Primary biliary cirrhosis and hepatic sarcoidosis – A case report

Primarna bilijarna ciroza i sarkoidoza jetre

Tamara Alempijević*, Aleksandra Sokić-Milutinović*, Ljubiša Tončev*, Aleksandra Pavlović-Marković*, Srdjan Djuranović*, Nada Tomanović†, Jelena Drulović‡

*Clinic for Gastroenterology and Hepatology, †Clinic for Neurology, Clinical Center of Serbia, Belgrade, Serbia; ‡Faculty of Medicine, University of Belgrade, Belgrade, Serbia

Abstract

Introduction. Primary biliary cirrhosis (PBC) is an immune-mediated chronic progressive inflammatory liver disease leading to destruction of small interlobular bile ducts. Sarcoidosis is a chronic disorder of unknown etiology characterized by non-caseous granulomas. Case report. We reported a 69-year-old female patient with abdominal pain, malaise, vertigo, headaches, hands tremor and partial loss of hearing. Initial laboratory findings revealed elevated liver function tests and cholesterol with positive antimitochondrial and antinuclear antibodies. Liver biopsy revealed granuloma typical for PBC and granulomatous lesions typical for sarcoidosis. Elevated serum angiotensin-converting enzyme and granulomatous lesion on the brain magnetic resonance imaging (MRI) were detected and the patient was diagnosed with overlap of PBC and liver sarcoidosis and neurosarcoidosis. The patient was treated with ursodeoxicholic acid (UDCA) and prednisolone. Six months later the patient was symptom-free with laboratory findings within normal range. Conclusion. In PBC patients it is important to consider coexisting granulomatous liver diseases if elevated liver function tests persist despite UDCA therapy.

Key words:

liver cirrhosis, biliary; sarcoidosis; diagnosis, differential; histological techniques; treatment outcome.

Introduction

Primary biliary cirrhosis (PBC)1, 2 is an immune-mediated chronic progressive inflammatory liver disease. In course of the disease destruction of small interlobular bile ducts together with progressive cholestasis is observed. If PBC is not treated it progresses to liver fibrosis and cirrhosis. PBC affects middle-aged women. Biochemical markers in PBC patients reveal cholestasis together with positive finding of serum antimitochondrial autoantibodies (AMA)3. Histological examination after liver biopsy reveals damaged biliary epithelial cells and loss of small intrahepatic bile ducts. In the portal tracts CD4+ and CD8+ T cells, B cells, together with macrophages, eosinophils and natural killer cells are found1, 4. Sarcoidosis is chronic granulomatous disease of unknown etiology that can affect different and sometimes multiple organs. It is most commonly diagnosed in patients aged 25 to 40, more often in women5. Pathogenesis of the disease is not completely clarified but it is probable that in geneti-
cally susceptible individual immunological response to yet unidentified antigen triggers of the disease exists. Loss of both regulatory and apoptotic mechanisms are also proposed as possible factors that play a role in the pathogenesis of this disease. Inflammatory process leading to granuloma formation is predominantly Th1 mediated and involves lymphocytes, macrophages and cytokines. Underlying mechanism responsible for chronic course and fibrosis in sarcoidosis patients is unclear. The majority of sarcoidosis patients remain asymptomatic despite the fact that hepatic granulomas are found after liver biopsy in 50–65% of patients and in autopsy series in 70% of cases. Liver function tests remain within normal range in the majority of cases and chronic intrahepatic cholestasis progressing to biliary cirrhosis is rare.

Since in many patients with PBC histological examinations of the liver reveal hepatic granulomas and taken into account similarities in clinical manifestation possible relation between PBC and sarcoidosis is presently under debate.

Nevertheless, evidence of overlap of these two diseases is extremely rare, with the majority of published data related to patients with skin sarcoidosis and PBC.

Case report

A 69-year-old female patient was referred to the Clinic for Gastroenterology, Clinical Center of Serbia, from regional hospital where, based on elevated liver function tests and positive AMA, PBC was diagnosed and the patient was started on standard dose of ursodeoxycholic acid (UDCA). The patient was referred to our Clinic for further diagnosis and treatment since laboratory findings did not improve in the course of UDCA therapy and the patient was experiencing clinical symptoms. On admission the patient reported abdominal pain localized in right upper quadrant, exhaustion, occasional vertigo, headaches localized in the occipital region, tremor of the hands and unilateral partial loss of hearing. The patient’s past medical history was not significant. Physical examination revealed xanthelasma on eyelids. Neurological examination revealed partial unilateral hearing loss and postural tremor of the hands. Initial laboratory findings revealed hemoglobin (Hgb) 100g/L (normal range 122–157 g/L), mean corpuscular volume (MCV) 74.6 (normal range 83–97.2 fL), hematocrit (Htc) 30% (normal range 35.6–47%), serum iron 4.2 μmol/L (normal range 7–28 μmol/L), total iron binding capacity (TIBC) 79.4 μmol/L (44.8–80.6 μmol/L), ferritin 3.1 μg/L (normal range 21.8–274.7 μg/L), aspartate aminotransferase (AST) 48 U/L (normal range 0–37 U/L), alanine aminotransferase 67 U/L (normal range 0–41 U/L), cholesterol 8.25 mmol/L (normal range 0–5.2 mmol/L). Hepatitis A, B and C profiles were negative. Alpha1 antitrypsin and ceruloplasmin were within normal range. Immunology profile revealed positive AMA-M2, 1:640, and antinuclear antibodies (ANA) – Hep2 IgG: cytoplasm + mitochondrial type 1:320. Further investigation revealed all tested tumor markers including AFP, CEA, CA 19-9 and CA 125 were within normal range. Chest X-ray and abdominal ultrasound were normal. On the esophagogastro-duodenoscopy multiple angiodysplasia in the duodenal mucosa were detected and treated with argon plasma coagulation. Colonoscopy and barium follow-through were normal. Video capsule endoscopy excluded the presence of other causes of anemia apart from previously diagnosed duodenal angiodysplasia. Percutaneous liver biopsy was performed and histological examination revealed granuloma typical for PBC (Figure 1) and unexpectedly also granulomatous lesions typical for sarcoidosis (Figure 2).

Since liver biopsy suggested overlap of PBC and sarcoidosis further diagnostic procedures were performed and revealed elevated serum angiotensin-converting enzyme (ACE) of 88 U/L (range 8–52 U/L), while chest computed tomography (CT) scan was normal thus excluding pulmonary sarcoidosis. Since the patient had neurological symptoms (headache, vertigo, unilateral partial loss of hearing and tremor of the hands) neurological workup was performed and it revealed ACE levels of 8 U/L in cerebrospinal fluid, while brain magnetic resonance imaging (MRI) revealed focal, nodular lesion localized in the right cavernous sinus near internal carotid artery and medial cerebral artery. This lesion had MRI characteristics of granulomatous lesion (Figure 3). In differential diagnosis aneurismatic dilation of blood vessel was considered but excluded after MRI brain angiography was normal. The diagnosis of neurosarcoïdosis was established.
After detailed diagnostic workup the patient was diagnosed with overlap of PBC and liver sarcoidosis and neurosarcoidosis. The patient was continued on UDCA and started on 20 mg of oral prednisolone. Six month later the patient was symptom-free and laboratory findings were within normal range.

Discussion

Gastrointestinal tract is rarely affected by sarcoidosis. Gastric sarcoidosis is diagnosed in 2.5%, and intestinal involvement in 3.4% of all sarcoidosis patients. As opposed to these findings liver involvement is diagnosed and granuloma typical for sarcoidosis detected after liver biopsy in 50–79% of patients, while autopsy reveals granuloma in 67–70% of patients.

Liver involvement is more frequent in African Americans than in Caucasians. Symptomatic liver disease is rare despite frequent granuloma detection. Abdominal pain and itching are more frequent than jaundice. Fever is more frequently seen in patients with liver sarcoidosis than in those without liver involvement. The responsible pathogenic mechanisms resulting in jaundice are intrahepatic cholestasis, but also hemolysis and hepatocellular dysfunction. Granulomatous hilar lymph nodes can also cause obstruction of extrahepatic bile ducts and result in jaundice.

Abnormal values of liver tests found in 35% of patients with sarcoidosis are not reliable predictors of clinical course and outcome of the liver disease. Approximately one quarter of sarcoidosis patients have liver involvement with no pulmonary disease. Enlarged liver is diagnosed during physical examination in one out of five patients while abdominal CT scans show liver enlargement in more than 50% of patients. Hepatic granuloma can be found on liver biopsy irrespective of the liver size thus biopsy should be performed in cases of suspected liver sarcoidosis even if the liver is not enlarged. Alkaline phosphatase is a more reliable marker of liver involvement than gamma glutamyl-transpeptidase.

Overlap syndrome or simultaneous presence of PBC and sarcoidosis has been previously reported, and the majority of cases were of skin and/or lung sarcoidosis, while the simultaneous presence of hepatic sarcoidosis and PBC is very rare. Namely Rajoriya et al. analyzed data from 1,510 patients with sarcoidosis aiming to identify disease association of sarcoidosis with different immune mediated and chronic inflammatory disease. Out of 1,510 patients only in 3 PBC was diagnosed and these results suggested that there was no significant association of PBC with sarcoidosis implying that this overlap is rare. To the best of our knowledge this is the first case of neurosarcoidosis described in PBC patient.

Histological similarities between PBC and sarcoidosis described more than 35 years ago tempted authors to speculate close relationship of the two diseases and to suggest possible common pathogenesis. Karlish et al. reported a female patient with cholestatic liver disease, enlarged hilar and paratracheal lymph nodes. The diagnosis of sarcoidosis was based on positive Kweim test, while positive AMA supported the diagnosis of PBC. A year later a case series was published demonstrating the simultaneous presence of PBC and liver sarcoidosis in 10% and PBC with lung sarcoidosis in another 10% of patients. Stanley et al., Rudzki et al. and Fagan et al. also reported small series of PBC patients with lung sarcoidosis, but none of these patients suffered from liver sarcoidosis. Hughes and McGavin reported a female patient diagnosed with sarcoidosis affecting her skin, nasal mucosa, lungs, lacrymal and parotid glands. In that patient granulomatous hepatitis with immunological features of PBC was diagnosed together with myositis.

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One of the most detailed reports published by Stanca et al. deals with a patient with progressive cholestatic liver disease that lead to liver transplantation. In this particular patient the differential diagnosis between liver sarcoidosis and PBC was not resolved during 24 years (from 1980 till 2004). Since the patient was diagnosed with lung sarcoidosis liver granuloma were considered to be related to sarcoidosis until the positive findings of AMA that confirmed the diagnosis of PBC.

The number of reported sarcoidosis and PBC overlap cases is too small to support the etiological link between the two diseases. The diagnosis of PBC is in 90% of patients confirmed by positive AMAs test result since AMA are negative in liver sarcoidosis.

Use of immunoblotting and enzyme-linked immunosorbent assay (ELISA) to detect M2-specific AMAs, as well as adequately performed and analyzed liver biopsy will probably result in precise establishing of the incidence of overlap between PBC and liver sarcoidosis, resulting in prompt treatment that will result in improved quality of life and prognosis of these patients.

**Conclusion**

It is of great importance to consider coexisting sarcoidosis and other liver diseases in PBC patients especially if elevated liver function tests persist despite the therapy.

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**REFERENCES**


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