CASE REPORT

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Isolated hepatic sarcoidosis

Izolovana sarkoidoza jetre

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Abstract

Introduction. Sarcoidosis is a multisystem granulomatous disease of unknown etiology. Although hepatic granulomas occur in 50–65% of patients with systemic sarcoidosis, isolated liver sarcoidosis is rare. Clinical presentation varies from asymptomatic to manifest. The diagnosis is based on a characteristic histopathological finding of liver biopsy. **Case report.** We reported a 69-year old man was admitted due to abdominal swelling and abdominal pain. Laboratory studies detected: cholestasis, pancytopenia and elevaton of angiotensin-converting enzyme. Abdominal imaging techniques showed liver cirrhosis, splenomegaly and ascites. The diagnosis of the hepatic sarcoidosis was confirmed by histopathological examination of liver biopsy. The patient was treated with corticosteroids. After 18 months the patient was without any subjective symptoms, and with biochemical and clinical improvement. **Conclusion.** Isolated hepatic sarcoidosis should be considered in the differential diagnosis of asymptomatic or simptomatic patients with hepatosplenomegaly and changes in liver functional tests. Only the timely diagnosis and proper treatment can lead to subjective and objective improvement of patients.

Key words:
sarcoidosis; liver cirrhosis; splenomegaly; ascites; diagnosis; histological techniques; treatment outcome.

Apstrakt

Uvod. Sarkoidoza je multisistemsko granulomatozno oboljenje nepoznate etiologije. Hepatični granulomi nalaze se kod 50–65% bolesnika sa sistemskom sarkoidozom, ali je izolovana hepatična sarkoidoza retka. Klinička slika varira od asimptomatske do manifestne. Dijagnoza se postavlja na osnovu karakterističnog patohistološkog nalaza. **Prikaz bolesnika.** Prikazan je muškarac, star 69 godina, primljen zbog oticanja trbuha i abdominalnih bolova. U laboratorijskim analizama imao je povišenje enzima holestaze, pancitopeniju i povišenje angiotenzin-konvertirajućeg enzima. Ultrasonografija i magnetna rezonanca abdomena ukazali su na cirozu jetre, splenomegaliju i ascites. Dijagnoza hepatične sarkoidoze potvrđena je patohistološkim pregledom bioptata jetre. Bolesnik je lečen kortikosteroidima. Nakon 18 meseci, bolesnik je bio bez tegoba, sa laboratorijskim i kliničkim poboljšanjem. **Zaključak.** Kod bolesnika sa hepatosplenomegalijom i poremećajima u hepatogramu, i kod onih bez simptoma, i onih sa simptomima oboljenja, u diferencijalnoj dijagnozi treba razmotriti izolovanu hepatičku sarkoidozu. Jedino pravovremena dijagnoza i adekvatna terapija mogu dovesti do subjektivnog i objektivnog poboljšanja.

Ključne reči:
sarkoidoza; jetra, ciroza; splenomegalija; ascit; dijagnoza; histološke tehnike; lečenje, ishod.

Introduction

Sarcoidosis is a multisystem granulomatous disease of unknown etiology [1]. The main characteristic of this disease is the presence of uncaseous epitheloid granuloma in the tissue. In 80–95% of patients, the changes affect the lungs and hilar lymph nodes [2, 3]. Extrapulmonal disease is often seen as part of systemic sarcoidosis and all the organs can be affected, particullary: skin, eyes, liver, spleen, lymph nodes and bone marrow [2, 4]. Although hepatic granulomas occur in 50–65% of patients with systemic sarcoidosis, isolated liver sarcoidosis is rare [4–8]. Hepatic events may be the first and only clinical sign of extrapulmonal sarcoidosis [9]. The clinical presentation varies from asymptomatic to symptoms and signs such as abdominal pain, nausea, vomiting, hepatosplenomegaly, clinical signs of cirrhosis and liver failure [7, 9, 10]. The diagnosis is based on

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clinical, laboratory and radiological findings with a characteristic histopathological finding of liver biopsy, if previously excluded other causes of hepatic granulomas [1].

We reported a patient with isolated liver sarcoidosis which was presented as decompensated liver cirrhosis.

Case report

A 69-year-old man was admitted to the Clinic for Gastroenterology, Clinical Center of Serbia, with abdominal swelling and abdominal pain located mostly in the left but also in the right hypohondrium. Symptoms lasted for two months before admission. The previous 6 years the patient had occasional mutual hypohondrial pain, but he did not find it significant. He denied other diseases, surgeries, and allergies. The family history was positive for cardiovascular diseases, but not for granulomatous or autoimmune disorders or any relevant disease of the gastrointestinal tract. Physical examination showed tenderness in the left upper quadrant. The liver was not enlarged, and the lower spleen border palpated 3 cm below the left costal margin. There were clinical signs of ascites.

Laboratory studies detected the elevation of cholestasis enzymes, with normal transaminase values. There were also signs of pancytopenia, prerenal azotemia, hypoproteinemia with hypoalbuminemia, sideropenia, elevated inflammatory markers and angiotensin converting enzyme (ACE) (Table 1). Other causes of liver diseases were excluded (no history of alcohol consumption, negative viral markers, autoantibodies and laboratory tests for metabolic liver diseases). Urine sample was normal. Stool sample was positive for muscle fibers and digested starch. The purified protein derivative test (PPD) was negative.

Abdominal ultrasonography and magnetic resonance imaging (MRI) showed the normal sized, inhomogeneous, macronodular liver with wavy edges and regular hypoechogenic nodules, surrounded by a thin hyperechoic bands (Figures 1 and 2). The gallbladder had no intraluminal content,

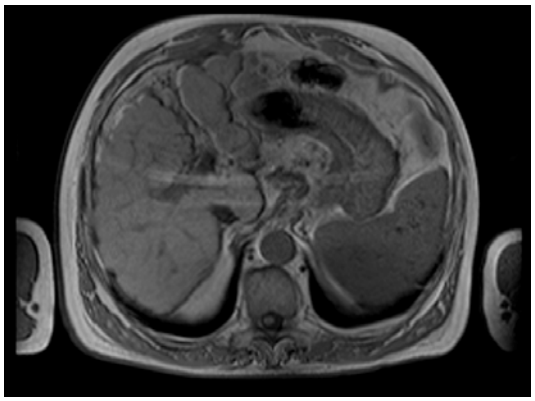


Fig. 1 – Abdominal magnetic resonance imaging showed normal sized, inhomogeneous, macronodular liver.

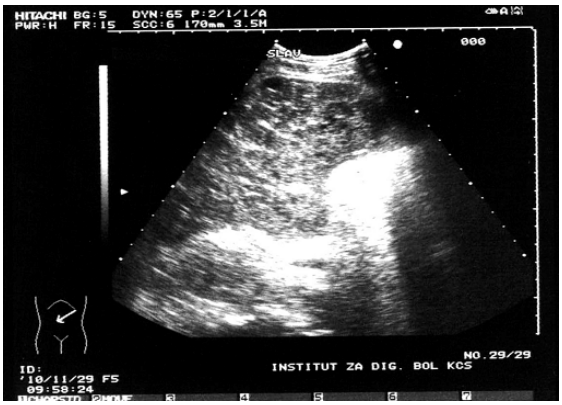


Fig. 2 – Abdominal ultrasound revealed the inhomogeneous liver with wavy edges and regular hypoechogenic nodules, surrounded by a thin hyperechoic bands.

Table 1

Laboratory analyses on admission and on control examination

Variables	On admission	After 18 monts	Reference range
Red blood cells (1×10^{12}/L)	3.7	4.1	4.3–5.7
Hemoglobin (g/L)	109.7	123	138–175
Hematocrit (L/L)	0.32	0.36	0.41–0.53
MCV (fL)	87.2	88	83–97.2
White blood cells (1×10^{9}/L)	2.3	4.6	3.4–9.7
Lymphocites (1×10^{9}/L)	0.4	0.7	2.1–6.5
Platelets (1×10^{9}/L)	74	64	158–424
Glucose (mmol/L)	6.0	10.5	4.2–6.1
Urea (mmol/L)	12.9	4.3	3.2–7.1
Creatinine (μmol/L)	97	73	62–133
Protein (g/L)	60	71	63–82
Albumin (g/L)	35	44	39–50
Iron (μmol/L)	4.7	11.1	8.8–32.4
TIBC (μmol/L)	45.2	60.5	44.8–80.6
Aspartate aminotransferase (U/L)	38	27	14–50
Alanine aminotransferase (U/L)	31	28	21–72
Alkaline phosphatase (U/L)	254	109	38–126
γ -glutamyl transferase (U/L)	157	83	8–78
Erythrocyte sedimentation rate (mm/h)	30	20	2–10
Fibrinogen (g/L)	4.7	4.2	2–4
Angiotensin-converting enzyme (U/L)	95	64	8–65
Hemoglobin A1c (%)		7.7	3.9–6.1

MCV – mean corpuscular volume, TIBC – total iron-binding capacity.

but its wall was irregularly thickened (5–13 mm). The spleen was enlarged, homogeneous, 180 mm in craniocaudal diameter (Figure 3). The portal (15 mm) and lienal vein (13.6 mm)

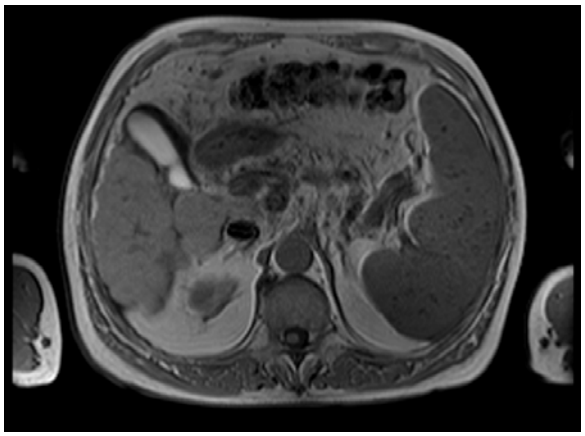
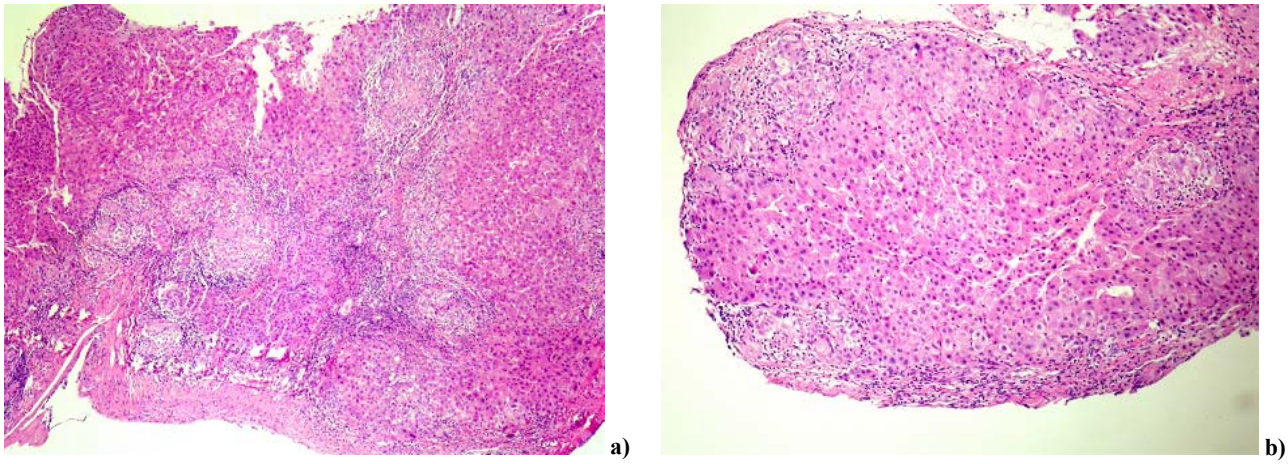


Fig. 3 –Abdominal magnetic resonance imaging showed splenomegaly.

were dilated. No intraabdominal lymphadenopathy was detected, but there was a reasonable amount of ascites. Transient elastography showed the signs of liver cirrhosis (Stiffness 20.6 kPa). During diagnostic laparoscopy regeneratory nodules with several centimeters in diameter were seen in the liver, with smooth capsule, and in some places covered with whitish planes. Biopsies were taken. Histopathological examination indicated chronic granulomatous hepatitis accompanied by an irregular sinusoidal dilation, but without other elements of Budd-Chiari syndrome. In some slices, the structure of the liver was changed showing regenerative nodules and cirrhotic changes parenchyma (Figure 4a). The dominant finding were numerous portal and periportal non-necrotizing granulomas, sarcoid type, consisting of epithelioid cells, macrophages, multinuclear giant cells with a few lymphocytes in the periphery and rarely partially fibrosing (Figure 4b). Staining with PAS (Periodic acid-Schiff) and Ziehl-Neelsen revealed no acid fast bacillus, nor other microorganisms. Esophagogastroduodenoscopy revealed varices of the oesophagus gradus III with "cherry red spots", varices of the cardia and portal hypertensive gastropathy. Chest X-ray and thoracic multi-detector computed tomography (MDCT) were normal. Histopathology finding of bone marrow did not show signs of granulomatous inflamation, but only reactive changes. The patient was treated with intravenous prednisolon (30 mg/day). On the day 6 of corticosteroid therapy hyperglycemia occurred, which was up to 32.6 mmol/L, so we started the therapy with metformine, long-lasting and short-lasting insulin. The dose of prednisolone was reduced to 20 mg a day. This therapy continued for the next 3 months and then corticotsteroid therapy gradually reduced to the maintenance dose of 5 mg a day. The patient was also treated with proton pump inhibitors, non-selective beta blocker, diuretic and supportive care. After 18 months, the patient was without any subjective symptoms, control laboratory tests were better than on admision, ACE was also normal (Table 1). Control abdominal MRI was without progression, the amount of ascites was reduced. Control chest radiography did not show signs of sarcoidosis/granulomas in the lung and hilar lymph glands. The maintenance therapy with prednisolone (5 mg a day) along with proton pump inhibitors, non-selective beta blocker and diuretic was continued.

Discussion

Sarcoidosis is a chronic multisystem disease. The incidence of this disease is 1–40 *per* 100,000 population [9, 11]. The highest incidence is in Scandinavian countries, the USA and Japan and the lowest in Asia and North America [12]. Most commonly it affects adults aged 20–40 years [12]. Sarcoidosis occurs equally in both genders, but sarcoid-related liver disease is more common in men [13]. The etiology of the disease is unknown but is expected to be multifactorial and includes genetic, environmental factors and infectious agents [14]. The clinical presentation of liver sarcoidosis can vary from asymptomatic to manifest. The dominant clinical manifestation of liver sarcoidosis is hepatomegaly, which occurs in 10–40% of patients [7, 9, 10], while splenomegaly is found in



a) b)

Fig. 4 – Liver histopathology: a) Regenerative nodules and cirrhotic changes of parenchyma. In some slices, the structure of the liver is changed and shows regenerative nodules and cirrhotic of changes parenchyma (HE, ×13); b) Numerous portal and periportal non-necrotizing granulomas, sarcoid type, consisting of epithelioid cells, macrophages, multinuclear giant cells with a few lymphocytes in the periphery (HE, ×52).

10–30% of patients [9]. Non-specific symptoms are: weight loss, abdominal pain, night sweats, erythema nodosum, fever and arthralgia [10]. Fever and arthralgias are more frequently seen in patients with liver sarcoidosis than in those with sarcoidosis without liver involvement [15]. The patient presented with nonspecific symptoms such as abdominal swelling and pain mostly in left hypohondrium which probably was caused by splenomegaly and ascites. Eventually decompensated liver cirrhosis with portal hypertension was diagnosed.

Liver cirrhosis occurs in 6–8% of patients with hepatic sarcoidosis [8, 16] mostly in advanced cases and may be accompanied by all its complications (portal hypertension, variceal bleeding, ascites, hepatic failure, etc.). Portal hypertension is a rare complication of liver sarcoidosis in patients with or without cirrhosis [8]. It occurs as a consequence of chronic hyperdynamic circulation in the portal system caused by arteriovenous shunts and/or compromited portal vein flow in the regions with the presence of granuloma, fibrosis and hyalinization of the portal triad which leads to the presinusoidal block [6]. Ascites occurs as transudate (portal hypertension, deterioration of right heart function) or exudate (peritoneal infiltration with sarcoid nodules) [17]. Rare clinical presentation of liver sarcoidosis are jaundice and Budd-Chiari syndrome [18]. Jaundice occurs as a result of direct affection of the biliary system (intrahepatic cholestasis, "vanishing" bile duct and ductopenia) [18]. If hepatic granulomas or enlarged lymph nodules compress the main biliary ducts, it may develop jaundice which corresponds to the differential diagnosis of cholangiocelular carcinoima [6, 19–21]. Budd-Chiari sindrome is caused by compromited hepatic veins blood flow and consequent development of thrombosis [18]. Blood analysis in patients with sarcoidosis can show leucopenia, lymphopenia, eosinophilia and monocytosis. ACE is elevated in around 70% of patients with hepatic sarcoidosis [6]. Elevation of alkaline phosphatase and γ-glutamyl transferase is found in 20–40% of patients [6, 10, 18, 22]. Transaminases may be normal or slightly elevated. Inflammatory markers (erythrocyte sedimentation rate, C-reactive protein) are normal or slightly elevated. Hypercalcemia may be present, as well as the increase in γ-globulins. Our patient had the elevation of alkaline phosphatase and γ-glutamyl transaminase, with normal transferase values . Regarding tha fact that we excluded alternate etiology of liver lesion (alcoholic, viral, autoimmune, cholestatic and metabolic liver disease), and a patient had an increase in ACE, we suspected on liver sarcoidosis. Abdominal imaging techniques [ultrasound, computed tomography (CT) and MRI] are used in setting the diagnose of liver sarcoidosis. Liver ultrasonography may indicate hepatomegaly, hyperechoic, inhomogeneous liver with or without nodules, denticulate edges and focal calcification [6, 23]. CT detect hepatic granulomas in less than 5%, since they are usually microscopic [18]. It can detect enlarged, homogeneous liver with diffuse, hypodense, various sized regenerative nodules, without contrast gain [6]. These nodules are low density in T2 sequences of MRI examination [6, 7]. Both imaging techniques can detect intraabdominal lymphadenopathy. The diagnosis of hepatic sarcoidosis is confirmed by pathological finding of uncaseous epithelioid granuloma, which are predominantly found in the portal and periportal areas [18]. Regarding the fact that granulomas can be found in other liver diseases, it is necessary to exclude other causes before the diagnosis of sarcoidosis. Epitheloid liver granulomas are with or without necrosis. Uncaseous granulomas without necrosis occur as a result of non-infectious diseases (sarcoidosis, primary biliary cirrhosis, drug-induced liver lesion) while granulomas without necrosis occur as a result of infectious genesis [24, 25]. In Western Europe and the USA sarcoidosis is in the second place (after primary biliary cirrhosis) as a cause of hepatic granulomas, accounting for 12–36% [12, 26, 27]. In the Middle East, the dominant cause of hepatic granulomas are infections diseases. In Saudi Arabia it is schistosomiasis (54%) [12], and in Iran the major cause is tuberculosis (52.8%) [28]. In presenting case imaging techniques indicated a modified cirrhotic liver, ascites and splenomegaly. Since the presence of ascites made percutaneous liver biopsy less desirable, we decided to go for laparoscopic liver biopsy. The diagnosis of liver sarcoidosis in our patient was confirmed based on histological findings of epithelioid granuloma in the portal and periportal areas, with the prior exclusion of other diseases that might cause similar changes. Normal finding of chest radiography and thoracic multislice computed tomografy (MDCT) excluded the diagnose of pulmonary sarcoidosis. Treatment of hepatic sarcoidosis depends on the clinical and laboratory presentations. Patients with histopathological finding of liver sarcoidosis, who are asymptomatic and had referent liver enzyms values need no therapy. Asymptomatic patients with mild elevation of liver enzymes but without clinical and laboratory sings of systemic sarcoidosis are suggested clinical and laboratory monitoring, without medication treatment with the possibility of a spontaneous resolution [6, 18, 29, 30]. In patients with refractory changes in liver enzyms values, clinical signs of cholestasis, cirrhosis, and systemic signs of sarcoidosis, corticosteroids are the treatment of choice. Most patients achieve satisfactory results with the low-dose prednisolone (10–15 mg/day), while in patients with jaundice and itching higher doses (40–60 mg/day) are used [18, 30]. Corticosteroids can not prevent disease progression including the development of portal hypertension, biliary duct depletion and fibrosis [8, 18]. Described cases of cholestasis enzymes normalization in patients with liver sarcoidosis responded to ursodeoxycholic acid therapy [8, 31]. Along the corticosteroid therapy immunomodulators (azathioprine, methotrexate, hydroxychloroquine, and infliximab) have a positive effect on symptoms, disorders of liver enzyms and hepatomegaly, but do not prevent disease progression [30]. The use of chloroquine, cyclosporine, cyclophosphamide, thalidomide and pentoxyphiline is also described but the strict guidelines do not exist [18]. In patients with advanced disease who do not respond to medical therapy, the only modality of treatment is liver transplantation [16]. Our patient was treated with prednisolone, which lowered the intensity of symptoms and improved laboratory findings. We started with diuretic therapy due to ascites, and propranolol due to portal hypertension with esophageal varices and gastric fornix varices. Clinical course was complicated by iatrogenic diabetes which was controlled by diet, oral antidiabetics and insulin.

Conclusion

Isolated hepatic sarcoidosis is a rare disease of unknown etiology which can lead to cirrhosis with all its complications. It should be considered in the making of differential diagnosis in both asymptomatic and symptomatic patients with hepatosplenomegaly and changes in the level of liver enzyms. Early diagnosis and appropriate therapy lead to subjective and objective improvement with a questionable effect on the progression of the disease.

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