American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2025; 26: e945175
DOI: 10.12659/AJCR.945175

Received: 2024.05.15
Accepted: 2025.01.15
Available online: 2025.01.27
Published: 2025.03.11

Hermansky-Pudlak Syndrome Type 1 Presenting with Interstitial Lung Disease: A Report of a Rare Case from Saudi Arabia

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Financial support: None declared
Conflict of interest: None declared

Patient: Male, 48-year-old
Final Diagnosis: Hermansky-Pudlak syndrome
Symptoms: Dyspnea
Clinical Procedure: —
Specialty: Pulmonology

Objective: Rare disease

Background: Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive disorder characterized by oculocutaneous albinism, bleeding diathesis, and potential multi-organ involvement such as pulmonary fibrosis and granulomatous colitis. While its incidence is globally low, it may be under-reported, particularly in regions with high rates of consanguinity, such as the Middle East. By reporting this case, we aim to increase awareness of this condition as well as its association with ILD.

Case Report: Herein, we present the case of a 48-year-old Saudi man of Arab descent with a 2-year history of progressive exertional dyspnea that recently worsened over the last 6 months, resulting in a Modified Medical Research Council (MMRC) dyspnea scale score increase from 2 to 3. Examination revealed signs consistent with albinism, accompanied by bibasilar end-inspiratory crackles on chest auscultation. Further evaluations revealed CT imaging consistent with non-specific interstitial lung pneumonia pattern (NSIP) with associated precapillary pulmonary hypertension. Notably, the patient exhibited oculocutaneous albinism, prompting consideration of Hermansky-Pudlak syndrome. Genetic testing confirmed an autosomal recessive HPS type 1 variant, a rarity in the Middle East.

Conclusions: HPS1 with ILD is rare in Saudi Arabia. This report describes such a case, offering important insight into its clinical presentation. Clinical management entails a multidisciplinary approach, including supportive care, preventive measures, and consideration of lung transplantation for severe cases. Consanguinity and endogamy, which are quite prevalent in the Middle East, probably means there is more prevalence of HPS and HPS-associated ILD than is recognized. Heightened awareness among healthcare providers is paramount for early diagnosis and optimal management of HPS-associated complications.

Keywords: Lung Diseases, Interstitial • Respiratory Function Tests • HPS1 Protein, Human

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/945175

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Introduction

HPS is characterized by oculocutaneous albinism, which includes a lack of pigmentation in the eyes, skin, and hair, along with bleeding diathesis due to dysfunctional platelets and, in some variations, additional complications such as neutropenia, pulmonary fibrosis, or granulomatous colitis [1]. Genotyping in HPS is clinically important and is crucial for accurate diagnosis and management, especially for those presenting with pulmonary fibrosis, as illustrated by the case presented here. Some genotypes are more associated with earlier onset and rapidly progressive pulmonary fibrosis [1]. HPS was first reported in 1959 by 2 Czechoslovakian physicians who documented patients with oculocutaneous albinism and associated bleeding disorders [2].

This case report of an individual initially presenting with interstitial lung disease underscores the clinical symptoms and diagnostic challenges of Hermansky-Pudlak syndrome, emphasizing the need for heightened clinical awareness and timely genetic testing.

Case Report

We present the case of a 48-year-old Saudi man of Arab descent, referred to our interstitial lung disease (ILD) service with progressive breathlessness on exertion. Though his symptoms had been ongoing for 2 years, they had become more noticeable over the preceding 6 months. His MMRC (Modified Medical Research Council) dyspnea scale score increased from 2 to 3. There were no potential triggers or exacerbating factors identified. A diagnosis of ischemic heart disease was considered at his local hospital, but he could not tolerate a cardiac exercise tolerance test due to shortness of breath and a coronary angiogram was planned. He had a non-productive paroxysmal cough, but had no history of constitutional symptoms or symptoms suggestive of connective tissue diseases or vasculitis. No significant history of occupational or recreational exposure was elicited. He denied any history of genital ulcerations. A review of other systems did not reveal any concerns.

There was no family history of similar respiratory symptoms. He is was born of a consanguineous marriage. His medical history included well-controlled type 2 diabetes mellitus, hypertension, gastroesophageal reflux, and a possible diagnosis of ischemic heart disease.

He was taking metformin, bisoprolol, clopidogrel, rosuvastatin, and budesonide/formoterol inhaler as maintenance medications.

On examination, he was comfortable at rest with oxygen saturation 87% on room air, respiratory rate 16/min, and BP 126/72 mmHg. There was no digital clubbing. His skin appeared very pale (**Figure 1**), his hair was ginger-colored, and his irises were pale (**Figure 2**) with evidence of conjugate horizontal nystagmus. No oral ulcers were seen. Chest auscultation

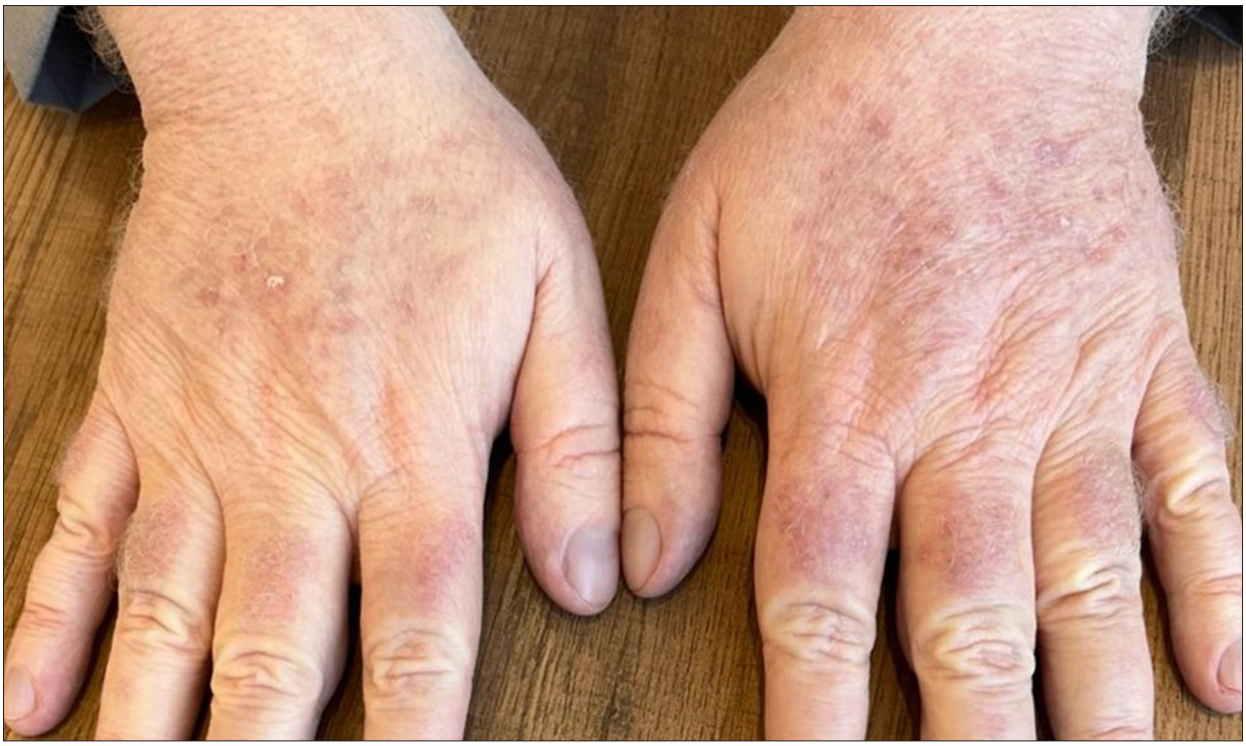

Figure 1. Hypopigmented hands.

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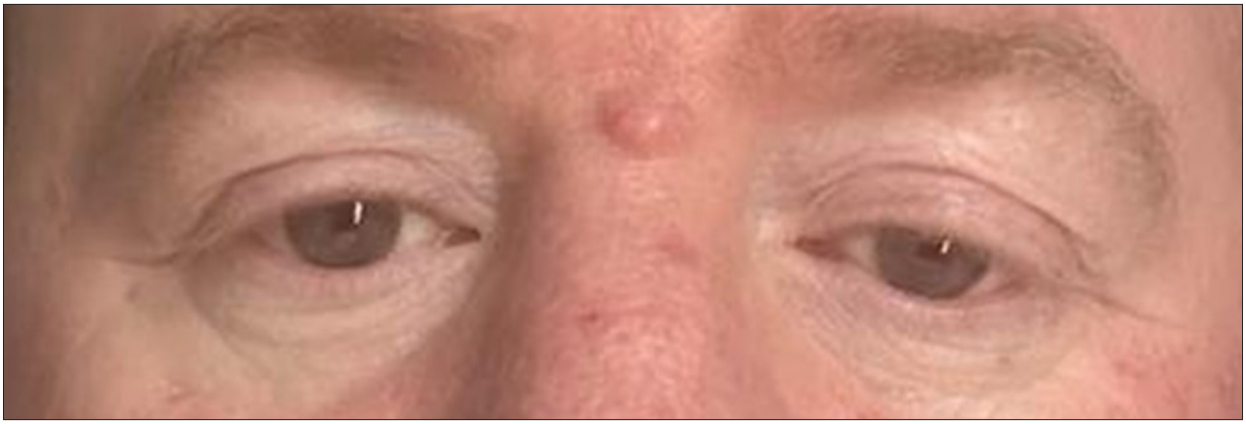

Figure 2. Hypopigmented irises.

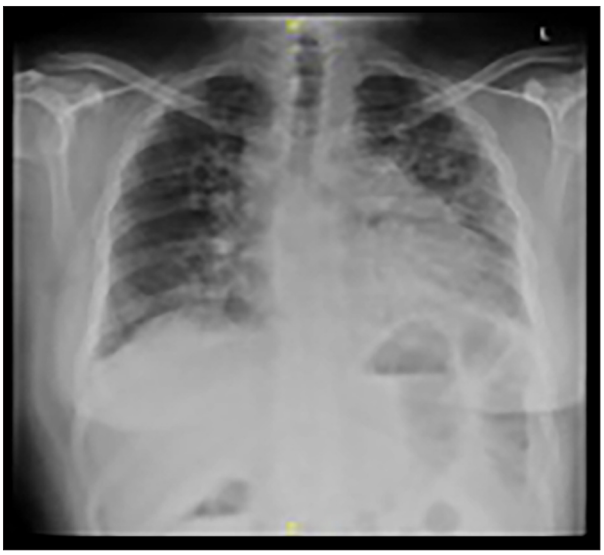

Figure 3. Chest X-ray showing changes consistent with interstitial lung disease.

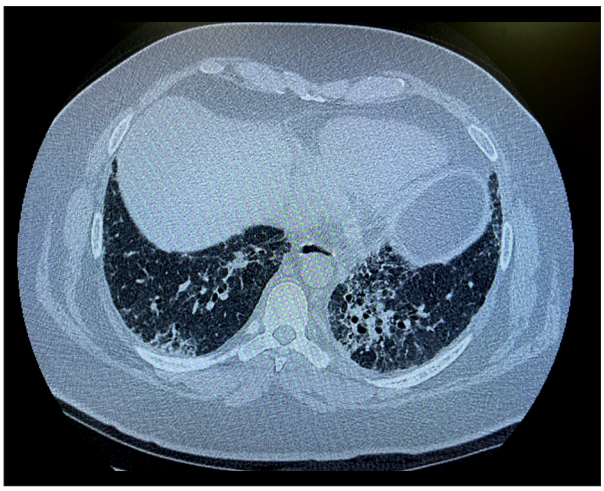

Figure 4. High-resolution CT showing lower-lobe predominant interlobular septal thickening with ground-glass attenuation, traction bronchiectasis and bronchiolectasis, without honeycombing.

revealed bibasilar end-inspiratory crackles. No signs of connective tissue disease, vasculitis, or local skin problems were seen. Fundal examination showed bilateral hypopigmentation. Neurological examination was unremarkable with no obvious muscle weakness.

Results of laboratory investigations, including complete blood count (CBC), renal, liver, and other biochemical parameters, were within normal ranges, and rheumatological panel tests for rheumatoid factor (RF), antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA), and extractable nuclear antigens (ENA) were negative. The virology panel, including human immunodeficiency virus (HIV) testing, yielded negative results.

A chest X-ray (**Figure 3**) revealed characteristic findings consistent with interstitial lung disease (ILD). High-resolution computed tomography (CT) scans (**Figure 4**) demonstrated lower-lobe predominant interlobular septal thickening with ground-glass attenuation, traction bronchiectasis and bronchiolectasis, with no evidence of honeycombing. A barium swallow indicated Grade 1 gastroesophageal reflux.

Further evaluations included bone densitometry and pulmonary function testing. Bone densitometry was normal. The results of the pulmonary function test revealed a restrictive defect, with forced expiratory volume in 1 second (FEV1) at 38% predicted, forced vital capacity (FVC) at 47% predicted, and a ratio of 96, along with a transfer factor of 44% predicted. During the 6-minute walking test, he walked 291 meters, experiencing significant desaturation from an initial oxygen saturation of 95% to 79% at the end of the test.

Although we were wary of having him undergo lung biopsy, we still offered it to him, but he refused. Lung biopsy is usually not recommended to establish a diagnosis of HPS pulmonary

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fibrosis given the high prevalence of pulmonary fibrosis in HPS. It is also a relative contraindication due to patients' increased tendency to bleed [3].

Cardiovascular assessments, including echocardiography and right-heart catheterization, were conducted. The echocardiogram showed normal left and right ventricular function. However, a short acceleration time at the right ventricular outflow tract suggested pulmonary hypertension, with the peak tricuspid regurgitation velocity (TRV) being unmeasurable. Subsequent right-heart catheterization confirmed precapillary pulmonary hypertension, with a mean pulmonary artery pressure (mPAP) of 32 mmHg, pulmonary capillary wedge pressure (PCWP) of 13 mmHg, and pulmonary vascular resistance (PVR) of 4.31 Wood units.

Genetic testing confirmed the diagnosis of autosomal recessive HPS type 1 variant c.972del p. (Met325Trpfs*6).

The history of progressive exertional dyspnea and findings of oculocutaneous albinism with variable hypopigmentation, conjugate horizontal nystagmus, and bibasilar crackles on chest auscultation led us to suspect HPS with ILD. This was confirmed by radiological and genetic studies. An additional complication of pulmonary hypertension was suspected when the patient presented with hypoxemic respiratory failure, which further worsened with exercise, and this was confirmed by echocardiography and right-heart catheterization.

The management of HPS-ILD and precapillary pulmonary hypertension in our patient included preventive measures, supportive care, and genetic counseling. Due to the risk of bleeding associated with HPS and the patient's use of clopidogrel, we decided not to administer nintedanib, despite its indication for progressive pulmonary fibrosis. Given the severity of the patient's disease, lung transplantation was considered, and a referral to our local lung transplant service was made.

Discussion

We present the case of a 48-year-old Saudi man of Arabic ethnicity born of a consanguineous marriage, diagnosed with Hermansky-Pudlak syndrome (HPS) type 1, confirmed by genetic testing to have HPS1 variant c.972del p. (Met325Trpfs*6), presenting with interstitial lung disease (ILD) and precapillary pulmonary hypertension.

Consanguinity and endogamy are prevalent in the Arab World. In Saudi Arabia, the prevalence of consanguineous marriage ranges between 42% and 67%, with different cities varying in estimated prevalence [4,5]. The incidence of HPS in the Arab world is unknown [6].

The case of an adolescent girl from Saudi Arabia with HPS-related lung disease was reported in 2015, but did not include genetic testing [7]. There is a report of HPS type 2 in a 6-year-old child who did not present with pulmonary fibrosis but had bleeding diathesis, clinical immunodeficiency, and recurrent infections [8]. Eight Omani cases with HPS (3 HPS type 2, 1 HPS type 3, and 4 HPS type 6) had been suspected clinically and confirmed through genetic mutation analysis; these patients had mild hemorrhagic phenotype, and variable platelet aggregation defects with different platelet agonists, and those with HPS 2 had severe neutropenia [9].

Pulmonary fibrosis is commonly associated with HPS types 1, 2, and 4, and has also been reported in a single case of HPS type 10; therefore, genotyping is important [1,10-15]. The HPS1 variant identified in our patient, c.972del p. (Met325Trpfs*6), is one of the 67 documented variations [16]. This highlights the genetic diversity within HPS1 mutations and underscores the importance of genetic testing in diagnosing HPS. However, while several HPS1 gene variations have been found, there have been no reports of any connections between these variations and the development of pulmonary fibrosis or other illness in individuals with HPS-1 [1].

The clinical management of HPS-ILD includes preventive measures and supportive care, while lung transplantation is considered for patients with severe disease [17]. These were provided to our patient. Additionally, genetic counseling was offered to our patient. Due to the risk of bleeding associated with HPS and the patient's use of clopidogrel, we opted against nintedanib, despite its indication for progressive pulmonary fibrosis [18,19]. While it is possible to deny the diagnosis of ischemic heart disease because the patient's dyspnea could be attributed to ILD and/or pulmonary hypertension and there was no evidence of ischemia on echocardiography, the patient was following in another institution and he elected to follow with them for this problem, and we therefore could not discontinue clopidogrel without their approval.

There is currently no approved medical therapy for HPS-ILD. A case report was published detailing long-term nintedanib treatment for progressive pulmonary fibrosis associated HPS 1 in a 44-year-old woman. She received it for more than 15 months, with diarrhea as a treatment adverse effect. It was notable that she did not develop bleeding during the course of treatment, but she eventually developed disease progression and underwent lung transplantation [20]. Another case was reported regarding the use of nintedanib in HPS-associated interstitial pneumonia (HPS type 4) [21]. Pirfenidone has shown mixed results in clinical trials, with some evidence suggesting it can slow lung function decline in mild to moderate cases, though its overall efficacy remains inconclusive [22,23].

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Given the severity of our patient's disease, lung transplantation was considered, and a referral to our local lung transplant service was made.

Conclusions

This report describes an extremely rare case of ILD in HPS 1 (HPS-1 variant c.972del p. (Met325Trpfs*6)) from Saudi Arabia. Health care personnel should be aware of this association and monitor patients accordingly. Consanguinity and endogamy, which are quite prevalent in the Middle East, probably means there is a higher prevalence of HPS and HPS-associated ILD than is recognized.

Department and Institution Where Work Was Done

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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