

## Budd-Chiari syndrome: an unusual presentation of multisystemic sarcoidosis

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### Abstract

Sarcoidosis is a multisystem granulomatous disease of unknown origin. All organs may be affected. Liver involvement is common but it is rarely symptomatic. Only a few cases of Budd-Chiari syndrome (BCS) secondary to a hepatic sarcoidosis have been described so far. We describe a case of multisystemic sarcoidosis presenting with BCS. A 42-year old female was referred to our department for chronic and anicteric cholestasis. Laboratory and imaging investigations disclosed features of chronic BCS associated with multisystemic sarcoidosis. The positive diagnosis was based on microscopic features, which showed hepatic, gastric and cutaneous non-caseating granulomas. Screening for an underlying thrombophilic disorder was negative. The diagnosis of BCS complicating hepatic sarcoidosis was the most likely. She was put on corticosteroids and anticoagulation therapy. To our knowledge, few cases of sarcoidosis-related BCS have been reported in the literature. In addition to being an uncommon presentation of sarcoidosis, this case illustrates the importance of recognizing an unusual cause of BCS and its therapeutic difficulties.

### Introduction

Sarcoidosis is a multisystem granulomatous disease of unknown origin that may affect any organ.<sup>1</sup> The lung is the most commonly involved, followed by the skin, eye, liver and peripheral lymph node.<sup>1</sup> The disease may present insidiously and the diagnosis is often made fortuitously upon routine chest radiography.<sup>2</sup> Liver involvement is common but is rarely symptomatic.<sup>3</sup> The most common abnormality consists of high levels of alkaline phosphatase (ALP). Few cases of Budd-Chiari syndrome (BCS) related to hepatic sarcoidosis have been described so far.<sup>4</sup>

In this report, we describe a case of multisystemic sarcoidosis presenting with BCS.

### Case Report

A 42-year old female was referred to our department for chronic anicteric cholestasis discovered fortuitously through a regular blood test. Her past medical history revealed diabetes mellitus evolving for 3 years; she had never received oral contraceptive therapy. She described progressive worsening cough and exertional dyspnea. She denied right upper quadrant pain, fatigue or pruritus. On examination, her liver span was 21 cm and spleen was palpable 4 cm below the left costal margin. Skin examination disclosed red-brown papular plates measuring 2 to 5 mm in diameter and having a predilection on scars and sites of trauma (Figure 1). Cardiovascular and respiratory examination was normal. Liver tests demonstrated increased cholestatic enzymes: a  $\gamma$ -glutamyl transferase level of 136 U/L (normal: 12-58) and ALP of 325 U/L (normal: 38-126) without hyperbilirubinemia (total bilirubin 13 mg/L; normal: 2-12); aminotransferases levels were normal. Other laboratory tests revealed normocytic inflammatory anemia with hemoglobin of 10.6 g/dL, mean corpuscular volume of 82.8 fL and serum ferritin of 150 g/L; white blood cell count of 4700/mm<sup>3</sup> and platelets count of 221,000/mm<sup>3</sup>. Erythrocyte sedimentation rate was 85 mm at 1 h. International normalized ratio was normal. Serum and urinary calcium were normal. Abdominal ultrasound with Doppler showed hepatomegaly with hypertrophied caudate lobe, splenomegaly and porto-systemic collateral circulation, while supra-hepatic veins were not demonstrated. Abdominal computed tomography (CT) confirmed these findings: the liver was multinodular, hepatic veins were also not visualized, which was consistent with the diagnosis of chronic BCS (Figure 2). Moreover, celiac, hepatic pedicle and lombo-aortic adenopathies were noticed. We completed with a CT scan of the chest, which demonstrated mediastinal and hilar adenopathies with multiple micronodular opacities on the lower pulmonary lobes. At screening upper endoscopy for portal hypertension, there were neither esophageal nor gastric varices but gastric mucosa was erythematous. Gastric biopsies were performed and disclosed non-caseating granuloma. Likewise, liver biopsy showed the presence of sarcoid granulomas consisting of a compact aggregate of large epithelioid cells, sometimes with multinucleated giant cells and a surrounding cuff of lymphocytes (Figure 3). These tend to be more frequent in portal tracts. Caseation or damage bile ducts were not present.

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Centrolobular hepatocytes were focally atrophic and replaced by fibrous and inflammatory septa. Some small hepatic veins were absent as they were incorporated into fibrosis (Figure 4). This granulomatous inflammation was also demonstrated on biopsy of skin lesions. These findings raised the possibility of systemic granulomatosis, in particular sarcoidosis. Additional examinations were then performed: tuberculin testing was negative, bronchoalveolar lavage did not show any acid-fast bacilli and angiotensin converting enzyme (ACE) was elevated: 201 UECA (normal: 12-68). The combination of pulmonary involvement and extra-pulmonary manifestations including liver, gastric, lymph nodes and skin, as well as raised ACE were highly suggestive of multisystemic sarcoidosis. This diagnosis was confirmed with histopathological examination of the liver, gastric and skin biopsies. As screening for an underlying thrombophilic disorder (JAK 2 mutation, flow cytometry, anticardiolipines and anti- $\beta$ 2 glycoprotein antibodies, lupus anticoagulant, factor V Leiden, antithrombin, protein S and C deficiency, homocysteinemia, bone marrow examination and celiac disease) failed to ascertain an underlying prothrombotic condition, the diagnosis of BCS complicating sarcoidosis was the most likely. Patient was started on oral prednisolone at a dose of 1 mg/kg and warfarin anticoagulation therapy.

### Discussion

We reported a case of multisystemic sarcoidosis presenting with BCS. Liver involvement in sarcoidosis is common but is rarely symptomatic.<sup>3</sup> A minority of patients will progress to severe cholestatic jaundice, portal hypertension and cirrhosis.<sup>4</sup> Moreover, BCS is

an exceptional complication of hepatic sarcoidosis. To the best of our knowledge, only 8 cases of BCS related to sarcoidosis have been reported in the literature.<sup>3,5-11</sup> The exact mechanism for BCS associated with hepatic sarcoidosis is unclear. It has been postulated that granuloma may cause external compression of the hepatic vein or involve the hepatic veins resulting in narrowing of the lumen leading to venous stasis and extensive thrombotic occlusion.<sup>3,5</sup> In the reported cases, BCS was the initial manifestation of sarcoidosis in 4 patients,<sup>5,6,8,10</sup> with a chronic presentation in all but one case that had an acute onset with ascites and deterioration of mental status.<sup>11</sup> Evidence-based guidelines for the treatment of

liver sarcoidosis are lacking.<sup>12</sup> Systemic corticosteroids are indicated in cases of severe liver involvement, whereas treatment of asymptomatic forms is controversial.<sup>12,13</sup> Furthermore, corticosteroids do not seem to prevent portal hypertension development.<sup>12</sup> On the other hand, treatment of BCS is better codified, based on anticoagulation therapy and treatment of the underlying condition; in case of failure, transjugular intrahepatic portosystemic shunt (TIPS) insertion and liver transplantation should be considered.<sup>14</sup> Regarding previous reported cases of BCS associated with sarcoidosis: 3 patients were treated with corticosteroids for liver involvement<sup>5,7,8</sup> associated with anticoagulation in one case<sup>8</sup> while 3

patients had liver transplantation (after TIPS failure for one)<sup>3,6,9</sup> and the 2 former had surgical portosystemic shunt.<sup>10,11</sup> Thus, this is the second case of BCS complicating hepatic sarcoidosis treated with anticoagulation and corticosteroids. In the first case, outcome was favorable, allowing normalization of liver tests and partial re-permeabilization of supra-hepatic veins.<sup>8</sup> Therefore, we believe that BCS complicating sarcoidosis should be treated initially with anticoagulation as it is the cornerstone for BCS treatment, associated with corticosteroid for the underlying disease in order to limit granuloma formation.



Figure 1. Red-brown papular plates on the leg.

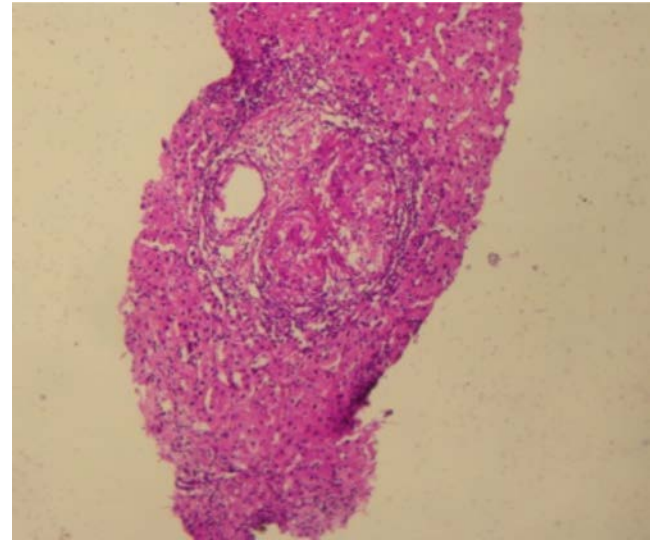


Figure 3. Liver biopsy demonstrating sarcoid granuloma in portal tract. Compact aggregate of irregularly arranged epithelioid cells with some multi-nucleated giant cells and a surrounding rim of lymphocytes (hematoxylin and eosin x200).

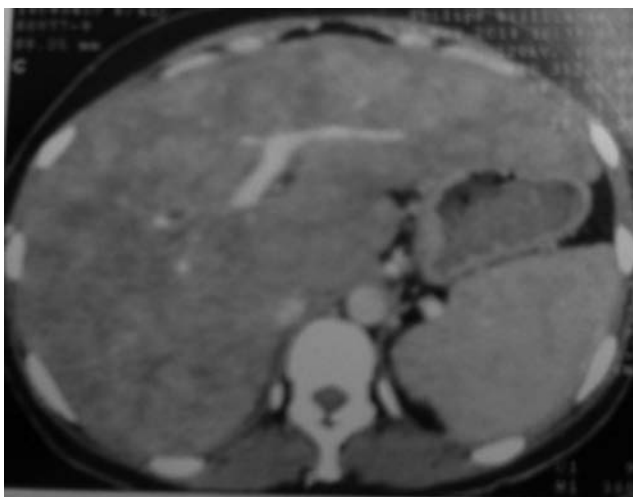


Figure 2. Abdominal computed tomography showing multinodular liver, hypertrophied caudate lobe, while hepatic veins are not visualized.

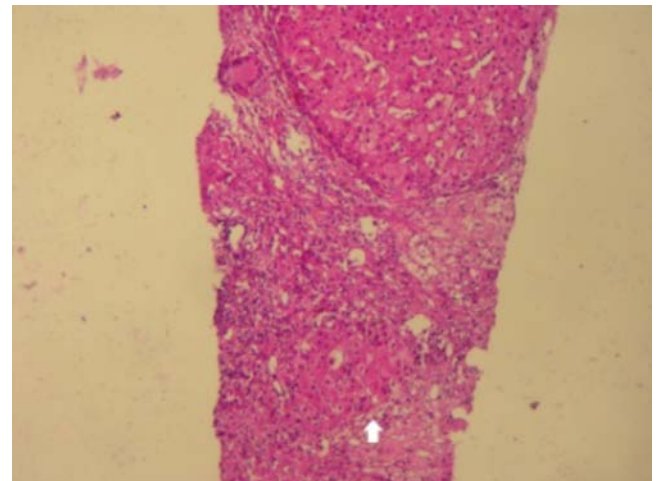


Figure 4. Liver biopsy showing focally atrophic hepatocytes, nodular transformation with fibrous and inflammatory septa entrapped regenerative hepatocellular plates (white arrow) (hematoxylin and eosin x200).

## Conclusions

The present patient belongs to a small group of patients reported with sarcoidosis-related BCS. In addition to being an uncommon presentation of sarcoidosis, this case illustrates the importance of recognizing an unusual cause of BCS and its therapeutic difficulties.

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