Hepatic Sarcoidosis : Clinico-pathological characterization of symptomatic cases

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Abstract

Aim : **The aim of this study was to investigate the clinical and pathological features of hepatic sarcoidosis in symptomatic cases.**

Methods : **Twenty-two symptomatic hepatic sarcoidosis cases were included in the study. Hepatic sarcoidosis was determined by typical imaging, histopathology, and high angiotensin-converting enzyme levels. Demographic data, laboratory data, imaging findings, liver biopsies, and clinical findings were analyzed. Portal hypertension (PH) was defined by the presence of ascites and/or varices ; imaging findings suggestive of PH-splenomegaly (> 12 cm on longest axis) ; portal vein dilation (> 13 mm) ; collateral vessel formation ; and hepatic venous pressure gradient ≥ 6 mmHg.**

Results : **Mean age was 49.63 ± 10.7 years. Liver tests showed elevated serum alkaline phosphatase and gamma-glutamyl transpeptidase levels (95%). Serum albumin levels were low (< 3 g/dl) in 32% of the patients. Histologically, hepatic granulomas were located in the portal/periportal areas, with or without parenchymal involvement (77%). Duct damage (27%), absent portal veins (32%), and hepatomegaly (41%) were also observed. Clinically, chronic cholestatic symptoms and PH features were observed in 41% and 50% of the patients, respectively. Three-quarters of patients with PH features were non-cirrhotic. Cirrhosis and bleeding varices were observed in 14%. Hepatic sarcoidosis overlaps with primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) was observed in two cases.**

Conclusion : **Sarcoidosis causes significant hepatic disease. PH and jaundice are main clinical presentations in liver sarcoidosis patients. Imaging findings of PH should be carefully reviewed, as it can occur even before the establishment of cirrhosis. Hepatic sarcoidosis mimics and overlaps with PBC and PSC.** (Acta gastroenterol. belg., **2015**, 78, **306-313**).

Key words : sarcoidosis, liver granuloma, portal hypertension, cirrhosis, cholestasis.

Introduction

Sarcoidosis is a multisystemic granulomatous disease. Sarcoidosis affects all races and ethnic groups (1). It manifests in younger age group of 20-40 years (1). Sarcoidosis mainly affects the lymph nodes and lungs ; other organs such as liver, skin, eyes, and nervous systems are also involved (1). Granulomatous liver involvement is seen in 50-90% cases, but it gets unnoticed because of minimal liver test abnormalities and absence of liver specific symptoms (2,3). Liver test abnormalities are detected in approximately 20-40% of all affected patients (3,4). Only 5%-30% of patients present with clinical signs and symptoms and majority of them have constitutional symptoms such as fever (60%) nausea, vomiting, abdominal pain in the right upper quadrant (15-30%), a painful liver during palpation, and hepatosplenomegaly (15-40%) (1,2,3). Only a minority of hepatic sarcoidosis patients have liver related specific clinical features. Those have liver specific clinical symptoms ; usually present with features of chronic cholestasis e.g. jaundice and pruritus, portal hypertension (PH), cirrhosis, and very occasionally ; Budd-Chiari syndrome (3,5). A diagnosis of hepatic sarcoidosis is established when clinico-radiological findings are supported by a compatible biopsy histology, after the exclusion of other causes of hepatic granulomas (6,7). In the present study, we systematically analyzed the clinical and histopathological characteristics of clinically apparent hepatic sarcoidosis cases.

Materials and Methods

Case selection

A retrospective search of the tertiary care liver hospital database was conducted for patients who had sarcoidosis. A total of 54 cases of hepatic sarcoidosis were enrolled in our institute over a period of four years. Thirty-two of the 54 cases were clinically asymptomatic and presented with a slightly deranged liver tests and their histopathology was not available. These asymptomatic cases were diagnosed as liver sarcoidosis based on the presence of non-necrotizing and Ziehl-Neelsen (ZN) stain negative solid granulomas obtained by fine-needle aspiration cytology on lymph nodes ; high angiotensin-converting enzyme (ACE) level ; and typical imaging features along with liver involvement. Thus, the study included 22 clinically symptomatic (> 3 times elevated serum alkaline phosphatase (SAP), fever, Jaundice, pruritus, and PH related findings) hepatic sarcoidosis cases diagnosed at our institute from January 2010 to December 2013. Liver sarcoidosis diagnosis in these cases were established based on liver biopsy findings of solid, non-necrotizing, epithelioid cell granulomas, typical of sarcoidosis ; high ACE levels ; and radiological findings of mediastinal/abdominal lymphadenopathy and lung involvement (the rationale behind the diagnosis is summarized in Table 1). Liver biopsies were obtained both for liver related clinical symptoms (jaundice, pruritus, pyrexia of unknown origin, PH related features and hepatosplenomegaly) and

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Table 1. — **Rationale for sarcoidosis diagnosis**

Diagnostic modality	Rationale
Histopathology in liver biopsy	Solid, non necrotizing, granulomas predominantly at the portal/periportal location with scarring are suggestive of sarcoidosis after excluding other causes of liver granuomas ; along with corroborative findings on imaging.
Serum Angiotensin converting enzyme levels	Serum Angiotensin converting enzyme is a useful tool for confirming the diagnosis of active sarcoidosis, since it distinguishes these patients from others with tuberculosis, lung cancer or lymphoma.
Imaging features	Bilateral hilar lymphadenopathy is the most common radiologic finding frequently associated with pulmonary infiltrates and a characteristic perivascular distribution at high resolution chest computed tomography suggestive of sarcoidosis along with histopathological findings.

abnormally deranged liver tests (> 3 times elevation of SAP and/or low albumin of < 2.5 g/dl). We carefully excluded the two common etiologies of liver granulomas : tuberculosis (based on negative QuantiFERON-Gold TB-PCR tests and negative ZN stains on biopsy) and schistosomiasis (absence of raised eosinophil counts and absence of liver biopsy findings typical of the same). We also excluded other cases of known etiologies (hepatitis B, C, and D ; human immunodeficiency virus (HIV) ; Epstein-Barr virus (EBV) ; cytomegalovirus (CMV) ; syphilis ; nonalcoholic steatohepatitis (NASH) ; and alcoholic liver disease). The patients were also negative for autoimmune serology. Anti-mitochondrial antibody-M2 (AMA-M2) was performed in cases with raised SAP to exclude possibility of primary biliary cirrhosis and it was negative in all cases except one was positive for AMA-M2. Drug history was also negative in all these cases.

Clinical data collection

We reviewed the hospital information system to gather the following information for each patient symptomatic for hepatic sarcoidosis : general demographic data, clinical presentation, data regarding the diagnostic procedures (laboratory abnormalities, endoscopic and radiological findings, liver biopsies), and treatment status details. Ultrasonographic, computed tomography, and/or magnetic resonance imaging findings were defined as positive (i.e., suggestive for hepatic sarcoidosis) in the presence of hyperechogenic or hypoechogenic spots (8). Hepatomegaly and splenomegaly were assessed and recorded based on palpation and imaging findings.

Portal hypertension assessment

Diagnoses of PH were made by using the following criteria, in isolation or in combination : (1) presence of ascites and/or varices in patients with cirrhosis (9) ; (2) imaging findings suggestive of PH- (spleen > 12 cm on the longest axis), portal vein dilation (> 13 mm), or collateral vessel formation (8-10) ; and (3) hepatic venous pressure gradient (HVPG) ≥ 6 mmHg, indicating PH, or HVPG ≥ 10 mmHg, indicating clinically significant PH (11-12) .

Histopathologic examination

Histological examinations were performed on formalin-fixed, paraffin-embedded tissue sections. The following histochemical stains were performed : hematoxylin and eosin for routine examination ; Masson's trichrome for fibrosis ; periodic acid-Schiff diastase reaction for fungal elements ; and ZN for acid-fast bacilli. Histopathological examinations were performed to evaluate the architecture of the liver ; presence and degree of inflammation, steatosis, and fibrosis ; and distribution of the granulomas. The granulomas were also assessed for presence of necrosis and inclusion bodies (Schaumann's bodies and asteroid bodies). The degree of inflammation was sub-typed as mild (no or minimal periportal inflammation), moderate (periportal and minimal lobular inflammation), or severe (periportal and lobular inflammation). Hepatic fibrosis was staged according to the five-point METAVIR scale, as follows : chronic hepatitis without fibrosis (F0) ; portal fibrosis without septa (F1) ; portal fibrosis with few septa (F2) ; septal fibrosis without cirrhosis (F3) ; and complete cirrhosis (F4) (13). Steatosis was determined according to the classification proposed by Kleiner *et al*. (14) : stage 0, less than 5% ; stage 1, 5%-33% ; stage 2, 33%-66% ; and stage 3, more than 66% of the parenchyma involved by steatosis.

Results

Baseline characteristics

Of the 22 patients in this study, 12 were female and 10 were male ; their mean age was 49.63 (range, 18-65) years. All of the patients were negative for hepatitis B and C, HIV, EBV, CMV, NASH, and alcoholic liver disease. Liver tests abnormalities were detected in 21 cases (95%), all of which displayed elevated SAP and gamma-glutamyl transpeptidase (GGT) level, with median values of 260 IU/L (Inter-quartile range (IQR) 175.2-402.5) and 137.42 IU/L (IQR 92-342), respectively (range : 109-542 IU/L and 38-720 IU/L ; normal ranges : 32-90 IU/L and 7-32 IU/L, respectively). The mean serum albumin level was 3.3g/dl ; seven of the patients (32%) had levels < 3 g/dl. The mean international normalized ratio (INR) was 1 ; it was elevated in three patients who

Table 2. — **Baseline characteristics**

Characteristics	Results
Male : female	10: 12
Age years ; mean ± SD ; (range)	49. 6 ± 10.7 (18-65)
Hepatoslenomegaly	Hepatosplenomegaly - 9 Splenomegaly - 5 Hepatomegaly - 1
Serum bilirubin ; median (IQR) ; range	1.3 mg/dl (0.8-2.1 mg/dl) ; 0.3-13.3
Serum alkaline phosphatase ; median (IQR)	260 IU/L (175.2- 402.5)
Serum gamma glutamyl transpeptidase ; median (IQR)	137.4 IU/L (92-342)
Serum Aspartate aminotransaminase ; median (IQR)	41 IU/L (30.4-56 IU/L)
Serum Alanine aminotransaminase ; median (IQR)	35.5 IU/L (26.5-62.5 IU/L)
Serum albumin ; mean ± SD (range)	3.3 g/dl ± 0.8 g/dl (1.6-4.3 g/dl)
INR, range	1.0 (1.0-1.2)
Serum angiotensin converting enzyme ; mean ± SD (range)	75.7 ± 16.7 microgram/L (27-143)
Lymphadenopathy and Lung involvement	Mediastinal lymphadenopathy and patchy pulmonary lesions-11 Only mediastinal lymphadenopathy-7 Only lung involvement -1 Only Abdominal lymphadenopathy-3

Key : SD, Standard Deviation ; IQR, Inter-quartile range.

also had ascites. Liver transaminases levels were elevated in 11 cases (50%), and serum ACE levels were elevated in 17 cases. Baseline characteristics are summarized in Table 2.

Clinical features

Nine patients presented with cholestatic symptoms (five : pruritus, two : pruritus with jaundice, and two : jaundice), with total bilirubin levels ranging from 1.8 to 13.3 mg/dL. Three patients had persistent fever of > 1 month. Endoscopy revealed esophageal varices in seven patients, three of which were having bleeding varices. Ascites present in three patients ; two were with gross ascites and one was detected on ultrasound examination. Clinical findings are summarized in Table 3.

Portal hypertension

PH features were documented in 11 cases (50%) according to the above-mentioned criteria. Ten patients had imaging features of PH, including splenomegaly (> 12 cm on the longest axis) with mean span of *17.4* cm (15.6-19.4 cm), portal vein dilatation (> 13 mm) with a mean value of *16.0* mm (15-17.2 mm), and collateral formation. Seven of the 11 patients had varices, and three had ascites. Bleeding varices were observed in three patients. HVPG was measured in six cases, and it was found to be elevated (> 6 mmHg) in three patients ; two of those also had esophageal varices, and one had imaging features of PH. HVPG of < 6 mm Hg was noted in three cases and they were considered as non-portal-hypertensive. Characteristics of the PH cases are summarized in Figure 1. Among the PH cases, liver biopsy examinations revealed the stage of fibrosis as follows- F1 : 1, F2 : 5, F3 : 2 and F4 : 3. Thus, in liver sarcoidosis, PH can occur even in the absence of significant fibrosis or cirrhosis.

Table 3. — **Clinical presentation of hepatic sarcoidosis patients**

Symptoms	Percentage* of patients (*n* = 22)
Cholestatic symptoms Pruritus Prutitus and jaundice Jaundice	 22.7% 9.0% 9.0%
Fever	13.6%
Varices	31.8%
Ascites	13.6%
Hepatosplenomeglay	68.2%
Deranged liver test	95.4%

*percentage not rounded to single digit

Histopathological findings

Biopsies were available in all 22 cases, and they showed presence of non-necrotizing granulomas. The granulomas were located in the portal/periportal region in 12 (55%) patients (Fig. 2A), portal/periportal region and parenchyma in five (22%) patients, in parenchyma only in three (14 %) patients (Fig. 2B), and perivenular spaces in two (9%) patients. All of the granulomas were reticulin-rich, with peripheral condensation of reticulin fibers. ZN stain was negative in all of the granulomas, and no fungal hyphae were revealed on periodic acid-Schiff staining. There was no evidence of schistosomial worm, ova, or eosinophil predominant inflammatory infiltrate in any of these cases. No Schaumann's bodies

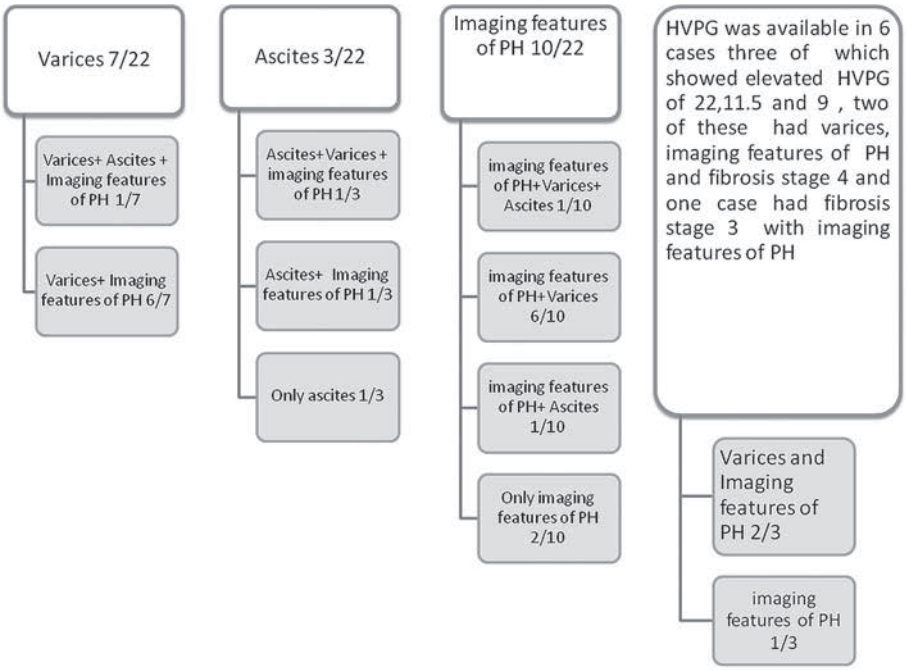

Fig. 1. — Portal hypertension findings

were seen, and asteroid bodies were observed in only one case. Duct destruction was seen in four (18%) patients (Fig. 2C), absence of duct profiles were noted in two (9%) patients, and portal tract vessels were not discernible in seven (32%) (Fig. 2D) ; three of them had inflammatory damage in the portal vein. Parenchymal cellular and canalicular cholestasis were observed in nine (41%) patients, necro-inflammatory activity was observed in nine (41%) patients, and central vein obliteration with sinusoidal dilatation was observed in three (14%) patients. Mild macrovesicular steatosis was noted in four (18%) patients. Fibrosis was staged according to the METAVIR scale and identified as follows : stage 0 in three patients, stage 1 in four patients, stage 2 in nine patients, stage 3 in three patients, and stage 4 in three patients.

Associated diseases/findings

Of the 22 patients, one 55-year-old woman had coexisting primary biliary cirrhosis (PBC) with presenting clinical manifestations of variceal bleeding, itching, and fatigue. Her serum AMA-M2 was positive, and her serum IgM level was 1.2 g/L (normal range : 0.03-0.3 g/L). She also had mediastinal lymphadenopathy, small liver and splenic lesions compatible with granulomas (Fig. 3A and B), lung lesions and raised ACE level of 110 μg/L (normal value : < 40 μg/L). On histopathological examination of her liver biopsy, this patient had cirrhotic nodules separated by very broad sclerotic fibrous septae and multiple epithelioid cell granulomas with focal duct loss. Based on the clinical, radiological, biochemical, and histopathological findings, the patient was diagnosed with primary biliary cirrhosis (PBC) associated with sarcoidosis. She was started on ursodeoxy-cholic acid (UDCA) and steroids ; subsequent clinical parameters showed an improvement.

A 48-year-old male patient presented with jaundice. His magnetic resonance cholangiopancreatography (MRCP) findings indicated primary sclerosing cholangitis (PSC) with skip areas of dilatation and narrowing involving bilobar intrahepatic biliary radicals, giving them a beaded appearance (Fig. 3C). He also had mediastinal lymphadenopathy and a raised serum ACE level of 98 μg/L. Sigmoid colon and rectal biopsies revealed features of active procto-colitis, but there was no definite evidence of inflammatory bowel disease. A liver biopsy showed portal/periportal sarcoid granulomas and METAVIR stage 2 fibrosis. Considering these findings, patient was diagnosed as PSC with sarcoidosis.

A 53-year-old male patient presented with itching, and MRCP revealed common bile duct stricture in the suprapancreatic region associated with upstream dilatation (Fig. 3D). Endoscopic ultrasound-guided fine-needle aspiration cytology was negative for malignancy. Multiple enlarged mediastinal and retropancreatic lymph nodes were observed. A liver biopsy showed multiple portal, periportal, and parenchymal solid, non-necrotizing, epithelioid cell granulomas, portal/periportal fibrosis, and cellular and canalicular cholestasis. The patient was diagnosed on imaging with bile duct stricture most likely due to extrahepatic bile duct involvement by sarcoidosis alongwith intrahepatic sarcoidosis on histopathological examination**.**

A 58-year-old female patient had secondary Sjogren's syndrome (dry mouth, dry eye and rheumatoid arthritis)

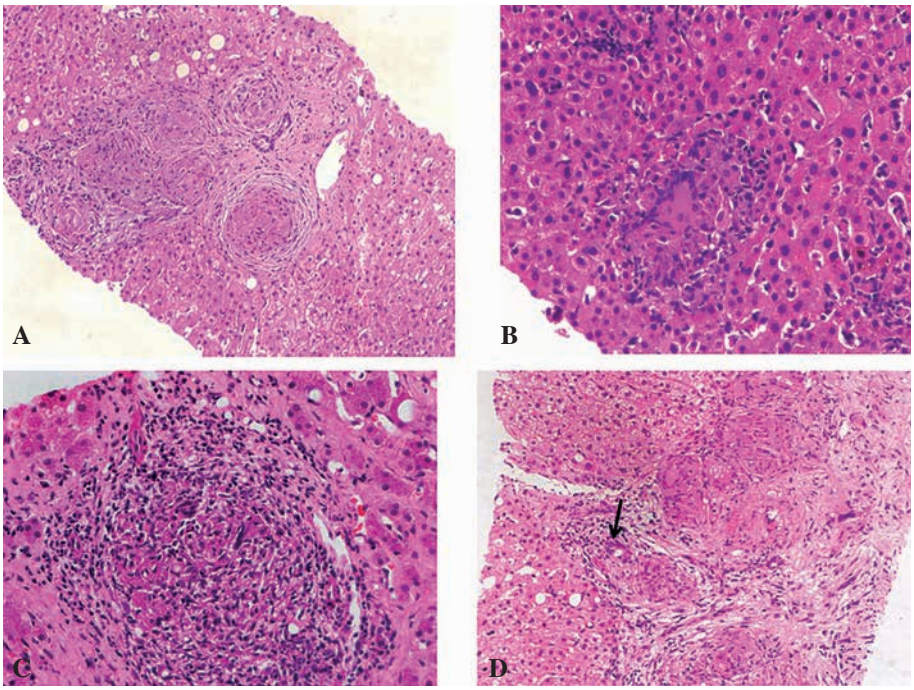

Fig. 2. — Liver Biopsy : 2A : Portal/Periportal sarcoid granulomas ; 2B : Parenchymal sarcoid granulomas ; 2C : Bile duct loss and sarcoid granuloma in portal tract ; 2D : Portal vessels not discernable and duct damage (arrow) (Hematoxylin and Eosin, 200× each).

with positive rheumatoid arthritis factor. Her liver biopsy showed multiple sarcoid granulomas in the portal/periportal, parenchymal, and perivenular regions. Her serum ACE level was 130 μg/L.

Discussion

Sarcoidosis is a systemic disorder of unknown etiology characterized by the presence of non-caseating epithelioid granulomas that disrupt the normal architecture and histology (6,15). The estimated prevalence of sarcoidosis is 1-40/100,000 population, and the average age of manifestation is 20-40 years (1,3, and 15). The etiopathogenesis of sarcoidosis is not clear. It has been proposed that individuals with class-1 HLA A1 and HLA B8, risk locus at 11q13.1 and 12q13.3-q14.1, ANXA11 gene on chromosome 10q22.3, truncating splice site mutation in BTNL2, altered CD4 :CD8 ratio, increased TH1 derived cytokines, common variable immunodeficiency, and local or systemic immunological abnormalities are genetically predisposed. Delayed hypersensitivity reaction to various environmental agents and pathogens, such as mycobacteria, rickettsiae, and propionibacteria, which cause sarcoidosis, is manifested in these individuals (16-21).

Granulomatous liver involvement in sarcoidosis is seen in 50-90% cases and 20-40% has liver test abnormalities (3,4). Most hepatic sarcoidosis patients are asymptomatic ; only 5%-30% present with clinical signs and symptoms (4). In very few cases, hepatic sarcoidosis can manifest as a severe and rapidly progressive disease, with the occurrence of chronic liver disease, cirrhosis, PH, chronic cholestasis, and very rarely, Budd-Chiari syndrome (4). In the present series, 40% of the hepatic sarcoidosis cases were symptomatic, and the incidence rate was comparable to those of other studies (4).

Depending upon the disease activity, liver tests are deranged, including liver transaminases, SAP and GGT. In about 90% cases of hepatic sarcoidosis, SAP levels are found be elevated (22). Serum ACE levels are elevated in most cases, but it is not a patho-gnomonic feature of sarcoidosis. In our series, 95% of the patients had elevated SAP levels, and 77.27% had elevated serum ACE levels. INR is typically normal in hepatic sarcoidosis cases, at least until liver failure sets in. This can be explained by the fact that sarcoidosis is more of a portal-based pathology, similar to non-cirrhotic PH.

Hepatomegaly is found in about 40% of patients on clinical examination, and in more than half of patients on abdominal computed tomography scans (3,23). In our series, hepatosplenomegaly was detected in 68% of the cases.

Hepatic sarcoidosis can also manifest as chronic cholestatic liver disease, which can be either intra- or extrahepatic in nature. Chronic intrahepatic sarcoidosis can mimic PBC and PSC and these can coexist with sarcoidosis (24-26). Chronic intrahepatic cholestasis in sarcoidosis appears to be due to progressive destruction of the bile ducts by portal and periportal granulomas. This is in contrast to PBC and PSC, in which non-suppurative bile duct destruction is responsible for cholestasis and vague PBC granulomas are secondary to the duct damage (27). In our experience, we have found that combined PBC-sarcoidosis pathology should be diagnosed

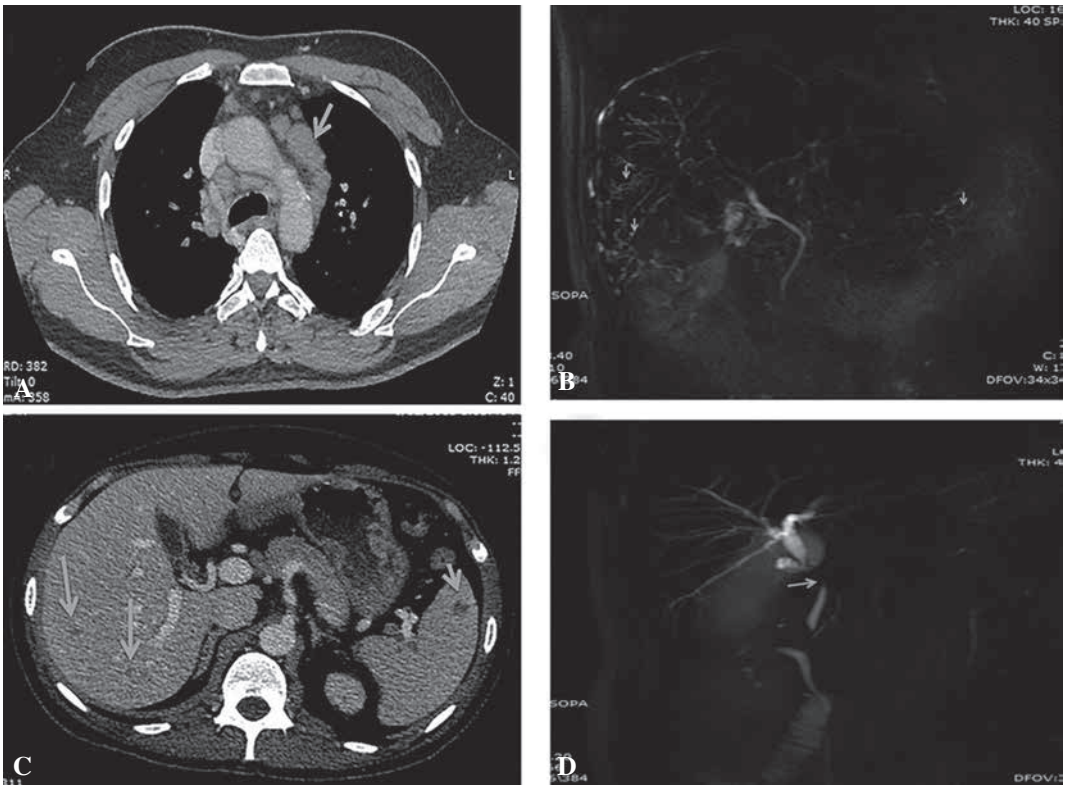

Fig. 3. — Imaging : 3A : Axial contrast-enhanced computed tomographic image of chest at the level of arch of aorta (upper) demonstrating multiple enlarged mediastinal lymph nodes ; 3B : Axial contrast-enhanced computed tomographic scan of abdomen (lower) showing few well defined subcentimeter sized hypodense non-enhancing nodular lesions involving both liver (long arrow) and spleen (short arrow) ; 3C : Two-dimensional magnetic resonance cholangiopancreatographic image showing skip areas of dilatation and narrowing involving bilobar intrahepatic biliary radicals giving them a beaded appearance (arrow) ; 3D : Two-dimensional magnetic resonance cholangiopancreatographic image showing stricture involving the supra-pancreatic common bile duct (arrow).

with positive AMA-M2 or raised IgM with definitive ductopenia and two features that suggest sarcoidosis ; including- elevated ACE levels, prominent solid hepatic granulomas, and additional mediastinal/abdominal lymphadenopathy or lung lesions. Sarcoidosis is differentiated from PSC by the absence of inflammatory bowel disease, lack of periductal fibrosis in histology, restricted narrowing of the bile duct to a single area of the biliary system, and improvement with steroid treatment (28). Combined pathology PSC-sarcoidosis might be considered if MRCP findings are suggestive of PSC with two features suggestive of sarcoidosis ; including-elevated ACE levels, prominent solid hepatic granulomas, and additional mediastinal/abdominal lymphadenopathy or lung lesions. Sarcoidosis can also cause extrahepatic biliary stricture, as in our patient who presented with itching and total bilirubin of 3.5 mg/dL. Only a few cases of sarcoidosis with biliary stricture have been reported in the literature. Sarcoid granulomas directly infiltrate the bile duct wall, and extrahepatic bile duct strictures develop with time and cause cholestatic symptoms (5). Abdominal lymphadenopathy, including portal and hilar lymphadenopathy is also seen in sarcoidosis. Despite the presence of hilar lymphadenopathy, extrahepatic cholestasis due to nodal compression is very rare, as the capsule of the lymph node is usually intact, and nodal adherence to adjacent structures does not occur (5).

Reports of the incidence of sarcoidosis with PH, with or without cirrhosis, have been increasing. Approximately half of patients with hepatic sarcoidosis may have PH without evidence of cirrhosis ; therefore, early detection by imaging methods is of utmost clinical importance, as development of cirrhosis carries a poor prognosis (4). In our case series, only three patients had histologically proven cirrhosis. Most of the portal hypertension cases (73%) were not having advanced fibrosis/cirrhosis. Thus, in liver sarcoidosis cases, PH can occur even in the absence of significant fibrosis or cirrhosis. Varices, ascites, splenomegaly, increased portal vein diameter with collateral formation, and increased HVPG are indicators of PH (11-14). Because there may be other causes of splenomegaly and ascites in sarcoidosis (5), the diagnosis of PH should be made based on imaging of the presence of splenomegaly along with increased portal vein diameter, collateral formation, varices, and increased HVPG. One of our patients only had ascites, which we considered to be due to PH, as serum-ascites albumin gradient was 1.1 g/dL. The exact pathophysiology of PH and cirrhosis

is not clear ; however, it may be due to (1) arterial-venous shunt formation in the region of granulomas and fibrosis, which leads to increased portal flow, and subsequently, intrahepatic pressure ; (2) increased scarring and fibrosis leading to architectural distortion, vascular remodeling of the liver parenchyma and flow resistance ; (3) inflammation and fibrosis that causes partial or complete obliteration of the portal vein, presinusoidal obstruction and subsequently increased portal pressure ; (4) hepatic and portal vein phlebitis and vascular scarring, which can lead to pre- and post-sinusoidal resistance ; (5) bile duct damage and obstruction, which may lead to secondary biliary cirrhosis, architectural distortion and resistant blood flow and (6) granulomas, inflammation, and scarring that may cause outflow obstruction and post-sinusoidal increase flow resistance (5). Hepatic vein occlusion and outflow obstruction might be due to extrinsic compression of granulomas. Vessel wall damage by inflammation or sarcoid granulomas can occur that will cause narrowing of the venous channels, venous stasis, and subsequent thrombosis (29).

Hepatic sarcoidosis is characterized by non-necrotizing portal-based granulomas. These can be seen in lobular parenchyma and perivenular region. In our series, sarcoid granulomas were densely clustered in the portal/periportal regions with hyaline fibrosis. Sarcoid granulomas can be differentiated from tubercular granulomas- as tubercular granulomas are predominantly parenchymal-based and exhibit variable amounts of necrosis, ZN staining positivity, and a reticulin-poor pattern ; they elicit a minimal amount of sclerotic fibrosis. Differentiating factors from PBC granulomas are described above. Parasitic-induced granulomas exhibit variable amounts of eosinophilic infiltrate, which is not seen in sarcoidosis (30).

A liver biopsy of hepatic sarcoidosis may show a variable presence of necroinflammatory activity, portal inflammation, and minimal to mild interface activity (31). Ductopenia/duct damage is found in approximately one-third of hepatic sarcoidosis patients presenting with cholestatic symptoms (31). In present series duct loss/damage was seen in 27% symptomatic cases. Steatosis may be seen as a coexistent finding.

This study has some limitations. HVPG data was available in only six cases, and presinusoidal, sinusoidal, and post-sinusoidal types of PH were not characterized. In addition, treatment and outcome data were not available for all the patients. However, the study provides an overall picture regarding the clinical and pathological findings of hepatic sarcoidosis and its potential complications and associated pathologies.

Conclusion

Clinical spectrum of hepatic involvement in sarcoidosis extends from asymptomatic “granulomatous hepatitis” to overt hepatic disease with chronic cholestasis, PH, cirrhosis, and very occasionally, Budd-Chiari syndrome. Chronic cholestatic liver disease is the main complication of hepatic sarcoidosis is observed in approximately half of clinically symptomatic cases. Extrahepatic biliary stricture may also occur in sarcoidosis cases. Hepatic sarcoidosis rarely occurs along with PBC or PSC, which should be diagnosed by a combination of clinical, serological, and histopathological findings. PH and cirrhosis are potential complications of liver sarcoidosis ; however, the majority of PH patients do not have cirrhosis. Liver biopsy examination in symptomatic cases is required to assess the extent of fibrosis and bile duct damage. A liver biopsy without evidence of cirrhosis does not rule out PH ; therefore, it is very important to look carefully for the imaging features that suggest PH.

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