



Case Report

Familial Pulmonary Fibrosis in 2 Mexican Sisters With Hermansky-Pudlak Syndrome

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ABSTRACT

Hermansky-Pudlak syndrome is an autosomal recessive disorder commonly found in individuals of Puerto Rican ancestry. We present 2 cases of familial pulmonary fibrosis in 2 Mexican sisters with Hermansky-Pudlak syndrome. Pulmonary fibrosis was biopsy-proven in 1 of the patients. This report shows that Hermansky-Pudlak syndrome may occur in individuals of Mexican ancestry.

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Fibrosis pulmonar familiar en 2 hermanas mexicanas con síndrome de Hermansky-Pudlak

RESUMEN

El síndrome de Hermansky-Pudlak (SHP) es una enfermedad autosómica recesiva que comúnmente se presenta en latinos de ascendencia puertorriqueña. Presentamos 2 casos clínicos de fibrosis pulmonar familiar en 2 hermanas mexicanas con SHP. La fibrosis pulmonar se confirmó por biopsia en una paciente. Esta comunicación demuestra que el SHP puede aparecer en población mexicana.

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Introduction

Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive disease characterized by albinism, hemorrhagic diathesis, and pulmonary fibrosis. Most cases reported in the medical literature correspond to individuals of Puerto Rican ancestry, and to date, no case of HPS with familial pulmonary fibrosis has been described in Mexicans. Therefore, we consider it extremely relevant to report the case of 2 Mexican sisters with this combination.

Case Description

Patient 1

A 60-year-old albino woman with epistaxis and purpura dating from 2 years previously had consulted 1 year earlier for shortness of breath when exercising and nonproductive cough. Lung function tests showed a severe restrictive pattern, with forced vital capacity of 42%, forced expiratory volume in 1 second of 50%, and carbon monoxide diffusing capacity of 60% of the theoretical value. A high-resolution CT scan (Figure 1A) showed discrete, diffuse ground-glass opacities, as well as patchy reticular opacity without honeycombing. The open lung biopsy showed predominantly subpleural fibrosing interstitial pneumonitis, microscopic honeycombing, and fibroblast foci. Areas of normal lung adjacent to lung areas with fibrosis were observed. In addition, patchy areas of pneumonia, type 2 pneumocyte

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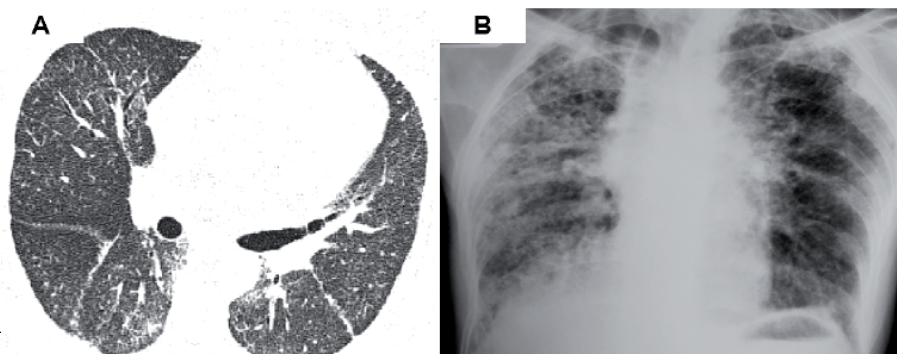


Figure 1. A, high-resolution CT scan showing discrete ground-glass attenuation and peripheral, patchy reticular opacity; no honeycombing can be observed. B, chest radiograph revealing decreased pulmonary volumes and reticulonodular infiltrates of apical predominance, as well as peripheral and bilateral basal honeycombing with enlargement of the pulmonary artery.

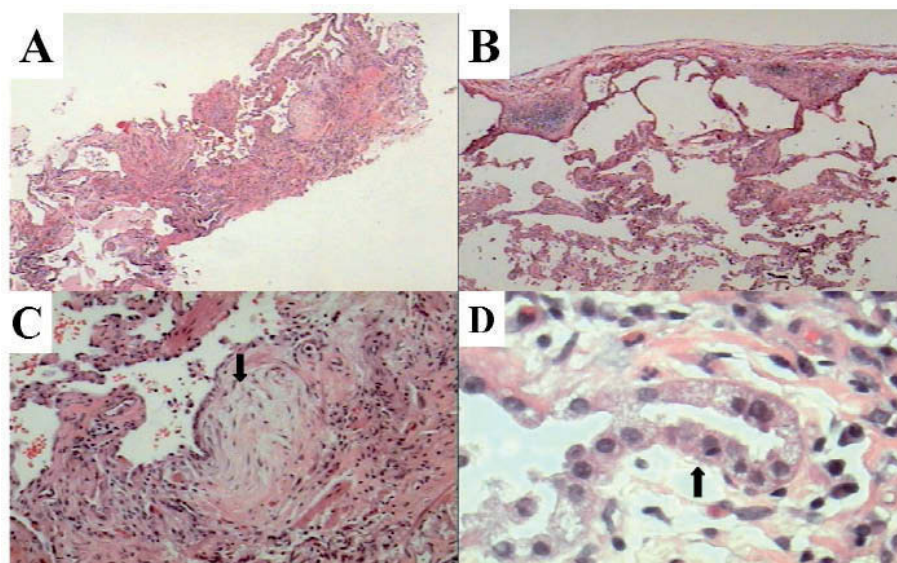


Figure 2. A and B, panoramic views showing predominantly peripheral involvement. (Hematoxylin-eosin, original augmentation $\times 1$ and $\times 10$.) C, image of a pocket of myofibroblasts (arrow) can be seen. (Hematoxylin-eosin, original augmentation $\times 10$.) D, image showing extensive hypertrophy and vacuolization of type 2 pneumocytes (arrow). (Hematoxylin-eosin, original augmentation $\times 40$.)

proliferation and vacuolization with areas of constrictive bronchiolitis, and bronchiolar metaplasia (Lambertosis) were observed. These findings were indicative of usual interstitial pneumonia, but with special characteristics (Figure 2). Because of the presence of albinism, a bone marrow aspiration was performed, showing megakaryocytes full of dense granules and lipofuscin bodies, confirming the diagnosis of HPS. The patient presented an aggressive, progressive course of dyspnea and died 1 month later.

Patient 2

A 56-year-old woman with oculocutaneous albinism, sister of patient 1, had been examined at our institution 10 years before the first patient was treated. She came to the office with a 10-month history of progressively worsening shortness of breath caused by exercise, dry cough, and chest pain. From 3 years previously, she had had hemorrhagic diathesis characterized by epistaxis, hematomas, and gingival bleeding. Spirometry revealed a severe restrictive pattern, with a forced vital capacity of 31% and forced expiratory volume in 1 second of 37% of the theoretical value. The blood work-up showed normal platelet count and coagulation time. The chest radiograph showed decreased pulmonary volumes and reticulonodular infiltrates of apical predominance, as well as

peripheral and bilateral basal honeycombing with enlargement of the pulmonary artery (Figure 1B). Because of advanced pulmonary damage, open lung biopsy could not be performed. Oxygen therapy was administered, the course was progressive, and the patient died 1 month after consultation.

Ten years later, when the presence of HPS in her sister (patient 1) was confirmed by bone marrow biopsy, we reassessed this second case, as the patient had had the same hematologic and pulmonary symptoms, as well as the phenotypic traits of albinism, that is, the triad of HPS consisting of albinism, hemorrhagic diathesis, and pulmonary fibrosis.¹

Discussion

HPS was first described in 1959, when Drs Hermansky and Pudlak reported the presence of a syndrome characterized by hemorrhagic diathesis and pulmonary fibrosis in albino patients.² In Puerto Rico, HPS occurs in 5 of every 6 albinos.³ At least 8 subtypes of HPS have been identified in people of different ethnic groups (in Puerto Rico, Japan, and Europe). Subtypes 1 and 4 are associated with more severe pulmonary fibrosis.⁴ In Mexico, HPS is extremely rare, and only 3 cases have been reported in the medical literature.^{1,5} The pulmonary fibrosis developed by our patients was very severe, which

indicates that they possibly had subtype 1 or 4. Nevertheless, neither of them had Puerto Rican ancestry, nor were they descendants of Mexican mestizos. This suggests that the syndrome may have resulted from a *de novo* mutation; in fact, the medical literature reports that 50% of patients of non-Puerto Rican origin can present *de novo* mutations.⁴

HPS is an autosomal recessive disorder that results from abnormal formation and transportation of intracellular vesicles in melanosomes, platelets, and lysosomes, leading to the accumulation of ceroid (lipofuscin) bodies.^{6,7} The pathogenesis of pulmonary fibrosis in HPS appears to be associated with the accumulation of these ceroid bodies inside type 2 pneumocytes, along with the accumulation of surfactant and other molecules in macrophages. Furthermore, a deficiency of surfactant secretion has been reported in animal models of HPS, which leads to the accumulation of giant lamellar bodies in type 2 pneumocytes.⁸ This abnormal accumulation of proteins in the endosomal compartment produces aberrant repair and fibrosis in response to an injury.^{9,10} It is interesting to observe that the pathogenesis of HPS is somewhat similar to proposed hypotheses in regard to the pathogenesis of familial pulmonary fibrosis, in which some proteins, such as surfactant protein C, do not function properly because of protein misfolding.^{11,12} This causes stress to the endoplasmic reticulum that induces an abnormal repair response and fibrosis.^{13,14}

Pulmonary fibrosis secondary to HPS has unique characteristics that distinguish it from usual interstitial pneumonia, which typically presents in patients with idiopathic pulmonary fibrosis. These characteristics are vacuolar degeneration of type 2 pneumocytes, constrictive bronchiolitis, and microscopic honeycombing that is not necessarily located at the periphery, as occurs in patients with idiopathic pulmonary fibrosis.^{9,15} The presence of HPS was suspected in patient 1 not only because of albinism, but particularly because the high-resolution CT scan was not typical of idiopathic pulmonary fibrosis associated with usual interstitial pneumonia, since it showed ground-glass attenuation without macroscopic honeycombing. Furthermore, histology revealed 2 of 3 of the pathologic characteristics of HPS: constrictive bronchiolitis and vacuolar type 2 pneumocyte degeneration. It should be mentioned that although these histopathologic changes are similar to those of usual interstitial pneumonia, disease course in our patients was considerably more aggressive than in patients with idiopathic pulmonary fibrosis associated with usual interstitial pneumonia: as is well known, these patients have a prognosis of 3 years from diagnosis.¹⁶

In conclusion, to our knowledge this is the first reported case of HPS associated with familial pulmonary fibrosis in the Mexican population. Although HPS is well recognized in Puerto Rican patients, the diagnosis should also be considered in Mexican and mestizo patients.

References

- Pierson DM, Ionescu D, Qing G, Yonan AM, Parkinson K, Colby TC, et al. Pulmonary fibrosis in Hermansky-Pudlak syndrome. A case report and review. *Respiration*. 2006;73:382-95.
- Hermansky F, Pudlak P. Albinism associated with hemorrhagic diathesis and unusual pigmented reticular cells in the bone marrow: report of two cases with histochemical studies. *Blood*. 1959;14:162-9.
- Witkop CJ, Nunez Babcock M, Rao GH, Gaudier F, Summers CG, Shanahan F, et al. Albinism and Hermansky-Pudlak syndrome in Puerto Rico. *Bol Asoc Med P R*. 1990;82:333-9.
- Oh J, Ho L, Ala-Mello S, Amato D, Armstrong L, Bellucci S, et al. Mutation analysis of patients with Hermansky-Pudlak syndrome: a frameshift hot spot in the HPS gene and apparent locus heterogeneity. *Am J Hum Genet*. 1998;62:593-8.
- Schallreuter KU, Frenk E, Wolfe LS, Witkop CJ, Wood JM. Hermansky-Pudlak syndrome in a Swiss population. *Dermatology*. 1993;187:248-56.
- Richmond B, Huizing M, Knapp J, Koshoffer A, Zhao Y, Gahl WA, et al. Melanocytes derived from patients with Hermansky-Pudlak Syndrome types 1, 2, and 3 have distinct defects in cargo trafficking. *J Invest Dermatol*. 2005;124:420-7.
- Huizing M, Gahl WA. Disorders of vesicles of lysosomal lineage: the Hermansky-Pudlak syndromes. *Curr Mol Med*. 2002;2:451-67.
- Guttentag SH, Akhtar A, Tao JQ, Atochina E, Rusiniak ME, Swank RT, et al. Defective surfactant secretion in a mouse model of Hermansky-Pudlak syndrome. *Am J Respir Cell Mol Biol*. 2005;33:14-21.
- Nakatani Y, Nakamura N, Sano J, Inayama Y, Kawano N, Yamanaka S, et al. Interstitial pneumonia in Hermansky-Pudlak syndrome: significance of florid foamy swelling/degeneration (giant lamellar body degeneration) of type-2 pneumocytes. *Virchows Arch*. 2000;437:304-13.
- Tang X, Yamanaka S, Miyagi Y, Nagashima Y, Nakatani Y. Lung pathology of pale ear mouse (model of Hermansky-Pudlak syndrome 1) and beige mouse (model of Chediak-Higashi syndrome): severity of giant lamellar body degeneration of type II pneumocytes correlates with interstitial inflammation. *Pathol Int*. 2005;55:137-43.
- Thomas AQ, Lane K, Phillips J III, Prince M, Markin C, Speer M, et al. Heterozygosity for a surfactant protein C gene mutation associated with usual interstitial pneumonitis and cellular nonspecific interstitial pneumonitis in one kindred. *Am J Respir Crit Care Med*. 2002;165:1322-8.
- Whitsett JA. Genetic basis of familial interstitial lung disease: misfolding or function of surfactant protein C? *Am J Respir Crit Care Med*. 2002;165:1201-2.
- Dong M, Bridges JP, Apsley K, Xu Y, Weaver TE. ERdj4 and ERdj5 are required for endoplasmic reticulum-associated protein degradation of misfolded surfactant protein C. *Mol Biol Cell*. 2008;19:2620-30.
- Nogee LM, Dunbar AE III, Wert SE, Askin F, Hamvas A, Whitsett JA. A mutation in the surfactant protein C gene associated with familial interstitial lung disease. *N Engl J Med*. 2001;344:573-9.
- Thomas de Montpréville V, Mussot S, Dulmet E, Darteville P. Pulmonary fibrosis in Hermansky-Pudlak syndrome is not fully usual. *Ann Pathol*. 2006;26:445-9.
- Flaherty KR, Thwaite EL, Kazerooni EA, Gross BH, Toews GB, Colby TV, et al. Radiological versus histological diagnosis in UIP and NSIP: survival implications. *Thorax*. 2003;58:143-8.