Sarcoidosis Presenting as Acute on Chronic Liver Failure–Report of the First Case

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Abstract

Sarcoidosis is a multi system disease with different clinical presentations. Asymptomatic presentation is the commonest, but others include jaundice with chronic cholestasis, cirrhosis, portal hypertension, hepatic venous outflow tract obstruction and extrahepatic biliary obstruction. Cirrhosis and portal hypertension are the rarest manifestation of hepatic sarcoid and represent less than 1% of all cases. Acute on chronic liver failure as a presentation of sarcoidosis has never been reported before. Here we present a patient of sarcoidosis presenting with acute on chronic liver failure, and in whom, steroid therapy improved liver failure with a good outcome.

Keywords: Sarcoidosis, ACLF, liver failure, jaundice, hepatic encephalopathy, granulomas

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Introduction

Sir Jonathan Hutchison first described sarcoidosis in 1878 in a 58 year old policeman who had skin, joint and renal manifestations of the disease. [1] Ernest Besnier, a French dermatologist first described sarcoid skin and coined the term 'lupus pernio' [2]. In 1892, Tenneson showed lupus pernio histologically as what sarcoid was later described [3]. Hutchison later on found a similar affliction in a middle aged woman, in 1898 and named the illness, 'Mortimer's Malady' [4]. Sarcoid histopathology was classically described by the Norwegian dermatologist, Cesar Boeck in 1899, who named it 'multiple benign lupoid' and later coined the term sarcoid, which means, 'flesh-like' [5]. Sarcoidosis is a multisystem disorder with hallmarks of non caseating granulomatous disease of incompletely understood etiology. It can involve the bone (first described by Kreibich in 1904), lung and lymph nodes (Schaumman in 1914, Pautrier in 1938) and eyes and salivary glands (uveoparotid involvement, Heerfordt 1909 and Miculicz 1937) and heart (John B Johnson, 1944) [6-10]. Liver involvement occurs in 50 to 90% of sarcoid patients, but mostly remains undiagnosed or asymptomatic [11]. van Beek and Haexl in 1943 reported characteristic sarcoid lesions in liver biopsy specimens obtained through needle biopsy aspiration. This was followed by positive biopsies for sarcoidosis in liver by van Buehem and later on by Volwiler and Scadding [12]. Hepatic manifestations of sarcoidosis are diverse. The most common presentation is asymptomatic with histopathology suggestive of sarcoid granulomas in the liver (seen in 75% of sarcoidosis) without liver function abnormalities. Clinical presentations include jaundice with chronic cholestasis, cirrhosis, portal hypertension, hepatic venous outflow tract obstruction and extrahepatic biliary obstruction. Cirrhosis and portal hypertension are most rare manifestations of hepatic sarcoid (< 1% of all cases.) Mino and Klatskin reported the association of portal hypertension with sarcoidosis in 1950. Here we describe a hitherto unknown presentation of hepatic sarcoidosis - acute on chronic liver failure in an elderly gentleman, who concomitantly had features of pulmonary sarcoidosis. This clinical presentation of systemic sarcoidosis, especially hepatic sarcoid, has never been reported in literature before.

The Case

A 52 year old man presented to us with complaints of progressive non cholestatic jaundice without prodrome for a period of 3 weeks. This was followed by painless abdominal distension without bilateral leg swelling or facial puffiness. There was no associated decrease in urine output, cola coloured urine or dysuria. The patient denied history of fever or loose stools prior to this episode and had no known addictions or co-morbidities. On further questioning, he stated that he had been suffering from intermittent bouts of dry cough since one year and has been on symptomatic treatment from a local practitioner who diagnosed his condition as 'seasonal allergy'. Four months prior to this presentation, the patient suffered an attack of syncope and was diagnosed with complete heart block for which he underwent permanent pacemaker implantation. He denied weight loss, bone pains, arthritis or bleeding diathesis at any point in time. His family history was non contributory. Our examination revealed a conscious and oriented, moderately built male with pallor, deep icterus, without cyanosis, with grade 2 clubbing and bilateral mild non tender pitting pedal edema in the absence of peripheral lymphadenopathy. His heart rate was 98 per minute, in sinus rhythm with a right brachial blood pressure of 122/68 mm of Hg in the sitting position. The neck was supple to palpation without thyromegaly. The abdominal examination revealed bilobar enlargement of liver, 4 centimetres below the right costal margin, which was firm in consistency with rough, non nodular surface and sharp, irregular margins. Grade 2 ascites was evident in the presence of splenomegaly and absence of tortuous veins over the abdominal wall. The respiratory system examination revealed bibasal fine expiratory crackles without other added sounds and the cardiovascular system examination was essentially normal. His baseline and follow up investigations are shown in Table 1. Evaluation for hepatitis B, C, A, E and HIV 1&2 were negative. A Mantoux test revealed no induration and sputum samples for acid fast bacilli were also negative on three occasions. His initial ultrasound imaging of the abdomen revealed a 12.5 cm liver which was irregular and lobulated with coarsened echotexture with left and cauadate lobe hypertrophy. The whole liver was heterogenous in appearance with multiple ill defined nodules studded throughout the liver parenchyma. The spleen was also enlarged in size and there was mild ascites noted; features that were confirmed on contrast enhanced computed tomography (CT) imaging of the abdomen revealed features of chronic liver disease with features of portal hypertension (abdominal collaterals, ascites and splenomegaly) with multiple small hypodense/hypoenhancing lesions

throughout splenic parenchyma with diffuse heterogenous parenchymal enhancement of the liver with areas of interlacing fibrosis and an upper gastrointestinal endoscopy that revealed grade 1 esophageal varices with mild portal hypertensive gastropathy. This was followed by a high resolution CT of the chest that revealed multiple enlarged bilateral hilar, right paratracheal, subcarinal and prevascular lymph nodes that showed foci of calcifications. This was also associated with peri-hilar bronchovascular interstitial thickening (left > right) with patchy areas of pulmonary fibrosis seen in both lower lobes, findings that were suspicious for thoracic sarcoidosis (Figure 1). Subsequently, the patient underwent a percutaneous liver biopsy (Figure 2) which showed evidence of prominent periportal well defined non caseating granulomas composed of hypertrophied epitheliod cells, multinucleated giant cells and fibrosis associated with distortion of acinar architecture with parenchymal replacement by fibro-collagenous tissue and incomplete regenerative nodule formation and acid fast staining for mycobacterium tuberculosis was negative–features suggestive of granulomatous pathology with advanced fibrosis secondary to sarcoidosis. Meanwhile, the serum angiotensin converting enzyme level was found to be 329 units/L (normal 8 to 52). Tumor marker levels in serum, such as alfa-fetoprotein, CA-19-9, carcinoembryonic antigen and prostate specific antigen were within normal limits. The patient was ultimately, based on historical, clinical and investigational analysis, diagnosed as a case of acute on chronic liver failure (ACLF) with acute insult being probable sarcoid flare and underlying chronic liver disease secondary to sarcoidosis with concomitant pulmonary sarcoidosis with lymph nodal involvement. He was started on weight based corticosteroid therapy, with prednisolone 60 mg per day along with proton pump inhibitors. The patient recovered clinically and manifestations of hepatic encephalopathy, deranged liver functions and coagulopathy improved substantially. Currently the patient is on 40mg of prednisolone and is on follow up on outpatient basis. Our plan is to maintain the patient on 40 mg of corticosteroid for the first 4 to 6 weeks and then taper off steroid to the minimum possible dose with 5 to 10 mg decrements every 4 to 8 weeks. In the event of corticosteroid failure, or dependency, the addition of a cytotoxic agent such as azathioprine will be contemplated.

Parameters	Normal	At admission	At 7 days	At 4 weeks
Hemoglobin	13-17 g/dL	10.2	9.8	9.0
TLC	4-9 x 10^9/L	9.8	13.4	12.2
DLC (N/L/M/E)	40-75/20-45/2-10/0-1 (%)	88/10/02	90/10/0	86/12/02
Platelet	150-450 x 10^9/L	90000	88000	88000
ESR	< 10 mm (first hour)	34	38	40
Total bilirubin	0.3-1.2 mg/dL	20.2	11.2	4.8
Direct bilirubin	0-0.2 mg/dL	13.8	7.8	3.3
Aspartate transaminase	5-40 IU/L	56	48	44
Alanine transaminase	10-40 IU/L	48	40	33
Alkaline phosphatase	32-92 IU/L	388	245	122
Gamma glutamyl transpeptidase	7-64 IU/L	122	98	56
Lactate dehydrogenase	265-500 IU/L	588	423	300
Blood urea	15-40 mg/dL	49	38	42
Creatinine	0.2-1 mg/dL	1.2	0.98	0.65
Procalcitonin	< 0.5	<0.5	<0.5	<0.5
INR	<1	3.46	2.2	1.86
Reticulocyte count	0.2 - 2%	1.63		
Calcium	8.4-10.2 mg/dL	9.2	8.8	7.6

TABLE 1: Baseline and follow up summary of investigations. TLC – total leucocyte count; DLC – differential leucocyte count, N – neutrophils, L – lymphocytes, M – monocytes, E – eosinophils; ESR – erythrocyte sedimentation rate; INR – international normalized ratio

PATHOPHYSIOLOGY OF PORTAL HYPERTENSION AND CIRRHOSIS IN SARCOID LIVER
Focal arterio-venous shunt formation at granulomatous regions, leading to increase in portal blood flow and compensatory increase in intrahepatic vascular resistance
Large, confluent granulomas producing intrahepatic sinusoidal obstruction leading to increase in sinusoidal pressure
Inflammation and healing fibrosis at sites of granulomas leading to portal central bridging fibrosis and cirrhotic remodelling
Granulomas as portal areas promoting increase in resistance to portal flow causing pre sinusoidal block/hypertension
Granulomatous phlebitis in liver parenchyma leading to inflammation, ischemia, fibrosis and cirrhosis; increase in pre and post sinusoidal resistance

TABLE 2: Pathophysiology of portal hypertension and cirrhosis in sarcoid liver

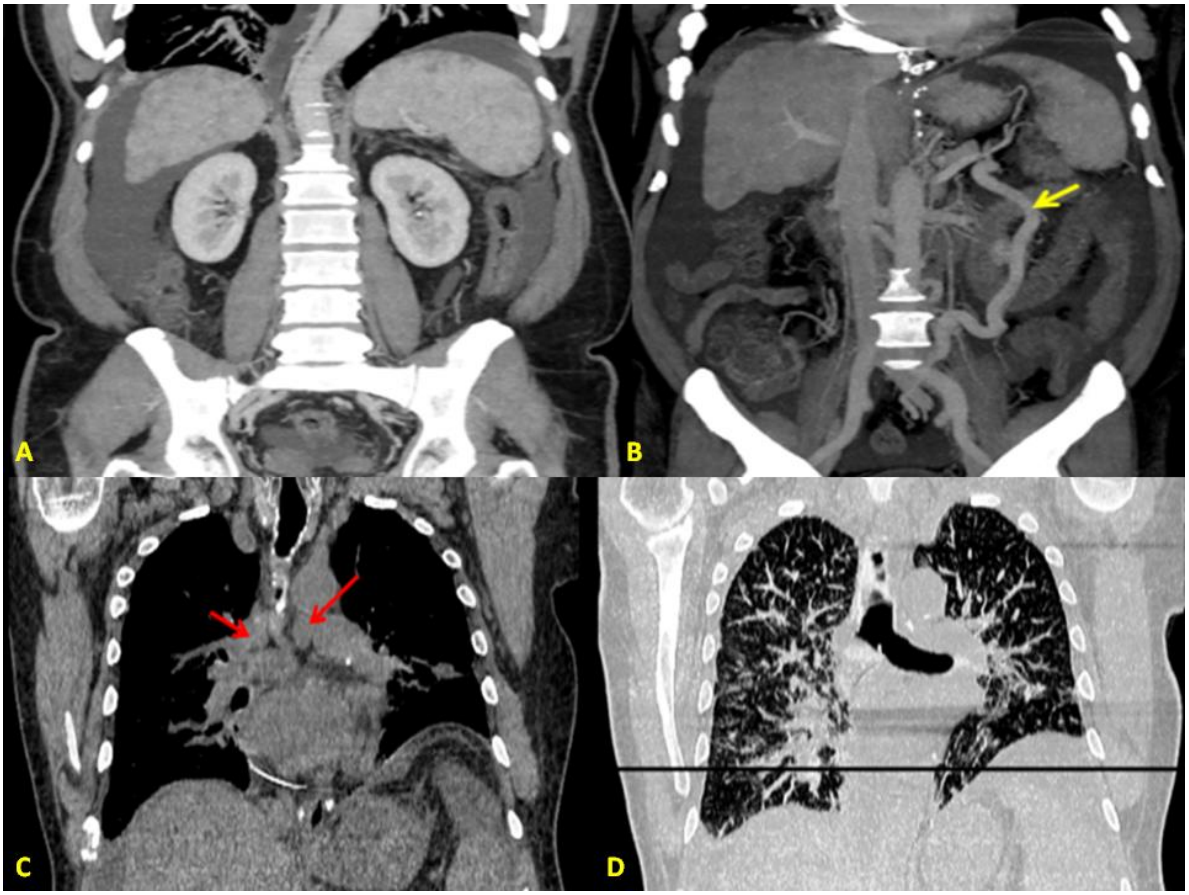

Figure 1. Computed tomography of abdomen and chest showing features of cirrhosis with multiple hypodense nodules in the liver (A) along with presence of abdominal collaterals (B, yellow arrow), multiple enlarged mediastinal nodes (C, red arrows) and extensive reticulonodular lesions in the lung (D), features suggestive of thoracic sarcoidosis.

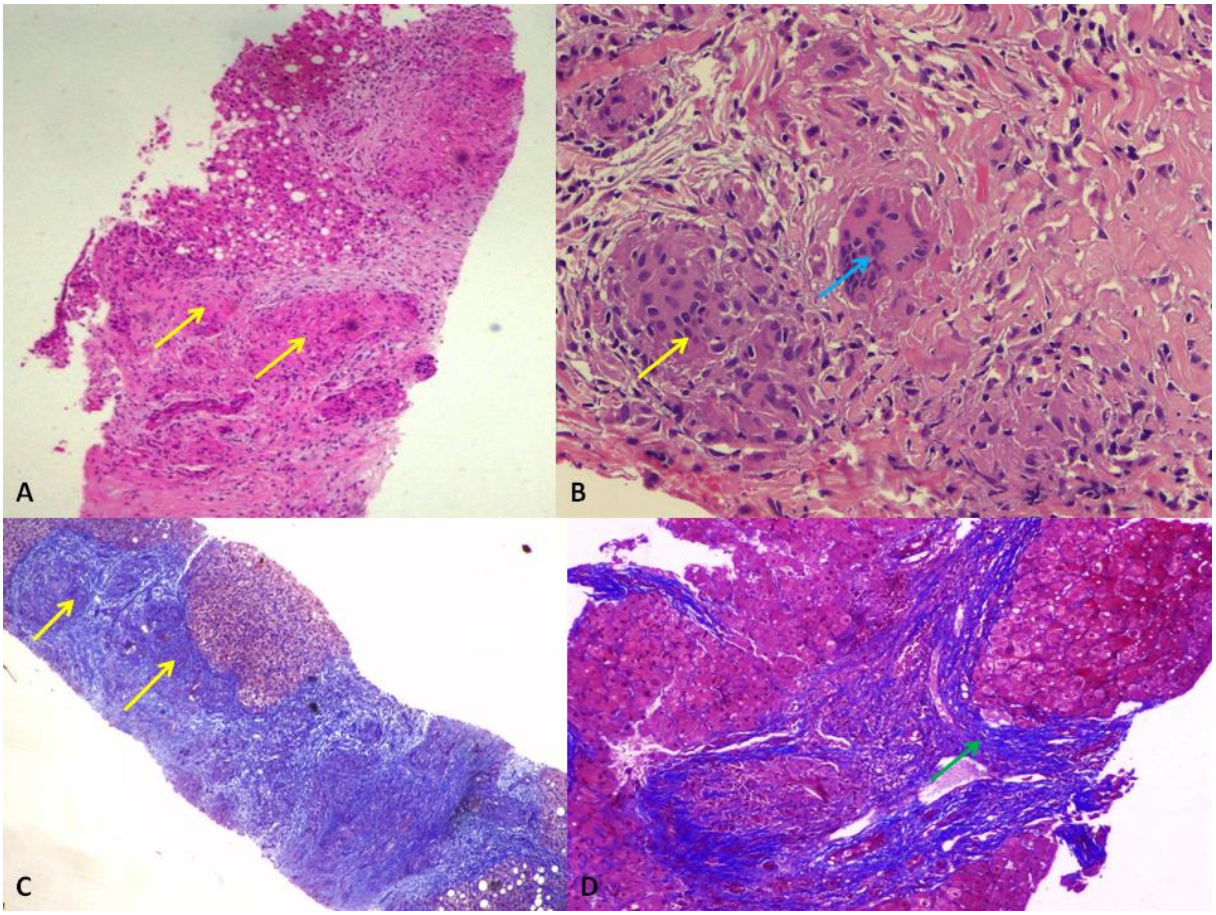

Figure 2. Histopathology of liver biopsy showing non caseating granulomas (A, yellow arrows, H&E 4X), presence of giant cells (B, blue arrow, H&E 20X), extensive fibrocollagenous areas with incomplete regenerative nodule formation (C and D, Masson trichrome stain, 4X and 20X respectively), features suggestive of hepatic sarcoidosis with advanced fibrosis and incomplete cirrhosis.

Discussion

Sarcoidosis is a chronic non caseating multisystemic disease that mostly affects females in the third to fourth decade, of suspected immunological etiology. It involves most commonly the lung, but can involve any part of the body. The disease is diagnosed mainly on the basis of systemic and pulmonary manifestations and histopathological evidence of non caseating granulomatous lesions in the lung, liver, lymph nodes, skin or uncommonly other tissues. The

spectrum of liver involvement in sarcoidosis ranges from asymptomatic granulomatous hepatitis to portal hypertension, intra and/or extrahepatic portal cholestasis to cirrhosis and portal hypertension. Portal hypertension and cirrhosis are uncommon complications of sarcoidosis. The presence of ascites and splenomegaly does not necessarily conclude presence of portal hypertension but evidence of esophageal varices is a strong indicator of it. Around 50% of patients with sarcoidosis present with portal hypertension in the absence of cirrhosis. Hence histopathology of liver tissue is important to showcase chronicity of liver disease [13-15].

The literature is rich with sarcoid liver presenting with the above mentioned complications. But none has provided insights into presentation of sarcoidosis as a syndrome of acute on chronic liver failure. It is believed that portal hypertension in sarcoid liver is as a result of multiple factors as shown in Table 2 [16-19]. Sarcoidosis presentation in the acute form include Lofgren's (erythema nodosum, bilateral hilar adenopathy and arthritis) and Heerfordt-Waldenstrom (parotidomegaly, fever, anterior uveitis and seventh nerve palsy) syndromes. Acute presentation represents 20 to 40% of all cases of sarcoid and has striking predominance of constitutional symptoms. Hepatic involvement in acute setting is rare and only 10 cases have been reported in literature. [20] Acute scenario commonly presents with jaundice, transaminitis and/or pruritus. The natural history of hepatic sarcoidosis usually is one of transaminitis that slowly and progressively leads to cirrhosis, portal hypertension and ultimately decompensation. The diagnosis of sarcoid related cirrhosis is usually made on pathological analysis of the explanted liver. An acute on chronic liver failure presentation is quite rare, as in this case. Histopathology in sarcoid liver has variable findings. In a study conducted by Devaney and co workers, granulomas were present in all of their patients, with space occupation ranging from less than 1 percent to more than 90 percent of tissue volume under examination. These granulomas were non caseating, most commonly seen in the portal/periportal region, were devoid of infectious particles and had three patterns on histology – necroinflammatory, vascular and cholestatic. Features of cholangiolitis, bile ductopenia, periductal fibrosis, chronic active hepatitis, nodular regenerative hyperplasia, and confluent sarcoidomas, bridging fibrosis or cirrhosis are also seen in variability [21,22]. Treatment of sarcoid liver mostly consists of glucocorticosteroids as the first line of treatment. Immunomodulators such as Azathioprine, TNF alpha antagonists, hydroxychloroquine and mycophenolate mofetil have also been found to be useful. Ursodeoxycholic acid in high doses

have been found to be beneficial in cholestatic presentations [23,24]. Our case report is unique in many ways. Firstly, sarcoid liver presentation as an acute on chronic liver failure syndrome has never been reported before. Secondly, the acute sarcoid related liver injury over a chronic sarcoid related cirrhosis is also novel. Thirdly, our patient had a very good outcome, once treatment with steroids were initiated thereby stating that prognosis of ACLF presentations in sarcoid liver may not be as dismal as seen with other etiologies. Clinicians need to consider common presentations of rare diseases in context, when conventional approach to diagnosis fails to identify the etiological agent.

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