A Diagnostic Dilemma: Pulmonary Involvement of Primary Biliary Cirrhosis or Coexistent Sarcoidosis?: Case Report

Tanısal İkilem: Primer Biliyer Siroz Akciğer Tutulumu veya Sarkoidoz Birlikteliği?

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ABSTRACT Primary biliary cirrhosis (PBC), is an autoimmune chronic cholestatic liver disease that granulomas may accompany. Sarcoidosis is a multisystem granulomatous disease that can involve all the tissues and organs. We present a case, with clinical findings of these two rare diseases. A 50 year-old female presented with dyspnea on exertion. Four years ago, she was diagnosed as autoimmune hepatitis (AIH)/PBC overlap syndrome and prednisolone, ursodeoxycholic acid and azathioprine had been initiated. She, herself, discontinued prednisolone for the last 1 year. Chest radiography demonstrated interstitial pattern. Bronchoalveolar lavage and transbronchial biopsy via fiberoptic bronchoscopy was consistent with sarcoidosis. Prednisolone therapy, re-started by gastroenterological indication, resulted in rapid radiological and clinical improvement also. The histologic similarity of sarcoidosis and PBC suggests that they might possess a common pathogenesis through a common process. The clinician should keep in mind the coexistence and the relationship of these two diseases.

Key Words: Sarcoidosis, pulmonary; liver cirrhosis, biliary; lung diseases, interstitial

ÖZET Primer biliyer siroz (PBS), genelde orta yaşlı kadınlarda rastlanan, safra kanallarının progressif harabiyeti ile karakterize, granülomların eşlik edebildiği kronik kolestatik otoimmun bir karaciğer hastalığıdır. Sarkoidoz öncelikle akciğerler ve lenfatik sistemi etkileyen, ancak tüm doku ve organları tutabilen multisistemik granülomatöz bir hastalıktır. Bu nadir iki hastalığa ait bulguların bir arada bulunduğu olgu, literatürler eşliğinde sunuldu. Elli yaşında kadın hasta kliniğimize eforla artan nefes darlığı ile başvurdu, 4 yıl önce otoimmun hepatit (OİH) ve PBS overlap sendromu tanısı ile ursodeoksikolik asit, azotiyoprin ve prednizolon tedavisi başlanmış, son 1 yıldır kendisi prednizolonu kesmişti. Fizik muayenesi normaldi ve PA akciğer grafisinde retikuler patern izlendi. Fiberoptik bronkoskopi eşliğinde uygulanan bronkoalveoler lavaj ve transbronşial biyopsi sonuçları sarkoidoz ile uyumluydu. Gastroenteroloji tarafından PBS/OIH nedeniyle tekrar prednizolon tedavisi başlanan olgunun pulmoner bulgularında da düzelme sağlandı. Sarkoidoz ve PBS'nin histolojik benzerliği ortak bir proseste ortak bir patogenezle birlikte olduklarını düşündürmektedir. Bu 2 nadir hastalığın ilişkisi unutulmamalıdır.

Anahtar Kelimeler: Sarkoidozis, akciğer; karaciğer sirozu, biliyer; akciğer hastalıkları, interstisyel

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Primary biliary cirrhosis (PBC), a chronic cholestatic autoimmune liver disease, may be associated with autoimmune diseases especially with Sjögren syndrome and autoimmune thyroiditis.[1] In the literature, case reports have been reported on lung involvement of PBC such as mild airflow obstruction, pulmonary hemorrhage.[2] Here, we present a case diagnosed as sarcoidosis coexisting with PBC autoimmune hepatitis (AIH) overlap syndrome. Consent for the publication had been obtained from the patient.

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CASE REPORT

A 50 year-old female patient was admitted to our clinic with complaints of dyspnea on exertion. There were no other respiratory symptoms. She was working as a housekeeping director in a hotel. She had never smoked and she was born and raised in İstanbul. Her mother had the diagnoses of restless legs syndrome whereas her father had hypertension, diabetes mellitus, chronic obstructive pulmonary disease. The patient's medical history was reviewed. At the age of 43, she had been investigated in another center due to epigastric pain. Liver function tests were elevated and improved with non-specific therapy in the follow-up. Three years later, she had been investigated with the complaints of intermittent epigastric pain, edema and diagnosed as autoimmune AIH/PBC overlap syndrome. Treatment with ursodeoxycholic acid (1250 mg/day), azathioprine (100 mg/day) and prednisolone (36 mg/day) had been initiated.

Her vital signs and physical examination was normal. The abnormal biochemical labarotory values were: alanine aminotransferase (ALT) 41 U/L (normal <40), alkaline phosphatase (ALP) 231 U/L (normal <128), gamma glutamyl transferase 230 U/L (normal <38). Complete blood cell count and the other laboratory tests were within normal limits.

Posteroanterior (PA) chest radiograph showed peripheral irregular reticular opacities evident in all areas of the lungs (Figure 1). Spirometric values were normal [FVC: 2.96 (89%), FEV_1: 2.34 (82%), FEV_1/FVC: 79%)], the carbon monoxide diffusing capacity (DLco) was decreased (77%). Thoracic high-resolution computed tomography (HRCT) demonstrated interlobular and intralobular septal thickening and subpleural micronodules were remarkable including fissures. In the mediastinal window, no lymphadenopathy was detected (Figure 2). Serum angiotensin converting enzyme (ACE) level was 83 (8-52) U/L, and calcium was 9.4 (8.5-10.5) mg/dL.

She admitted that she discontinued prednisolone therapy for 1 year that had been started with the diagnosis of AIH/PBC overlap syndrome. She was still under ursodeoxycholic acid (1250 mg/day), azathioprine (100 mg/day) treatment. We consulted the patient with a gastroenterologist and liver biopsy specimens were re-evaluated. Biopsy findings confirmed the diagnosis, anti-liver-kidney microsomal 1 (LKM-1) and anti-mitochondrial antibody (AMA) were also detected as positive.

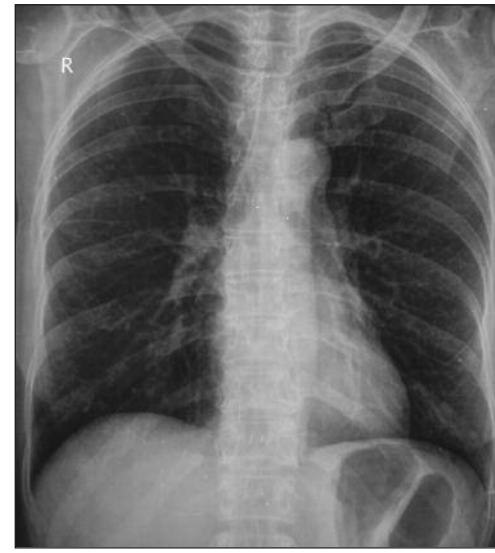

FIGURE 1: The chest radiograph at initial presentation demonstrates peripheric, extended, irregular opacities.

To investigate the etiology of interstitial lung disease, rheumatologic markers were studied and found to be negative. The rheumatologists did not affirm any rheumatic disease. Bronchoalveolar lavage (BAL) from the right middle lobe and transbronchial biopsy (TBB) were performed from the right lower lobe via fiberoptic bronchoscopy, no endobronchial lesion was detected. Lavage was negative for acid fast bacilli (AFB). The mean total cell count in the BAL fluid was 365/mm^3, mean cell fraction rates for lymphocytes, neutrophils, macrophages and eosinophils were 38%, 41%, 16% and 5% respectively. The ratio of CD4 cells to CD8 was 4.36. Biopsy revealed granulomas consistent with sarcoidosis.

Stage III sarcoidosis diagnosis was established on the basis of the clinical, radiological, laboratory and pathologic findings. Neurologic, ophthamologic and cardiac consultations excluded extrapulmonary involvements.

Gastroenterology re-started prednisolone treatment with 32 mg/day. Steroid therapy provided clinical and radiological improvement in the

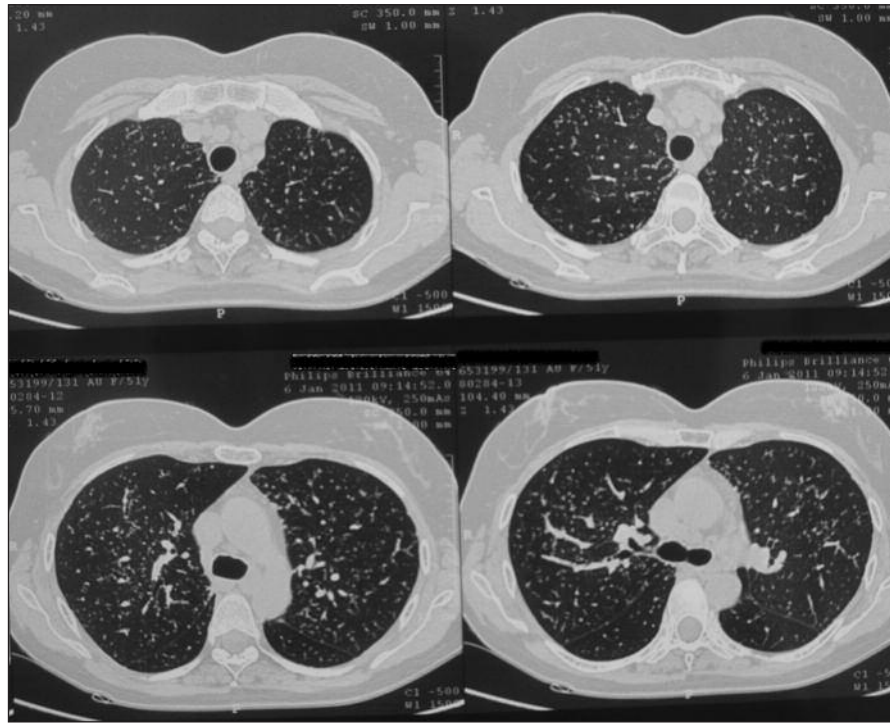

FIGURE 2: Computed tomography at presentation shows extended micronodules and interlobular and interlobular septal thickenings.

first month and near-complete radiological regression in the 1st year (Figure 3). Still, in the 3rd year of regular follow-ups, the patient remains stable without respiratory symptoms or radiological progression (Figure 4). Currently she is under ursodeoxycholic acid (1250 mg/day), azathioprine (100 mg/day) and low dose prednisolone (4 mg/day) and she is followed by both pulmonology and gastroenterology clinics.

DISCUSSION

Autoimmune hepatitis is an autoimmune liver disease of unknown etiology due to hepatocellular inflammation. The disease is characterized by the seropositivity of antinuclear antibody (ANA), anti smooth muscle antibody (ASMA), LKM-1, systemic lupus erythematosus (SLE) autoantibodies, hypergammaglobulinemia and histologically periportal hepatitis.[3] Serological subtypes of AIH are commonly described as: Type 1 (ANA and ASMA positive), Type 2 (LKM-1 positive), Type 3 (SLA positive). The term 'overlap syndrome' is used to describe the coexistence of AIH with PBC and primary sclerosing cholangitis.[4] Our case was evaluated as Type 2 AIH with the seropositivity of LKM-1 and interface hepatitis on liver biopsy.

Primary biliary cirrhosis is an autoimmune chronic cholestatic liver disease characterized by progressive inflammatory destruction in the small and medium intrahepatic bile ducts, which may deteriorate to fibrosis and cirrhosis causing liver failure.[5] PBC is encountered usually in middle-aged women.[6] The annual incidence was reported as 0.33 to 5.8 per 100 000.[7] Three diagnostic criteria are described, of which at least 2 must be provided for the diagnosis: the ALP and GGT elevation in biochemical studies showing cholestasis, AMA seropositivity which is specific to the disease and compatible histology on liver biopsy.[8] Histologically, the most consistent finding is chronic nonsuppurative cholangitis which may include granulomas indicating destruction of biliary epithelial cells; decreased number of small bile ducts and portal inflammatory cell infiltration.[9,10] In our case, liver biopsy manifested focal inflammation in periportal, portal and lobular areas; without granuloma structure. In our case, PBC/AIH overlap syndrome was diagnosed on AMA seropositivity, the ALP and GGT elevation, and consistent biopsy findings.

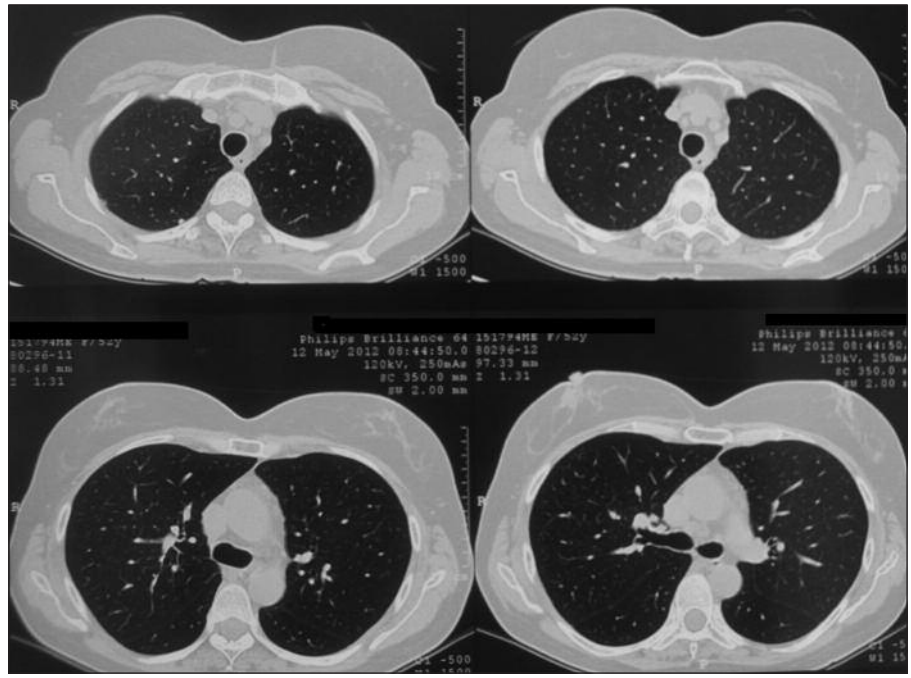

FIGURE 3: Computed tomography at the end of the 1st year of the prednisolone therapy manifests regression.

Approximately 41% of PBC, may be associated with other autoimmune diseases, most commonly Sjögren syndrome (21-80%) and autoimmune thyroiditis (6-17%).[1] There are limited number of studies and case reports in the literature on PBC and concomitant pulmonary disease. Mild airway obstruction, pulmonary hemorrhage, decreased DLco, lung granulomas and subclinical lymphocytic alveolitis in BAL fluid had been reported.[2] The coexistence of PBC with interstitial lung disease is found in 10-15% of patients, and 40% of them were reported as asymptomatic.[11,12]

Granuloma occurs as a response of the immune system against impurities that can not be digested by macrophages nor inflammatory cells. Other than the lungs and its associated lymph nodes, the liver is one of the organs that granulomas is most often seen due to the rich blood supply and intense reticuloendothelial cells.[13] Drebben et al. had analysed 215 PBC preparations and found granuloma structure in 48% of them.[14] The first case describing the relationship between sarcoidosis, granuloma structures, and PBC is reported in 1969 by Karlish et al. in a 47-year-old female patient with hilar and paratracheal lymphadenopathy, progressive liver disease and AMA

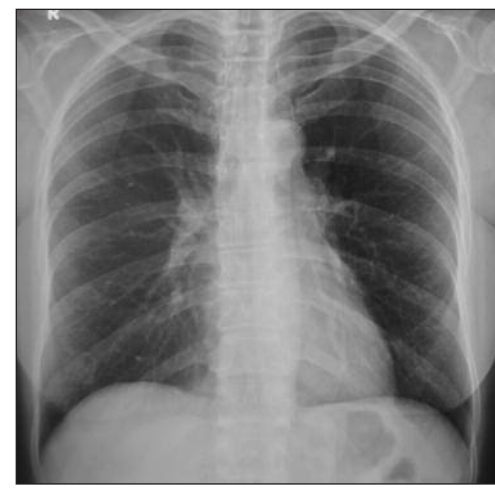

FIGURE 4: Chest radiograph at the end of the 2nd year.

seropositivity, and Kveim test conveniency.[15] Stanley et al. reported patients with pulmonary infiltration and pulmonary granulomas found at autopsy who were diagnosed as PBC previously.[16] Lung granulomas were found in 3 out of 4 female AMA seropositive patients, who have located granulomas on liver biopsy and interstitial involvement on chest radiographs.[17]

In a series of 4 consecutive PBC and radiological interstitial lung disease, lymphocytic intersti-

tial pneumonia, lymphocytic predominance in BAL fluid, granuloma structures, Sjögren's syndrome, and fibrosis have been reported.[18] Also high levels of lymphocytes and elevation in CD4/CD8 ratio in BAL fluid, biopsy-proven lymphocytic bronchitis/bronchiolitis had been shown in PBC patients without respiratory symptoms.[19-21]

Sarcoidosis is a systemic granulomatous disease affecting most commonly the lungs and lymphatic system. The incidence is considered as 1-40/100 000 depending on factors such as race, gender, age. The diagnosis is challenging principally because there is no specific reliable diagnostic test available. In the differential diagnosis, PBC must be considered as well as infectious and the other diseases.[22-24] Hepatic granulomas were reported in up to 60% of the sarcoidosis patients without clinical signs.[25] Rarely, liver failure may develop as a result of chronic intrahepatic cholestasis and biliary cirrhosis in patients with sarcoidosis.[26] In a study evaluating 20 patients with sarcoidosis and chronic liver disease PBC was found in two.[27]

As a result, the histologic similarity of sarcoidosis and PBC suggests that they might possess a common pathogenesis through a common process. We assumed our case as 'coexistence of sarcoidosis and PBC' due to the clinical, radiographic findings and elevated serum ACE levels. But when considered in the light of the literature, the pulmonary findings of our case might have also been 'pulmonary involvement of PBC' and it does not seem possible to certainly figure out. Either way, corticosteroid treatment, used for gastroenterologic indication, also provided a response in pulmonary findings.

REFERENCES

1. Allan PF, Powers CR, Morris MJ. Pulmonary manifestations of primary autoimmune hepatobiliary disease. Clin Pulm Med 2005;12(4): 232-45.
2. Chatté G, Streichenberger N, Boillot O, Gille D, Loire R, Cordier JF. Lymphocytic bronchitis/bronchiolitis in a patient with primary biliary cirrhosis. Eur Respir J 1995;8(1):176-9.
3. Abdollahi MR, Somi MH, Faraji E. Role of international criteria in the diagnosis of autoimmune hepatitis. World J Gastroenterol 2013;19(23): 3629-33.
4. Rust C, Beuers U. Overlap syndromes among autoimmune liver diseases. World J Gastroenterol 2008;14(21):3368-73.
5. Smyk DS, Bogdanos DP, Pares A, Liaskos C, Billinis C, Burroughs AK, et al. Tuberculosis is not a risk factor for primary biliary cirrhosis: a review of the literature. Tuberc Res Treat 2012;218183.
6. Smyk DS, Rigopoulou EI, Pares A, Billinis C, Burroughs AK, Muratori L, et al. Sex differences associated with primary biliary cirrhosis. Clin Dev Immunol 2012;2012: 610504.
7. Boonstra K, Beuers U, Ponsioen CY. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review. J Hepatol 2012;56(5):1181-8.
8. Kaplan MM, Gershwin ME. Primary biliary cirrhosis. N Engl J Med 2006;354(3):314.
9. Neuberger J. Primary biliary cirrhosis. Lancet 1997;350(9081):875-9.
10. Heathcote EJ. Management of primary biliary cirrhosis. The American Association for the Study of Liver Diseases practice guidelines. Hepatology 2000;31(4):1005-13.
11. Shen M, Zhang F, Zhang X. Primary biliary cirrhosis complicated with interstitial lung disease. J Clin Gastroenterol 2009;43(7):676-9.
12. Liu B, Zhang FC, Zhang ZL, Zhang W, Gao LX. Interstitial lung disease and Sjögrens syndrome in primary biliary cirrhosis: a causal or casual association? Clin Rheumatol 2008;27(10):1299-306.
13. Senol S, Tasbakan MI, Pullukçu H, Yamazhan T, Büke Ç, Ulusoy S, et al. [Granulomatous liver diseases: three cases]. Ege Journal of Medicine 2007;46(3):167-70.
14. Drebber U, Kasper HU, Ratering J, Wedemeyer I, Schirmacher P, Dienes HP, et al. Hepatic granulomas: histological and molecular pathological approach to differential diagnosis--a study of 442 cases. Liver Int 2008;28(6): 828-34.
15. Karlish AJ, Thompson RPH, Williams R. A case of sarcoidosis and primary biliary cirrhosis. Lancet 1969;2(7620):599.
16. Stanley NM, Fox RA, Whimster WF, Sherlock S, James DG. Primary biliary cirrhosis or sarcoidosis or both? N Engl J Med 1972;287(25): 1282-4.
17. Fagan EA, Moore-Gillon JC, Turner-Warwick M. Multiorgan granulomas and antimitochondrial antibodies. N Engl J Med 1983;308(10): 572-5.
18. Bartosiewicz M, Siemion-Szcześniak I, Jędrych M, Radwan-Röhrenschef P, Lewandowska K, Langfort R, et al. [Interstitial lung disease in patients with primary biliary cirrhosis]. Pneumonol Alergol Pol 2012;80(5): 471-81.
19. Ichikawa Y, Saisho M, Koga H, Tokisawa S, Tokunaga N, Oizumi K. Lymphocytic alveolitis associate with asymptomatic primary biliary cirrhosis. Kurume Med J 1993;40(2):59-63.
20. Spiteri M, Johnson M, Epstein O, Sherlock S, Clarke SW, Poulter LW. Immunological features of lung lavage cells from patients with primary biliary cirrhosis may reflect those seen in pulmonary sarcoidosis. Gut 1990;31(2):208-12.
21. Jastrzębski DT, Musialik JA, Ziora DI, Niepsui GS, Okiek K, Petelenz MI, et al. [Lung function tests and bronchoalveolar lavage (BAL) findings in patients with primary biliary cirrhosis]. Wiad Lek 2002;55(9-10):516-24.
22. Statement on Sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. Am J Respir Crit Care Med 1999;160(2):736-55.
23. Baughman RP, Culverf DA, Judson MA. A concise review of pulmonary sarcoidosis. Am J Respir Crit Care Med 2011;183(5):573-81.
24. Judson MA. Advances in the diagnosis and treatment of sarcoidosis. F1000Prime Rep 2014;6:89.
25. Klatskin G, Yesner R. Hepatic manifestations of sarcoidosis and other granulomatous diseases: a study based on histological examination of tissue obtained by needle biopsy of the liver. Yale J Biol Med 1950;23(3):207-48.
26. Rudzki C, Ishak KG, Zimmerman HJ. Chronic intrahepatic cholestasis of sarcoidosis. Am J Med 1975;59(3):373-87.
27. Maddrey WC, Sha E, Keeffe E. When sarcoidosis overlaps primary biliary cirrhosis. J Respir Dis 1985;6:41-5.