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Hepatic sarcoidosis resembling primary sclerosing cholangitis

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SUMMARY

We report the case of a 29-year-old man who presented with progressive weight loss, night sweats, abdominal pain and pruritus who was found to have obstructive jaundice and cholestatic pattern of liver injury on laboratory workup. Though findings on magnetic resonance cholangiopancreatography were initially concerning primary sclerosing cholangitis, he was ultimately diagnosed with biliary sarcoidosis after a liver biopsy. This case brings attention to the rare phenomenon of hepatic sarcoidosis causing hyperbilirubinemia and highlights the importance of reaching the correct diagnosis early, as the patient's symptoms improved after initiation of steroids.

BACKGROUND

Sarcoidosis is a multisystemic granulomatous disease of unknown origin that affects individuals worldwide, with highest incidence and prevalence in African Americans.¹ It is characterised by the presence of non-caseating granulomas on tissue biopsy and can involve any organ, including the liver. Hepatic sarcoidosis was found in 11.5% of patients with sarcoidosis and clinical manifestation vary significantly; most of the patients are asymptomatic but 5%–15% develop signs and symptoms of cholestasis, portal hypertension, cirrhosis and Budd-Chiari syndrome.^{2–7}

Cholestatic liver disease in hepatic sarcoidosis could be intrahepatic or extrahepatic. Intrahepatic sarcoidosis can resemble primary sclerosing cholangitis (PSC) or in rare circumstances these two entities can coexist.^{8–12}

We present a case report of a patient with radiological findings 'typical' for PSC and liver biopsy showed non-caseating granulomas consistent with hepatic sarcoidosis.

CASE PRESENTATION

A 29-year-old man with no significant medical history presented to the emergency department as referred by his general practitioner for scleral icterus. His symptoms began 6 months ago with shortness of breath, dry cough, nausea, vomiting, epigastric abdominal pain, fatigue and night sweats along with unintentional weight loss of 60 lbs. For the past 3 weeks he experienced intense body itching that is worse at night and unalleviated with over-the-counter antihistamines. He also noticed yellow discolouration of his eyes 3 days ago. He does not take any prescription medications or herbal supplements. He denies tobacco,

alcohol, or recreational drug use. Family history is insignificant.

On review of vital signs, the patient was afebrile, normotensive with blood pressure 132/82 mm Hg and heart rate of 87 bpm. Physical examination was pertinent for icteric sclera, but otherwise unremarkable.

INVESTIGATIONS

Initial laboratory analysis was significant for alanine aminotransferase of 98 U/L, aspartate aminotransferase of 124 U/L and alkaline phosphatase (ALP) of 790 U/L demonstrating a mixed pattern cholestatic and hepatocellular liver injury. Furthermore, total bilirubin was 11.1 mg/dL with a direct bilirubin of 8.1 mg/dL. The rest of the initial laboratory workup can be found in [table 1](#).

Chest X-ray demonstrated bilateral hilar lymphadenopathy. A right upper quadrant abdominal ultrasound showed no stones within the gallbladder, a normal common bile duct measuring 0.2 cm and no intrahepatic biliary ductal dilatation.

Further testing revealed absence of autoantibodies, including negative antinuclear antibody, PR3-ANCA, anti-liver-kidney-microsomal antibody, anti-mitochondrial antibody (AMA) and smooth muscle antibody. The patient had a normal IgG4 level. Eventually, an ACE level returned elevated at 104 U/L, and soluble interleukin-2 receptor levels elevated to 2576 U/mL. He underwent Magnetic resonance cholangiopancreatography (MRCP) which showed peripheral intrahepatic biliary ductal dilatation consistent with changes of primary sclerosing cholangitis ([figure 1](#)). A liver biopsy performed by the interventional radiology team showed non-caseating granulomas ([figure 2A,B](#)). A CT of the chest without contrast confirmed bilateral hilar and mediastinal adenopathy, but showed no parenchymal lung disease. Given the diagnostic uncertainty, he underwent a colonoscopy, which was unremarkable.

DIFFERENTIAL DIAGNOSIS

The differential is broad in a patient presenting with jaundice and pruritus whose laboratory workup show conjugated hyperbilirubinemia. A useful branch point is determining if the obstruction is extrahepatic or intrahepatic. A history that is inconsistent with an acute presentation and an unremarkable right upper quadrant ultrasound narrows the differential to intrahepatic causes of cholestasis. With findings of ductal dilatation and



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Table 1 Laboratory work at admission

Variable	On admission	Reference range
Sodium (mEq/L)	134	135–145
Potassium (mEq/L)	4.3	3.5–5.0
Chloride (mEq/L)	97	98–108
Carbon dioxide (mEq/L)	23	20–30
BUN (mg/dL)	9	5–20
Creatinine (mg/dL)	0.89	<1.30
ALP (U/L)	790	<130
AST (U/L)	124	<50
ALT (U/L)	98	<40
Albumin (g/dL)	3.1	3.5–5.0
Total bilirubin (mg/dL)	11.1	<1.2
Direct bilirubin (mg/dL)	8.1	<0.5
Cholesterol (mg/dL)	>600	0–200
Triglycerides (mg/dL)	305	20–190
HDL (mg/dL)	13	55–999
LDL (mg/dL)	>526	0–129

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, Blood urea nitrogen; HDL, High density lipoprotein; LDL, Low density lipoprotein.

non-necrotising granulomas on biopsy, the leading differential for our patient included primary sclerosing cholangitis, primary biliary cholangitis, and biliary sarcoidosis.

TREATMENT

Patient found mild symptomatic relief with cholestyramine and ursodiol. After a negative fungal workup, he was discharged home on budesonide 3 mg two times a day.

OUTCOME AND FOLLOW-UP

On outpatient follow-up, he reported doing well since discharge. His jaundice and pruritus have improved. Three months after



Figure 1 Peripheral intrahepatic biliary ductal strictures and dilatation concerning for changes of PSC. There is no extrahepatic biliary dilatation. No focal hepatic lesions. Liver shows normal portal vein and hepatic vein enhancement.

starting steroids, his transaminases also normalised (table 2). Interestingly, ALP level remained elevated.

DISCUSSION

Though systemic sarcoidosis can frequently involve the liver, the granulomatous infiltration is only clinically significant in 5%–15% of cases.⁵ Biliary sarcoidosis leading to symptoms of cholestasis have been reported in literature in a dozen of cases; among many of these an alternative diagnosis was first considered, PSC being the top contender.^{11–15} Overall, patients' presentations ranged from minimal symptoms to biliary sepsis,¹⁶ however, jaundice and elevated ALP levels are common findings. Non-invasive (ie, MRI) and biliary tree imaging (ie, MRCP) demonstrate stricture or 'beading' of intrahepatic biliary ducts, and less commonly, extrahepatic involvement.¹³ Interestingly,

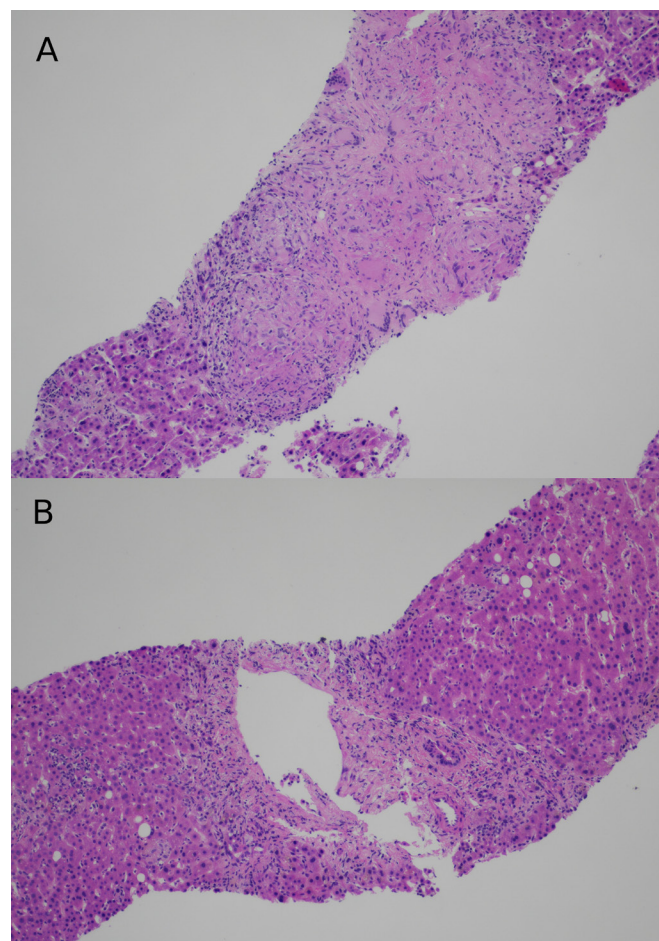


Figure 2 (A) This is a representative picture of the liver biopsy, demonstrating a granulomatous nodule forming in a background of otherwise unremarkable hepatic parenchyma. The granuloma consists of an aggregate of histiocytes (cells with eosinophilic cytoplasm and elongated nuclei) and giant cells (large eosinophilic cells with numerous nuclei arranged in crescent shape). This finding is characteristic, while not specific, for sarcoidosis. (H&E stain, 100× magnification). (B) The representative picture of the portal tract of the liver biopsy shows a mild ductular reaction (bile duct proliferation) and mild lymphocytic infiltration of the portal tract. There is a lack of inflammation of the bile duct, however, as the lymphocytes are not infiltrating the ductal epithelium. Moreover, the characteristic periductal fibrosis (onion-skinning) typically seen in primary sclerosing cholangitis is not observed in the entire biopsy. (H&E stain, 100× magnification).

Table 2 Hepatic function tests on discharge prior to steroids initiation and at 3 months and 6 months

Variable	At discharge	3 months follow-up	6 months follow-up
Albumin (g/dL)	3.1	3.6	3.8
Total bilirubin (mg/dL)	7.8	0.6	0.7
Direct bilirubin (mg/dL)	6.6	0.4	0.4
ALP (U/L)	576	552	410
AST (U/L)	191	46	48
ALT (U/L)	169	62	44

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

most reported cases proceed to Endoscopic retrograde cholangiopancreatography (ERCP) after a cross-sectional imaging modality. While more invasive, ERCP has the ability to obtain brush cytology in cases where cholangiocarcinoma is high on the differential. As a sum, these cases demonstrate that the correct diagnosis can save the patient from invasive procedures, emotional stress in cases of misdiagnosed cholangiocarcinoma,¹⁷ and even surgery, such as liver transplantation and exploratory laparotomies.¹⁸

The leading mimicker PSC is a chronic, progressive disease that insidiously destroys the biliary ducts and eventually leads to cirrhosis and liver transplantation. It is more common in men than women and has a strong association with inflammatory bowel disease. Anti-neutrophil cytoplasmic antibodies, and more recently, the subtype PR3-ANCA, are specific but poorly sensitive (38.5%) for PSC.¹⁹ Unlike sarcoidosis, PSC does not have systemic manifestations, but instead it is associated with other autoimmune diseases such as hypothyroidism, type 1 diabetes mellitus and autoimmune hepatitis.²⁰ Interestingly, granulomas can be found in 5% of liver biopsies in patients with confirmed PSC.²⁰ Of note, at least two cases of coexisting diagnosis of PSC and sarcoidosis have been described. In one, a patient with ulcerative colitis was diagnosed with PSC, and 1 year later developed pulmonary sarcoidosis.²¹ Another case featured a patient with 6-year history of sarcoidosis who was found to have PSC

and succumbed to cholangiocarcinoma.²² Both authors propose shared pathogenesis in immunological pathways. On liver biopsy, neither patient had granulomas. A brief overview of the similarities and differences of PSC and hepatic sarcoidosis have been summarised in table 3.

Other granulomatous diseases of the liver exist, such as primary biliary cholangitis. The two can be differentiated based on the characteristics of the granuloma—in PBC, granulomas tend to be portal based and poorly formed whereas in sarcoidosis granulomas are well formed and associated with presence of giant cells.²³ Additionally, AMA is 90% sensitive and specific to PBC. The role of ACE in diagnosing sarcoidosis is limited due to its high levels in other granulomatous diseases and its low sensitivity, around 40%–60%.²⁴ Biopsy is the gold standard for establishing the diagnosis, but a biopsy taken at the time of extensive cholestatic injury may only show nonspecific changes, and occasionally a second biopsy after the initial insult has resolved is needed for diagnosis.^{14 16 25}

Oral glucocorticoids are the most common first-line treatment. Response to steroid therapy varies; most patients with biliary sarcoidosis in case reports have resolution of symptoms and improvement in liver function tests with a single short course.^{11 13 15} More extensive pulmonary involvement appears to predict persistent symptoms and liver enzyme elevations after steroids.²⁶ There have not been trials to study treatment in biliary sarcoidosis. In a retrospective study of 27 patients with hepatic sarcoidosis, 83% responded to medical treatment with either oral glucocorticoids, anti-metabolites or biological agents. In this group, 40% (9 out of 22) of patients who initially presented with elevated ALP had levels that were lowered but not normalised, similar to that in our patient.⁵ In a similar study, 345 patients with sarcoidosis at a single US centre were screened for hepatic involvement—19 patients had abnormal liver tests, liver imaging or abnormal liver at autopsy (3 patients).²⁷ Of the patients who received oral glucocorticoids, 27% of patients had lower but not normalised ALP at the end of follow-up. Lack of normalisation of the ALP was not correlated with worse outcome (ie, development of cirrhosis) in this study.²⁷

Both studies were conducted to identify hepatic involvement retrospectively in patients with sarcoidosis. None of

Table 3 Comparison of PSC and hepatic sarcoidosis

	PSC	Hepatic sarcoidosis
Epidemiology	Incidence: ~1 in 100 000. Men in fourth decade of life. Strong association with IBD.	Incidence of sarcoidosis: 1–40 in 100 000 with symptomatic liver involvement in 5%–30% (up to 80% have asymptomatic involvement). Women > men. 3× higher incidence in AA.
Clinical presentation	Abdominal pain, pruritus, diarrhoea, jaundice, fatigue and fever, but many patients are asymptomatic and diagnosed on incidental laboratory work.	Jaundice, nausea, vomiting, abdominal pain and hepatosplenomegaly.
Serological markers	Elevated ALP, elevated aminotransferase levels but less than three times upper limit. Bilirubin is normal in 60% of patients. Positive ANCA (84%), anticardiolipin antibodies (66%) and ANA (53%).	Elevated ALP, ALT and AST. Negative ANA, AMA and ASMA. Normal IgG, normal or elevated ACE. Normal or elevated calcium and vitamin D.
Imaging features	Multifocal intrahepatic and/or extrahepatic biliary strictures. 'Beading appearance'.	No imaging findings are sensitive or specific for diagnosis. May show diffuse heterogeneity of the hepatic parenchymal on cross-sectional imaging.
Histology	Cholangitis, periductal fibrosis, ductular reaction and ductopenia. 'Onion skin' appearance (specific but not sensitive).	Non-caseating granulomas with macrophages with surrounding inflammatory cells.
Natural history	Progresses to end-stage liver disease requiring liver transplant. At increased risk of developing cholangiocarcinoma.	3%–18% develop portal hypertension.
Treatment	No targeted medical therapy. Liver transplantation only curative treatment.	Corticosteroids normalise liver tests and reduce granulomas, but they may not prevent progression.

AA, African americans; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, Antimitochondrial antibody; ANA, Antinuclear antibody; ANCA, Antineutrophil cytoplasmic antibodies; ASMA, Anti-smooth muscle antibody; AST, aspartate aminotransferase; IBD, Inflammatory bowel disease; PSC, primary sclerosing cholangitis.

the patients in the Ungprasert study presented with jaundice or pruritus, and only a quarter in Sedki's group experienced cholestatic symptoms. Consequently, the conclusions drawn from these patients may not apply to patients whose disease primarily involves the biliary tree. An early response to steroids and the lack of extensive systemic involvement seems to predict a better outcome, however, it is not known what factors predict a favourable response to steroids. More research is needed to delineate the optimal treatment and natural history of sarcoidosis involving the hepatobiliary system.

Learning points

- ▶ Systemic sarcoidosis can frequently involve the liver and granulomatous infiltration is only clinically significant in 5%–15% of cases.
- ▶ A multisystemic approach is required to establish the diagnosis of hepatic sarcoidosis that may resemble primary sclerosing cholangitis on imaging studies.
- ▶ While glucocorticoids are the most used first-line therapy, there are no randomised controlled trials for their use in hepatic sarcoidosis. Levels of alkaline phosphatase may remain elevated even after treatment with glucocorticoids. The significance of this finding is unclear.

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