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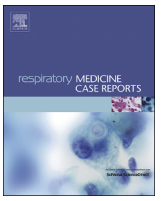

Case Report

Hermansky-Pudlak Syndrome: An unusual pattern of pulmonary fibrosis

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ABSTRACT

Hermansky-Pudlak Syndrome is a rare genetic cause of pulmonary fibrosis, associated with albinism, nystagmus, and a bleeding diathesis. Histologically, Hermansky-Pudlak Syndrome Pulmonary Fibrosis (HPS-PF) typically resembles usual interstitial pneumonia (UIP), however radiologically this is not always the case with a range of features described in the current literature. HPS-PF typically occurs earlier in life than idiopathic pulmonary fibrosis (IPF) and there is limited evidence to support the use of antifibrotic therapy. Given the rarity and potential clinical outcomes of the disease, further research is required. This may be aided by the inclusion of patient with HPS-PF in registry databases.

1. Introduction

Hermansky-Pudlak Syndrome (HPS) is a rare autosomal recessive disorder characterised by oculocutaneous albinism, nystagmus, a bleeding diathesis, and in some, pulmonary fibrosis. Hermansky-Pudlak Syndrome Pulmonary Fibrosis (HPS-PF) has been described as a histological mimic of idiopathic pulmonary fibrosis (IPF), however the clinical features, disease progression and radiological appearance can differ significantly. We present a case of HPS-PF without a usual interstitial pneumonia (UIP) pattern and discuss the literature surrounding this condition.

2. Case report

A thirty-nine-year-old Caucasian man from rural Australia with a clinical diagnosis of HPS was referred for review at the Alfred Hospital Interstitial Lung Disease Clinic. At birth he demonstrated albinism and a mild bleeding diathesis leading to his diagnosis, with genetic testing unavailable at that time. There was no history of consanguinity, neither parents were affected by the condition, and neither were his two elder siblings nor any other extended family members. He presented to his general practitioner with a 2-week history of coryzal symptoms, dry cough, and exertional dyspnoea. He had no other associated cardiopulmonary, infective or constitutional symptoms. He was a distant ex-smoker with a five-year pack history, and brief low intensity marijuana use in his 20's. He had no exposure to other recreational inhaled products or vaping, and no history of intravenous drug use. He was employed as an osteopath and had no previous occupational exposures including fibrogenic dusts or gases. He had no exposure to birds or moulds, or other risks within the home or via avocational activities, and no previous treatment with a fibrogenic agent. He had no gastrointestinal symptoms, no history of colitis or peri-anal disease. His bleeding diathesis was mild, manifesting as a slightly prolonged bleeding

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time in the event of minor trauma. He had suffered no clinically apparent bleeding of note. He had never required platelet transfusion, desmopressin, or tranexamic acid.

On examination he demonstrated albinism, left beating horizontal nystagmus, and clubbing of the fingers, but no manifestations of an underlying rheumatological or connective tissue condition. His oxygen saturation (SpO2) was 95 % on a fraction of inspired oxygen (FiO2) 21 %. His heart rate was 65 beats per minute and blood pressure was 125/80 mmHg. He had fine crepitations audible in the left mid and upper zones, and at the right base. Visual acuity was 6/60 on the right, and 3/60 on the left without corrective eyewear.

A connective tissue screen including anti-nuclear antibodies (ANA), extractable nuclear antigen antibodies (ENA), perinuclear and cytoplasmic anti-neutrophil cytoplasmic antibodies (p-ANCA and c-ANCA) was negative. Platelet aggregometry revealed normal platelet aggregation with adenosine diphosphate, adrenaline and ristocetin, but reduced aggregation was seen with both arachidonic acid and collagen. Pulmonary function tests performed according to the ATS/ERS criteria (Platinum DL 1, MGC Diagnostics) were suggestive of a restrictive defect with a forced vital capacity (FVC) of 3.42L (65 % predicted) and forced expiratory volume in 1 second (FEV_1) of 2.76L (65 % predicted), however no total body plethysmography was performed. He had a reduced carbon monoxide diffusion capacity (DLCO) of 19.76 ml/mmHg/M (63 % predicted). A six-minute walk test revealed a walk distance of 703 m with an end Borg Score of 0.5 for dyspnoea, and 6 for leg fatigue, and exertional hypoxaemia was noted with an SpO2 nadir of 82 %. A transthoracic echocardiogram demonstrated normal left ventricular size and function, with an estimated ejection fraction of 60 %, and normal right ventricular size and function. The right atrium was of normal volume, and the estimated pulmonary arterial pressure was 27 mmHg.

A high-resolution computed tomography (HRCT) demonstrated maintained lung volumes, with bilateral symmetric, pulmonary infiltrates with no zonal gradient. The distribution was slightly more peripheral at the bases but did involve the peribronchovascular interstitium particularly in the upper lobes. Imaging also demonstrated fine lace-like reticulations with airway dilatation, and mild upper lobe honeycombing. There was an absence of honeycombing at the bases and no evidence of an airway centred inflammatory process with no centrilobular ground glass nodules, airway thickening, nor air trapping on expiratory films (see Fig. 1).

The patient was discussed in a specialised interstitial lung disease multi-disciplinary meeting attended by respiratory physicians specializing in interstitial lung disease and an expert thoracic radiologist. The radiological pattern of disease was felt to be inconsistent with any of the idiopathic interstitial pneumonias, including usual interstitial pneumonia (UIP) and non-specific idiopathic pneumonia (NSIP). The diagnosis assigned was HPS-PF with a radiological pattern of unclassifiable interstitial lung disease. A repeat HRCT performed 6 months later demonstrated no progression of disease. Repeat pulmonary function tests with total body plethysmography performed according to the ATS/ERS criteria (Platinum DL 1, MGC Diagnostics) revealed a restrictive ventilatory defect with an FEV_1 of 2.63L (62 % predicted), FVC of 3.41L (65 % predicted), total lung capacity (TLC) of 5.06L (70 %), and a significantly reduced DLCO of 15.87 ml/mmHg/M (51 % predicted). Genetic testing revealed a deletion, and a variant of uncertain significance in the HPS-1 gene confirming the diagnosis of HPS and HPS-PF. The patient and his family are undergoing genetic counselling. Given clinical and radiological stability, and a limited evidence base to support it, antifibrotic therapy has not been commenced.

3. Discussion

Hermansky-Pudlak Syndrome (HPS) is a rare autosomal recessive disorder with an estimated global prevalence between 1 in 500,000 and 1 in 1,000,000 [1]. There is a clustering of cases in Puerto Rico where the prevalence is as high as 1 in 1800 [1,2]. HPS is

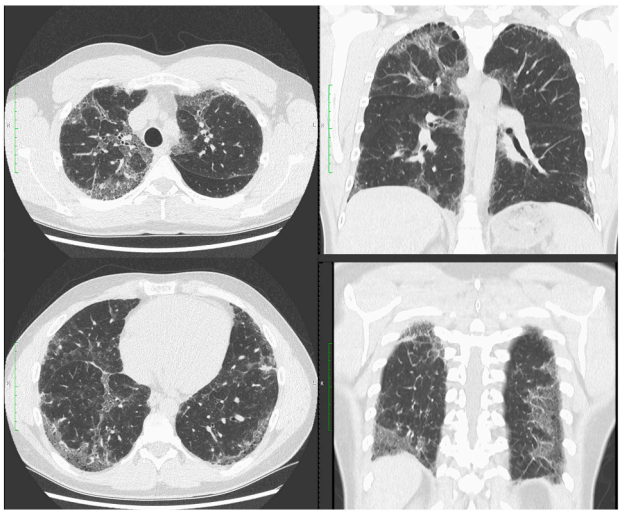

Fig. 1. Axial and coronal high resolution computed tomography images demonstrating bilateral pulmonary infiltrates without clear zonal gradient. There is involvement of both the peripheries at the bases, and the peribronchovascular space in the upper zones. Features of fine lace-like reticulations, upper lobe honeycombing without lower lobe involvement, and an absence of airway cantered inflammation or ground glass infiltrates. This pattern is not consistent with either UIP or NSIP, and was determined to be radiologically unclassifiable.

characterised by oculocutaneous albinism, nystagmus, and bleeding diathesis. Patients can also develop granulomatous colitis and pulmonary fibrosis. Ten subtypes have been identified and nine individual genes implicated in the condition. HPS-1, HPS-2, and HPS-4 are associated with the development of pulmonary fibrosis, with all patients of HPS-1 subtype developing the disease [3,4]. HPS genes encode for proteins which contribute to the formation of biogenesis of lysosome-related organelle complexes (BLOCs). Lysosome related organelles (LROs) are a diverse class of subcellular carriers responsible for transporting various substances within cells [5]. Dysfunction of melanosomes and platelet dense granules (both LROs affected by HPS) result in the characteristic albinism and platelet dysfunction.

Hermansky-Pudlak Syndrome Pulmonary Fibrosis (HPS-PF) is incompletely understood but is thought to occur due to disruption of lamellar bodies, an LRO within type II pneumocytes responsible for the synthesis and storage of surfactant [6]. This triggers macrophage mediated inflammation and fibroblast proliferation, resulting in the development of pulmonary fibrosis [7]. HPS-PF has traditionally been seen as a similar entity to idiopathic pulmonary fibrosis (IPF), although typically manifests in the fourth and fifth decade of life (rather than the sixth onwards) and carries with it a better prognosis [3,8,9]. The rate of decline in lung function and associated mortality appears to differ significantly between individual patients, however there is an approximate 2-year survival once forced vital capacity reaches 50 % predicted [9].

Histologically, HPS-PF is typically described as a 'mimic' of usual interstitial pneumonia (UIP) [10], however features of non-specific interstitial pneumonia (NSIP) and desquamative interstitial pneumonitis (DIP) have also been reported [11]. Given this association, an expectation that HPS-PF might follow a radiological UIP pattern is not unreasonable, although some differences between the two conditions do occur [3]. Features of UIP on HRCT typically include a basal predominant pattern with subpleural reticular opacities, honeycombing, and traction bronchiectasis [3,8]. All these features have been described in HPS-PF, however additional abnormalities including pleural thickening, subpleural cysts, and peri-bronchovascular thickening have also been described [12,13]. A study examining HRCTs of sixty-seven patients with HPS described the appearance and defined patterns of radiological disease progression [12]. Early stages of disease were characterised by septal thickening, ground glass opacities and mild reticulations. Patients with more advanced stages of disease demonstrated findings of moderate to severe reticulation, bronchiectasis, subpleural cysts, and peri-bronchovascular thickening [12]. Findings were evenly distributed throughout the lungs, however appeared to affect the middle and lower zones more commonly, with a tendency for peripheral areas [12]. The characteristic CT findings of UIP and HPS-PF, in addition to those of the present case are presented in Table 1. The radiological findings present in this case were not typical of those previously described in HPS. Given the rarity of this condition, alternative diagnoses must be considered. In the current case, pertinent radiological differentials included UIP, NSIP and chronic hypersensitivity pneumonitis (CHP). Additional relevant differential diagnoses including connective-tissue disease related interstitial lung disease (CTD-ILD) must be excluded. The diagnosis of unclassifiable ILD refers to an inability to assign a diagnosis with greater than 50 % confidence. It is important to assign a working diagnosis in this patient group to allow the opportunity to provide treatment that may stabilise or slow disease progression. The prognosis in those assigned a diagnosis of unclassifiable ILD is slightly better than in those with IPF, however the mortality rate remains high (31 % at 5 years) [14].

The definitive management for HPS-PF is lung transplantation [17,18]. The utility of the anti-fibrotic pirfenidone has been evaluated with conflicting results. In 2002, Gahl et at demonstrated a reduction in rate of decline of FVC by 5 % per year when treated with Pirfenidone compared with placebo [9], however a subsequent 2011 study by the same group was abandoned early due to lack of treatment effect [19]. One very small open-label case-control trial consisting of three patients compared against historical controls demonstrated that treatment with Pirfenidone was well tolerated long term and may slow decline in both FVC and DLCO [20]. In the three patients treated with pirfenidone the rate of FVC change was between −0.80 % and 1.8 % per year, while the rate of DLCO change was between −2.5 % and 1.2 % per year. In comparison, among patients who were not treated with pirfenidone both the median rate of change in FVC and DLCO was −3.0 % predicted per year. The benefit of treatment with Pirfenidone therefore remains unclear but appears to be safe for use in this cohort. The Efficacy and Safety of Pirfenidone Treatment in HPS-ILD (NCT NCT04193592)

Table 1
High resolution computed tomography findings of usual interstitial pneumonia (UIP), Hermansky-Pudlak Syndrome Pulmonary Fibrosis (HPS-PF) and current case [3,8,12,15,16].

	Usual Interstitial Pneumonia	Early HPS-PF	Late HPS-PF	Current Case
Distribution	Subpleural and basal predominance Heterogenous with areas of normal lung	Even distribution Slight predilection for middle and lower lungs Slight peripheral tendency	Peripheral changes progress toward the centre of the lung	No zonal gradient Slightly more peripheral at bases but not central sparing
Reticular Opacities	Common	Mild	Moderate	Fine, lace-like reticulations
Consolidation	Not present	Not usually present	May be present	Not present
Honeycombing	Distinguishing feature	Can be present	Common	Present at the apices but absent at the bases
Traction Bronchiectasis	Present	Not present	Present	Present
Ground Glass Opacities	Mild, if prominent feature consider other diagnosis	Seen across spectrum of disease	Seen across spectrum of disease	Not present
Peri-bronchovascular Thickening	Not present, suggestive of alternative diagnosis	Not present	Present	Not present
Pleural Thickening	Not present, suggestive of alternative diagnosis	Not present	May be present	Not present
Loss of Lung Volume	Present	May be present	May be present	Not present

or PEARL trial is currently underway evaluating the use of pirfenidone in this patient cohort. There is little evidence to support the use of nintedanib in HPS-PF, with some concerns regarding the potential bleeding risk associated with the bleeding diathesis common to the condition [21]. Itano et al. described the case of a patient with HPS-4 treated with first pirfenidone, then nintedanib with apparent delaying of lung function decline [22].

HPS is an exceedingly rare condition, even more so outside of Puerto Rico. The Australasian Interstitial Lung Disease Registry (AILDR) is contributed to by more than 20 sites across two countries and includes more than 3000 registered participants with ILD [23]. To date, this patient remains one of only several recorded case of HPS in Australasia, and the only patient on the AILDR [24]. Given the global prevalence, it is expected that more cases exist in the region. Inclusion within the AILDR would provide opportunity for better understanding of disease behaviour and allow enrolment of patients into clinical trials of novel antifibrotics that may help advance the care of patients with HPS.

Ethics statement

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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Nil.

CRediT authorship contribution statement

Matthew Donnan: Conceptualization, Writing – original draft. **Samantha Ellis:** Conceptualization, Supervision, Writing – review & editing. **Ian Glaspole:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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