

## Hermansky's Hypoxia: A Brain Teaser

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### Abstract

Hermansky-Pudlak syndrome (HPS) is a rare heterogeneously inherited autosomal recessive group of disorders presenting with oculocutaneous albinism, bleeding diathesis and pulmonary disease. HPS is thought to occur as a consequence of disturbed formation of intracellular vesicles, most importantly, melanosomes, platelet dense granules and lysosomes. These abnormalities contribute to the morbidity associated with the disease, as ceroid lipofuscin deposits in lysosomes affect many organ systems. This is especially evident in the lungs where it is often associated with severe pulmonary fibrosis and premature death. Clinical recognition of HPS is critical as it facilitates genetic counseling, aids in prognostication and directs medical management as in our patient who presented with end stage fibrosis and severe hypoxia.

**Keywords:** Hermansky; Albinism; Hypoxia; Hypopigmentation; Lysosomes; Genetic; Ceroid

### Introduction

Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive disorder presenting with oculocutaneous albinism, bleeding diathesis and pulmonary disease. HPS is thought to occur as a consequence of disturbed formation of intracellular vesicles, most importantly melanosomes, platelet dense granules and lysosomes. The latter finding, in particular, contributes much to the morbidity associated with the disease as ceroid lipofuscin deposits in lysosomes affect many organ systems. This especially affects the lungs where it is often associated with severe pulmonary fibrosis and premature death.

### Case Report

A 44-year-old male presented for the evaluation of worsening shortness of breath associated with clear productive cough for 1 year. He denies any fevers, chest pains orthopnea or swelling of legs. He did mention poor vision and light patches over the skin. His family history was significant for light colored skin spots in brother, and there was no history of blood clots. He denied smoking cigarettes. On admission he had a HR of 110/min, BP 113/67 mm Hg, RR 20/min, T 98.6 °F and he was saturating 86% on room air. Upon physical examination the patient looked anxious. There was hypopigmentation of iris and strabismus of the right eye with left gaze preference was noticed. His visual acuity was only 20/100. Diffuse bilateral rales were appreciated on lung auscultation. Examination of the extremities was significant for hypopigmented hair and multiple skin spots. Labs were significant for WBC, 12,700  $\mu$ L (lymphocytes 2%, bands 11%, neutrophil 82%), and electrocardiography showed sinus tachycardia. Arterial blood gases showed PH 7.34, PCO<sub>2</sub> 29.4, PO<sub>2</sub> 53.3, HCO<sub>3</sub> 20.7 and SO<sub>2</sub> 86% on room air. Chest X-ray showed diffuse interstitial lung disease and low lung volumes. A chest CTA was negative for pulmonary embolism and revealed advanced interstitial pulmonary fibrosis, honeycombing and bronchiectasis (Fig. 1a, b). ECG showed mild pulmonary hypertension and normal ejection fraction. The patient was started on antibiotics and oxygen supplementation. Further workup revealed negative anti-nuclear antibodies. 1,25-dihydroxyvitamin D, ACE levels were normal. He underwent biopsy of the lung which showed subpleural fibrosis and microscopic honey comb appearance. Pathology demonstrated mild to moderate lymphocytic infiltrates. The bronchioles contain mucus admixed with scattered neutrophils along with bronchial metaplasia of the adjacent alveoli. Peribronchiolar smooth muscle hyperplasia was also seen. The alveoli contained foamy macrophages, neutrophils and fibrous plugs. Many foci of the alveoli were lined with vacuolated pneumocytes (Fig. 2a, b). No granulomas, or foreign bodies nor crystalloid material was seen. No fungal elements were demonstrated with GMS stain. These pathological findings were suggestive of HPS. The patient underwent genetic testing and was found to be homozygous for the 16 bp duplication in the HPS1 gene, consistent with the diagnosis of HPS.

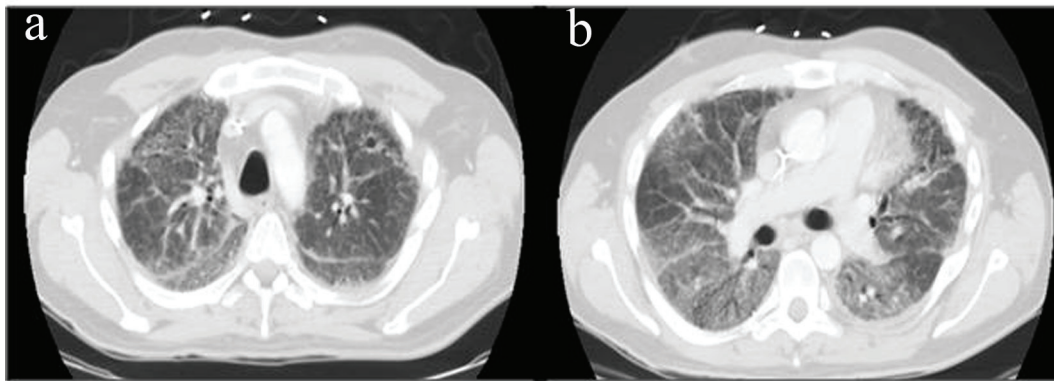
The patient was discharged on home oxygen and referred

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**Figure 1.** (a, b) CT of chest showing interstitial pulmonary fibrosis, honeycombing, bronchiectasis.

for a lung transplant.

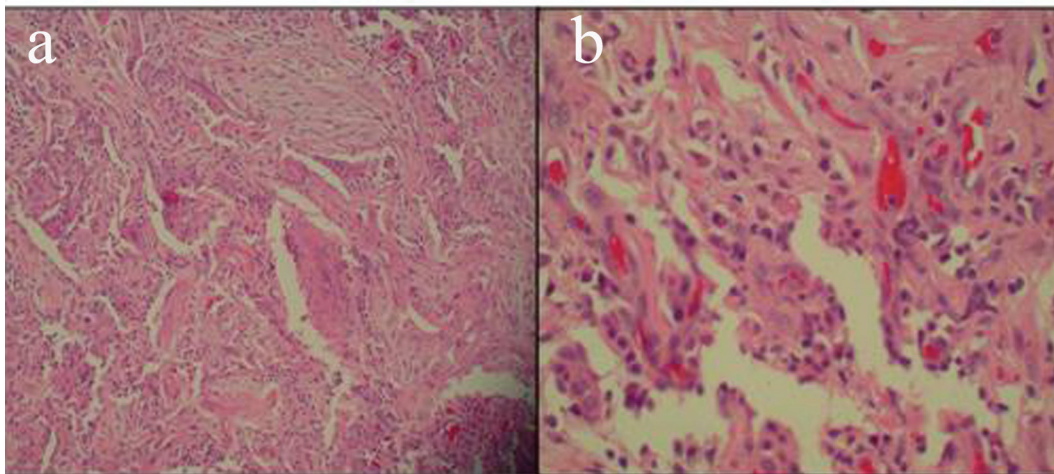
## Discussion

HPS is also known as “albinism with hemorrhagic diathesis and pigmented reticuloendothelial cells” and “delta storage pool disease”. It is a hereditary multisystem disorder, characterized by oculocutaneous albinism and platelet storage deficiency, in which prolonged bleeding, pulmonary fibrosis and granulomatous colitis may also occur. Although the first patients with this disorder were reported from Czechoslovakia, most of the subsequent patients have come from Puerto Rico. There are nine types of human HPS reported to date, based on the genetic mutation from which the disorder stems [1].

The HPS1 subtype is the most common HPS genetic mutation. Patients with HPS1 characteristically develop severe pulmonary fibrosis. Colitis occurs in about 15% of these cases. In HPS, there is variable impairment of the lysosomal system with subsequent ceroid deposition affecting many tissues of the body. This deposition is particularly toxic to the

lungs, where intracellular disruption of type II pneumocytes by ceroid triggers a cascade of inflammation, cytokine production and fibroblast proliferation, ultimately culminating with development of fibrosis [2].

Patients with HPS are predisposed to numerous medical conditions and therefore need a multidisciplinary approach. Their deficiency in melanin production leads to an increased risk of skin cancers, requiring regular dermatological examinations. All HPS patients have some type of visual impairment, as normal melanin production is mandatory for healthy retinal and neural development between the eye and brain. Ophthalmologic findings are quite variable, even in patients homozygous for the same mutation, ranging from mild decreased acuity to legal blindness, commonly not ameliorated by corrective lenses. Horizontal nystagmus is often the rule, but strabismus and other manifestations are common [2]. HPS patients should also be aware of their bleeding diathesis which stems from dysfunction occurring in platelet aggregation. In a hypopigmented patient, the current absolute prerequisite for a diagnosis of HPS is absence or marked diminishment in number or size of platelet dense bodies by electron microscopy. Although



**Figure 2.** (a, b) Interstitial fibrosis, lymphocytic infiltrates, smooth muscle hyperplasia suggestive of HPS.

in actual clinical practice, the combined presence of albinism with prolonged bleeding time and normal prothrombin and activated partial thromboplastin times usually serve as sufficient corroborating evidence of disease [2].

Because HPS is inherited there is currently no known way to prevent the condition. Recognition of the existence of this rare disorder is imperative for provision of much needed genetic counseling and supportive system-wide care. Known carriers could be offered options of various intrauterine tests such as amniocentesis, chorionic villus sampling and preimplantation genetic diagnosis.

For those with debilitating pulmonary involvement, lung transplantation may be a treatment option. Although long-term outcome of any prophylactic pharmaceutical intervention is currently unclear, early trial results with pirfenidone, an anti-inflammatory, antioxidant and antifibrotic agent, appear to hold some promise in preventing or minimizing pulmonary fibrosis. Also gene therapy may provide the means for HPS patients to benefit from normal gene delivery to disease-prone lungs [2].

In conclusion multidisciplinary approach should be well established in follow-up and treatment of patients diagnosed with HPS with ample consideration given to lung transplanta-

tion earlier in the course of diagnosis.

### Conflict of Interest

None.

### Funding

None.

### References

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