IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Case Report: Progressive Liver Disease With Hypercalcemia Due To Hepatic Sarcoidosis

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Abstract

We report a case of 77-year-old man who presented with fatigue, jaundice, pruritus, abdominal pain, progressive weight loss and cholestatic pattern of liver injury. Clinical findings and imaging was suggestive of Chronic Liver disease, and liver biopsy confirmed sarcoidosis. This case brings attention to hepatic sarcoidosis as a cause of progessive liver failure and highlights the importance of reaching the correct diagnosis early.

Keywords: Noncaseating granulomas, hepatic failure, cirrhosis, tuberculosis, cholestasis.

Introduction:

Sarcoidosis is a multisystemic granulomatous disease of unknown etiology[1] with liver being one of the most common organs affected. It is seen worldwide, with highest incidence and prevalence in African Americans[2]. It is characterised by the presence of non-caseating granulomas[3-5] on tissue biopsy and involvement any organ, third most common being the liver[6-7]. Granulomas can be found in approximately 75% of patients with sarcoidosis[3-5].

Hepatic involvement was found in 11.5% of patients with sarcoidosis and clinical manifestations vary significantly; most of the patients are asymptomatic but 5–15% develop signs and symptoms of cholestasis, portal hypertension, cirrhosis or Budd-Chiari syndrome.[2, 8-11]

Cholestatic features in sarcoidosis could be intrahepatic or extrahepatic. Intrahepatic sarcoidosis can resemble primary sclerosing cholangitis (PSC) or in rare circumstances these two entities can coexist.[12-16]

We report a patient with features of Chronic liver disease and liver biopsy demonstrating non-caseating granulomas consistent with hepatic sarcoidosis.

Case presentation

A 77-year-old man with diabetes, hypertension and hypothyroidism, presented to Medical Gastroenterology department after being referred by the general practitioner for scleral icterus. His symptoms began 1 month ago with generalized weakness, nausea, epigastric pain and night sweats and weight loss of 5kgs. For the past 3 weeks he experienced intense body itching that is worse at night and unalleviated with antihistamines. There was yellow discoloration of sclera, dark yellow urine since 2 weeks. He is a nonalcoholic and on regular treatment for diabetes, hypertension and hypothyroidism. Family history is noncontributory.

Physical examination was normal except for jaundice.

Laboratory analysis revealed elevated bilirubin and alkaline phosphatase suggesting cholestatic liver injury. The laboratory results are shown in **TABLE NO.1**

Haemoglobin	12.10g/dL
Complete Urine Examination	bilirubin +
Glucose Random	181mg/dL
ESR	104mm 1st hr
Anti HAV IgM	Negative
Anti HEV IgM	Negative
Anti HCV	Non reactive
HBsAg	Non reactive
PT	16.5 sec
INR	1.18
aPTT	41.7 sec
S.Creatinine	1mg/dL
$Na^+/K^+/Cl^-$	135/4.10/105 (in mmol/L)
HbA_1C	5.60 %
S. Calcium	10.50 mg/dL
Ca 19-9	94 U/mL
ANA	negative
Anti LKM-1 antibody	0.32
AMA	negative
IgG4	0.72 g/dL
cANCA	negative
pANCA	negative
ACE	87 U/L
Total Bilirubin	8.40mg/dL
Direct Bilirubin	3.90mg/dL
Indirect Bilirubin	1mg/dL
Alkaline Phosphatase	312 U/L
SGOT	48 U/L
SGPT	33 U/L
GGT	58 U/L

TABLE NO:1

Chest X-ray demonstrated bilateral hilar lymphadenopathy.

Abdominal ultrasound showed parenchymal liver disease, mild splenomegaly, normal gallbladder, common bile duct (0.2 cm) and no intrahepatic biliary ductal dilatation.

CECT abdomen (Triphasic) showed features of CLD in the form of micronodularity, surface irregularity, volume redistribution and mild splenomegaly.

MRCP findings were suggestive of Chronic Hepatic parenchymal disease with portal HTN and mild splenomegaly, with no bile duct abnormalities.

Liver ARFI ranged from 2.00 to 2.90 m/sec with a mean value of 2.40 m/sec, suggesting severe fibrosis.

PET-CT whole body showed cirrhotic changes in the liver parenchyma. No definite scan evidence of FDG avid lesion in the whole body.

ACE levels found to be 87 U/L and Serum Calcium was 10.5mg/dL.

Liver biopsy war performed with a suspcion of sarcoidosis in view of elevated calcium and serum ACE. Liver biopsy showed non-caseating granulomas suggestive of sarcoidosis (Fig 1 & 2).

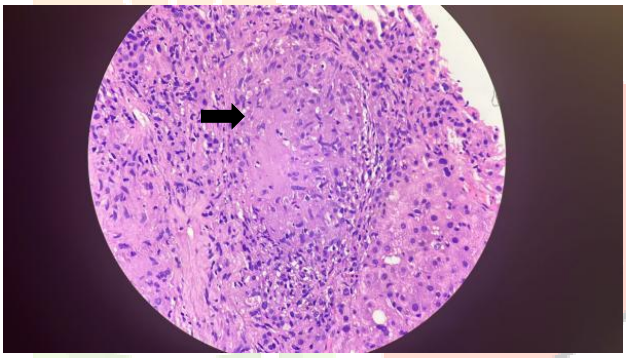

Fig 1: High power shows epitheloid histiocytes aggregates

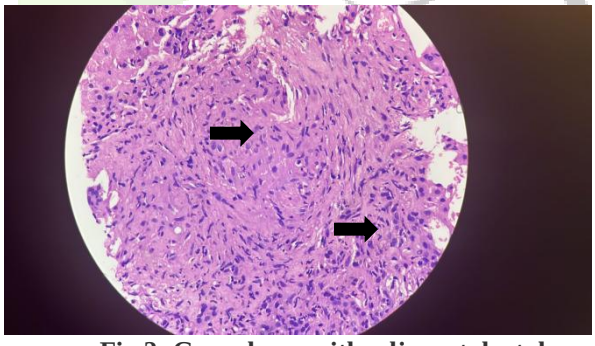

Fig 2: Granuloma with adjucent ductular reaction

The differential dignosis is broad in a patient presenting with jaundice and pruritus with laboratory results showing conjugated hyperbilirubinemia. A useful 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 reaction and non-necrotising granulomas on biopsy, the leading differential for our patient included primary sclerosing cholangitis, primary biliary cholangitis, and hepatic sarcoidosis.

There was mild symptomatic relief with cholestyramine and UDCA. He was initiated on prednisolone 40 mg per day.

On follow-up, his jaundice and pruritus had regressed. One month after starting steroids, his liver enzymes also normalised and had significant recovery. Serum ACE levels normalized.

Discussion

Sarcoidosis is a systemic disease of unknown etiology characterized by granulomatous inflammation which most frequently affects the lungs, followed by the lymphoid tissue. In more than 90% of cases it is characterized by the presence of noncaseating granulomas[3-5] containing activated T lymphocytes and mononuclear phagocytic cells in the lungs and lymph nodes, and may also involve skin and eyes. The most affected intraabdominal organs are liver, spleen, and lymph nodes. Liver is the third most frequently involved organ[6-7]. The most frequent sign of hepatic involvement in sarcoidosis is hepatomegaly, seen in more than 50% of cases. Multiple nodules formed by the aggregation of granulomas may be observed in the liver[17]. Hepatic sarcoidosis mostly affects the younger population group between 20 and 40 years of age. Most of these lesions are usually asymptomatic, with 5–30% presenting with atypical clinical signs and symptoms including nausea, vomiting, jaundice, abdominal pain and hepatosplenomegaly[7].

Most cases of Sarcoidosis with hepatic involvement have a subtle clinical course. In some cases, jaundice, chronic cholestasis, portal hypertension, or Budd-Chiari syndrome may develop[17-18]. Cirrhosis is a rarely seen entity in less than 1% of cases[7].Early detection is crucial since the development of cirrhosis carries a poor prognosis.

The first report of portal hypertension associated with sarcoidosis was published in 1949 by Mino et al. followed by Klatskin in 1950[3]. Granulomas are the characteristic histological feature in sarcoidosis. In liver biopsies, granulomas have been reported in 60% to 80% of patients with sarcoidosis[7].

However, palpable hepatomegaly and/or lab evidence of liver involvement is detected in only 20% to 30% of patients. Rarely, hepatic involvement might be the only manifestation of disease. Sarcoidosis frequently affects the periportal areas. Isolated granulomatous hepatitis may be seen.

If active hepatic inflammation is present, fever and upper right quadrant tenderness may be observed. In hepatic sarcoidosis, abnormalities in liver function tests may be detected. The level of bilirubin and transaminases may be increased, and typically the values are greater than those of ALP and GGT. Cholestatic pattern has also been observed[1-6]. In hepatic sarcoidosis, granulomatous lesions are often very small and clinically asymptomatic.

Asymptomatic hepatic involvement and slightly increased transaminases do not require treatment; however, in cases with a marked increase in transaminases or severe hepatic dysfunction, steroids are used. With treatment, the levels of enzymes normalize. If chronic granulomatous inflammation in the liver persists, progressive hepatic damage, intrahepatic cholestasis, and portal hypertension may develop. Frequently, intrahepatic cholestasis is seen in biopsy. Cholestasis may develop as a consequence of hepatic granulomas, sarcoidotic involvement of intra- or extrahepatic biliary ducts, or compression of the common biliary duct by enlarged perihilar lymph nodes. In our case extrahepatic biliary obstruction was excluded. In addition to foci of granulomatous inflammation, grade 3 macrovesicular steatosis was present. The relationship between sarcoidosis and hepatosteatosis is not known. However, microgranulomas may accompany hepatosteatosis. Both these conditions may lead to increased hepatic enzyme levels. The differential diagnosis of hepatic granulomas include autoimmune diseases (sarcoidosis, primary biliary cirrhosis, Wegener's granulomatosis), bacterial infections (mainly tuberculosis); viral infections (cytomegalovirus, Epstein-Barr virus infections, hepatitis A,B,C infections) fungal infections (histoplasmosis, cryptococcosis), parasitoses (toxoplasmosis, schistosomiasis), malignancies (especially Hodgkin's lymphoma), medications, and idiopathic causes. When establishing a diagnosis, other clinical and laboratory findings of the patient in addition to histopathological characteristics are important.

The follow-up this patient with significant recovery after steroid therapy also favours the etiology as hepatic sarcoidosis.

Conclusion: Hepatic Sarcoidosis is a potentially reversible cause of liver injury and requires a high index of supsicion for diagnosis as evident in our case. Adequate therapy may present progression to liver failure.

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