Case Report:
Hermansky Pudlak Syndrome Associated Pulmonary Fibrosis

Authors:
Navakumar Manickam, Assistant Professor,
Kannan Gopalan, Professor,
Vandhana Manoharan, Final Year Junior Resident,
Seethalakshimi Ganga Vellaisamy, Professor,
Department of Skin & STD, Vinayaka Mission's Kirupananda Vyarai Medical College & Hospital, Vinayaka Mission's Research Foundation (Deemed to be University), Salem - 636308, Tamil Nadu.

Address for Correspondence
Navakumar Manickam,
Moolapathai,
Edappadi Taluk,
Salem - 637102
Tamil Nadu.
E-mail: dmava2k3@gmail.com.

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Abstract: Hermansky-Pudlak syndrome (HPS) was first described by Dr. Frantisek Hermansky and Dr. Paulus Pudlak in 1959. HPS is relatively common in Puerto Rico, in the north-western region of the island. Other regions where HPS was reported include India, Japan, the United Kingdom and Western Europe. HPS is a rare autosomal recessive genetic disorder associated with mutations in nine distinct HPS gene subtypes, characterized by constellation of findings such as oculocutaneous albinism, bleeding diathesis, interstitial pulmonary fibrosis, granulomatous colitis, neutropenia, and rarely renal failure and cardiomyopathy. The graviest complication of the syndrome is interstitial lung disease leading to irrecoverable pulmonary fibrosis. HPS-1, HPS-2 and HPS-3 subtypes are associated with pulmonary fibrosis. We report a rare case of HPS in a 43 year old female associated with pulmonary fibrosis (PF).

Key Words: Hermansky-Pudlak syndrome, Pulmonary fibrosis, Oculocutaneous albinism, Interstitial lung disease, Bleeding diathesis, Rare disease.

Introduction:
Hermansky Pudlak syndrome is a rare autosomal recessive genetic disorder characterized by the combination of oculocutaneous albinism and prolonged bleeding due to abnormal platelet function. It is associated with mutations in nine distinct HPS genes leading to spectrum of manifestations mainly due to deficiencies in the biogenesis of lysosome-related organelles that include melanosomes, platelet dense granules, lamellar bodies of type II alveolar epithelial cells and lytic granules of cytotoxic T lymphocytes and natural killer cells. Albinism and bleeding diathesis are common to all forms of HPS. In addition to this, PF is characteristic for HPS-1, HPS-2 and HPS-4 subtypes. Thus, early screening of HPS patients for PF is recommended as early intervention with long term oxygen therapy and antifibrotics will significantly reduce the morbidity.
Manickam N, Gopalan K, Manoharan V, Vellaisamy SG. Hermansky Pudlak Syndrome Associated Pulmonary Fibrosis.

**Figure 1**: Oculocutaneous albinism with hypopigmented skin and light brown hairs

**Figure 2**: Fundoscopy showing albinotic fundus in both eyes

**Figure 3**: HRCT showing features of pulmonary fibrosis

**Discussion**

Genes associated with HPS encode for formation of lysosome-related organelles required for normal breakdown of liposomes, defect of which leads to a storage disorder. Mutation in the genes causes accumulation of a wax-like substance (ceroid lipofuscin) in the body tissues leading to systemic complications such as PF and colitis.[7] Ten mutant HPS genes associated with ten clinical subtypes of HPS have been described.[8,9][Table 2] HPS-1 mutation was the most common, seen in approximately 75% of cases from Puerto Rico. Other regions where HPS was reported include India, Japan, the United Kingdom and Western Europe. [10]

<table>
<thead>
<tr>
<th>Table 1: Ophthalmic examination of both eyes</th>
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<td><strong>Ophthalmic Examination</strong></td>
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<tr>
<td>Best Corrected Visual Acuity</td>
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<tr>
<td>Lids And Conjunctiva</td>
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<tr>
<td>Cornea</td>
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<tr>
<td>Iris</td>
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<td>Anterior Chamber</td>
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<td>Pupil</td>
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<tr>
<td>Lens</td>
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<td>Spectral Domain Optical Coherence Tomography</td>
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Dilated Fundus on 90d Lens

- Media: Clear Albinotic hypopigmented blonde fundus.
- Optic disc: Normal with 0.3:1 C:D ratio
- Foveal reflex: Absent.
- Choroidal vasculature seen.
- Reduced retinal pigment.

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Individuals with HPS-1, HPS-2 and HPS-3 subtypes are at risk of developing pulmonary fibrosis. HPS associated with PF has a poorer prognosis compared with other subtypes of HPS. Clinical manifestations of pulmonary fibrosis usually occur in the fourth or fifth decade of life.[11-13] The average life expectancy of HPS patients is 40-50 years with the main cause of death being PF.[14, 15] HRCT of lung reveals abnormalities in 82% of patients. Reticular opacities involving the entire lung with lower zone predominance, subpleural honey combing, and traction bronchiectasis are typical of PF.[15] Spirometry shows restrictive pattern of disease. A lung biopsy is not required in case of typical radiographic findings.[7,15] Antifibrotic agent Pirfenidone has been found to delay fibrosis progression, but only in patients who have well-preserved residual lung volume.[13,16] Thus, lung transplantation remains the only option of prolonging the survival in HPS patients with advanced pulmonary fibrosis.[17] The severity of ocuclorcutaneous albinism is variable in HPS with hair color ranging from white to brown and skin color ranging from white to olive in colour. HPS-1 and HPS-4 subtypes typically have pronounced pigmentation abnormalities. Constant sun exposure leads to coarse, rough, and thick skin (pachydermia), and also predisposes to premalignant conditions such as solar keratoses and skin cancers such as basal cell carcinoma and squamous cell carcinoma.[8,18] Early sun protection with regular sunscreen application will prevent the later development of premalignant and malignant skin cancers and also will protect against severe photaging of skin. All subtypes present with ocular involvement such as nystagmus, strabismus, photophobia, decreased visual acuity, foveal hypoplasia, albinotic fundi and translucent iris. Children have nystagmus at birth and also have periodic alternating nystagmus, wandering eye movements, and lack of visual attention. The nystagmus can be very fast in early life, and becomes slow with time, but all patients have nystagmus throughout their lives. Nystagmus is more marked when an individual is tired or anxious, and less marked when they are resting and relaxing.[19,20] Photophobia may accompany severe foveal hypoplasia. Iris colour may be blue or change to a green/hazel or brown/tan color. Visual acuity is seen between 20/50 and 20/400 and it usually remains constant after early childhood.[21] Bleeding diathesis results from absent or deficiency of dense granules in platelets.[22] Patients may have easy bruising first appearing at the time of ambulation, epistaxis during childhood which diminishes after adolescence, gingival bleeding, postpartum hemorrhage, colonic bleeding, and prolonged bleeding may occur during menstruation, after dental extraction, circumcision, and other surgeries. They bleed longer than usual but heal normally. Procoagulants and platelet transfusions for severe bleeding are recommended.[23,24] Aspirin and indomethacin are contraindicated in HPS patients as they exacerbate the platelet abnormality. The diagnosis of HPS is established by the typical skin, hair, and ocular hypopigmentation and absent dense bodies on electron microscopy of platelets. In resourceful settings, evaluation should include electron microscopic study of platelets, genetic linkage analysis, desmopressin trial and bone densitometry.

**Conclusion**

The diagnosis of HPS is considered in our case based on features of ocuclorcutaneous albinism such as hypopigmentation of skin, hair, iris and albinotic retina with foveal hypoplasia associated with interstitial lung disease, visual defects and bleeding diathesis due to platelet dysfunction. Periodic follow up is necessary in all HPS patients to look for any systemic complications particularly lung involvement. HPS should be considered in the differential diagnosis of all cases with pulmonary fibrosis.

**References**