

Sarcoidosis mimicking primary biliary cirrhosis- A clinico-pathological description

We present an unusual case of sarcoidosis presenting with biliary cirrhosis requiring liver transplantation.

Case report

A 52-year-old man presented with jaundice and abdominal distention in May 2011 and underwent further investigations in an outside hospital. His liver function showed a bilirubin of 2.8mg/dL, ALT 26U/L, AST 59 U/L, alkaline phosphatase 236U/L, albumin 2.1gm/L, globulin 4.9gm/dL and GGT 80U/L. His CT scan abdomen showed cirrhotic liver with free fluid and splenomegaly. Investigations for chronic liver disease etiology revealed a positive AMA with a titre of 1:100. Other auto-antibodies and viral serological markers were negative. He had a percutaneous needle liver biopsy which showed advanced fibrosis, expanded portal tract and inflammatory infiltrate mainly composing lymphocytes with insignificant bile duct damage. There was also the occasional periportal non-caseating epithelioid granuloma. A diagnosis of primary biliary cirrhosis

was considered. He later presented with spontaneous bacterial peritonitis (SBP) and septicemia and subsequently had a life-threatening variceal bleed, which required intubation and ventilation for management. He was transferred to our center for consideration of liver transplant. A pre-transplant work up was undertaken and the patient was placed on the waiting list for deceased donor liver transplantation (DDLT). During follow up in the waiting period, thrombus in the IVC was noted. The patient underwent liver transplantation. During the operation a shrunken, nodular and firm liver was seen, with hugely hypertrophied caudate lobe. Anorthotopic liver transplantation was done along with classical caval replacement and inferior vena caval thrombectomy.

The explant liver weighed 1400g and measured 20 cm x 15 cm x 10cm. The cut surface was firm, nodular, and showed diffuse fibrosis. The hilum showed few dilated hilar ducts containing bilirubin casts (**Figure 1A**). The sections showed biliary cirrhosis with marked distortion of portal and lobular architecture with formation of variable sized regenerative nodules demarcated with fibrous septa. Foci of bridging fibrosis and incomplete nodularity were also noted. The portal tracts and septa were expanded and showed prominent bile ductular reaction, ectatic vascular channels, with moderate inflammatory cell infiltrate comprising of lymphocytes, few

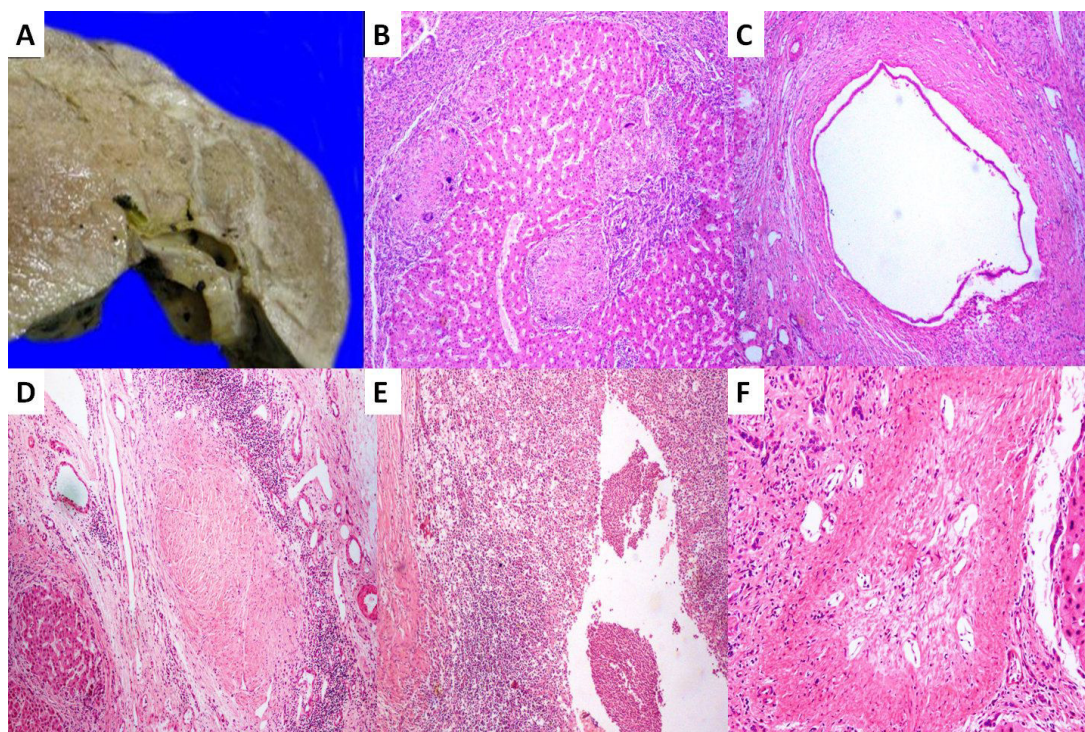


Figure 1: Gross specimen demonstrating thickened hilar ducts with bile impregnation (1A). Multiple portal and periportal granulomas (1B, H&E, X100). Bile duct with epithelial atrophy and surrounded by dense collagen (1C, H&E, X100). Dense fibrous rounded scars demonstrating complete obliteration of the bile duct (1D, H&E, X100). Ulceration of large hilar ducts (1E, H&E, X100). Hepatic veins with phlebitis and fibrous obliteration (1F, H&E, X100)

plasma cells along with some polymorphs and occasional eosinophils. Multiple lymphoid aggregates were noted. Multiple portal and periportal granulomas composed of epithelioid histiocytes admixed with multinucleated giant cells in few were noted (**Figure 1B**). Few granulomas show central granular necrosis. Periductal fibrosis with epithelial atrophy was also noted in multiple portal tracts (**Figure 1C**). Distorted septal and larger ducts were noted. Larger portal tracts showed loss of bile ducts, the site indicated by fibrous rounded scars (**Figure 1D**). There was ulceration of large hilar ducts with cholangitic abscesses, duct wall thickening with bile impregnation and intrahepatic bile sludge (**Figure 1E**). Xanthogranulomatous cholangitis, a lesion consisting of exuberant granulation tissue with prominent foamy macrophages, acute and chronic inflammation, fibrosis and foreign-body giant cells, were also found at the liver hilum. Hyperplastic arterioles were noted. Portal vein intimal fibrosis was also noted. Few foci show spill over of portal/septal inflammation into adjacent periportal/periseptal parenchyma. The hepatic parenchyma showed focal ballooning of hepatocytes and patchy lobular inflammation with spotty necrosis. There were sinusoidal dilatation, lymphocytosis and hyperplastic Kupffer cells. Scattered apoptotic hepatocytes were noted in nodules. Multiple lobular granulomas composed of epithelioid histiocytes admixed with multinucleated giant cells were identified. Occasional asteroid bodies were also noted in giant cells. Few hepatic veins showed phlebitis with fibrous obliteration (**Figure 1F**). The granulomas showed increased reticulin fibres. The sections from hilar region showed cystically dilated and ulcerated/ruptured large ducts, with biliary sludge, and xanthogranulomatous inflammatory reaction along with veins and arteries. Focal squamous metaplasia of the duct epithelium was noted. The duct also showed periductular fibrosis with epithelial atrophy. There was no significant iron overload. There was increase in stainable copper/copper associated protein in periportal/periseptal hepatocytes (Grade 2/3). The final impression was released as hepatobiliary sarcoidosis with secondary sclerosing cholangitis with no morphological evidence of PBC.

Discussion

Liver disease due to sarcoidosis is probably under reported. Hepatic involvement by sarcoidosis is highly variable but the patterns of hepatic injury have been well described.¹ Three major histological patterns are described including chronic

intrahepatic and rarely extrahepatic cholestasis, necro-inflammatory and vascular changes.^{1,2} Granulomatous involvement of the bile ducts resembles primary biliary cirrhosis. Periductal fibrosis with epithelial atrophy and nodular scars resembles primary sclerosing cholangitis. Cholestatic changes also include progressive diminution in the number of interlobular bile ducts, periportal fibrosis, and the eventual development of a micronodular biliary cirrhosis.³ Occasional cases of cholestasis in sarcoidosis are the result of a mass effect of sarcoid nodules at the hilum of the liver with bile duct obstruction. Vascular changes in hepatic sarcoidosis manifest mainly in sinusoidal dilatation/congestion and nodular regenerative hyperplasia.⁴ Granulomatous phlebitis may also be noted. The classic granuloma in sarcoidosis is mainly found in the portal triads with a cluster of large epithelioid cells, often with multinucleated giant cells. The granulomas of sarcoidosis may exhibit focal granular necrosis of minimal amount.¹ In cases with granulomas that exhibit a greater degree of necrosis an infective etiology should be strongly suspected. A variety of inclusions may be present, including Schaumann's bodies, asteroid bodies, birefringent crystals, and Hamazaki-Wesenberg bodies. The granulomas of sarcoid are reticulin rich.

The present case also posed a diagnostic challenge between the chronic cholestatic syndrome of sarcoidosis and primary biliary cirrhosis considering the serological positivity of AMA. A positive mitochondrial antibody titer is characteristic of primary biliary cirrhosis and is present in > 90% of cases. On rare occasions, differentiation between sarcoidosis and primary biliary cirrhosis may be impossible because cases have been described with clinical and histologic features of both conditions where mitochondrial antibody was positive or negative.^{1,5} AMAs are usually absent in patients with sarcoidosis and cholestatic liver disease. To be precise, however, anti-M2 AMAs are specific for PBC. Non-M2 AMAs are found in a small percentage of normal individuals. The widely used commercial immuno-fluorescence tests for AMAs do not distinguish between M2 and non-M2 auto antibodies. Instead, a titer above 1:40 is used as an arbitrary cutoff value to identify patients with PBC. Our patient had an AMA titer of 1:100, well above the cutoff value. There is an overlap of the histopathology of these two conditions, although they differ in their typical forms⁵. In primary biliary cirrhosis, there is non suppurative destructive cholangitis also termed as florid duct lesion. Granulomas are usually few in number, poorly defined and are usually associated with bile ducts. Comparatively in

sarcoidosis, if bile duct damage is present it is less conspicuous; granulomas are abundant and well-formed. Lobular granuloma commonly occur in sarcoidosis and are rare in PBC.

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A fatal case of disseminated aspergillosis in an immune-competent patient- An autopsy case report

Introduction

Invasive aspergillosis has emerged as a cause of severe infection in immune-compromised patients. The lungs are

primarily affected, likely due to its portal of entry through the respiratory tract. Very few cases in the literature show primary involvement of the gastrointestinal tract.¹ Also disseminated aspergillosis in the immune-competent state is rare.²⁻³

Case report

A 70-year old male patient, admitted to our tertiary care hospital, had chief complaints of pain in abdomen and inability to pass stools for 8 days. He had no complaints of fever, nausea, vomiting, yellowish discoloration of urine or stools or any significant past surgical or medical history of tuberculosis, diabetes mellitus, hypertension or bronchial asthma. He was afebrile and conscious with pulse of 98 beats/min and blood pressure of 110/70 mmHg. His abdomen was distended and tender, with guarding and absent bowel sounds. His hemoglobin was 10.7 g/dL, WBC count of 10,700/mm³ (Polymorphs-89%, Lymphocytes-8%, Eosinophils-3%) and platelet count of 1.43 x10⁵/mm³. Random blood sugar level was 167g/dL. The serology status of the patient was negative for HIV, HCV and HBsAg. Ultrasonography of the abdomen showed distended bowel loops with gas shadows, suggestive of partial intestinal obstruction. Immediate emergency laparotomy showed 0.5 cm x 0.5 cm perforation, 50 cm proximal from the ileocaecal junction with dense adhesions and perforative peritonitis.

A primary closure of the perforation site was performed with drain in situ. The postoperative general condition was moderate and the patient was afebrile. But, a leak from the drain was noted. Re-exploration showed new serosal tear of the small intestine, for which primary suturing was done. His general conditions were stable. From post-operative day five, he developed intermittent spikes of high blood pressure. Electrocardiogram showed depression in leads II and III. Troponin-T was positive. He developed pleural effusion with consolidation, bilaterally. WBC counts increased to 18,360/mm³. Tracheal SCAST was positive for *Klebsiella pneumoniae* species. He died on twelfth post-operative day.

At autopsy, the stomach fundus showed a large necrotic ulcer, with multiple small ulcers along its lesser curvature. Small and large intestine showed pre-gangrenous changes with serosa covered with greenish yellow exudates and thinned out, dusky mucosa containing altered blood (**Figure 1**). Also, the small intestine showed suture-site covered with similar exudates and few tiny small ulcers. Bilateral lungs showed target lesions, characteristic of angio-invasive aspergillosis (**Figure 2**). The heart showed small endocardial vegetations