

Interstitial Lung Disease in Primary Biliary Cholangitis

Enfermedad pulmonar intersticial en colangitis biliar primaria

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ABSTRACT

During the course of PBC, interstitial lung involvement may develop: organizing pneumonia, interstitial fibrosis, lymphoid interstitial pneumonia, or non-specific interstitial pneumonia. Although the diagnosis of PBC usually precedes pulmonary manifestations, the opposite can occur. The frequency of interstitial disease in patients with PBC is not exactly known. It may or may not be associated with other connective tissue diseases; therefore, it is necessary to carry out a systematic search of these diseases and the pulmonary manifestations of this entity. We present the case of a patient with a previous diagnosis of PBC, who developed interstitial lung involvement during the course of the disease.

Key words: Primary biliary cholangitis; Interstitial lung disease; Crazy paving.

RESUMEN

Durante el transcurso de la colangitis biliar primaria se puede desarrollar compromiso intersticial pulmonar: neumonía organizada, fibrosis intersticial, neumonía intersticial linfocítica, neumonía intersticial no específica. A pesar de que el diagnóstico de colangitis biliar primaria usualmente precede a las manifestaciones pulmonares, puede ocurrir lo inverso. La frecuencia de enfermedad intersticial en pacientes con colangitis biliar primaria no es conocida con exactitud. Puede estar o no asociada a otras enfermedades del tejido conectivo; por lo tanto, es necesario realizar una búsqueda sistemática de estas y de las manifestaciones pulmonares de dicha entidad. Presentamos el caso de una paciente con diagnóstico previo de colangitis biliar primaria, la cual desarrolla durante el curso de su enfermedad, afectación pulmonar intersticial.

Palabras clave: Colangitis biliar primaria; Enfermedad pulmonar intersticial; Crazy paving

INTRODUCTION

Primary biliary cholangitis (PBC) is an autoimmune, chronic, progressive disease of unknown etiology. It predominantly affects middle-aged women and is characterized by cholestasis caused by diffuse inflammation, destruction and fibrosis of intrahepatic bile ducts, ultimately leading to

cirrhosis, portal hypertension, and hepatic failure.¹

The diagnosis of PBC must meet at least two of the following three criteria: 1) Chronic cholestasis with elevated serum alkaline phosphatase and/or gamma-glutamyl transpeptidase; 2) Presence of anti-mitochondrial antibodies (AMA); and 3) Hepatic histopathological characteristics indicative of PBC.²

Autoimmune diseases can be observed in up to 84% of patients, with 41% having more than one concomitant associated autoimmune condition.^{3,4}

PBC can also involve the impairment of other organs, including the respiratory system.

There is limited literature regarding the pulmonary manifestations that can occur in patients with PBC, and it is often challenging to distinguish lung involvement solely due to PBC from that associated with another connective tissue disease. This is the reason why the exact frequency of interstitial lung disease (ILD) is unknown.

Throughout the course of PBC, several types of interstitial involvement can develop, including organized pneumonia, interstitial fibrosis, lymphoid interstitial pneumonia, non-specific interstitial pneumonia, and granulomatous disease. These entities have been described in different studies. Alveolar hemorrhage, airway obstruction, pulmonary hypertension, and pleural effusion can also be observed, though less frequently.³ Despite the fact that the diagnosis of PBC usually precedes pulmonary manifestations, the opposite can occur.⁵

We present the case of a patient with a previous diagnosis of PBC, who developed interstitial lung involvement during the course of the disease.

CASE REPORT

A 50-year-old female patient with a history of smoking and diagnosed with PBC in 2017, along with portal hypertension and computed tomography showing initial signs of bibasal interstitial disease, presented with a 3-day history of abdominal distension and dyspnea.

Upon admission, the patient exhibited hypoxemia, signs of ascites, and bibasal crackling sounds. Initial laboratory tests revealed thrombocytopenia, leukocytosis, elevated C-reactive protein, and normal NT-proBNP (N-terminal pro-brain natriuretic peptide) levels. The chest X-ray showed bilateral alveolar infiltrates. The ascitic fluid indicated predominantly mononuclear cellular content.

The patient began antibiotic therapy and treatment with diuretics, with a slow evolution of her condition. Subsequently, a chest CT scan was performed, revealing interstitial infiltrates with a bilateral crazy-paving pattern (Figure 1). Nasopharyngeal swabs for SARS-COV-2, mycoplasma, chlamydia, and influenza were all negative. The immunological profile showed a positive antinucle-

ar antibody (ANA) at a titer of 1/320, positive anticentromere antibody, positive anti-mitochondrial antibody, and elevated rheumatoid factor.

Systemic corticosteroid therapy was initiated, leading to significant improvement in oxygen levels. However, after 48 hours of noticeable clinical improvement, the patient experienced upper gastrointestinal bleeding and cardiac arrest. Despite resuscitation efforts, the patient did not respond and passed away.

DISCUSSION

PBC is an autoimmune liver disease characterized by the progressive destruction of intrahepatic bile ducts, leading to cholestasis and fibrosis, which can ultimately result in cirrhosis and hepatic failure.³

It predominantly affects women in their fourth to sixth decades of life. Anti-mitochondrial antibodies have high specificity and are present in 90-95% of patients.⁶

Extrahepatic manifestations occur in over 70% of cases, mainly due to the association with other autoimmune diseases such as Sjögren's syndrome (being the most commonly associated entity), hypo or hyperthyroidism, systemic sclerosis, rheumatoid arthritis, and lupus.⁷

In a prospective study by Min Shen et al, which included 178 PBC patients from a Beijing hospital between 2001 and 2007, it was observed that 84.4% of patients had an association with other connective tissue diseases.⁸

There isn't much data in the literature regarding the prevalence of interstitial lung disease in patients with PBC, but it is estimated to affect around 15% of the cases.⁹

In 1970, Mason et al published the first report of interstitial lung disease in the course of PBC.¹⁰

In a retrospective study by Chen et al, which included 136 patients with an average follow-up of 8.76 years from 1999 to 2014, they found that 11% of the cases had ILD.⁶

In a study by Wang et al, involving a cohort of 332 patients in China, it was revealed that 46.6% had one or more associated autoimmune diseases. The most frequent was Sjögren's syndrome (121 cases, 36.2%). There were 9 cases of systemic sclerosis (2.8%), 12 cases of systemic lupus erythematosus (3.7%), 9 cases of rheumatoid arthritis (2.8%), and 10 cases of polymyositis (3.1%). When compared to patients with PBC alone, those with

associated Sjögren's syndrome or systemic sclerosis had a higher frequency of ILD.¹¹

In the study by Min Shen et al, where patients with conditions that could confound the diagnosis of ILD were excluded, they found that 15% of patients had interstitial lung disease. While in most cases there was an association with another connective tissue disease (mainly Sjögren's syndrome), 42.8% of the patients didn't show any association with another condition. The risk factors that are mostly associated with the development of ILD were: having an associated autoimmune disease and the Raynaud's phenomenon.⁸

The most commonly observed CT patterns in associated ILD during the course of PBC include reticular opacities (39%), patchy opacities (25%), nodular opacities (25%), ground-glass infiltrates (18%), interlobular septal thickening (18%), and honeycombing (11%).⁹

It was believed that the histological variant of fibrosis associated with PBC was similar to usual interstitial pneumonia.¹²⁻¹⁴ Several reports describe that interstitial fibrosis, lymphoid interstitial pneumonia (LIP), and organizing pneumonia are the most frequent patterns in PBC. LIP can be associated with both PBC and Sjögren's syndrome. In a study by Sheng et al, lung biopsies were performed on 5 patients with ILD, revealing interstitial infiltrates predominantly composed of lymphocytes, suggestive of LIP, in 3 patients. The other 2 biopsies were compatible with interstitial fibrosis, vascular hyperplasia, and thickened vascular walls.⁸ Organizing pneumonia can be a manifestation of PBC, especially in patients with an associated connective tissue disorder.¹⁵ Davison and Epstein reported a case of recurrent organizing pneumonia in a patient with PBC, CREST syndrome, and chronic pancreatitis.¹⁶ However, it can also occur in isolated cases of PBC. Almonte Batista et al reported a case of a patient with PBC and organizing pneumonia, without evidence of associated underlying connective tissue disorder.¹⁷

Among the differential diagnoses for the crazy-paving pattern, the following should be considered: cardiogenic or non-cardiogenic pulmonary edema, pneumonia (viral, bacterial, or fungal - such as PCP [pneumocystis carinii pneumonia]), alveolar hemorrhage, adult respiratory distress syndrome (ARDS), vasculitis, and alveolar proteinosis, among others. For proper characterization and distinction, it's important to separate acute causes

from subacute or chronic ones. Similarly, the etiology can be categorized based on infectious origins (pneumonia), oncological causes, idiopathic factors (organizing pneumonia, proteinosis, sarcoidosis, NSIP [non-specific interstitial pneumonia]), inhalation-related factors (hypersensitivity pneumonitis, lipid pneumonia), or blood-related factors (ARDS, alveolar hemorrhage syndromes).¹⁸⁻¹⁹

Information about the treatment of ILD in the course of PBC is very limited. The response to agents like corticosteroids and other immunosuppressants can be favorable. However, the recurrence rate is high, and unfortunately, corticosteroid therapy doesn't halt the progression of the liver disease.⁹

CONCLUSION

The frequency of interstitial disease in patients with PBC is not exactly known. It may or may not be associated with other connective tissue diseases; therefore, it is necessary to carry out a systematic search of these diseases and the pulmonary manifestations of this entity.

In our patient, no clinical or laboratory evidence of associated connective tissue disease or other differential diagnoses with that CT pattern were found. Therefore, initially, the ILD manifesting as a crazy-paving pattern corresponds to a pulmonary manifestation specific to PBC.

Conflict of interest

Authors have no conflicts of interest to declare.

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