

**Małgorzata Bartosiewicz¹, Izabela Siemion-Szcześniak¹, Małgorzata Jędrych¹,
Piotr Radwan-Röhrenscheff¹, Katarzyna Lewandowska¹, Renata Langfort², Karina Oniszh³,
Monika Franczuk⁴, Jan Kuś¹**

¹Department of Pulmonary Diseases, National Tuberculosis and Lung Diseases Research Institute
Head: Prof. J. Kuś, MD, PhD

²Department of Pathomorphology, National Tuberculosis and Lung Diseases Research Institute
Head: R. Langfort, MD, PhD

³Department of Radiology, National Tuberculosis and Lung Diseases Research Institute
Head: I. Bistry, MD

⁴Department of Respiratory Pathophysiology, National Tuberculosis and Lung Diseases Research Institute
Head: S. Wesółowski, MD, PhD

Interstitial lung disease in patients with primary biliary cirrhosis

Zmiany śródmiąższowe w płucach u chorych na pierwotną żółciową marskość wątroby

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Abstract

Primary biliary cirrhosis (PBC) is a chronic autoimmune disorder of unknown etiology. The disease affects middle-aged women and is characterized by the destruction of the intralobular bile ducts that causes consequent cholestasis. AMA is a hallmark of PBC, composed mostly of IgG and IgM class. The M2 antibody is the most specific one, with sensitivity range of 54–98% depending on type of test used. PBC is often accompanied by other autoimmune diseases, such as Sjögrens syndrome, thyroiditis, rheumatoid arthritis, dermatomyositis, polymyositis. Interstitial lung disease (ILD) has been reported in patients with primary biliary cirrhosis but its frequency and nature are poorly understood. We report pulmonary involvement in the course of PBC in 4 middle-aged women. Histopathological examination of lung specimens was available in three patients: two presented with sarcoid — like granulomas, one with lymphocytic interstitial pneumonia (LIP). In one patient the diagnosis of pulmonary fibrosis was based on clinical and radiological features. Because of abnormal pulmonary function tests (PFT) results all the patients were treated with prednisone, one, additionally with azathioprine. The treatment was successful in all of the patients.

Key words: primary biliary cirrhosis, liver, interstitial lung disease, connective tissue disease

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Introduction

Lung involvement in the course of the other organ disorders may appear in various forms and cause a lot of diagnostic difficulties. Respiratory symptoms often precede the symptoms of the primary condition, e.g. alimentary tract disease, haematological disorders or connective tissue disease, and cause patients to seek medical help from

chest physicians. Chest physicians should always remember about the possibility of a secondary character of a pulmonary problem.

One of the diseases that may cause interstitial changes in lungs is primary biliary cirrhosis (PBC). PCB is a chronic, cholestatic, autoimmune liver disease. It is characterised by progressive and irreversible destruction of intrahepatic bile ducts. PCB may be accompanied by other disorders of

Address for correspondence: Prof. Jan Kuś, MD, PhD, I Department of Pulmonary Diseases, National Tuberculosis and Lung Diseases Research Institute, ul. Płocka 26, 01–138 Warszawa, tel.: +48 (22) 431 21 43, fax: +48 (22) 431 24 43, e-mail: j.kus@igichp.edu.pl

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autoimmune aetiology like Sjogren's syndrome (SS), rheumatoid arthritis, systemic lupus erythematosus, scleroderma polymyositis and dermatomyositis, undifferentiated connective tissue disease, common variable immune deficiency, thyroiditis of Hashimoto type, and HIV infection — especially in children [1–9].

The diagnosis of PCB must fulfil at least 2 out of 3 of the following criteria: 1) features of chronic cholestasis with elevated alkaline phosphatase (ALP) and/or gamma-glutamyl transpeptidase (GGT) persistent for more than 6 months, 2) the presence of antimitochondrial antibodies (AMA), and 3) a histopathological study of a liver specimen biopsy indicating PCB [10]. In the course of PCB various types of interstitial lung diseases (ILD) may develop, such as interstitial fibrosis, organising pneumonia, lymphoid interstitial pneumonia (LIP), or sarcoid reaction. Less commonly, alveolar bleeding, airway obstruction, and severe pulmonary hypertension may appear [1–4, 11–17].

We report on four cases of interstitial lung disease in patients fulfilling the criteria of PBC, each of them with a different clinical and radiological picture. In all cases the diagnosis of PBC was confirmed by specialists from gastroenterological centres with special interest in liver disorders.

Table 1 presents abnormalities in laboratory tests suggestive of PCB.

Case reports

Case 1

A 50-year-old female, free of any addictions, was admitted to the I Pulmonary Department of the National Tuberculosis and Lung Diseases Institute in September 2005 due to abnormalities present in chest X-rays from Feb 2005. The abnormalities included widened left hilum shadow and the presence of a small round opacification in the lower area of the right lung.

Chest computed tomography (CT) performed in February 2005 showed infiltrating lesion in the 3rd segment of the left lung and a single small parenchymal opacification in the lower right lobe. Mediastinal and hilar lymph nodes were not enlarged. The imaging studies were suggestive of left lung tumour with metastases in both lungs. In March 2005 right-sided video-assisted thoracoscopy was performed. Histopathological study of biopsied tissue excluded the neoplasm in the right lung. In April 2005 left-sided thoracotomy and wedge resection of the infiltrating lesion from the 3rd left segment was performed. The histopathological examination revealed chronic inflammation rich in lymphocytes and histiocytes, obscuring the structure of pulmonary tissue. Lymphoid interstitial pneumonia was recognised, and at that stage the patient was referred to our centre. At the time of admission to our department she was in good condition, complained of shortness of breath and decrease in exercise capacity, low-grade temperature up to 38^o C, itching of the skin, general weakness, and body weight loss. The chest X-ray showed elevated diaphragm, linear opacities in lower areas of the lungs, bilaterally, and pleural abnormalities on the right side (Figure 1). Ultrasound (US) examination excluded the presence of fluid in the right pleural cavity. Chest CT scan confirmed the existence of linear parenchymal opacities with air bronchograms, bilaterally, most intense in the lower part of the right lung (Figure 2). Pulmonary function tests (PFT) indicated pulmonary restriction with total lung capacity (TLC) of (2.76 L) — 65% of the predicted value, and a marked decrease in diffusing capacity for carbon monoxide (DLCO) — (3.29 mmol/min/KPa) — 45% of the predicted value. In 6-minute walking test (6MWT) the patient covered a distance of 448 metres, and oxygen saturation dropped from 96 to 89%. There were no alterations in fibre-optic bronchoscopy (FOB). Lymphocytes accounted for 26.5% of the cell count of bronchoalveolar lavage (BAL) fluid, and the CD4/CD8 ratio was 0.64. The results of additional

Table 1. Biochemical, immunological and histological data in PBC patients

Case	FA (35–104) U/l	GGT (12–43) U/l	IgM (40–230) mg/dl	ANA	AMA	AMA M2	RF	Liver biopsy
1	257	344	1741	1:5120	1:640	1:640	+	No
2	53	77	1023	1:1280	1:640	1:640	–	No
3	257	269	Not defined	1:640	Not detected	Not detected	–	Yes
4	154	259	416	1:320	1:1280	1:1280	–	Yes

FA — alkaline phosphatase; GGT — γ -glutamyltranspeptidase; IgM — immunoglobulin; ANA — antinuclear antibodies; AMA — antimitochondrial antibodies, AMA M2 — antimitochondrial antibodies subtype M2; RF — rheumatoid factor; in parantheses reference values



Figure 1. Posteroanterior chest X-ray (2005) — bilateral linear opacities above elevated diaphragm corresponding to parenchymal consolidations and right sided pleural lesions

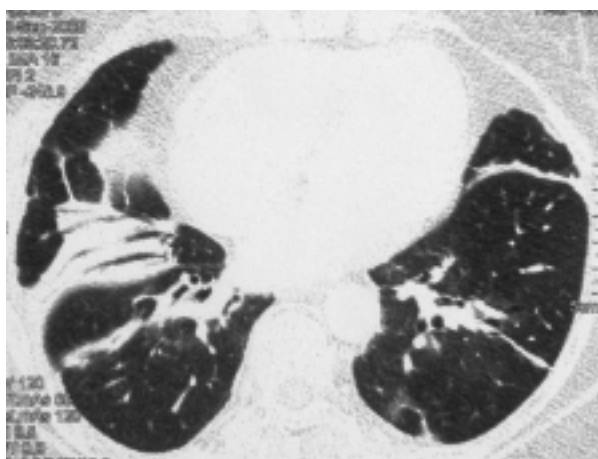


Figure 2. Chest CT scan (2005) — shows linear parenchymal consolidations with air bronchogram involving lower zones, the right lung predominantly

tests indicating PBC can be found in Table 1. The abdomen US and CT scans showed features of liver cirrhosis. The patient's medical records from the past revealed that hepatic pathology had been most likely present since the late 1990s. The laboratory tests from that period showed elevated ESR and liver parameters. The preliminary diagnosis of PBC based on the presence of the cholestasis and high titre of AMA and AMA M2 was later confirmed by a gastroenterologist. Lymphocytic interstitial pneumonia in the course of PBC was recognised on the basis of the clinical and radiological picture, biochemical and immunological tests, and, mainly, histopathological study of the previous lung biopsy. Treatment with prednisone 40 mg once a day was commenced. The follow-up tests

at 3 and 6 months, with the prednisone dose being reduced gradually to 20 mg once a day, initially revealed a partial and subsequently complete regression of radiological abnormalities, and improvement in PFT indices (increase of vital capacity — VC, TLC, and DLCO). After 20 months of the treatment, on the prednisone maintenance dose of 20 mg daily, progression occurred. The immunosuppressive therapy was intensified. Azathioprine was added to prednisone. As the radiologic studies and PFT stayed stable for another 12 months, we decided to withdraw azathioprine and reduce prednisone to 10 mg daily. The patient remains under the care of gastroenterologists. She has been treated with ursodeoxycholic acid (UDCA) since PBC was diagnosed.

Case 2

A 53-year-old female patient, without any addictions, was admitted to I Pulmonary Department in March 2006 due to the presence of multiple round opacities of various sizes in both lungs, seen in chest imaging studies since Aug 2005 (Figures 3, 4).

She gave a history of chronic cough with purulent sputum, deteriorating exertional breathlessness, general weakness, sweating, fever, loss of appetite, and recurrent pains of the joints, especially in her hands. Before she was referred to our centre, toxocariasis and tuberculosis were recognised. Albendazole, antituberculous medications, and glucocorticosteroids were used, resulting in a transient improvement only, most prominent after glucocorticosteroids. In September 2005 video-assisted thoracotomy with lung biopsy was performed. Histopathological examination revealed multiple diffuse non-caseating granulomas, and areas of interstitial inflammatory reaction with alveolar involvement. In January 2006 advice was sought in our centre for the first time. The recommendation to investigate toward PCB was given as the clinical course, and all the results available at the time were highly suggestive of it (Table 1). In February 2006, after glucocorticosteroids were stopped, the radiological abnormalities progressed. Parenchymal, partly confluent opacities appeared in the lower lobes and in the middle right lobe. Moderate hypoxemia — pO_2 58 mm Hg was noted. Decreased VC — 67% of predicted value, and decreased forced expiratory volume in 1 second (FEV_{1s}) — 76% of predicted value, were present in the spirometry. Lymphocytes accounted for 60% of the BAL fluid cell count. No final diagnosis was made, and in March 2006 the patient was referred and admitted to our centre. The PFT showed moderate decrease of DLCO (4.84 mmol/min/KPa) —



Figure 3. Posteroanterior chest X-ray (2005) — multiple, round opacities with central lucency, confluent in lower lung zones

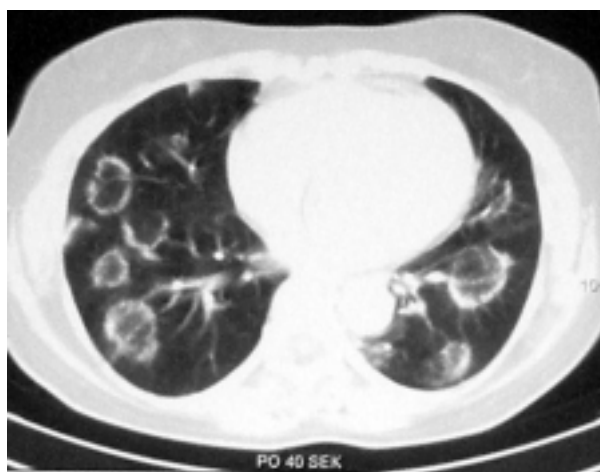


Figure 4. Chest CT scan (2005) — shows bilateral, multiple, big, ring shaped foci of various size; the biggest one in the right lower lobe

60% of predicted value; in 6MWT she covered distance of 415 m without any significant desaturation. On the basis of the clinical and radiological picture, together with results of additional tests, preliminary diagnosis of PBC was established. Later on, it was confirmed by gastroenterologists. We diagnosed pulmonary sarcoid reaction secondary to PBC. Treatment with prednisone, in doses being gradually reduced down to 20 mg daily, was commenced. After 3 months almost complete regression of radiological changes and significant improvement in PFT were achieved. The prednisone therapy was ended in June 2008. Six months later changes in chest X-ray reappeared and PFT deteriorated. The prednisone was reintroduced

with good clinical effect and regression of abnormalities in imaging studies. The patient was also treated with UDCA since the diagnosis of PBC was established.

Case 3

A 64-year-old female patient, without any addictions, was admitted to our department in April 1998, due to diffused abnormalities in a chest X-ray. In 1968 the patient was treated for tuberculosis without bacteriological confirmation. In 1996 PBC was recognised on the basis of the presence of the cholestasis and histopathological examination of the liver biopsy specimen (diagnostic process conducted by gastroenterologists). She had been treated with UDCA since then.

The results of additional tests suggestive of PBC are shown in Table 1.

On admission she gave a one-month history of dry cough, progressing exertional breathlessness, and general weakness. In chest X-ray performed before the admission, linear and nodular opacities with calcifications in the left apex, and linear opacities above the left hemidiaphragm, were seen. High resolution CT (HRCT) scan revealed post-tuberculosis fibrosis in the apex zone of the left lung and ground-glass opacifications and honeycombing in both lower lobes, lingula, and right middle lobe. These changes indicated interstitial pulmonary fibrosis. The mediastinal and hilar lymph nodes were not enlarged. PFTs showed moderate impairment of DLCO (4.31 mmol/min/kPa — 55% of predicted value), and the remaining parameters were within normal limits. There was no exertional desaturation recorded during 6MWT. Chronic inflammatory changes were seen in the airways during FOB. Lymphocytes accounted for 47% of the cell count in BAL fluid, and the CD4/CD8 ratio was low (0.11). Taking into consideration the whole clinical picture and the results of additional tests, a diagnosis of pulmonary interstitial fibrosis in the course of PBC was established. At that point the patient was left without treatment. In July 1998, however, treatment consisting of prednisone in a dose of 20 mg daily, and subsequently with methylprednisolone 12 mg daily, was commenced due to the occurrence of a fever up to 39°C, intense dry cough, and joint pains.

In January 2002 she was admitted to our department again. The chest X-ray appearance was stable in comparison to previous studies. In HRCT scan, however, areas of ground-glass opacifications and honeycombing were more extensive in the lower areas of the lungs, when compared to the study from 1998. The partial remission of interstitial

changes in the upper parts of the lungs was seen. In 6MWT she covered a distance of 437 m and desaturated from 97 down to 91%. In PFT, as before, DLCO was decreased (3.94 mmol/min/kPa — 52% of predicted value) and other parameters stayed within normal limits. The continuation of treatment with methylprednisolone was recommended.

In Septmeber 2003 the patient was admitted to the Institute of Rheumatology, due to swollen and painful hands joints, myalgia, and progressive general weakness lasting for several months. Dermatomyositis and secondary Sjogren's Syndrome were recognised. The dose of methylprednisolone was increased to 16mg daily.

In February 2006 the patient was in our department for the third time. The chest X-ray and HRCT scan (Figures 5, 6) were stable when compared to images from 2002. Further deterioration of DLCO (2.59 mmol/min/kPa — 37% of predicted value) was noted in PFT. The distance covered in 6MWT was longer (517 m) but the exertional drop of saturation was greater (down to 87%) than during previous hospitalisation. Because stabilisation of the radiological picture was achieved and the patient was free from any respiratory symptoms the treatment with methylprednisolone 16 mg daily was continued as ordered by rheumatologist.

Case 4

A 53-year-old female patient, an ex-cigarette smoker, was admitted to our department in October 2008, due to suspicion of the neurosarcoidosis. She had undergone a peripheral facial diplegia, uveitis of the right eye, and recurrent pains of ankles and knees in the past. She denied fever, cough, or breathlessness. In March 2008 she was admitted to a neurological department with suspicion of borreliosis. However, investigation excluded borreliosis and tick-borne encephalitis. Short treatment with prednisone resulted in partial remission of facial diplegia. In a chest X-ray from August 2008 widening of mediastinal and hilar shadows, as well as subtle diffused abnormalities in middle zones of the lungs, could be seen. A chest CT scan revealed enlarged mediastinal lymph nodes of all groups, and a bilateral diffuse nodular pattern. The clinical and radiological picture was highly suggestive of sarcoidosis with central nervous system involvement. For further investigation the patient was referred to our centre. An endobronchial ultrasound-guided transbronchial needle aspiration of a mediastinal lymph node was performed. The histopathological findings of non-necrotizing epithelioid cell granulomas confirmed the diagnosis of sarcoidosis. PFT results were normal.



Figure 5. Chest X-ray (2006) — linear and reticular opacities within both lower lung zones, small nodules within right apex under thickened pleura

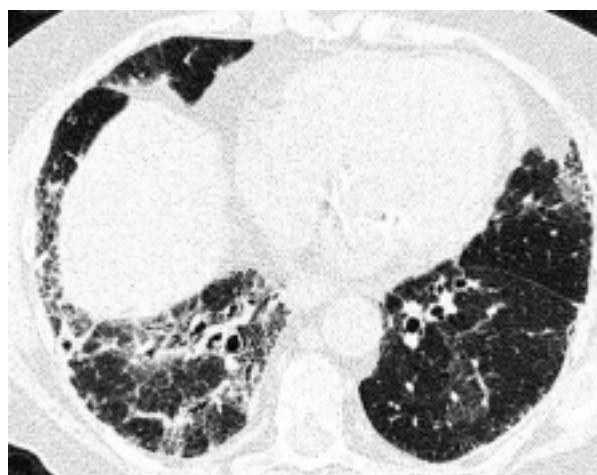


Figure 6. HRCT of the lungs (2006) — shows thickened interlobular septa with traction bronchiectasis and small foci of honeycombing corresponding to interstitial pulmonary fibrosis

In 6MWT she covered a distance of 527 m without a significant drop in oxygen saturation. The results of additional tests suggestive of PBC are shown in table 1. A liver biopsy was performed in April 2009 by gastroenterologists, and it confirmed the diagnosis of PBC. Taking into consideration the entire clinical and radiological picture, together with all performed additional studies, the sarcoid-like reaction in the course of PBC was recognised. Because of normal PFT results the decision not to treat was made at that time. In January 2010 chest imaging studies showed a prominent progression of diffuse interstitial opacity (Figures 7, 8). A decrease of DLCO down to 66% of the predicted value



Figure 7. Chest X-ray (2010) — enlarged left hilum; bilateral linear and nodular opacities within lower-lung zones

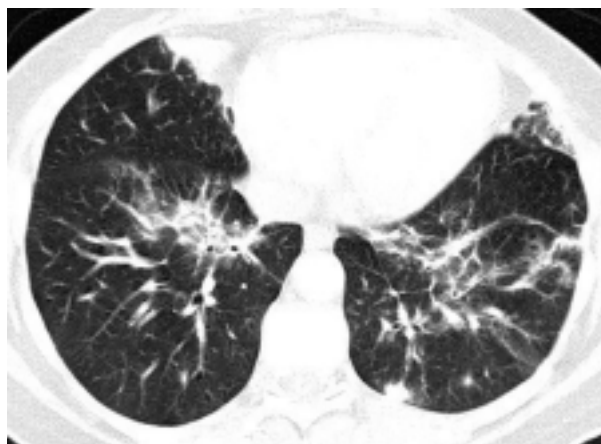


Figure 8. Chest CT scan (2010) — linear opacities corresponding to fibrosis and nodular air-space consolidation in lower lung zones

was noted. The US study showed enlargement of peripheral lymph nodes: cervical, submandibular, supraclavicular, and abdominal. The fine-needle biopsies of a right-sided supraclavicular lymph node and a left-sided submandibular one revealed epithelioid cell granulomas. Because of the deterioration seen on chest imaging studies and in PFT, treatment with prednisone in an initial dose of 40 mg a day was commenced. The dose was subsequently gradually reduced down to a maintenance dose of 5 mg a day. The check-ups after 3, 6, and 12 months of the treatment showed marked regression of diffuse opacifications and improvement of PFT parameters — DLCO increased to 87% of the predicted value. The patient remains under the care of a gastroenterologist, taking UDCA since the PBC was diagnosed.

Discussion

Primary biliary cirrhosis is a chronic, systemic disease that affects mainly middle-aged women. The criteria of diagnosis were listed in the ‘Introduction’ section. All patients reported above had fulfilled the enzymatic criteria of PBC, and three of them had elevated titre of AMA and AMA M2. In two cases a liver biopsy was performed and the diagnoses were confirmed by a histopathological examination. The PBC is usually accompanied by other disorders of autoimmune background — most frequently Sjögren’s syndrome (seen in 21–80% of patients with PBC [18]) and autoimmune thyroiditis (6–17% of patients [19]). In 41% of PBC patients more than one autoimmune disease coexists [1].

Among our patients, the first one suffered from a dry-eye syndrome (the results of immune tests did not allow for recognition of a secondary Sjögren’s syndrome). The second one had an elevated titre of anticardiac and antithyroid antibodies, but no specific autoimmune disease was found at that time. The third patient had dermatomyositis and Sjögren’s syndrome diagnosed ultimately.

Turner-Warwick was the first to pay attention to the coexistence of chronic liver diseases and interstitial lung fibrosis in 1968 [20]. In 1979 Mason et al. published a first case report of interstitial pulmonary disease in the course of PBC [21]. It is estimated that the prevalence of interstitial lung diseases among PBC patients is above 15%. A total of 54% of patients report symptoms related to the respiratory tract, and around 40% stay asymptomatic [22]. Liu et al. found features of interstitial lung disease in HRCT scans in 10% of 109 patients with PBC [23].

As mentioned above, more than half of patients with ILD in the course of PBC have symptoms related to the respiratory tract — most commonly they complain of breathlessness (> 50% of patients) and cough (35% of patients). Physical examination reveals bilateral basal crackling in 35% of patients [22]. Three of our four patients complained of symptoms related to the respiratory tract (dyspnoea, cough, impaired exercise tolerance). In the 2nd and 3rd cases bilateral basal crackling was heard on auscultation. In the 1st case dullness and reduced breathing sounds were present in the lower zone of the right lung. The last of the presented patients did not have any symptoms related to respiratory system initially, and the subtle bilateral basal crepitation appeared after around 1.5 years of follow-up, together with

radiological abnormalities. HRCT scan allows for early detection of ILD, and helps in determining its extent. The most common patterns seen in ILD in the course of PBC include: reticular opacities (39% of patients), patchy opacities (25%), nodular opacities (25%), ground-glass opacifications (18%), thickening of interlobular septa (18%), and honeycombing (11%). In more than 60% of patients these changes can be seen in a classic chest X-ray [23]. All of our patients had abnormalities in chest X-rays and CT scans. In the 1st case the initial radiological appearance was highly suggestive of a neoplastic process, subsequently the features of ILD occurred. In the remaining patients the radiological picture was typical for ILD from the beginning. The pattern of changes in HRCT scans corresponds to the degree of the fibrosis in histopathological study. The first of our patients developed lymphocytic interstitial pneumonia, in 2nd and 4th cases it was a sarcoid-like reaction, and in the 3rd case it was pulmonary fibrosis. The lymphocytic interstitial pneumonia was confirmed by histopathological examination. Lymphocytic interstitial pneumonia was first described in 1969 by Liebow and Carrington. It is a benign lymphoproliferative disease limited to the lungs, and usually accompanies various autoimmune disorders [24], just like in the case we presented. Many papers reporting that interstitial fibrosis, LIP, organising pneumonia, and sarcoid-like reactions are the most common pulmonary complications in PBC, have been published [4, 13, 19, 22, 25]. There has been a long discussion about whether pulmonary complications in patients with PBC are a result of chronic inflammation in the liver, or could be associated with other autoimmune diseases coexisting with PBC. In 1981, Rodriguez et al. stated that pulmonary complications occur only in patients with coexisting Sjogren's symptoms [26]. A study conducted many years later showed that in the group of 109 PBC patients, the ratio of ILD was 21.7% in patients with coexisting SS, whereas in patients without SS it was only 1.6% [23]. In a study from 2009 that included 178 PBC patients, pulmonary complications developed in 40% of patients without any other additional autoimmune disease. Lymphocytic infiltrations and LIP were commonly seen in the lung biopsy in these patients [14]. In the opinion of those authors, PBC should be considered as a classic autoimmune disease on its own, which, similarly to connective tissue disease and Sjogren's syndrome, may be accompanied by the development of pulmonary complications, sometimes very severe [16].

The coexistence of ILD and PBC has been reported on rarely [17]. PBC is often accompanied by other autoimmune diseases. In our 3rd case, features of ILD appeared 2 years after PBC diagnosis, and after a few more years a connective tissue disease was recognised. It is not possible to tell whether chronic immune process taking place in the liver was the sole reason for pulmonary interstitial changes in this case, or whether those pulmonary changes were the first symptom of dermatomyositis (frequently accompanied by ILD). It seems that severe general autoimmune disturbances could lead to multi-organ and systematic manifestation of the disease in the presented patient.

The first description of alterations in PFT in patients with PBC came from Rodriguez et al. [26]. They found that the impairment of DLCO is the most typical abnormality. All of our patients had decreased DLCO: moderately in 2 patients (case 2 and 4) and severely in another 2 (case 1 and 3). Krowka et al. revealed a positive correlation between the degree of gas exchange impairment and intensity of changes in the histopathological examination of the specimen from liver biopsy, as well as with the Mayo index (a tool for the assessment of death risk using demographic and biochemical data) [27, 28]. Among our patients, the biochemical hepatic abnormalities were the greatest in patient no. 1. This patient also had the most prominent alterations in PFT parameters — DLCO decreased to 45% of the predicted value and there was moderate restriction (TLC 65% of the predicted value). The DLCO impairment was of moderate degree in cases 2 and 4 (60% and 66% of predicted value, respectively), where the liver indices were normal or nearly normal. In case no. 3, the one with the long history of the disease and biochemical features of cholestasis, the decrease of DLCO was significant. In a study by Rodriguez et al., decreased DLCO was present only in patients with PBC and coexisting Sjogren's syndrome or dryness syndrome. PBC patients without other autoimmune diseases had DLCO within normal range. The authors suggested that lowered parameters of PFT reflected the degree of activity of Sjogren's syndrome or dryness syndrome, and not chronic hepatic pathology [26]. That hypothesis was supported in 2008 by studies of Liu et al. [23]. Our patients nos. 2 and 4 had moderately decreased DLCO, despite suffering neither from SS nor from dryness syndrome. In cases 1 and 3, dryness syndrome and SS coexisted with PBC, which would be in favour of Rodriguez's hypothesis.

Hypoxemia of moderate degree ($pO_2 < 70$ mm Hg) is not a common finding in patients with PBC.

It occurs in 14–40% of patients, depending on the severity of the liver disease [11]. Hypoxemic respiratory failure was not present in our first patient, despite abnormal liver tests and alterations in a radiologic study and PFT. In the second patient moderate hypoxemia was present, although PBC was not very advanced. Severe hypoxemia with $pO_2 < 50$ mm Hg in the course of a liver disease is very rare, mainly in patients with hepatopulmonary syndrome. Among 178 PBC patients, moderate (pO_2 60–80 mm Hg) and severe ($pO_2 < 60$ mm Hg) hypoxemia was present in 29% and 14%, respectively [22].

In BAL fluid of patients with PBC and lymphocytic interstitial pneumonia the percentage of lymphocytes and CD4/CD8 ratio are usually increased. The presence of lymphocytosis in BAL fluid is not always accompanied by visible changes in imaging studies [29, 30]. The advanced alterations in a chest X-ray and clinical symptoms, such as breathlessness, cough, and decreased exercise capacity, were present in all our patients. In the 4th patient clinical symptoms appeared when the radiological progression of lung disease took place. In all patients who had BAL fluid examined, the percentage of lymphocytes was increased. In the patient with LIP, lymphocytes accounted for 26% and the CD4/CD8 ratio was 0.64. In the patient with a sarcoid-like reaction, lymphocytes constituted 60% of cell count in BAL fluid. In the 3rd case it was 47% (LIP was not diagnosed in that patient, the radiological picture corresponded to interstitial fibrosis, and dermatomyositis with a secondary Sjogren's syndrome was diagnosed few years later). Spiteri et al. performed BAL in 10 respiratory symptom-free patients with PBC. In 6, a significant increase of lymphocyte number ($> 15\%$) and CD4/CD8 ratio up to 4:1 was found. Similar alterations were seen in sarcoidosis patients, but they were not present in a control group [31]. Authors of that study suggested that the immune mechanisms involved in the formation of granulomas are similar in sarcoidosis and PBC. In almost all patients with lymphocytosis and increased CD4/CD8 ratio, chest CT scans showed abnormalities, despite normal chest X-rays and PFTs. Similar results were achieved by Waalert et al. [32]. Studies in recent years have confirmed that lymphocytic infiltrations and LIP are the most common pathologic changes in patients with PBC [22].

Jastrzebski et al. investigated a differential cell count in BAL fluid in 13 women with histopathologically confirmed PBC, but without symptoms from the respiratory system. In 38% of patients the

percentage of lymphocytes was higher than in a control group. In addition, a lower content of CD8 subpopulation in the group of patients was found [29]. Chatte et al. reported on infiltrations rich in plasmatic cells and lymphocytes in a histologic examination of lung biopsy specimens. CD8 cells dominated in 2/3 patients and CD4 cells in the remaining patients [33].

The data on the treatment of the lung disease in the course of PBC is limited. Most commonly GCs and other immunosuppressive medications, i.e. azathioprine, cyclophosphamide, methotrexate, cyclosporine, and colchicine, are used. Usually, the response to such treatment is good; however, lung changes have a high tendency for recurrence. Unfortunately, GCs do not stop liver pathology [1, 11].

Conclusions

Many abnormalities in respiratory system functioning are seen in patients with liver diseases. Their pathogenesis remains not fully explained. The range of lung pathology in the course of PBC is very broad. It appears as radiological changes, PFT abnormalities (most frequently decreased DLCO), and alterations of differential cell count in BAL fluid (CD4 lymphocytosis). Some authors believe that the degree of lung involvement is independent of PBC severity [26, 27, 29, 32]. Interstitial lung disease is a serious complication, which usually has a mild course, but on occasions may even be fatal. In around 12% of PBC, pulmonary hypertension develops [14], more frequently in patients with features of ILD, Raynaud's syndrome, Sjogren's syndrome, and portal hypertension. Pulmonary hypertension significantly worsens the prognosis. The only effective therapy for PBC is a liver transplantation. Five-year survival rate is more than 90%, but PBC may reoccur in an implanted liver [8, 34].

Conflict of interest

The authors declare no conflicts of interest.

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