

# Pulmonary involvement in primary biliary cirrhosis

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**ABSTRACT** The association of pulmonary fibrosis and primary biliary cirrhosis (PBC) remains controversial. To determine the frequency of pulmonary fibrosis in PBC, a carefully selected series of 14 PBC patients, seven patients with Sicca complex, and 14 control subjects have been studied. Seven of the 14 patients with PBC had Sjögren's syndrome, four of whom had some clinical evidence of pulmonary disease. Evaluation of ventilatory capacity, gas transfer factor, arterial blood gases, and lung mechanics were performed. Gas transfer was reduced in patients with PBC associated with Sjögren's syndrome and in patients with the Sicca complex. These results suggest that the respiratory, clinical, and functional abnormalities found in PBC are related to the presence of an associated Sjögren's syndrome.

The frequency and nature of pleuropulmonary manifestations in primary biliary cirrhosis (PBC) are poorly documented. The finding of both an interstitial pattern on chest radiographs and a restrictive ventilatory impairment with a gas transfer defect on routine lung function tests in some cases of chronic active hepatitis and PBC has led some authors to suggest that fibrosing alveolitis could be associated with chronic liver disease,<sup>1 2</sup> although others have been unable to find such an association.<sup>3 4</sup> Furthermore, PBC is frequently associated with Sjögren's syndrome, an entity in which the interpretation of lung disease remains difficult.<sup>5</sup> In the present study we have investigated to what extent PBC is associated with pulmonary signs, symptoms, radiological and functional abnormalities and have made comparisons with a healthy control population and with a group of patients affected by the so-called Sicca complex, a limited variant of Sjögren's syndrome.

## Methods

The following categories of patients, matched for sex, age, height, and socioeconomic status were studied: seven with PBC and Sjögren's syndrome, seven with PBC alone, seven with Sicca complex, and 14 normal subjects (table 1). All were non-smokers who gave no history of alcoholism, occupational

Table 1 *Physical data in groups investigated*

Category	Sex (F/M)	Age (years $\pm$ SD)	Height (cm $\pm$ SD)
Healthy control subjects (n=14)	13/1	46.9 $\pm$ 9.4	154.6 $\pm$ 4.1
Primary biliary cirrhosis (PBC) (overall series)	13/1	46.3 $\pm$ 10.3	154.9 $\pm$ 5.8
PBC without Sjögren's Syndrome (n=7)	7/0	42.9 $\pm$ 10.0	153.1 $\pm$ 3.4
PBC with Sjögren's Syndrome (n=7)	6/1	49.7 $\pm$ 10.0	156.5 $\pm$ 7.4
Sicca complex (n=7)	7/0	48.7 $\pm$ 7.1	152.4 $\pm$ 5.7

exposure to dusts known to cause lung damage, cardiopulmonary or autoimmune diseases, or previous medication with potentially fibrogenic drugs.

The diagnosis of PBC was based on clinical and morphological data. All patients had a serum alkaline phosphatase level higher than 300 mU/ml (normal <85 mU/ml) and a positive antimitochondrial antibody test. Eight of them had a serum bilirubin higher than 34  $\mu$ mol/l. According to the liver biopsy three were stage I, five stage II, five stage III, and one stage IV. The diagnosis of Sicca complex was accepted when both keratoconjunctivitis and xerostomia were present (table 2). The diagnosis of keratoconjunctivitis was based on the presence of clinical symptoms, an abnormal Schirmer's test (wetting of a paper strip 5 mm or less in 5 min) and Rose bengal ocular staining in the conjunctival sac.<sup>6</sup> Xerostomia was recognised by clinical history, by abnormal bilateral parotid gland scintigrams after

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Table 2 Investigation of keratoconjunctivitis and xerostomia

Cases	Lacrimal gland symptoms	Schirmer's test	Rose Bengal stain	Salivary glands symptoms	Parotid gland scintigram	Lip biopsy
<b>PBC without Sjögren's syndrome</b>						
1	-	-	-	-	-	ND
2	-	-	-	-	-	ND
3	-	-	+	-	-	ND
4	-	-	-	-	+	-
5	-	-	-	-	-	+
6	-	-	-	-	-	ND
7	-	-	-	-	-	ND
<b>PBC with Sjögren's syndrome</b>						
1	-	-	-	-	+	+
2	+	+	+	+	-	NR
3	+	-	-	+	-	+
4	+	+	-	+	ND	ND
5	+	+	+	-	-	+
6	+	+	+	-	-	+
7	-	+	+	+	+	+
<b>Sicca complex</b>						
1	+	-	+	+	+	+
2	+	-	+	+	+	+
3	+	+	+	+	+	ND
4	+	+	+	-	+	+
5	+	+	+	+	+	ND
6	+	-	+	+	+	+
7	+	-	+	+	-	+

ND=not done; NR=not reliable; (-)=absent; (+)=present.

intravenous administration of 4 mCu of  $^{99m}\text{Tc}$  pertechnetate,<sup>7</sup> and by abnormal lip biopsy.<sup>8</sup> The diagnosis of both keratoconjunctivitis and xerostomia required the presence of at least two of their respective diagnostic criteria. Sjögren's syndrome was considered to be present when keratoconjunctivitis or xerostomia or both occurred with PBC.<sup>5</sup> Control subjects were judged to be normal on the basis of negative histories of acute and/or chronic diseases, normal physical examination, and normal chest roentgenograms.

On the day of study each participant was submitted to a modified respiratory questionnaire<sup>9</sup> and was examined by two chest physicians. Posteroanterior chest radiographs were performed, and each examined and graded independently by five experienced observers according to the 1971 ILO-U/C standard classification.<sup>10</sup>

Lung function studies were performed as follows: (1) arterial  $\text{PaO}_2$  and  $\text{Paco}_2$  (72, Radiometer); (2) thoracic gas volume ( $V_{\text{Tg}}$ ) and airway resistance ( $R_{\text{aw}}$ ) using a constant-volume body plethysmograph (Body-Pneumotest, E Jaeger)<sup>11</sup>, the results being reported as specific airway conductance ( $sGaw$ ); (3) total lung capacity (TLC) and residual volume (RV) were calculated from  $V_{\text{Tg}}$ ; (4) single-breath transfer factor ( $TLCO$ ) (Resparameter MK-IV, Morgan) with correction for anaemia<sup>12</sup> and calculation of transfer coefficient ( $KCO$ ); (5) Forced vital capacity (FVC), forced expiratory volume in one second ( $FEV_1$ ), peak flow (PEF), forced mid-expiratory flow ( $\dot{V}_{25-75\%}$ ), forced end-expiratory flow ( $\dot{V}_{75-85\%}$ ), and

maximal flow rates at 50% and 75% of the FVC ( $\dot{V}_{50\%}$  and  $\dot{V}_{75\%}$ , respectively) (Fleisch pneumotachograph, HP 47304 A); (6) static expiratory compliance of the lung (Cstat) close to functional residual capacity was recorded using an oesophageal latex-balloon and a shutter interrupter (E Jaeger), according to the method of Milic Emili *et al.*<sup>13</sup>

The pulmonary function tests ( $sGaw$ ,  $V_{\text{Tg}}$ , DLCO, static lung volumes, and MEFV curves) were performed on two separate occasions in each control subject and on three occasions in the groups of patients. Arterial blood gases and Cstat (only reliable in 11 out of 14 cases) were measured on two separate occasions in patients with PBC. The data analysed for each participant were the average of two or three values. In each subject lung function studies and clinical and radiological examination were performed on the same day by separate observers and no results were revealed until the study was completed.

Statistical analysis of the results used one-way analysis of variance with a priori contrast, and with Pearson's lineal correlation coefficients.

Written informed consent was obtained from all subjects.

## Results

### CLINICAL AND RADIOLOGICAL FEATURES

The pulmonary clinical and radiological characteristics of the patients with PBC and of those with Sicca complex are summarised in table 3. Signs and

**Table 3** Prevalence of abnormal respiratory clinical and radiological features in patients with primary biliary cirrhosis and Sicca complex.

Features	PBC without Sjögren's syndrome (n=7)	PBC with Sjögren's syndrome (n=7)	Sicca complex (n=7)
Cough	0	1	4
Sputum	0	1	2
Dyspnoea	0	1	0
Clubbing	1	2	0
Wheezing	0	0	0
Crackles	0	0	1
Abnormal chest radiograph	0	1*	0

\*Graded 1/1<sup>18</sup>

symptoms were uncommon among patients with liver disease alone but were present in four out of the seven with associated Sjögren's syndrome. One patient had mild dyspnoea, another had cough with scanty phlegm, and two others had finger clubbing; one of whom had an abnormal chest film, which was graded 1/1 (ILO-U/C)<sup>16</sup>. Only one patient with PBC but no Sjögren's syndrome showed digital clubbing. Five patients with the Sicca complex had signs and/or symptoms: two had dry cough, two had a slight productive cough, and one had unilateral crackles.

#### PULMONARY FUNCTION TESTING

The mean FVC, FEV<sub>1</sub>, and FEV<sub>1</sub>/FVC% of the 14 healthy subjects investigated were 106%, 95%, and 86% of their predicted values<sup>14</sup> respectively; V<sub>T</sub>, TLC, VC, RV, and RV/TLC% were 119%, 111%, 109%, 119%, and 108% of their respective predicted values<sup>15</sup>; DLCO and Kco were 114% and 113% of their respective predicted values<sup>16 17</sup>; and PEF,  $\dot{V}_{25-75\%}$ ,  $\dot{V}_{75-85\%}$ ,  $\dot{V}_{50\%}$ , and  $\dot{V}_{75\%}$  were 94%, 67%, 52%, 72%, and 40%, of their predicted values respectively.<sup>14 18</sup> When these data were compared between the groups studied, no significant differences were found for maximal mid and end-expiratory flow rates, static lung volumes, and sGaw. Static lung compliance and in all but two cases Pao<sub>2</sub> and Paco<sub>2</sub> were within predicted normal limits.<sup>16</sup> Mild hypoxaemia (10kPa) was observed in two 45-year-old women with PBC with and without Sjögren's syndrome respectively. No differences in arterial blood gases and Cstat were observed between any patient group.

Mean TLCO was significantly lower both in patients with PBC plus Sjögren's syndrome ( $20.5 \pm 1.6$  ml min<sup>-1</sup> mmHg) and in patients with Sicca complex ( $20.4 \pm 1.1$  ml min<sup>-1</sup> mmHg<sup>-1</sup>), than in controls ( $25.8 \pm 1.6$  ml min<sup>-1</sup> mmHg<sup>-1</sup>) ( $p < 0.02$  and  $p < 0.016$ , respectively). Mean TLCO in PBC patients without Sjögren's syndrome, ( $24.7 \pm 0.6$  ml min<sup>-1</sup> mmHg<sup>-1</sup>) was normal. Mean Kco was also significantly lower in patients with PBC plus Sjögren's

syndrome ( $5.3 \pm 0.4$  min<sup>-1</sup> mmHg<sup>-1</sup>) than in those without it ( $6.4 \pm 0.3$  min<sup>-1</sup> mmHg<sup>-1</sup>), but mean Kco did not differ significantly from controls in either of these groups.

#### Discussion

The first account of a clinical association between lung fibrosis and PBC was given by Mason *et al*<sup>2</sup> in 1970, Turner-Warwick<sup>1</sup> having previously drawn attention to the association of pulmonary fibrosis with other chronic liver diseases. Later Golding *et al*<sup>19</sup> added further observations and reported the presence of gas transfer defects, with either an abnormal chest film or a restrictive ventilatory impairment, in several patients with chronic liver disease including PBC. However in two patients with PBC who came to necropsy Stanley *et al*<sup>3</sup> found widespread intra-pulmonary granulomas without fibrosis, one subject having an interstitial radiographic pattern and an impairment of the transfer factor.

The present study suggests that the incidence of clinical, radiographic and functional abnormalities is very low and that when present it may be related to the existence of an associated Sjögren's syndrome. Only four out of 14 patients with PBC had one or more clinical and/or radiological manifestations of pulmonary disease and all had keratoconjunctivitis sicca, xerostomia or both. Digital clubbing was observed in one patient with PBC not associated with Sjögren's syndrome but this feature cannot be related specifically to pulmonary disease.

The only consistently abnormal lung function finding was the reduction of gas transfer factor which was observed in patients with PBC associated with Sjögren's syndrome and in patients with the Sicca complex. These data suggest that the development of an abnormal diffusing capacity in patients with PBC, is somehow related to an associated Sjögren's syndrome and not to liver disease itself.

Comparisons of the results of the present investigation with previous reports cannot be made because of differences in format and because in papers previously reporting an association between PBC and lung fibrosis it has not been stated that factors noxious to the lung such as tobacco, alcohol, occupational or nonoccupational exposure to dust, associated clinical conditions, and iatrogenic factors have been excluded. Furthermore the presence of an associated Sicca complex, to which pulmonary impairment may be related, has not been investigated previously. Recently Clarke *et al*<sup>20</sup> have reported a high incidence of mild scleroderma in a series of patients with PBC in some of whom respiratory functional abnormalities, such as gas transfer impairment and airway obstruction were detected.

A wide range of pulmonary abnormalities has been reported in patients with the Sicca complex, either in isolation or in association with a connective tissue disorder—that is, Sjögren's syndrome.<sup>5</sup> Some of these are purely morphological, such as lymphocytic and plasma cell infiltration of the trachea and the large and small airways. Others have clinical relevance—for example, diminished mucous secretions caused by bronchial mucous gland destruction in large airways, bronchopulmonary infections related to dryness of the respiratory tract, pleural effusions, fibrosing alveolitis of both the mural and desquamative types, and lymphocytic interstitial pneumonitis.

In a few pulmonary function studies of patients suffering from different connective tissue disorders, the existence of a gas transfer defect with or without ventilatory impairment has been noted in some patients with Sjögren's syndrome.<sup>21–23</sup> In a series of patients with the Sicca complex, studied by Newball and Brahim,<sup>24</sup> almost one-half had small airways dysfunction unassociated with chronic obstructive lung disease.

However, most of these studies failed to exclude a number of factors which could have contributed to the development of lung disturbances, particularly those clinical conditions chiefly related to chronic liver disease such as renal failure, fluid retention, or hepatic encephalopathy, or those connective tissue disorders which are frequently associated with Sjögren's syndrome and have a fairly high prevalence of pleuropulmonary manifestations such as rheumatoid arthritis and systemic lupus erythematosus.

In our study mean TLCO was significantly lower only in patients with the Sicca complex and in those with PBC associated with Sjögren's syndrome. No differences were observed in any other parameter of lung function, except for hypoxemia in two patients and a difference in mean Kco between PBC patients with and without Sjögren's syndrome, the interpretation of which is uncertain. Maximal and mid-expiratory flow rates, considered to be a sensitive test for early detection of small airway dysfunction, were mostly below 70% of their respective predicted values in all groups studied, including the control group. Although the discriminant value of these measurements is still controversial,<sup>25</sup> it is possible that exposure to industrial or urban pollutants,<sup>26</sup> or the influence of hitherto unidentified environmental factors, could be the cause of these mild respiratory functional abnormalities.

Although any conclusion concerning cause and mechanism is premature, the presence of a gas transfer defect in Sjögren's syndrome might represent a response to a variety of respiratory injuries. The absence of any significant ventilatory impairment in

our series and its presence in patients studied by others would suggest that Sjögren's syndrome is a progressive disorder with a wide spectrum of pulmonary functional abnormalities.

In conclusion, it appears that the clinical, physiological, and radiographic manifestations of pulmonary disease observed in patients with PBC are the result of an associated connective tissue disorder, such as Sjögren's syndrome, rather than the result of PBC per se.

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