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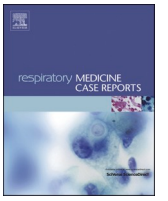

Case Report

Usual interstitial pneumopathy in a patient with hypersensitivity pneumonitis and microscopic polyangiitis. Case report

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ABSTRACT

One of the most frequent diffuse interstitial lung diseases is hypersensitivity pneumonitis. It is related to exposure to diverse antigens, causing fibrosis in advanced stages, making the differential diagnosis with interstitial pulmonary fibrosis difficult as it overlaps with the usual interstitial pneumonia pattern. On the other hand, there are interstitial lung diseases associated with ANCA, such as microscopic polyangiitis, which is also related to the usual interstitial pneumonia pattern. We present the case of a 74-year-old male patient with chronic dyspnea, history of smoking and exposure to organic particles, in addition to a pattern suggestive of moderately severe restriction. The diagnosis was confirmed by histology of hypersensitivity pneumonitis by presenting granules, however, anti MPO and p-ANCA positivity was found, integrating the simultaneous diagnosis of microscopic polyangiitis. This is a case of difficult diagnosis since these pathologies have not been previously reported to coexist.

1. Introduction

Interstitial Lung Disease (ILD) are a diagnostic challenge due to their multifactorial etiology and not being mutually exclusive. One of the most frequent ILD is Hypersensitivity Pneumonitis (HP), triggered by exposure to antigens causing T-cell hyperactivation and bronchioloalveolar inflammation. Centrilobular nodules, ground-glass opacities, air trapping, and mosaic perfusion characterize Computed Axial Tomography (CAT) of inflammatory or cellular HP. The "tri-density pattern," which combines areas of ground-glass opacification, lobar areas of low attenuation, and normal lung, has a specificity of 93 % for the diagnosis of inflammatory HP. Otherwise, the coexistence of pulmonary fibrosis and inflammation with signs of bronchiolar obstruction is highly suggestive. The honeycomb pattern and traction bronchiectasis are associated with severe cases [1]. On the other hand, histopathological non-fibrotic HP is characterized by bronchiolocentric cellular interstitial pneumonia and cellular bronchiolitis with a predominantly inflammatory infiltrate of lymphocytes, poorly formed granulomas, and multinucleated giant cells. Fibrotic HP may overlap with a tomographic pattern of usual interstitial pneumopathy (UIP), making differential diagnosis with idiopathic pulmonary fibrosis (IPF) difficult [1].

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Recently, ILDs associated with Antineutrophil Cytoplasmic Antibodies (ANCA) have been given importance due to their poor prognosis [2].

Vasculitis is characterized by causing multisystemic diseases with pulmonary involvement, such as microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA), with an incidence of 15-16, 1.9–13 and 0.8–4 per million person-year, respectively [3]. It mainly affects patients older than 65 years and presents with progressive dyspnea (50–73 %), non-productive cough (21–60 %), alveolar hemorrhage, and hemoptysis (5 %) [2,5]. In addition, involvement of the skin (8–31 %), peripheral nervous system (8–53 %), kidney (57–100 %), joints, and muscles (23–31 %) has been described [5]. Because it is related to the infiltration of inflammatory cells, lymphoid follicles with germinal centers, and cellular bronchiolitis, mortality is higher, reaching 61.1 % at five years [1,4]. UIP is observed in 50–78 %, while up to 58 % have nonspecific interstitial pneumopathy (NSIP) and desquamative interstitial pneumopathy (14 %) [1,4]. The therapeutic approach includes anti-inflammatory agents such as corticosteroids, cyclophosphamide, rituximab, mycophenolate, and azathioprine [3]. Patients who benefit from biologic therapy have fibrosis extension more significant than 10 % on CAT, with clinical signs of progression despite treatment [6,7]. Thus, in this work, we present a case report from a patient in whom histopathology showed the presence of granulomas, integrating the diagnosis of hypersensitivity pneumonitis. However, p-ANCA and positive MPO were found in the approach, which resulted in a diagnostic and therapeutic challenge.

2. Case

A 74-year-old male patient came for evaluation due to chronic dyspnea of 10 years of evolution; he has a history of smoking with a rate of 20 pack/year, suspended 30 years ago, in addition to exposure to organic particles and work with poultry for five years, as well as recurrent lower respiratory tract infections (Fig. 1). DIPD approach was performed with spirometry, reporting: exhaled volume in the first second (FEV1) 55 %, FVC 52 %, FEV1/FVC 0.82, concluding a pattern suggestive of moderately severe restriction. An extended panel of antibodies was performed, which included: P-ANCA 1:640 (positive), C-ANCA (negative), anti-protease 3 (PR3) antibodies 16 AU/mL (negative), anti-myeloperoxidase (MPO) antibodies 1203 AU/mL (positive), anti-glomerular basement membrane antibodies 10 AU/mL (negative), rheumatoid factor 8.6 (negative) and anti-CCP 60.5 (positive). Thorax tomography reported areas of cysts with predominantly subpleural and lower lobe penalization, inflammatory mediastinal adenopathy, pulmonary flow cephalization, traction bronchiectasis predominantly in the lower lobes, and diffuse interlobular septal thickening (Fig. 2). Also, echocardiogram was performed and showed left ventricular ejection fraction (LVEF) 54 %, pulmonary systolic pressure 25 mmHg, right ventricle without dilatation or alteration in its mobility, normal tricuspid annular systolic excursion, tricuspid regurgitation index of 3.1 m/s, estimated pulmonary artery systolic pressure of 55 mmHg and mean pulmonary artery pressure of 36 mmHg. Subsequently, an open lung biopsy was requested, and a diagnosis of “acute and chronic extrinsic allergic alveolitis” was made (Fig. 3), initiating treatment with mycophenolate mofetil, deflazacort, budesonide-formoterol, and supplemental oxygen. Therapeutic administration of an antifibrotic Nintedanib started in order to reduce the accelerated loss of lung function and quality of life.

3. Discussion

The diagnosis of hypersensitivity pneumonitis is initially suspected by characteristics in the pattern observed in the CAT, in

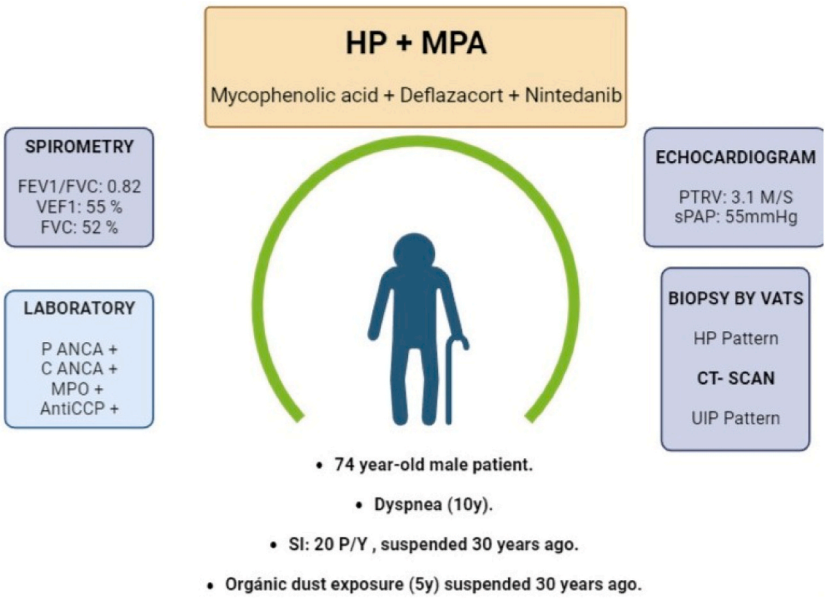

Fig. 1. Graphical description of the clinical case presented in this study.

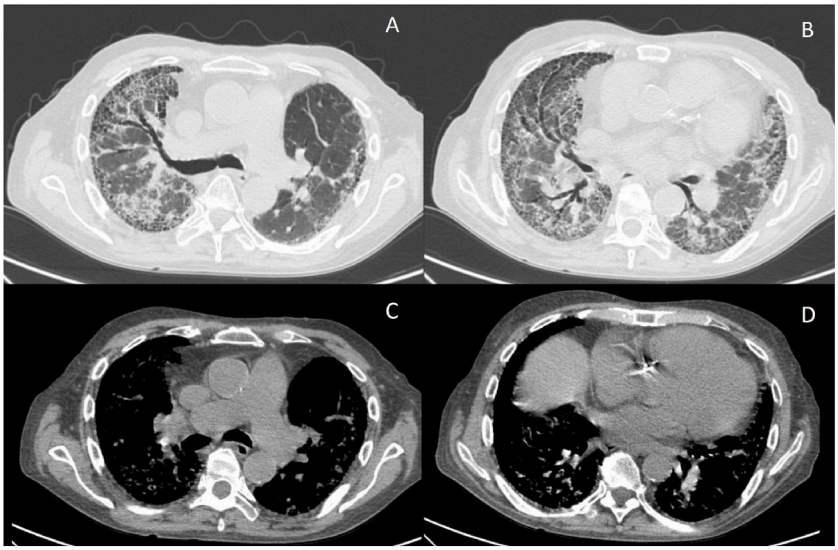

Fig. 2. Chest magnetic resonance imaging of the patient presented in this case. Areas of groundglass pattern in the bilateral axial interstitium were observed. There were also several subpleural cyst mainly in the lower lobes associated with traction bronchiectasis.

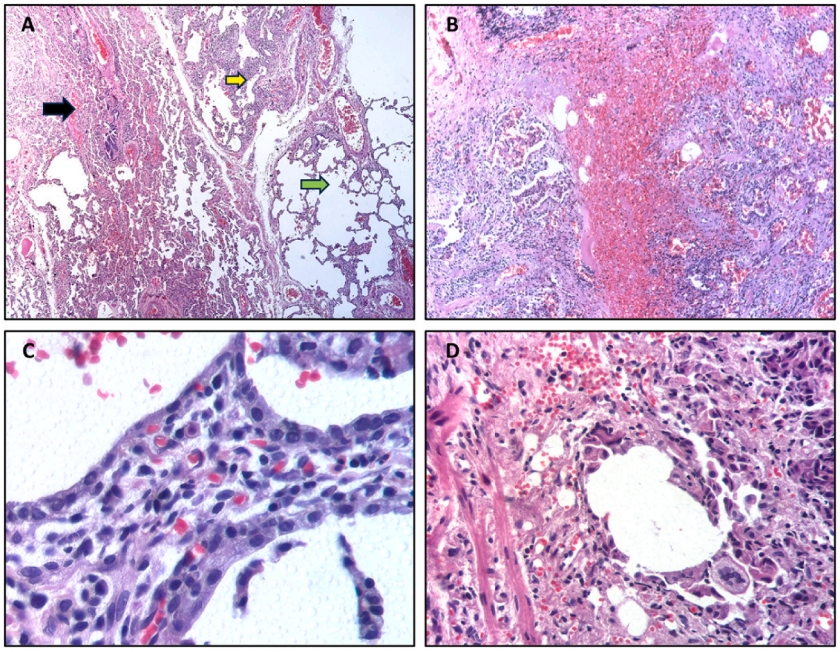

Fig. 3. Lung biopsy was processed and stained with H&E technique. (A) 4X. The lung parenchyma shows different patterns of damage, as shown by thickened alveolar septum (Yellow Arrow). Also, some alveolar spaces are dilated and damaged (Green Arrow). Additionally, peribronchial inflammation is present (Black Arrow). (B) 10X. The lung parenchyma is infiltrated with erythrocytes and leukocytes. (C) 40X. Interstitial inflammation infiltrated includes lymphocytes, plasma cells, neutrophils, and fibroblast. (D) 40X. Finally, In the interstitium layer and the air spaces, multinuclear cells can also be seen. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.

addition to risk factors such as exposure to antigens and compatible biopsy when acute and chronic extrinsic allergic alveolitis is reported [6]. HP is an immunologic pathology secondary to exposure to allergens acquired in the environment or occupationally, mainly in previously sensitized susceptible patients. Although it is a pathology frequently diagnosed in the fourth decade of life, it can present at any age, as in the present case, in which symptoms began in the seventh decade. It has been described that up to 50 % of patients start with chronic respiratory symptoms causing pulmonary fibrosis, which progressively causes a decrease in lung function.

Characteristically, patients with hypersensitivity pneumonitis and fibrosis show NSIP or UIP pattern, in addition to poorly formed non-necrotizing granulomas and multinucleated giant cells and fibrotic bronchiolocentric accentuation on biopsy [5]. The patient

presented multiple granulomas, so hypersensitivity pneumonia was initially suspected; however, the CT scan was consistent with UIP, leading to the search for differential diagnoses such as vascular diseases, drug toxicity, asbestosis, and IPF. Among the histological signs suggestive of underlying connective tissue disease, conclusive with vasculitis, are lymphocytic cellular interstitial infiltrate, plasma cells, cellular bronchiolitis, centrilobular fibrosis, pleuritis, and coexistence of one or more patterns in the same biopsy, without finding interstitial or peribronchial granulomas, findings not detected in the patient by histopathology [8]. However, the presence of MPO (observed in 60 % of MPA, with a sensitivity of 73 % and specificity of 97 %) resulted in a diagnostic challenge for the multidisciplinary team [3,9] since these are pathologies that have not previously been reported to coexist.

In addition, elevated anti-citrullinated antibodies (anti-CCP) related to rheumatoid arthritis were identified; although, the patient did not present clinical data suggesting it. An incidence of anti-CCP seropositivity of up to 4.07 % has been described in patients aged 65–74 years, related to hypoalbuminemia (CI 2.72–15.34, $p < 0.001$), glomerular filtration rate (GFR) less than 60 mL/min/m2 and inflammatory state (CI 1.013–1.053, $p < 0.01$), being then considered as an epiphenomenon, as is the case of our patient [10].

From the clinical criteria of vasculitis, the patient presented pulmonary involvement and acute kidney injury, reaching a GFR of 58ml/min/m^2, which has improved with the elevation of mycophenolate mofetil dose, with a current GFR of 98ml/min/m^2. The patient presented compromised pulmonary function, which could be associated with both entities, so it was concluded with an underlying diagnosis of HP plus MPA. On the one hand, the DIDP itself induces the production of MPO-ANCA, explaining the appearance of ANCA after the onset of DIDP [5]. The patient has a history of smoking, which stimulates MPO expression in epithelial cells due to smoking toxicity and chronic ischemia of the lung parenchyma. At the same time, pro-inflammatory cytokines can trigger an autoimmune response against the expressed MPO [2,5]. The patient is suspected to be predisposed, so the production of MPO-ANCA gave rise to ANCA vasculitis [5]. Pulmonary fibrosis may result from iterative episodes of intra-alveolar hemorrhages that the patient presented. The presence of MPO-ANCA has been directly associated with pulmonary fibrosis, due to the production of oxidant products that trigger fibroblast proliferation, in addition to releasing proteolytic enzymes, injuring lung tissue [2].

This patient started with dyspnea, frequent infections, and pulmonary involvement at the age of 60 years. He had initially been treated with deflazacort and mycophenolate mofetil when the diagnosis of HP was confirmed by biopsy with a report of acute and chronic extrinsic allergic alveolitis. Due to pulmonary progression, the dose of mycophenolate mofetil was increased, achieving normalization of renal function by quantifying GFR of 98 ml/min/m^2; however, tomographic changes due to pulmonary fibrosis were observed, as well as images suggestive of bronchiectasis and traction bronchiectasis. The patient has had a rapidly progressive decrease in pulmonary function due to the degree of pulmonary fibrosis, so treatment with nintedanib will be initiated [7].

Ethics approval statement and patient consent statement

An informed consent was shown and accepted by the patient participating in this case report.

Data availability statement

The data used to support the findings of this study are available from the corresponding author upon request.

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CRediT authorship contribution statement

Ana Gabriela Pérez-Romero: Methodology. **Ulices Alejandro Barajas-Hernández:** Investigation. **Felipe de Jesús Contreras-Rodríguez:** Methodology. **Alfredo Salazar de Santiago:** Writing – original draft, Writing – review & editing. **Dulce M de Jesús Macìas-Díaz:** Methodology. **Juan Manuel Diaz:** Writing – original draft, Writing – review & editing. **Silvia Denise Ponce-Campos:** Investigation, Methodology, Supervision.

Declaration of competing interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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