Pulmonary Manifestations among Patients with Primary Biliary Cirrhosis

Deniz Koksal*1, Aydin Seref Koksal2,3 and Ahmet Gurakar3

1Department of Chest Diseases, Hacettepe University School of Medicine, Ankara, Turkey; 2Department of Gastroenterology, Sakarya University School of Medicine, Sakarya, Turkey; 3Division of Gastroenterology and Hepatology, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland, USA

Abstract

Primary biliary cirrhosis (PBC) is a chronic progressive cholestatic liver disease caused by diffuse inflammation, destruction and fibrosis of the intrahepatic bile ducts, ultimately leading to cirrhosis, portal hypertension and liver failure. The pathogenesis of PBC is incompletely understood, but current data suggest roles for genetic susceptibility and environmental factors. PBC is often thought of as an organ-specific autoimmune disease, which mainly targets the liver; however, lung tissue is also a site for autoimmune involvement of PBC. The pulmonary manifestations of PBC include abnormalities in gas transfer and pulmonary function, subclinical alveolitis, interstitial lung disease, granulomatous lung disease, airway disease, pulmonary hypertension, pulmonary hemorrhage and pleural effusion.

Introduction

Primary biliary cirrhosis (PBC) is a chronic progressive cholestatic liver disease caused by diffuse inflammation, destruction and fibrosis of intrahepatic bile ducts, ultimately leading to cirrhosis, portal hypertension and liver failure. The typical patient is a middle-aged woman, presenting with fatigue and itching or asymptomatic with an unexplained elevation in alkaline phosphatase level.1,2 Anti-mitochondrial antibodies (AMAs) are detected in more than 95% of the patients and are considered as a diagnostic hallmark of PBC.

The pathogenesis of PBC is incompletely understood. Current data suggest that it is an autoimmune disease and involves genetic susceptibility and environmental factors.3,4

It is more common in individuals with a family history of PBC and often associated with other autoimmune diseases. Autoimmune diseases can be seen in up to 84% of PBC patients, with 41% having more than one concomitant autoimmune disease.5,6 In a recent population-based cohort study, among 322 Chinese patients with PBC, 46.6% had one or more connective tissue diseases (CTDs). The most common CTD was Sjögren’s syndrome (36.2%), followed by systemic lupus erythematosus (3.7%), polymyositis (3.1%), progressive systemic sclerosis (2.8%) and rheumatoid arthritis (2.8%).7

PBC is often thought of as an organ-specific autoimmune disease, which mainly targets the liver. However, lung tissue is also a possible site for autoimmune involvement of PBC and there is accumulating evidence indicating that PBC may involve multiple systems, including the pulmonary system.8 Therefore, physicians should be aware of potential pulmonary manifestations. Although the diagnosis of liver disease usually precedes pulmonary manifestations, the reverse can also occur.9 Sometimes, concomitant autoimmune diseases, which may be a contributor or primary etiology of a clinically apparent pulmonary disease, makes it difficult to discriminate PBC-associated lung involvement and other autoimmune diseases.10

The aim of this manuscript is to review pulmonary manifestations of PBC (Table 1). The pulmonary manifestations of PBC include abnormalities in gas transfer and pulmonary function, subclinical alveolitis, interstitial lung disease, granulomatous lung disease, airway disease, pulmonary hypertension, pulmonary hemorrhage and pleural effusion. Despite the main target of pulmonary involvement being the pulmonary parenchyma, the airways, pulmonary vasculature and pleura are also affected rarely. In the current literature, there is not much data about the pulmonary manifestations that occur among patients with PBC. Most of the literature has included small case series, case reports and scarce postmortem studies. Apart from this, it is difficult to discriminate sole pulmonary involvement of PBC from associated clinical conditions such as CTD-associated interstitial lung disease or portal hypertension related pulmonary hypertension. For these reasons, the frequency of pulmonary involvement in PBC is not known exactly.

Gas transfer and pulmonary function abnormalities

Gas transfer abnormalities can be investigated by measuring diffusing capacity for carbon monoxide. Subclinical lung impairment, mostly represented by a reduced diffusion of
alveolar gasses, is a recognized complication of PBC.\(^{11,12}\) Rodriguez-Roisin et al.\(^{13}\) were the first to study lung function tests in patients with PBC. They compared 4 subgroups, all of which were non-smokers matched by age, sex, height and socioeconomic status. The groups included 7 sole PBC patients, 7 concurrent PBC and SS patients, 7 sole sicca complex patients, and 14 healthy controls. There was no significant difference in the mean pulmonary function test values, but the mean diffusion capacity for carbon monoxide was significantly reduced in those PBC patients with concurrent PBC and SS or with sole sicca complex. The authors concluded that the respiratory, clinical and functional abnormalities found in PBC were related to the presence of an associated SS.\(^ {13}\) Later on, Uddenfeldt et al.\(^{14}\) investigated lung function abnormalities in a small number of patients with PBC (n=25) and in age- and sex-matched healthy controls (n=17). The PBC group was divided into two groups: symptomatic (n=18) and asymptomatic (n=7). The prevalence of lung function impairment was 56%. Almost all abnormal lung function data were found in the symptomatic (i.e. pruritis, xanthoma, xanthelasmata, jaundice, hyperpigmentation, hepatosplenomegaly) patients. In the symptomatic PBC patients, there was a mean reduction in diffusion capacity and an elevated residual volume suggestive of hyperinflation, compared to the control group of patients. The authors suggested that PBC might be associated with a distal airway obstruction. However, they did not control the groups for smoking history or consider the presence of hepatoportal syndrome, which can cause a reduced diffusion in symptomatic, advanced PBC patients.\(^ {14}\) Krowka et al.\(^ {11}\) investigated the relationship between hepatic and pulmonary functions in never-smoked patients with PBC. They studied 67 patients, of who 20 were transplant candidates, and determined a significant relationship between the histological stage, disease severity of PBC and the steady-state diffusion capacity. Progressive deterioration of diffusion capacity was found to be associated with increasing severity of PBC. There was no relationship found between pulmonary function and the presence of sicca complex, SS or the clinical manifestations of portal hypertension.\(^ {11}\) In another study that included 61 patients with different stages of PBC, the diffusion capacity was reduced in 24 (39%) of the patients. There was no significant relationship between diffusion capacity, advancement of liver disease and concomitant SS. However, reduced diffusion capacity showed a significant correlation with the presence of complete or incomplete scleroderma (also known as CREST syndrome, standing for calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) and with the presence of circulating anti-centromere antibodies.\(^ {12}\)

### Subclinical alveolitis

PBC is characterized by continued assault of T lymphocyte-mediated attack on the small intralobular bile ducts, eventually leading to their gradual destruction.\(^ {1,2}\) It is suggested that lymphocytic infiltration of PBC may not be limited to the liver but may also involve the lungs.\(^ {15}\) In a study aiming to determine whether subclinical inflammatory alveolitis is associated with PBC, the authors compared the number and types of cells in bronchoalveolar lavage (BAL) fluid from patients with PBC, patients with alcoholic cirrhosis, and healthy controls. They found a subclinical alveolar inflammation comprised of T lymphocytes, mainly of the CD4 type, and activated alveolar macrophages in a high proportion of patients with PBC.\(^ {16}\) One of the limitations of that study was the concomitant presence of SS in 7 out of 12 patients with PBC. Since it has been reported that up to 44% of patients with SS have subclinical alveolitis, it was difficult to discriminate the exact etiology.\(^ {17}\) Spiteri et al.\(^ {18}\) also studied BAL-derived cellular inflammatory patterns among patients with sarcoidosis, patients with PBC but without clinical lung involvement, and healthy controls. All patients with pulmonary sarcoidosis had lymphocytic alveolitis, with a proportion of 29.2%. Six out of 10 patients with PBC showed evidence of alveolitis, with an elevated lymphocyte count of 27.6%. Upon comparison of the patients with PBC and sarcoidosis, an overlap was found in the CD4/CD8 lymphocyte ratio predominance (4.13 vs. 5.6). The authors realized that, despite normal findings from physical examination and chest x-ray, 5 of 6 patients with alveolitis on BAL had an evidence of interstitial lung disease on subsequent computed tomography of the thorax.\(^ {18}\)

### Interstitial lung disease (ILD)

PBC has been reported as associated with various ILDs, such as pulmonary fibrosis, lymphoid interstitial pneumonia (LIP), non-specific interstitial pneumonia (NSIP) and bronchiolitis obliterans with organizing pneumonia (BOOP).\(^ {10,19}\) Concomitant SS increases the risk of ILD in patients with PBC.\(^ {20}\) In a study composed of 109 consecutive PBC cases, concomitant SS was seen in 46 patients (42.2%). While the frequency of ILD was 21.7% in PBC patients with SS, it was only 1.6% in those without SS.\(^ {21}\)

The findings of both radiographic interstitial pattern and restrictive ventilatory impairment with gas transfer defects in some of the patients with chronic active hepatitis and PBC has led some authors to suggest an association of pulmonary fibrosis with chronic liver disease.\(^ {22–24}\) Although the prevalence of pulmonary fibrosis was poorly defined, one review estimated it to be less than 5%.\(^ {25}\) One of the reasons for this uncertainty could be the presence of concomitant CTDs, which would cloud the assumption of sole PBC attributable pulmonary fibrosis.\(^ {10}\) In a necropsy series of 120 patients with PBC, none of the cases demonstrated pulmonary fibrosis findings.\(^ {26}\) Golding et al.\(^ {24}\) reported that 9 (13%) out of 70 patients with

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**Table 1. Pulmonary manifestations of primary biliary cirrhosis**

| 1) Gas transfer abnormalities |
|-----------------------------|
| 2) Subclinical alveolitis    |
| 3) Interstitial lung disease |
| 4) Granulomatous lung disease |
| 5) Airway disease           |
| 6) Pulmonary hypertension    |
| 7) Pulmonary hemorrhage      |
| 8) Pleural effusion          |

- Pulmonary fibrosis
- Lymphoid interstitial pneumonia
- Nonspecific interstitial pneumonia
- Bronchiolitis obliterans with organizing pneumonia
- Pulmonary fibrosis
- Lymphoid interstitial pneumonia
- Nonspecific interstitial pneumonia
- Bronchiolitis obliterans with organizing pneumonia
PBC had both radiological and pulmonary functional changes suggestive of pulmonary fibrosis; however, only 2 of them had biopsy-proven pulmonary fibrosis. The histological variant of fibrosis in association with PBC was believed to be similar to usual interstitial pneumonitis. Shen et al. systematically addressed the development of ILD as a complication of PBC in a prospective study. The study included 178 consecutive PBC patients who were followed for 6 years. The incidence of ILD was 15.7% (n=28). Of the patients with ILD, 53.6% had pulmonary symptoms and 88.2% had diffusion and restrictive ventilation impairment on pulmonary function tests. Although 42.9% of the patients with ILD did not have any other CTD, presence of Raynaud phenomenon and association with other CTDs were the risk factors for PBC patients to develop ILD.

LIP is obviously associated with PBC and SS. Up to 25% of LIP cases occur in association with SS, and complete or incomplete SS can be noted in 84% of PBC patients. Shen et al. performed lung biopsies in 5 patients with ILD. Histopathologic investigations revealed interstitial infiltrations with mainly lymphocytes suggestive of LIP in 3 patients. The other 2 biopsies were compatible with interstitial fibrosis, vascular hyperplasia and thickened vascular walls.

BOOP may be one of the non-hepatic complications of PBC, especially in patients associated with other CTDs. Davison and Epstein reported a case of relapsing organizing pneumonia in a man with PBC, CREST syndrome and chronic pancreatitis. BOOP can also manifest in isolated PBC cases. Chest radiographs show multiple, bilateral, peripherally distributed interstitial opacities. BOOP must be considered in the differential diagnosis of unresolved pneumonia in patients with PBC and respiratory symptoms. Strobel et al. reported an interesting case of PBC, for which the patient’s open lung biopsy revealed BOOP, LIP and destructive bronchiolitis. This dual histopathology was also reflected in a bimodal clinical phase and gave a viewpoint about the therapy. The first phase was probably BOOP characterized by dramatic response to corticosteroid treatment (within a 1-week period) and the second phase was probably LIP characterized by a slow normalization (over a 1-year period). All recognizable signs of lung disease slowly and completely resolved after addition of azathioprine to the therapeutic regimen.

Data about the management of pulmonary involvement in the course of PBC is very limited. Review of the literature revealed that patients experience a widely variable response to therapeutic agents such as steroids, cyclosporine and azathioprine. This heterogeneity might be due to different histopathological patterns that could not be clinically distinguishable. The case presented by Strobel et al. also supported this hypothesis.

**Granulomatous lung disease (GLD)**

Sarcoidosis is a granulomatous disorder of unknown etiology that characteristically involves any organ of the body, but mainly the lungs. Although sarcoidosis does not meet the criteria for an autoimmune disorder, it can coexist with a wide variety of autoimmune diseases. There is also an association reported between PBC and sarcoidosis. A number of patients have features of both diseases, raising the question of whether they are within the spectrum of one disease or are two distinct clinical disorders that may share an autoimmune pathogenesis with some overlapping symptoms. Kishor et al. reviewed 17 patients with sarcoidosis and PBC and suggested that a common pathway contributes to granuloma formation in both disorders. The prevalence of GLD related to PBC is not known, but it seems to be rare based upon case reports and case series. A large necropsy series of 120 PBC patients reported only 2 patients (1.6%) with widespread intrapulmonary granulomas without fibrosis; one of these patients had interstitial pattern on chest radiography and impaired gas transfer. Wallace et al. described 4 patients with PBC and concomitant SS, in whom symptomatic pulmonary involvement developed; three of these patients died of respiratory failure. The types of pulmonary involvement were interstitial fibrosis with accompanying vasculitis, which was thought to be a variant of idiopathic pulmonary fibrosis, lymphocytic bronchiolitis and GLD. GLD seems to be a steroid-responsive condition. Apart from steroids, other immunosuppressive drugs can also be used.

**Airway disease**

Airflow obstruction has occasionally been reported in patients with PBC. Mild airway obstruction was present in 4 patients with concomitant sicca syndrome in a series of 67 patients with PBC. Obstructive lung disease was also reported in a patient with PBC and SS, secondary to an autoimmune process documented by immunofluorescent staining of lung parenchyma. Lympohcytic bronchitis/bronchiolitis is a non-specific type of airway disease characterized by infiltration of the large and small airways by lymphocytes. It was also described in a patient with PBC, suggesting that lymphocytic bronchitis/bronchiolitis may be part of a generalized autoimmune process in PBC.

**Pulmonary hypertension**

Pulmonary vascular abnormalities have been noted in the course of PBC. There is a well-recognized association between portal hypertension of cirrhosis and an increased incidence of pulmonary hypertension. In patients with liver disease, portal hypertension plays an important role in the pathogenesis of pulmonary hypertension, namely porto-pulmonary hypertension. In a prospective study including 178 consecutive PBC patients with a follow-up of 6 years, the incidence of pulmonary hypertension was 11.8% (n=21). Among these patients, 4 had moderate to severe pulmonary hypertension, and 1 patient died of right heart failure, indicating a poor prognosis. Pulmonary hypertension was closely associated with portal hypertension and immunological dysregulation. It was noteworthy that more than 30% of the patients with pulmonary hypertension did not show any evidence of portal hypertension, suggesting that other mechanisms may also be involved in the pathogenesis of pulmonary hypertension in PBC patients. However, there are a few case reports with PBC-associated pulmonary hypertension concomitant with normal portal venous pressure. This rarity might be due to dismissal of primary pulmonary hypertension since most of the patients had associated portal hypertension due to liver disease.

**Pulmonary hemorrhage**

Diffuse alveolar hemorrhage associated with PBC has been reported in 2 case reports. However, in both cases, there are some conflicting data for an associating pulmonary hemorrhage directly to PBC itself. Bissuel et al. reported a
41-year-old woman presenting with life threatening intrapulmonary hemorrhages. The presence of antineutrophil cytoplasmic antibodies, focal segmental glomerulonephritis, and cutaneous leukocytoclastic vasculitis were all suggestive for the presence of a systemic vasculitis rather than PBC-associated alveolar hemorrhage. Komatsu et al. reported a patient with both PBC and Goodpasture syndrome. Postmortem examination of both lungs revealed diffuse hemorrhage probably due to pulmonary vasculitis related to the Goodpasture’s syndrome.48

**Pleural effusion**

Hepatic hydrothorax is defined as a pleural effusion in patients with cirrhosis, without a primary cardiac or pulmonary disease. The estimated prevalence of hepatic hydrothorax is about 5-10% in patients with cirrhosis.49,50 There are only a few case reports of PBC-associated hepatic hydrothorax.51,52 Other than hepatic hydrothorax, pleural effusion was described in a patient with LIP. Lymphocytic infiltration was shown in the thoracoscopic biopsy of the visceral pleura of the patient.53

**Conclusions**

In conclusion, PBC is a chronic progressive cholestatic liver disease caused by diffuse inflammation, destruction and fibrosis of intrahepatic bile ducts, ultimately leading to cirrhosis, portal hypertension and liver failure. The pathogenesis of PBC is incompletely understood. Current data suggest that it is an autoimmune disease involving genetic susceptibility and environmental factors. It is more common in individuals with a family history of PBC and often associated with other autoimmune diseases. PBC is often thought of as an organ-specific autoimmune disease, which mainly targets the liver. However, lung tissue is also a site for autoimmune involvement of PBC. The main target of pulmonary involvement is the pulmonary parenchyma, but the airways, pulmonary vasculature and the pleura can also be affected rarely. Currently, the frequency of pulmonary involvement in PBC is not known exactly and there is no data for the presence of autoantibodies to diagnose PBC-related pulmonary involvement.

**Conflict of interest**

None

**Author contributions**

Writing content and formatting the table in the manuscript (DK), drafting sections of the document (ASK), critical revision and administration during manuscript writing (AG).

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