CASE BASED DISCUSSIONS

Hermansky-Pudlak syndrome with a novel genetic variant in HPS1 and subsequent accelerated pulmonary fibrosis: significance for phenocopy diseases

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ABSTRACT

The Hermansky-Pudlak syndrome (HPS) is a collection of autosomal-recessive disorders characterised by tyrosinase-positive oculocutaneous albinism (OCA), bleeding diatheses and, in selected individuals, early-onset accelerated pulmonary fibrosis, neutropaenia and granulomatous colitis. We describe a young man who presented following a self-directed literature review prompted by severe bleeding complications following minor surgical and dental procedures in the context of OCA. HPS was clinically suspected, with subsequent genetic testing confirming biallelic mutations in the *HPS1* gene. Of interest, this is the only described HPS type 1 patient with two different (compound heterozygote) splice site variants in *HPS1*. In addition to detailing a novel genetic result and outlining the progressive clinical course of disease in this case, we discuss the management of HPS, the prognostic value of subtype analysis and the technical difficulties relating to transplantation in the case of HPS-associated advanced pulmonary fibrosis. This case also illustrates the concept of lung phenocopy relationships and the potential for elucidating the pathogenesis of more common pulmonary disorders by studying genetic diseases that result in similar phenotypes. Furthermore, it re-emphasises the importance of the patient voice, particularly with regard to complex diagnoses and rare diseases.

The patient: Arriving at my diagnosis marked the end of a long road. Although the diagnosis itself was personally devastating, it afforded me the opportunity to engage with the help needed to take the best possible care of my lungs going forward. I first underwent specialist review by a haematologist in the late 1990s, following several episodes of prolonged bleeding. After the completion of many tests, no bleeding issues was identified. I also have albinism with associated visual impairment. At several of these consultations, I enquired as to whether my albinism and bleeding difficulties might be linked by a rare disease. I felt that these concerns were dismissed without adequate consideration, particularly since I had spent a great deal of time researching the area. Several years later, a severe bleeding episode following a tooth extraction that required blood transfusions prompted my dental surgeon to suggest

that it would be worth re-attempting to find a team able to diagnose my bleeding issues.

Dr Oliver J McElvaney (OJMcE): A 28-year-old Caucasian Irish man with oculocutaneous albinism (OCA) self-referred to our clinic in 2003 with a history of epistaxis and significant haemorrhagic complications following minor surgical and dental procedures. A standard evaluation for platelet dysfunction and coagulopathy at another hospital was negative. Family history was unremarkable and he was a lifelong non-smoker and non-drinker. On examination, periodic alternating nystagmus and bilateral lower limb petechiae were noted.

The differential diagnosis for OCA includes X-linked OCA, Chediak-Higashi syndrome, Griscelli syndrome, Cross syndrome and haemophagocytic lymphohistiocytosis. Given the history and examination findings, however, the Hermansky-Pudlak syndrome (HPS) was suspected. This was despite his ethnicity, since the condition occurs almost exclusively in individuals of Puerto Rican ancestry. Electron microscopy studies of platelet-rich plasma demonstrated an absence of platelet dense bodies, enabling a working diagnosis of HPS to be made. He was referred to our colleagues at the National Institutes of Health, USA for further studies.

Dr Marjan Huizing (MH) and Professor William A Gahl (WAG): The patient underwent genetic testing which revealed biallelic mutations in the *HPS1* gene (figure 1). The compound heterozygous splice site variants identified confirmed the clinical diagnosis of HPS-1, a particularly rare finding in the Caucasian population and the first Irish case on record. Furthermore, they continue to represent the only described patient with HPS-1 with two different compound heterozygous splice site variants in *HPS1*. Variant c.1857+2T>C (IVS18 +2 T>C) is a novel variant. This variant changes splice site prediction from 99% (wild type) to 0%, essentially deleting the splice site. While variant c.1744-2A>C (IVS17-2A>C) has previously been described in subjects of Caucasian descent, no effect of splice site on cDNA had been published previously. We calculated splice site strength using Human Splice Site Prediction by Neural Network, comparing wild-type sequence to variant sequence.

Dr Deirdre Horan (DH): While no signs or symptoms suggestive of pulmonary involvement

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Figure 1 Progressive HPS-associated fibrotic lung disease. Genetic sequencing revealed the first case of two different compound heterozygous splice site variants in the *HPS1* gene, including a previously undescribed novel variant (panel A; [†]Exp. Splice Effect: as reported in literature: ND; Yes, i.e., splice site effect was demonstrated experimentally. [‡]Using Human Splice Site Prediction by Neural Network, comparing wild-type sequence to variant sequence). Predicted Splice Site Scores are visualised as follows: green (high splice site prediction >80%), yellow (medium splice site prediction 50%–80%) and red (low splice site prediction <50%). The patient underwent monitoring with serial HRCT thorax imaging (panel B), spirometry with DLCO (panel C), FVC (panel E) and cardiopulmonary exercise testing (panel D). Despite brief improvement following commencement of pirfenidone (asterisk), steady decline in these indices over time can be observed. DLCO, diffusing capacity of the lung for carbon monoxide; EXP, experimental; FVC, forced vital capacity; *HPS1*, Hermansky-Pudlak syndrome gene; HRCT, high-resolution CT; ND, not done.

were present initially, mild bronchiectasis was noted on thoracic high-resolution CT (HRCT) scan the following year. By 2008, aged 33, the patient displayed early clubbing, and 2 years later HRCT changes consistent with pulmonary fibrosis were apparent, later matched by progressively worsening, fine end-inspiratory crackles.

Prior to the development of significant fibrosis, *N*-acetyl-cysteine had been prescribed. As the patient began to exhibit symptoms and signs of progressive pulmonary fibrosis, pirfenidone therapy was commenced. Despite this intervention, the patient experienced progressive exertional dyspnoea, decreased exercise tolerance and declining cardiopulmonary exercise test performance over the course of the ensuing decade, with a marked reduction in diffusing capacity of the lung for carbon monoxide.

Dr P Mark Logan (PML): Serial HRCT imaging confirmed worsening fibrotic lung disease over time with associated traction bronchiectasis. HRCT is more sensitive than chest radiography in evaluating the extent of pulmonary disease in patients with HPS and provides a useful means of assessing disease status

and progression that can be correlated with pulmonary function testing. Chest radiographic findings seen in HPS include bilateral reticulonodular interstitial patterns, perihilar fibrosis and pleural thickening. HRCT may reveal septal thickening, ‘ground-glass’ opacities (likely microfibrosis beyond the resolution of CT) and peribronchovascular thickening, in the context of fibrotic changes that are most frequently bilateral with a basal predominance. Radiologically HPS can differ somewhat from idiopathic pulmonary fibrosis (IPF). For example, honeycombing appears to be more common in IPF than HPS, while cysts and mosaic pattern may be more common in HPS than IPF.

OJMcE: The patient has subsequently been listed for lung transplantation, having undergone an extended workup for same. This process was commenced prior to qualification for the transplant list, in light of his overwhelming likelihood of progression to end-stage fibrotic lung disease.

DISCUSSION

OJMcE: The HPS is a collection of autosomal-recessive multi-system disorders characterised by tyrosinase-positive OCA,

bleeding diatheses and, in selected individuals, neutropaenia, early-onset pulmonary fibrosis and granulomatous colitis.¹⁻³ The HPS spectrum includes 10 disorders (HPS-1 to HPS-10). HPS-1 and HPS-4 are associated with the poorest prognosis, due to the occurrence of accelerated fibrotic lung disease in these subtypes.¹⁻³

Presentation usually occurs following clinically significant bleeding in the context of some degree of hypopigmentation. Patients may report epistaxis, soft-tissue ecchymosis or prolonged bleeding following dental extractions, minor surgical procedures or childbirth. Women may also present with prolonged menstrual bleeding. Decreased visual acuity, often to the level of legal blindness, is generally accompanied by horizontal nystagmus. Early-onset pulmonary fibrosis in the context of OCA should prompt suspicion of the diagnosis.

WAG: Approximately 75% of the HPS population will die of causes directly related to the condition, in particular pulmonary fibrosis, haemorrhagic episodes and granulomatous colitis.³ Clinical manifestations of HPS-associated pulmonary fibrosis classically occur in the fourth or fifth decades of life. Mean life expectancy remains below 50 years of age.³

MH: The diagnosis is achieved by demonstrating the absence of platelet dense bodies on whole mount electron microscopy with confirmatory genetic testing. Subtype identification has prognostic and therapeutic implications, and should be sought wherever possible. Where disease-causing mutations have been identified in families, antenatal testing is available.

OJMcE: Lung transplantation is the only definitive treatment for HPS-associated pulmonary fibrosis and has been performed in subtypes 1, 2 and 4.³ Several challenges exist with respect to this option. First, the absence of dense bodies in HPS platelets impairs the normal secondary aggregation response, with subsequently increased mucosal bleeding. This may necessitate additional use of intraoperative platelet transfusions and prophylactic desmopressin and/or recombinant factor VIIa. Second, uncertainty exists as to whether allograft recurrence of disease occurs. A third issue exists regarding the timing of referral for lung transplantation. Patients with HPS-1 and HPS-4 in particular should be referred early in the clinical course of their disease given the accelerated nature of fibrosis in these subtypes and the need for a comprehensive preoperative haematological workup and bleeding risk assessment. Finally, the presence of cutaneous hypopigmentation increases the risk of skin malignancy in immunosuppressed transplant recipients. While pirfenidone may anecdotally offer temporary improvement or slow the progression of fibrosis, HPS-specific clinical trials have not been definitive.⁴ Steroid therapy is not effective.³

Professor Noel G McElvaney (NGMcE): This case raises two further issues. The first is the opportunity afforded to research clinicians by genetic conditions when it comes to understanding the pathogenesis of more common, phenotypically similar, non-genetic diseases, or 'phenocopies'. To use this particular case as an example, our patient was virtually certain to develop early onset-pulmonary fibrosis by virtue of his HPS subtype. This enables the research clinician to assess the prefibrotic course in detail, rather than beginning the research process after the proverbial die is cast and established pulmonary disease has already taken hold. The collection of biological samples such as bronchoalveolar lavage fluid, brushings and blood stands to provide valuable information, which may be used to identify potential biomarkers that herald the onset of disease, and reveal aspects of the pathophysiology underlying the fibrotic process. Such discoveries may then in turn be applicable to other fibrotic conditions, such as IPF.

Dr Emer P Reeves (EPR): Other examples of lung phenocopies include emphysema and alpha-1 antitrypsin deficiency (AATD), and bronchiectasis and cystic fibrosis (CF).

NGMcE: AATD is an autosomal-co-dominant genetic disorder. The most common severe deficient variant (PiZZ) is caused by a single-nucleotide polymorphism in *SERPINA1* resulting in the substitution of glutamic acid for lysine at residue 342. The primary function of AAT is to inhibit neutrophil elastase (NE) to prevent NE-induced tissue damage. In PiZZ homozygotes the mutant Z protein polymerises in hepatocytes leading to liver disease and a decreased anti-NE protective screen in the lung. The obvious phenocopy is smoking-induced emphysema, since smokers without antigenic deficiency of AAT may still have a functional deficiency in the lung due to oxidative inactivation of AAT by oxidants from cigarette smoke.⁵ There is currently an effective treatment for AATD whereby weekly plasma-purified AAT, given intravenously, decreases progression of emphysema as assessed by CT densitometry. This approach may be of future use in a chronic obstructive pulmonary disease/smoker population.

EPR: A further phenocopy relationship is that between non-CF bronchiectasis (NCFB) and CF. CF is an autosomal-recessive chloride channelopathy resulting from mutations in the *CFTR* gene on chromosome 7q resulting in a multisystem disorder characterised in the lung by severe bronchiectasis. Therapeutic advances for CF pulmonary manifestations have benefitted NCFB, although not all CF treatments are readily transferable. The advent of ion channel modulators has helped clarify the normal function of CFTR and generated discussion that CFTR function may be diminished by inflammation in conditions such as bronchiectasis and chronic bronchitis, contributing to a CF-like phenotype.

NGMcE: The second issue highlighted in this paper is the critical value of listening to the patient voice, which may frequently inform the clinician as to the diagnosis. This has added relevance when it pertains to the diagnosis and assessment of genetic and rare diseases. The individual described in this report displayed exceptional persistence, diligence and involvement in his own condition. He had, on several occasions, reported his concerns to medical professionals and proposed the possibility of a unifying diagnosis linking OCA and a bleeding diathesis, only to be rebuffed, in large part due to his ethnicity. Without his consistent efforts to find a diagnosis, it is likely that monitoring for onset and progression of pulmonary fibrosis would not have been undertaken, nor would pre-emptive referral and specialised workup for transplantation.

The patient: This journey was an arduous one initially. It featured what felt like the futile re-running of the same tests over and over again and dismissals of the possibility of me having HPS on the basis that I am not of Puerto Rican extraction. Times have changed, however. Doctors these days are more open to listening to what a patient has to say, a trend that I hope is here to stay.

Patient information regarding the diagnosis of HPS, platelet EM testing and genetic panels for OCA and HPS can be found at www.HPSnetwork.org

Patient and public involvement

The involvement of the patient in the preparation and writing of this manuscript has been acknowledged by co-authorship. It is our belief that patient involvement strengthens the message of research, and we acknowledge the work done by *Thorax* and the BMJ group as a whole to promote the patient voice as a matter of policy.

Contributors OJMcE: the lead author and corresponding author. MH and WAG: performed genetic analyses. PML: evaluated serial imaging. PO'D and DH: contributed to writing and fact-checking the manuscript. EPR and NGMcE: share senior authorship.

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