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29-Year-Old Man Presenting With Progressive Dyspnea, Oculocutaneous Albinism, and Epistaxis

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A 29-year-old man with a history of oculocutaneous albinism presented to the ED complaining of progressive dyspnea on exertion. One month prior to admission, the patient had begun to experience worsening dyspnea provoked by routine household activities. Additionally, he had developed a nonproductive cough, exacerbated by cold weather. He denied associated chest pain, hemoptysis, fever, chills, or night sweats. He denied any new exposures or sick contacts in the recent past. A review of systems was significant for a history of epistaxis and frequent bruising. Born in Honduras, he had immigrated to the United States approximately 10 years prior to his presentation to our facility. Furthermore, there was no family history of albinism, bleeding disorders, or pulmonary disease.

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Physical Examination Findings

Physical examination revealed an albino man in no acute distress. He was afebrile, with a pulse of 72 beat/min, BP of 125/72 mm Hg, respiratory rate of 20 breaths/min, and oxygen saturation of 90% on room air. Central cyanosis and digital clubbing were noted. Ocular examination revealed a horizontal nystagmus and red reflexes bilaterally. Cardiopulmonary auscultation was notable for Velcro-like inspiratory rales at bilateral lung bases and a prominent second heart sound. The remainder of his examination was unremarkable.

Diagnostic Studies

Laboratory investigation revealed a normal blood cell count and basic chemistry panel. Routine bacterial, fungal, and mycobacterial cultures of sputum were negative, as were serology testing for HIV, coccidioidomycosis, TB, and histoplasmosis. The admission chest radiograph is shown in Figure 1. High-resolution CT scan of the chest was performed; representative sections are shown in Figure 2. Echocardiography revealed

a pulmonary artery systolic pressure of 90 mm Hg and right ventricular strain. Right-sided heart catheterization revealed a pulmonary artery systolic pressure of 70 mm Hg and a pulmonary capillary wedge pressure



Figure 1 – Chest radiograph showing low lung volumes and diffuse bilateral reticular and ground-glass opacities.

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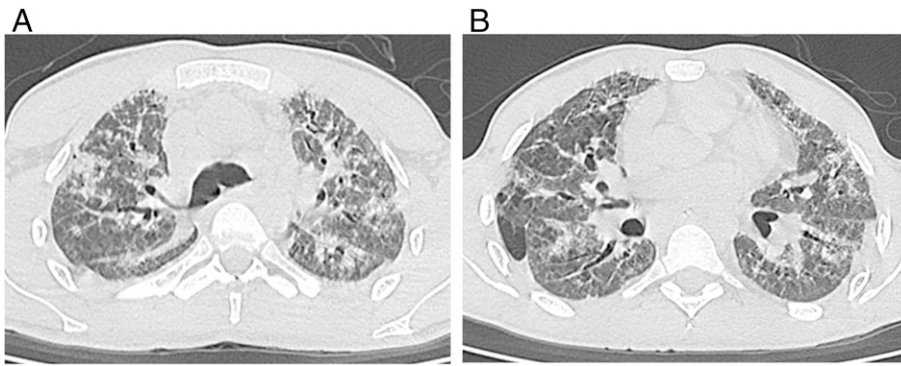


Figure 2 – A, Chest CT scan showing upper lung field septal thickening, traction bronchiectasis and bronchiolectasis, and ground-glass opacities. B, CT chest scan showing mid-to-lower lung field septal thickening, traction bronchiectasis, mild pleural thickening, and peribronchovascular ground-glass opacities.

of 7 mm Hg. Pulmonary function testing showed an FVC of 28% predicted, total lung capacity of 35% predicted, and diffusion capacity of 33% predicted. Six-minute walk distance was markedly reduced; additionally, arterial oxygen saturation of 71% was noted during exercise. During further investigation, electron microscopy of the platelets showed absence of dense granules (Fig 3).

What is the diagnosis?

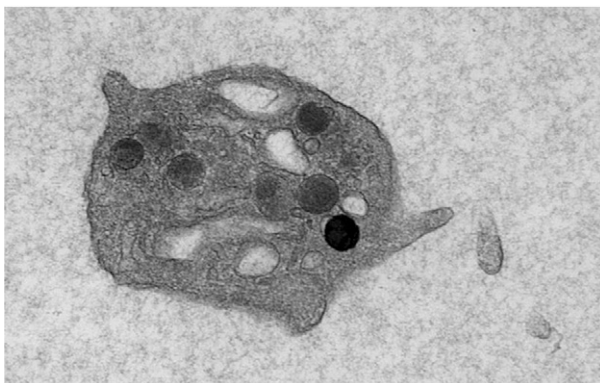


Figure 3 – Electron microscopy showing abnormal platelets with absence of dense granules (magnification $\times 26,000$).

Diagnosis: Hermansky-Pudlak syndrome with associated pulmonary fibrosis

Discussion

Hermansky-Pudlak syndrome (HPS) is a rare, heterogeneously inherited, autosomal recessive disorder estimated to affect one in 500,000 to 1 million individuals worldwide. HPS most commonly affects those of Puerto Rican descent, with a prevalence of one in 1,800 in that population. This disorder consists of nine subtypes; HPS-1 is the most common subtype and has the highest associated mortality. This mutation is associated with pulmonary fibrosis in approximately 75% of the affected individuals. The clinical extent of pulmonary disease varies by ethnicity in the patient population with HPS. Individuals from Puerto Rico and Japan have a more progressive clinical course caused by unknown factors associated with this condition. Sporadic cases of HPS complicated by pulmonary fibrosis affecting individuals of non-Puerto Rican or non-Japanese descent have been rarely reported. The patient was from Honduras and presented with the classic symptoms of the disease, as well as the HPS-1 mutation.

HPS can manifest with various dermatologic, hematologic, and pulmonary signs and symptoms. The first, and often most telling, clue in establishing the diagnosis of HPS is the dermatologic manifestation of the disease. All patients with HPS have some degree of oculocutaneous albinism, characterized by hypopigmentation of the skin, hair, and eyes, caused by a defect in the tyrosine transport system and impairment in the melanin production pathway. Ocular changes such as nystagmus, strabismus, and decreased to complete loss of visual acuity may also be observed.

Bleeding diathesis is the second most common presenting symptom of HPS, with the affected individuals experiencing easy bruising, epistaxis, and gingival bleeding. This is often attributed to platelet dysfunction caused by the lack of dense granules within the platelets. The third, and the most detrimental, set of presenting symptoms of HPS are those caused by pulmonary fibrosis, which are most commonly attributed to a sporadic mutation in the HPS-1 gene. Patients often present with insidious, yet progressive, worsening of dyspnea caused by the development of pulmonary fibrosis within the third or fourth decades of life.

The severity of pulmonary fibrosis in patients with HPS often correlates with the degree of ceroid deposition. Ceroid lipofuscin, a lipid protein complex, can deposit in numerous organs of patients with HPS. These

particles form residues within the lysosomes of affected patients and are the primary contributor to the morbidity associated with the HPS. It is hypothesized that the deposition of these lipid-filled lysosomes into type 2 pneumocytes and alveolar macrophages triggers a cascade of inflammation, cytokine production, and fibroblast proliferation, ultimately culminating in the development of pulmonary fibrosis.

More recent studies have focused on lysosome-related organelles (LROs) as a cause of the signs and symptoms of certain subgroups of patients with HPS. LROs are very similar in function to lysosomes, and any disturbance in their function could lead to problems with cellular trafficking and transport. It is speculated that mutations in HPS genes could lead to defects in the LROs within melanosomes of the melanocytes, δ granules of platelets, and lamellar bodies of type 2 epithelial cells of the lungs, leading to the clinical findings of HPS.

High-resolution CT scanning of the chest is the modality of choice when evaluating the extent of pulmonary fibrosis in patients with HPS. In the early stages of the disease, imaging reveals septal thickening, ground-glass attenuation, and mild reticulation in the peripheral lung fields. With disease progression, the central portions of the lungs become increasingly involved, with moderate to severe reticulation, traction bronchiectasis, subpleural cysts, and peribronchovascular thickening. Unlike this patient, most individuals with HPS who are under the age of 30 years have only minimal amounts of pulmonary fibrosis. Electron microscopy can confirm the diagnosis by demonstrating the absence of platelet-dense bodies.

Despite the interest in the clinical consequences of pulmonary fibrosis in HPS, treatment options remain sparse. In patients with idiopathic pulmonary fibrosis, pirfenidone, an antifibrotic agent that inhibits tumor growth factor- β -mediated fibroblast proliferation and collagen synthesis, has been shown to reduce disease progression as reflected by lung function and exercise tolerance. In a 2002 study of patients with HPS-associated pulmonary fibrosis, pirfenidone, compared with placebo, was shown to slow the rate of decline in FVC. However, in a more recent study evaluating a similar cohort of patients with HPS-associated pulmonary fibrosis, treatment with pirfenidone exhibited no significant benefit compared with placebo.

Although lung transplant is a consideration for patients with advanced pulmonary fibrosis of diverse causes, the

bleeding diathesis associated with HPS has been viewed as a contraindication. Because the severity of platelet dysfunction varies among patients with HPS, those patients with only mild bleeding diathesis should be considered. To our knowledge, there is at least one reported case of successful bilateral lung transplantation in a patient with HPS. In this case, the patient was supported through surgery with platelet transfusions. Desmopressin administration also temporarily corrects the platelet dysfunction associated with HPS and could be used to support select patients through major surgical procedures such as transplant. Unfortunately, lung transplant centers are rarely accessible to patients from the geographic areas where HPS is most prevalent.

Clinical Course

The patient was informed of his diagnosis of HPS-1-associated pulmonary fibrosis. Treatment with oxygen and pulmonary rehabilitation were initiated. The patient opted to return to Honduras where he was to receive regular pulmonary care.

Clinical Pearls

1. HPS should be suspected in a patient presenting with oculocutaneous albinism, easy bruising, and interstitial lung disease.
2. Electron microscopic examination of the platelets revealing the absence of dense granules is necessary to confirm the diagnosis of HPS.
3. HPS is associated with nine distinct gene mutations; the HPS-1 mutation is the most common with the highest incidence of pulmonary fibrosis and the poorest prognosis.
4. Data on the efficacy of pirfenidone in treating HPS-associated pulmonary fibrosis are conflicting.

5. The bleeding risk associated with HPS has been viewed by many centers as a contraindication to lung transplantation. Nonetheless, successful transplantation has been documented, and bleeding risk can potentially be attenuated with platelet and/or desmopressin support.

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Suggested Readings

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