Idiopathic interstitial pneumonia in a patient with von Hippel–Lindau syndrome: a first case

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To the Editor:

Interstitial lung diseases (ILD) are a large group of pulmonary disorders characterised by the cardinal involvement of the pulmonary interstitium. Although multiple predisposing factors have been associated with these diseases, no evidence is currently available regarding the coexistence of pulmonary fibrosis and von Hippel–Lindau (VHL) syndrome.

We hereby present a case of idiopathic interstitial pneumonia in a patient known for VHL and deficiency of carnitine palmitoyltransferase type II (CPT2). VHL disease is an inherited, autosomal dominant syndrome that causes benign and malignant tumours. CPT2 deficiency is an autosomal recessive disorder affecting skeletal muscle and represents the most common inherited long-chain fatty acid oxidation disorder.

A 30-year-old Caucasian male affected by VHL syndrome, thalassaemia trait and CPT2 deficiency (homozygous mutation S113L gene CPT2, myopathic form) [1] developed episodes of worsening dyspnoea and dry cough in 2018. The diagnosis of VHL was confirmed in 2002 through genetic testing (VHL P86A mutations of exon 1) based on family history and the presence of retinal haemangioblastomas and pancreatic tumours. The patient worked as an employee in an office and had no particular hobbies. He was a never-smoker and did not refer to exposure to any substance that could cause lung damage. As a consequence of the onset of respiratory symptoms, he performed pulmonary function tests (PFTs) that unveiled a moderate–severe restrictive respiratory pattern (forced vital capacity (FVC) 48% and total lung capacity (TLC) 52% of the predicted value, forced expiratory volume in 1 s (FEV_1)/FVC ratio 77%) and a chest computed tomography (CT) scan showing bronchiectasis of the middle and lower lobes, without any sign of ILD (figure 1, A1–A3). The family history was negative for respiratory diseases. The echocardiogram was normal. Autoimmune screening was negative, which included antinuclear antibodies, antineutrophil cytoplasmic antibodies, extractable nuclear antigen, circulating anticentromere, anti-double-stranded deoxyribonucleic acid antibodies, antibodies against La/SSB autoantigens, antibodies against Ro/SSA autoantigens, antibodies against histidyl tRNA synthetase, antinuclear ribonucleoprotein antibody, anti-topoisomerase I antibody (Scl70) and antibodies against Smith antigen. The 6-min walk test was interrupted due to hypoxia (oxygen saturation measured by pulse oximetry 76%) and normalised with oxygen supplementation. At that time the only specific treatments received were long-term oxygen therapy and respiratory rehabilitation.

Given the worsening of symptoms at the beginning of 2019, he was prescribed a course of oral steroids (prednisone 25 $mg \cdot day^{-1}$) in suspicion of an underlying inflammatory disease, with no significant change. After 6 months, he underwent a follow-up chest high-resolution CT scan, which showed mosaic attenuation in the right and left lower lobes, thickening of the interlobular septa and traction bronchiectasis in the middle lobe and in the lateral segments of the lower lobes (figure 1, panels B1–B3). The diameter of the pulmonary artery was 38 mm (normal values <30 mm). He also performed a bronchoalveolar lavage, which showed a neutrophilic alveolitis (neutrophils 28%), whereas microbiological examination results were negative.

Because of the deterioration of respiratory symptoms, he was hospitalised in November 2019. During hospitalisation he stopped prednisone and underwent a CT scan revealing a hypoexpansion of the left lung, without parenchymal thickening, no opacification defects of the pulmonary arteries and branches, no

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Although the mechanisms are not known, this is a case of progressive interstitial lung involvement, with a NSIP radiological pattern, evolving in pulmonary fibrosis in a patient with von Hippel–Lindau syndrome, without extrapulmonary fibrosis. https://bit.ly/3QlNStu

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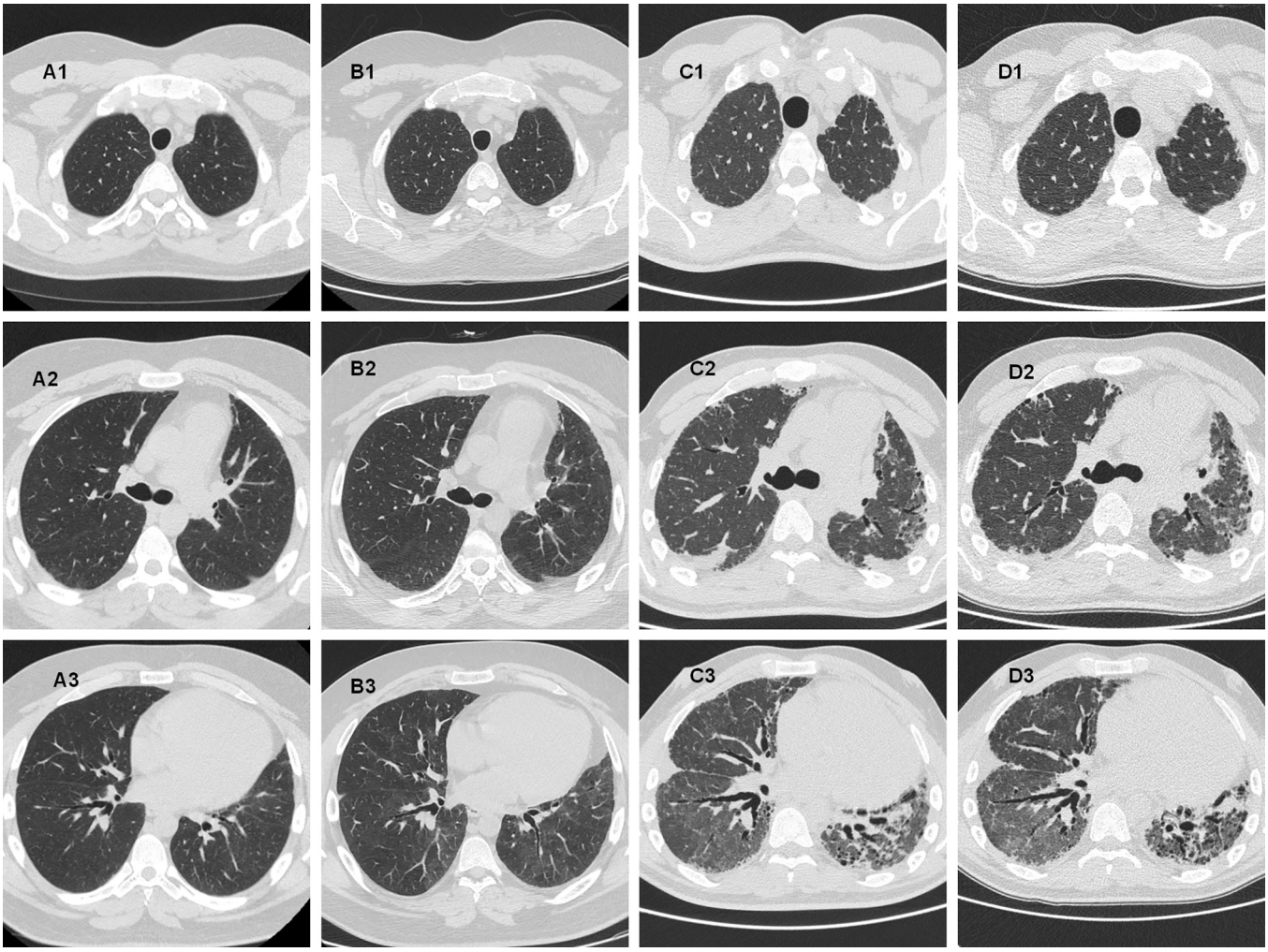

FIGURE 1 Radiological progression of fibrotic interstitial lung disease (ILD) in male patient between 2018 and 2021. Axial high-resolution computed tomography scans at the level of apices (A1, B1, C1, D1), carina (A2, B2, C2, D2) and atria (A3, B3, C3, D3).

lymphadenomegaly, no effusions and regular hypopharyngeal structures. He also underwent electromyography, but results were unremarkable. He was discharged with oxygen therapy of 5 $L \cdot min^{-1}$ only on exertion.

After discharge from hospital, he underwent an echocardiogram showing a left ventricle ejection fraction of 55%, estimated pulmonary arterial systolic pressure (PASP) of 50 mmHg, tricuspid annular plane excursion of 21 mm and right ventricular hypertrophy.

After 1 month, the patient was rehospitalised because of further worsening of the respiratory symptoms. A chest CT was performed at admission, showing a nonspecific interstitial pneumonia (NSIP) pattern mainly in the left lung together with traction bronchiectasis. He underwent PFTs revealing a further deterioration of the restrictive ventilatory pattern (FVC 49%, FEV_1 34%, FEV_1/FVC ratio 98%, TLC 44%, diffusing capacity of the lungs for carbon monoxide diffusion capacity: not detectable). An echocardiogram showed severe pulmonary hypertension with an estimated PASP of 70 mmHg. He was therefore treated with methylprednisolone (1 $mg \cdot kg^{-1}$) with improvement of symptoms. After a few weeks the chest CT showed an improvement of the NSIP pattern with reduction of ground-glass opacities (GGOs) and the appearance of pneumomediastinum and subcutaneous emphysema. Clinical and arterial blood gases improvement was obtained with steroids only. In the suspicion of an idiopathic fibrotic ILD, the patient was discharged with prednisone (25 $mg \cdot day^{-1}$) and referred to the lung transplant centre.

In March 2021 the patient was hospitalised due to a further deterioration of respiratory symptoms during steroid tapering. The chest high-resolution CT scan showed a worsening of pulmonary fibrosis (with

extension and progression of subpleural distortion and traction bronchiectasis) and more conspicuous GGO; no signs of pneumomediastinum and subcutaneous emphysema were observed (figure 1, panels C1–C3). He was treated with methylprednisolone (1 $mg \cdot kg^{-1}$) and discharged with a medium–high dose of steroids until the next visit to the transplant centre.

The disease continued to progress despite prolonged high-dose steroids, and it was not possible to discharge the patient from the hospital due to elevated oxygen requirement at rest. Therefore, he was listed and transplanted in May and June 2021, respectively. Before the lung transplant, he underwent a right heart catheterisation that did not confirm the values suggested by the previous echocardiograms (estimated PASP 88 mmHg), but showed pre-capillary pulmonary hypertension (mean pulmonary arterial pressure 24 mmHg, pulmonary artery wedge pressure 7 mmHg, pulmonary vascular resistance 3.24 WU). Testing for telomere-related gene mutation was also performed and results were negative, while the analysis for surfactant-related gene mutations was not performed. The last high-resolution CT scan in June 2021 showed further progression of pulmonary fibrosis with lung volume reduction and subpleural honeycombing (figure 1, panels D1–D3). After transplant, a pathological examination of the explant revealed a significant fibrosing interstitial process, with intra-alveolar macrophage infiltrate suggesting an NSIP anatomopathological pattern. The explant was not studied for the expression of VHL protein.

To our knowledge, this is the first description of a progressive fibrotic ILD in a patient affected by VHL syndrome.

The VHL gene was first identified in patients with VHL syndrome, an autosomal dominant disease with an incidence of one in 36 000 births [2]. Germline mutation of the VHL gene, which is located in human chromosome 3p25 [3], predisposes individuals to various benign or malignant tumours and cysts in many organs [4].

In a microarray study, Pardo and colleagues [5] showed that lungs of idiopathic pulmonary fibrosis patients expressed higher levels of VHL protein (pVHL) mRNA than lungs of control individuals. Specifically, lungs of fibrotic patients expressed elevated levels of pVHL in fibroblastic foci. Overexpression of pVHL in lung fibroblasts increased the expression of fibronectin, collagen and the α5 integrin subunit as well as lung fibroblast proliferation [6]. On the contrary, the suppression of pVHL production in fibroblasts has been shown to protect against bleomycin-induced pulmonary fibrosis in a mouse model [7]. pVHL is also necessary for fibroblast proliferation after treatment of transforming growth factor-β1, a potent pro-fibrotic cytokine. These results suggest that elevated expression of pVHL results in aberrant fibronectin expression and activation of integrin/FAK signalling, leading to fibroblast proliferation and fibrosis [6].

On the basis of this pathogenetic background, we support a possible causal relationship between VHL and the fibrotic NSIP, rather than a random association. In fact, NSIP is considered a distinct clinical entity with specific clinical, radiological and pathological features. It occurs predominantly in older patients compared to our clinical case, in general in the sixth decade of life [8]. Therefore, because of the lack of a family history for ILD, the absence of environmental factors, including inorganic and organic dusts, the negative testing for telomere-related genes, together with the negative autoimmune panel and the young age of the patient, we believe that a relationship between VHL and the fibrotic NSIP pattern can be suggested. Furthermore, our observation is supported by the human and animal models suggesting that overexpression of pVHL acts as a fibrogenic trigger in the lungs.

When considering fibrosis in other organs, such as liver or kidney, pVHL and the VHL gene showed contrasting effects.

In experimental models of liver fibrosis, liver sections from patients with liver fibrosis had a lower level of pVHL compared with healthy sections, a finding which was confirmed in mice. On the contrary, overexpression of VHL attenuated liver fibrosis, downregulated fibrogenic genes, and inhibited liver inflammation, apoptosis and angiogenesis [9].

In the kidney, the tumour suppressor VHL gene acts as a gatekeeper of renal tubular growth control. Knockout of the VHL gene in the mouse tubular apparatus enables hypoxia-inducible transcription Factor (HIF)-2α expression [10]. Continuous transgenic expression of HIF-2α leads to renal fibrosis and failure together with the formation of multiple renal cysts. Despite these multiple effects of biallelic VHL inactivation in patients with hereditary VHL syndrome, our patient did not show multi-organ fibrosis.

In conclusion, this case report is the first to describe the development of a progressive fibrotic ILD in a young patient affected by VHL syndrome, without detection of extrapulmonary fibrosis. Although the disease mechanisms are not known, we believe that this description is important to draw attention to common signs and symptoms, along with proper utilisation of diagnostic tests, to diagnose a fibrotic ILD in the early phase.

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