neck showed adenoid hypertrophy. Patient underwent adenotonsillectomy with bilateral grommet insertion.

Discussion

Hermansky-Pudlak syndrome type 2 (HPS-2) is a rare autosomal recessive disorder characterized by oculocutaneous albinism, bleeding diathesis, and neutropenia. Eleven types of HPS associated with mutations in 11 different genes have been recognized, each mutation causing altered biogenesis of lysosomes and lysosome-related organelles and defective intracellular protein trafficking.(8) Molecular genetic testing for mutations in various genes can be used to confirm the diagnosis.

This disorder is found more commonly in individuals from Puerto Rico(9), however, we describe a case presenting in South-Asia which was initially diagnosed at the age of 4 years and eventually followed over the course of 9 years due to multiple complications including miliary TB and TB lymphadenopathy,initially thought to be lymphoma prior to biopsy– a common association with HPS-2 (10).

Hermansky-Pudlak syndrome can often be a diagnostic dilemma as it's symptoms can be similar to those of other disorders such as Chediak-Higashi syndrome, which was considered. In the present case however, an interesting finding was upper extremity x-rays which demonstrated bullet shaped phalanges; this was more consistent with findings seen in Mucopolysaccharidosis (MPS). HPS was diagnosed due to the characteristic skin and hair hypopigmentation and ocular findings such as a grey iris and nystagmus, bleeding diathesis and neutropenia without granules on peripheral smear. The patient was categorised under the HPS2 subtype which has mild immunodeficiency as seen in this case by recurrent respiratory tract and skin infections along with HPS morphological features.

HPS is usually associated with neutropenia and hence pyogenic infections as demonstrated by a study that showed that HPS1 deficiency leads to an altered metabolic program and Rab32-dependent amplified mTOR signalling, facilitated by the accumulation of mTOR on lysosomes. This pathogenic mechanism translates into aberrant bacterial clearance, Rab32-mediated mTOR signalling acts as an immuno-metabolic checkpoint, adding to the evidence that defective bioenergetics can drive hampered anti-microbial activity and contribute to inflammation(11). Another study demonstrated the same via a candidate gene approach and found that canine cyclic neutropenia is the equivalent of the rare human Hermansky Pudlak syndrome type 2 (HPS2), with both diseases resulting from homozygous inactivating mutations of AP3B1, encoding the beta subunit of the adaptor protein 3 (AP3) trafficking complex (12).

The present case, however, was associated with recurrent tuberculosis infection, he was initially treated for miliary tuberculosis shows for 2 years after which he had recurrence of symptoms after 1.5 years despite being treated adequately, giving rise to the possibility of a T-cell defect. This finding has also been demonstrated by a study that reported the occurrence of nodular lymphocyte predominance type Hodgkin lymphoma in two siblings affected by HPS2, by analysing peripheral blood immune cells they found that NK and iNKT cells from HPS2 patients were significantly impaired in their number and function.

By immunohistochemistry, CD8 T-cells from HPS2 NLPHL contained an increased amount of perforin (Prf) + suggesting a defect in the release of this granules-associated protein and peripheral blood immune cell analysis revealed a significant reduction of circulating NKT cells and of $CD56^{bright}CD16^{-}$ Natural Killer (NK) cells subset. In summary suggesting that a combined defect of innate and adaptive effector cells explains susceptibility to infections and lymphoma (10). The vulnerability in the present case maybe due to this defect.

IFN-γ plays a pivotal role in protective immunity against intracellular pathogens, specifically Mycobacterium tuberculosis infection(13). IFN-γ is an important mediator of macrophage activation(14) and humans deficient in either the gene for IFN-γ or the IFN-γ receptor show enhanced susceptibility to mycobacterial infections(15). IFN-γ also has a unique capacity to prime dendritic cells (DCs) for high IL-12 production. HPS2 patients demonstrate a complete defect in IL-12 production by moDCs, and hence likely display impaired T helper 1 polarization likely explaining the impaired immune mechanism in this patient which lead to the susceptibility to recurrent TB infections(16).

Prandini A et all and others studied monocyte derived dendritic cells and plasmacytoid dendritic cells in HPS2 siblings, which found that T-cell costimulatory activity measured by mixed lymphocyte reaction assay was lower in patients with HPS2, suggesting that function and maturation of DCs is abnormal in these patients. It was concluded that AP-3 deficiency resulted in abnormal maturation of monocyte derived DCs and impaired total antigen-presenting cell activity. This impairment of DC activity contributes to susceptibility to bacterial and viral infections, which is well demonstrated in the present case(16)

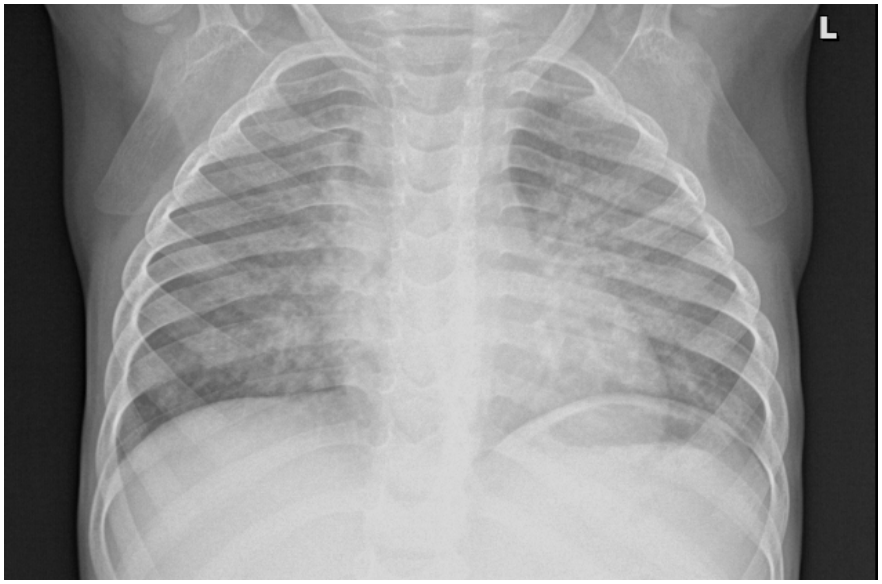

Figure B: Chest X-Ray of the patient suggestive of miliary tuberculosis

	Hermansky-Pudlak Syndrome	*Chediak-Higashi Syndrome (CHS)*
Oculocutaneous albinism	Present	Present
Cytoplasmic granules in platelets and neutrophils	*Always absent*	*Characteristic finding*
Intellectual disability/ Neurological findings	May or may not be present	Present in all
Hepatosplenomegaly	May or may not be present	Maybe present
Hemophagocytic lympohistiocytosis	May or may not be present	Also called the accelerated phase of CH

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