



Early View

Research letter

Idiopathic interstitial pneumonia in a patient with Von Hippel-Lindau syndrome: a first case

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TITLE

Idiopathic interstitial pneumonia in a patient with Von Hippel-Lindau syndrome: a first case report

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Take-home message: Although the mechanisms are not known, we describe 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.

Interstitial lung diseases (ILD) are a large group of pulmonary disorders characterized histologically 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 tumors. CPT2 deficiency is an autosomal recessive disorder affecting skeletal muscle and represents the most common inherited long-chain fatty acid oxidation disorder.

A 30-years-old caucasian male affected by VHL syndrome, thalassemia trait and CPT2 deficiency (homozygous mutation S113L gene CPT2, myopathic form) [1] developed episodes of worsening dyspnea 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 hemangioblastomas and pancreatic tumors. The patient worked as an employee in an office and he had no particular hobbies. He was a never smoker and did not refer 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 the 1st second (FEV1)/FVC ratio 77%) and a chest CT scan showing bronchiectasis of the middle and the lower lobes, without any sign of ILD, Figure 1 (panels A1-A3). The family history was negative for respiratory diseases. Echocardiogram was normal. Autoimmune screening – including antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), extractable nuclear antigen (ENA), Circulating anticentromere (CENP), anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies, antibodies against La/SSB autoantigens (SSB-La), antibodies against Ro/SSA autoantigens (SSA-Ro), antibodies against histidyl tRNA synthetase (anti-Jo-1), antinuclear ribonucleoprotein antibody (anti-RNP), Anti-topoisomerase I antibody (Scl70) and antibodies against Smith antigen (SmD) - was negative. The six minute walking test was interrupted due to hypoxia (SpO2 76%) and normalized with oxygen supplementation. At that time the only specific treatments received were long-term oxygen therapy and respiratory physiotherapy.

Given the worsening of symptoms at the beginning of 2019, he was prescribed a course of oral steroids (prednisone 25 mg/day) in suspicion of an underlying inflammatory disease, with no significant change. After six months, he underwent to a follow-up lung high resolution CT scan showing mosaic attenuation in the right and left lower lobes, thickening of the interlobular septa, 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 broncho-alveolar lavage that showed a neutrophilic alveolitis (neutrophils 28%), while microbiological examination resulted negative.

Because of the deterioration of respiratory symptoms, he was hospitalized in November 2019. During the hospitalization he stopped prednisone, and performed a CT scan revealing a hypoexpansion of the left lung, without parenchymal thickening, no opacification defects of the pulmonary arteries and branches, no lymphadenomegaly, no effusions and regular hypopharyngeal structures. He underwent also electromyography that resulted unremarkable. He was discharged with oxygen therapy 5L/m only on exertion.

After the hospitalization, he performed an echocardiogram showing a left ventricle ejection fraction 55%, estimated pulmonary arterial systolic pressure (PASP) 50 mm Hg, tricuspid annular plane excursion (TAPSE) 21 mm and right ventricular hypertrophy.

After one month, the patient was rehospitalized because of further worsening of the respiratory symptoms. A chest CT was performed at admission, showing a non-specific 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%, FEV1 34%, FEV1/FVC ratio 98%, TLC 44%, diffusing capacity of the lungs for carbon monoxide diffusion capacity, DLCO: not detectable). An echocardiogram showed severe pulmonary hypertension (PH) with an estimated PASP of 70 mm Hg. He was therefore treated with methylprednisolone (1 mg/kg) 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 gasses improvement was obtained with steroids only. In the suspicion of an idiopathic fibrotic ILD, the patient was discharged with prednisone (25 mg/day) and referred to the lung transplant center.

In March 2021 the patient was hospitalized due to a further deterioration of the 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/kg) and discharged with a medium-high dose of steroids until the next visit to the transplant center.

The disease continued to progress despite prolonged high dose steroids and the patient became not dischargeable from the hospital due to elevated oxygen requirement at rest. Therefore, he was eventually listed and transplanted in May and June 2021, respectively. Before the lung transplant, he underwent a right heart catheterization that did not confirm the values suggested by the previous echocardiograms (estimated PASP 88 mm Hg) but showed pre-capillary pulmonary hypertension (mean pulmonary arterial pressure 24 mm Hg, pulmonary artery wedge pressure 7 mm Hg, pulmonary vascular resistance 3.24 WU). Testing for telomere-related genes mutation was also performed and resulted 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 the transplant, the explant underwent a pathologic examination showing 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 36000 births [2]. Germline mutation of the VHL gene, which is located in human chromosome 3p25 [3], predisposes individuals to various benign or malignant tumors and cysts in many organs [4].

In a microarray study, Pardo and colleagues showed that lungs of idiopathic pulmonary fibrosis patients expressed higher levels of VHL protein (pVHL) mRNA than lungs of control individuals [5]. 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 $\alpha 5$ 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 TGF- $\beta 1$, a potent pro-fibrotic cytokine. These results suggest that elevated expression of pVHL results in the aberrant fibronectin expression and activation of integrin/FAK signaling, 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, radiologic, and pathologic 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 relation between the VHL and the fibrotic NSIP pattern can be suggested. Furthermore, our observation is supported by the human and animal models suggesting that over-expression of pVHL acts as a fibrogenic trigger in the lungs.

When considering fibrosis in other organs, such as liver or kidney, pVHL and 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 tumor suppressor VHL gene acts as a gatekeeper of renal tubular growth control. Knockout of VHL gene in the mouse tubular apparatus enables hypoxia-inducible transcription factor (HIF)-2 α expression [10]. Continuous transgenic expression of HIF-2 α 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 utilization of diagnostic tests, to diagnose a fibrotic ILD in an early phase.

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Figure 1. Radiological progression of fibrotic ILD between 2018 and 2021

Footnotes: Axial High Resolution CT scans at the level of apices, (A1; B1; C1; D1), carina (A2; B2; C2; D2) and atria (A3; B3; C3; D3).

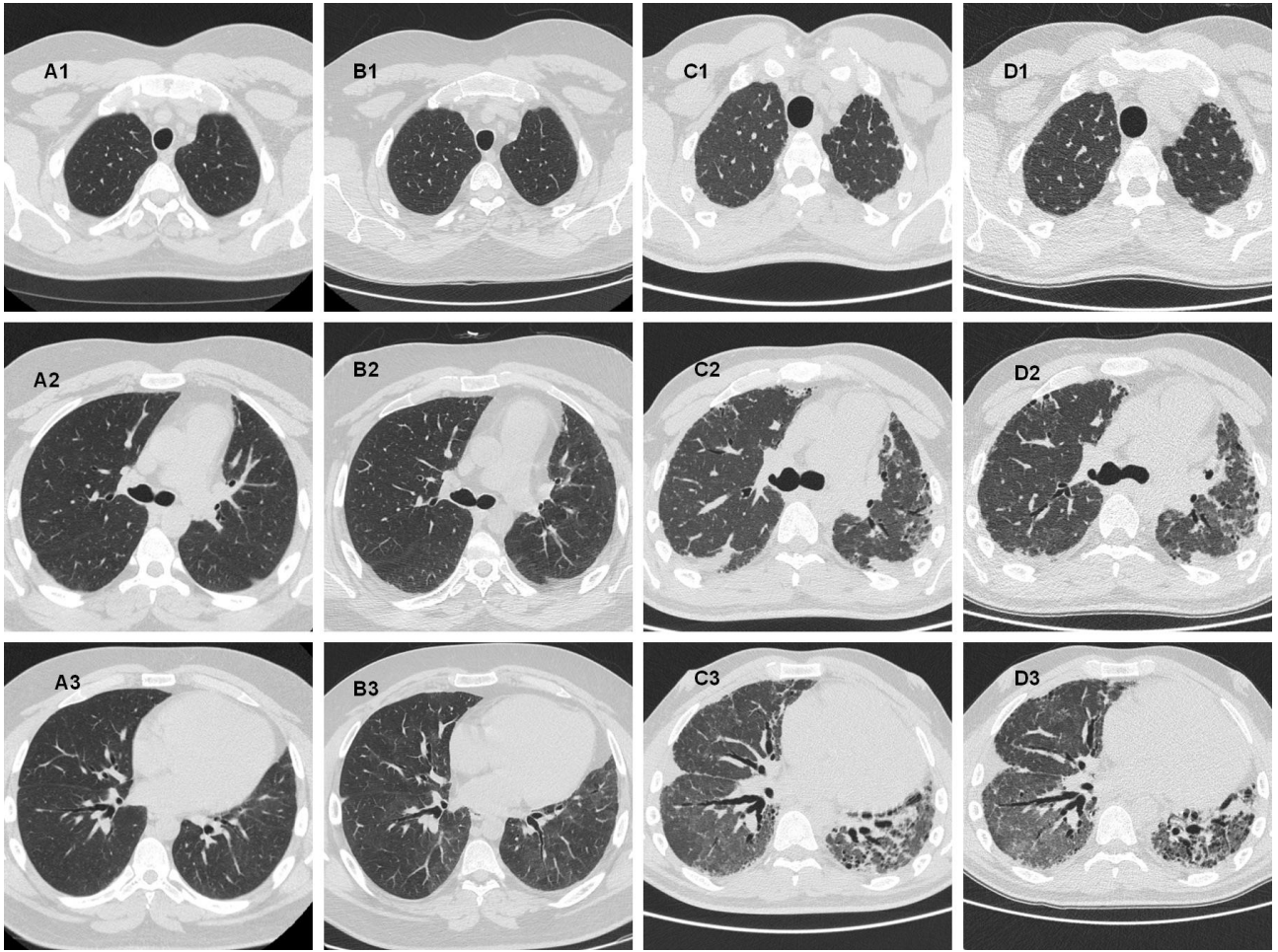


Figure 1