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Pulmonary Fibrosis in Hermansky-Pudlak Syndrome Type 2: A Very Rare Association

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Abstract **Case Report**

Background: Hermansky-Pudlak Syndrome (HPS) is a rare autosomal recessive disorder affecting lysosomal-related organelles, leading to variable clinical manifestations. HPS type 2 (HPS2) is exceptionally associated with pulmonary fibrosis. ***Case Presentation*:** We present a 25-year-old male with HPS2, exhibiting progressive dyspnea and interstitial lung disease. Clinical assessment revealed oculocutaneous albinism, digital clubbing, and thoracic deformities. High-resolution computed tomography (HRCT) demonstrated fibrosing interstitial lung disease with reticulations, septal thickening, and traction bronchiectasis. Genetic testing confirmed a deleterious *AP3B1* mutation. The patient was managed with symptomatic treatment, vaccination updates, and consideration for antifibrotic therapy and lung transplantation. ***Conclusion*:** This case highlights the clinical complexity of HPS2 and its rare pulmonary manifestations, emphasizing the importance of multidisciplinary management.

Keywords: Hermansky-Pudlak Syndrome, Pulmonary Fibrosis, *AP3B1* Mutation, Interstitial Lung Disease, Rare Genetic Disord.

INTRODUCTION

Hermansky-Pudlak Syndrome (HPS) is a rare autosomal recessive genetic disorder primarily affecting lysosomal-related organelles involved in protein storage and dense granules in platelets. Multiple genes have been identified as causative for different forms of this syndrome, with each mutation leading to varied clinical manifestations. HPS type 2 (HPS2) is rarely associated with pulmonary fibrosis.

We report a case of HPS2 illustrating the diversity of its clinical manifestations, particularly pulmonary involvement, and the different aspects of its management.

CASE REPORT

A 25-year-old male, born from a first-degree consanguineous marriage, presented with a history of recurrent respiratory infections in childhood, chronic diarrhea, epistaxis, and psychomotor and growth retardation. Over the past two years, he developed progressive dyspnea (mMRC grade 1) and a dry cough.

Clinical examination revealed oculocutaneous albinism, erythematous macules with overlying telangiectasias on the face suggestive of photo-induced rosacea (Fig1C), and marked digital and toe clubbing (Fig1A). Thoracic examination showed pectus carinatum, right-convex scoliosis (Fig1B), and bilateral basal crackles.

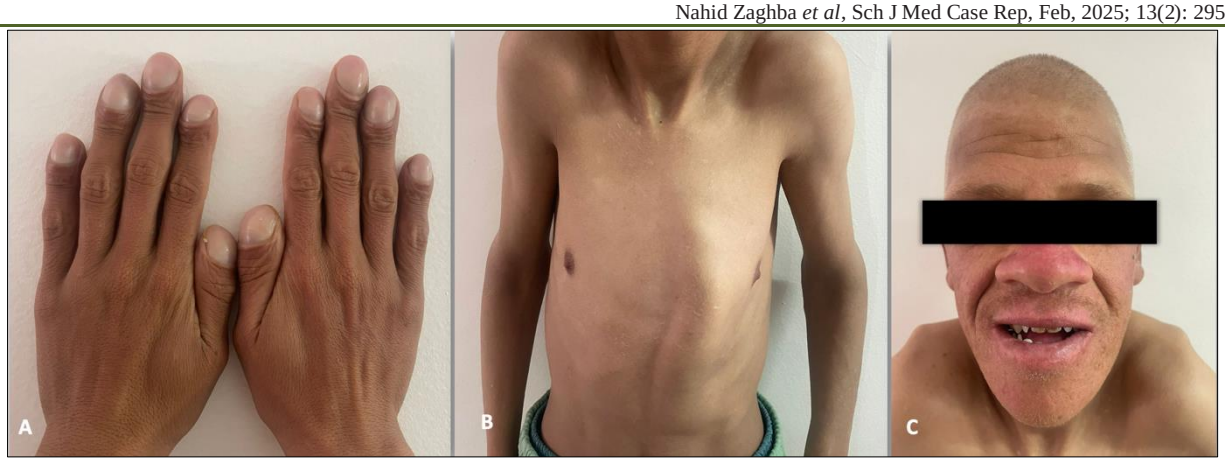

Figure 1 : Clinical abnormalities: A: marked digital and toe clubbing, B: pectus carinatum, right-convex scoliosis, C: oculocutaneous albinism and photo-induced rosacea

High-resolution chest computed tomography (HRCT) showed fibrosing interstitial lung disease without a specific pattern, with reticulations, septal thickening, traction bronchiectasis, honeycombing, and scattered ground-glass opacities (Fig2).

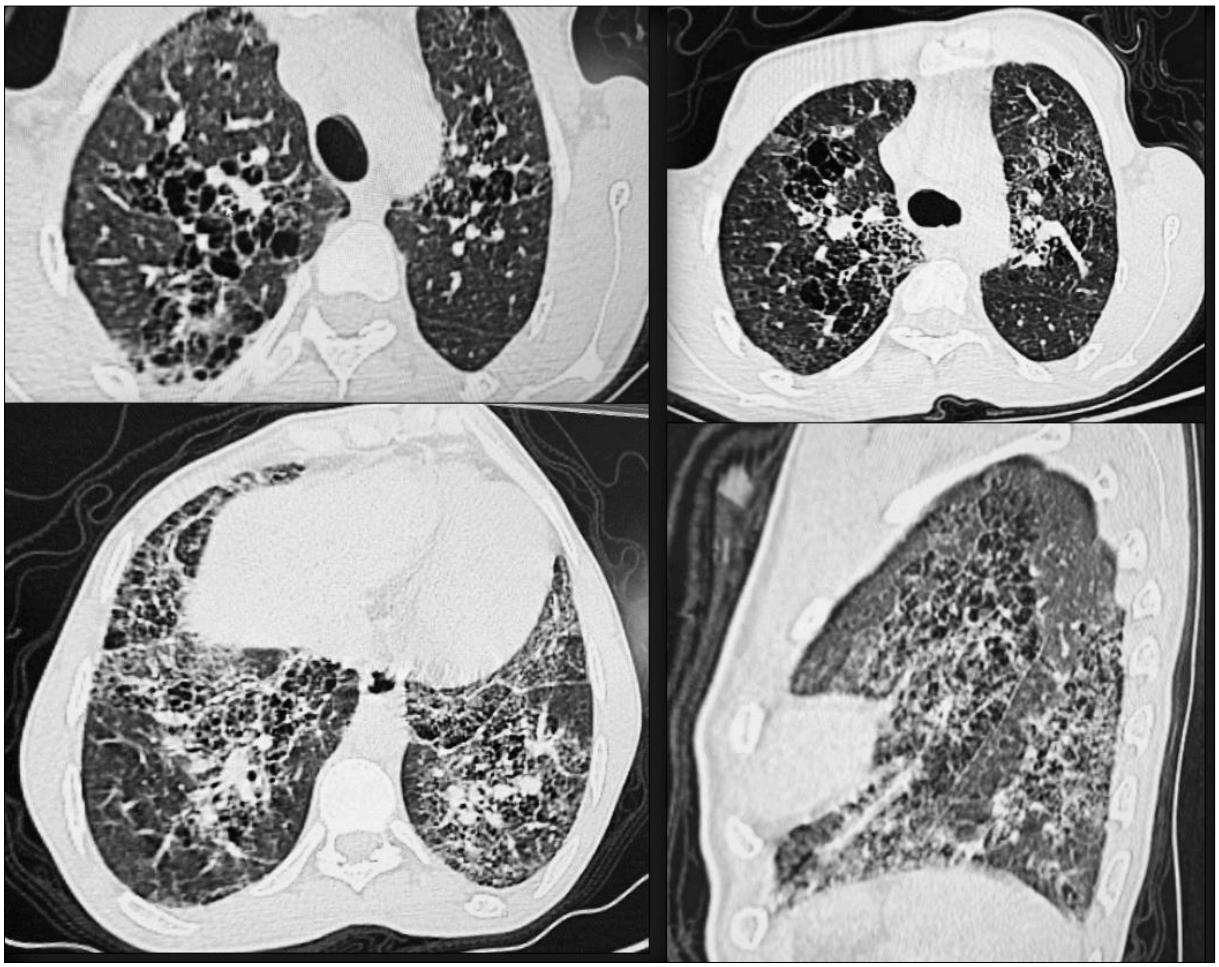

Figure 2 : High-resolution chest computed tomography (HRCT) showing fibrosing interstitial lung disease without a specific pattern, with reticulations, septal thickening, traction bronchiectasis, honeycombing, and scattered ground-glass opacities

Complete blood count, coagulation profile, and platelet aggregation test were normal. Functional protein C assay was 72% (normal: 80-130%). Flexible bronchoscopy was normal; bronchoalveolar lavage (BAL) analysis revealed 15% neutrophils and 15%

eosinophils. Bronchial biopsies showed nonspecific chronic inflammatory changes.

Ophthalmologic examination revealed horizontal nystagmus, visual acuity of 1/10 in both eyes, and retinal hypopigmentation. Electroretinography (ERG) demonstrated impaired retinal electrophysiology affecting both photopic and scotopic systems in both eyes. Due to thoracic deformity, bone densitometry showed osteopenia at the lumbar spine and left femoral neck.

Cardiac evaluation was normal. Pulmonary function tests suggested probable restrictive ventilatory impairment (FVC = 37%), arterial blood gases were normal, and the six-minute walk test was terminated prematurely due to oxygen desaturation to 92% at the fourth minute. Genetic testing identified a deleterious mutation in the *AP3B1* gene: c2757del (p. Ile919Metfs*8), confirming the diagnosis of HPS2. The patient was started on symptomatic treatment, including optical correction, photoprotection, and preventive measures. A multidisciplinary discussion (MDD) recommended optimizing respiratory function and updating influenza, pneumococcal, and COVID-19 vaccinations before considering antifibrotic treatment and, subsequently, lung transplantation preparation.

DISCUSSION

Hermansky-Pudlak Syndrome exhibits significant clinical heterogeneity with 11 different subtypes, each associated with specific mutations. Mutations in *HPS1* and *HPS4* are particularly linked to severe pulmonary and gastrointestinal complications, whereas *HPS2* mutations predispose to aggressive pulmonary fibrosis [1]. The prevalence is higher in Puerto Rican and Ashkenazi Jewish populations, estimated at 1 in 1,800 to 1 in 23,000 individuals [2].

The clinical presentation includes oculocutaneous manifestations common to other forms of albinism, which can be a major disability for patients [3]. Coagulation disorders in HPS patients result from a deficiency of dense granules in platelets, leading to a bleeding diathesis despite normal platelet counts [4]. These patients require specific precautions to prevent hemorrhage, particularly before surgical interventions. Granulomatous colitis is another specific involvement, affecting approximately 15-20% of *HPS1* and *HPS4* patients, often mimicking Crohn's disease [5].

Pulmonary fibrosis is the most severe complication. Unlike other forms of pulmonary fibrosis, particularly idiopathic pulmonary fibrosis (IPF), HPS-associated fibrosis typically manifests earlier (between 30 and 50 years) and progresses rapidly to chronic respiratory failure and death [6]. The pathophysiology involves excessive accumulation of intralysosomal material in alveolar macrophages due to *HPS* gene mutations (*HPS1* and *HPS4* in particular), leading to chronic inflammation. These macrophages release inflammatory mediators (TGF-β and other cytokines), triggering fibrotic processes [7]. HRCT is crucial, often showing UIP (usual interstitial pneumonia), NSIP (nonspecific interstitial pneumonia), and DIP (desquamative interstitial pneumonia) patterns. However, ILD in HPS may be unclassifiable or present atypical features, as observed in our patient.

Identification of pathogenic biallelic variants in associated genes confirms the diagnosis [8]. Genetic subtypes influence the likelihood and severity of pulmonary fibrosis. *HPS1* and *HPS4* subtypes have a high predisposition to early-onset pulmonary fibrosis, whereas *HPS3* and other subtypes show little to no established link with fibrosis, emphasizing the rarity of our case. *HPS2* is caused by mutations in the *AP3B1* gene, encoding a subunit of the adaptor protein complex 3 (AP-3), which is crucial for intracellular trafficking of lysosomes and similar organelles. This leads to abnormal macrophage and natural killer (NK) cell function, making *HPS2* the only subtype associated with increased susceptibility to bacterial and viral infections, as seen in our patient.

There is no curative treatment for HPS or its associated manifestations. Preventive and supportive care improve quality of life and reduce complications. The response of HPS-associated pulmonary fibrosis to therapy is limited; corticosteroids have little effect, and antifibrotics like pirfenidone and nintedanib are used with variable and limited efficacy. Tyrosine kinase inhibitors are potential therapeutic candidates [9]. Lung transplantation remains the treatment of choice for patients with advanced fibrosis, although bleeding complications related to platelet abnormalities in HPS require meticulous preoperative management. Recent research explores gene therapy targeting hematopoietic stem cells to correct mutations, though these approaches remain experimental [10, 11].

CONCLUSION

This case highlights the complexity and clinical diversity of Hermansky-Pudlak Syndrome, necessitating precise diagnostic approaches and multidisciplinary management. Antifibrotic treatments and gene therapy research offer promising prospects, though their availability remains limited. Regular pulmonary, hematological, and gastrointestinal follow-up is essential to improve quality of life and anticipate severe complications.

DECLARATIONS

Ethical Approval: Not required.

Consent for Publication: Written informed consent was obtained from the patient.

Competing Interests: The authors declare no competing interests.
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Authors' Contributions: All authors contributed to the study concept, diagnosis, treatment, and manuscript preparation.

REFERENCES

1. Gahl, W. A., Huizing, M., & Malicdan, M. C. V. (2019). Genetic disorders of organelles involved in the storage and function of proteins. *The Journal of Clinical Investigation*, 129(3), 1013-1023.
2. López, D., Rodriguez, V., & Sierra, V. (2020). Hermansky-Pudlak Syndrome in the Puerto Rican population: Genetic insights and public health impact. *Genetics in Medicine*, 22(5), 841-847.
3. Arveiler, B., Lasseaux, E., & Morice-Picard, F. (2017). Clinical and genetic aspects of albinism. *Presse Med*, *46(*7-8 Pt 1), 648-654.
4. Huizing, M., & Gahl, W. A. (2020). Hermansky-Pudlak syndrome: Clinical and molecular perspectives. *Blood*, 135(1), 37-45.
5. Girot, P., Le Berre, C., De Maissin, A., Freyssinet, M., Trang-Poisson, C., & Bourreille, A. (2019). Crohn's-like acute severe colitis associated with Hermansky-Pudlak syndrome: A case report. *World J Gastroenterol*, *25*(8), 1031-1036.
6. Sivapalan, A. S., Nielsen, M. F., & Langberg, C. M. (2022). Evaluation of antifibrotic treatment in Hermansky-Pudlak syndrome: Current evidence and future directions. *Respiratory Research*, 23(1), 200.
7. Velázquez-Díaz, P., Nakajima, E., Sorkhdini, P., Hernandez-Gutierrez, A., Eberle, A., Yang, D., & Zhou, Y. (2021). Hermansky-Pudlak Syndrome and Lung Disease: Pathogenesis and Therapeutics. Front. Pharmacol. 12:644671.
8. Introne, W. J., Huizing, M., & Malicdan, M. C. V. Hermansky-Pudlak Syndrome. 2000 Jul 24, GeneReviews : University of Washington, Seattle; 1993-2024.
9. Yokoyama, T., & Gochuico, B. R. (2021). Hermansky-Pudlak syndrome pulmonary fibrosis: a rare inherited interstitial lung disease. *Eur Respir Rev*, *30*(159), 200193.
10. Young, L. R., Thomas, M. S., & Ferreira, R. (2021). Pulmonary complications of Hermansky-Pudlak syndrome and treatment options. *American Journal of Respiratory and Critical Care Medicine*, 203(8), 998-1006.
11. Nieto-Alamilla, G., Behan, M., Hossain, M., Gochuico, B. R., & Malicdan, M. C. V. (2022). Hermansky-Pudlak syndrome: Gene therapy for pulmonary fibrosis. *Mol Genet Metab*, *137*(1-2), 187-191.