

Non-cirrhotic hepatic sarcoidosis induced portal hypertension: Nine case reports

Safia Elaboudi*, Imane Benelbarhdadi, Fatima-zohra Ajana

Department of gastro-enterology "C", Ibn Sina university hospital, Mohamed V University, Rabat, Morocco

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*Corresponding author: Safia Elaboudi

Abstract

Sarcoidosis is a systemic granulomatous disease of unknown etiology and involves many organs. The liver is the third most commonly involved organ after the lymph nodes and the lungs, usually clinically silent. As in the other organs, liver sarcoidosis is characterized histopathologically by non-caseating granulomas. In rare instances (5% of cases), liver sarcoidosis is complicated by portal hypertension or chronic cholestasis. The aim of this study is to show that liver sarcoidosis can cause portal hypertension without progression to cirrhosis.

Keywords: Hepatic sarcoidosis, portal hypertension, granuloma, cholestasis, corticosteroid.

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INTRODUCTION

Sarcoidosis is a systemic non-caseating granulomatous disease involving many organs [1]. The typical manifestation of sarcoidosis is the presence of non-caseating granulomas, affecting the lungs and lymph nodes in more than 90% of cases, but it can involve any organ system [2, 3, 4]. The liver is the third most commonly involved organ after lymph nodes and lungs; hepatic granulomas can be found in up to 50–79 % of all people with sarcoidosis. Despite this, hepatic sarcoidosis is not commonly described.

Most cases of hepatic involvement from sarcoidosis are clinically silent, with only a few patients developing jaundice, chronic cholestasis, portal hypertension and/or Budd-Chiari syndrome [1, 2], or Cirrhosis which is a very rare complication of liver sarcoidosis found in less than 1% of cases [3, 5]. We present 9 case of granulomatous liver disease secondary to sarcoidosis complicated with portal hypertension without liver cirrhosis.

MATERIALS AND METHODS

A retrospective and descriptive study, including nine patients with systemic sarcoidosis and liver involvement, diagnosed between January 2003 and May 2018. The diagnosis of sarcoidosis was suspected by the association of clinical, biochemical and radiologic features of sarcoidosis, and confirmed by histology showing non-caseating granulomas. Diagnosis of liver involvement was based on the presence of non-caseating granuloma on liver biopsy.

Others causes of granulomatous hepatitis (mainly tuberculosis, primary biliary cirrhosis, viral hepatitis B and C and drugs) were investigated and excluded. Clinical, biochemical, imaging and pathological features were detailed. Treatment was specified as well as the outcomes. Response to treatment was evaluated after 12 months of therapy. Complete response was defined by normalization of biochemical markers, partial response by biochemical improvement without normalization, and refractoriness with stagnation or worsening biochemical parameters.

RESULTS

Nine patients were included, all of them were women aged between 23 and 65 years old. One of them has celiac disease. The patients were admitted for hematemesis in 4 cases, left hypochondrial pain was manifested in 1 case, right upper quadrant pain in 2 cases and for abnormalities liver tests (intrahepatic cholestasis) in 2 cases. Physical examination was normal in 2 patients, splenomegaly was found in 6 cases and hepatomegaly was found only in 1 case. Abnormal liver tests have been noted including intrahepatic cholestasis in 5 cases with normal bilirubin level. Amino transferases were raised in 3 cases (1,5N-6N). The prothrombin ratio and albumin level were normal in all cases. Abdominal ultrasound had revealed portal hypertension signs in 6 patients and had eliminated supra and infra hepatic obstacle. The gastroscopy in the patients with portal hypertension signs had shown esophageal varices associated with hypertensive gastropathy in 2 cases. Histopathologic

evaluation of the liver biopsy specimen revealed granulomatous hepatitis in all patients. Tuberculin skin test, sputum smears and cultures for acid-fast bacilli (AFB) were negative in all patients. The activity of the angiotensin-converting enzyme was high in 4 cases between 93 and 147 U / l (usual values: 18-60 U / l). Chest X-ray showed bilateral hilar lymph node enlargement in 3 patients. Bronchoscopy with bronchoalveolar lavage and endobronchial biopsies were launched in all cases. Non caseating epithelioid granulomas were found in 6 cases. Salivary glands biopsy was done in all patients and was positive in 3 cases. Fundoscopy revealed evidence of previous right uveitis in 2 patients. All these arguments concluded to liver sarcoidosis diagnosis. Patients with active sarcoidosis were treated by corticosteroids. Specific treatment of esophageal varices was established in patients with hematemesis. Patients follow-up showed a normalization of the liver tests and no one had developed cirrhosis, however some corticosteroids related complications were noticed.

DISCUSSION

Sarcoidosis, a systemic granulomatous disease, classically affects the chest; however, sarcoidosis can involve any organ system [1,2]. Extra thoracic sarcoidosis is fairly common, with the liver being the third most commonly involved organ after lymph nodes and lungs. Hepatic sarcoidosis mostly affects the younger population group between 20 and 40 years of age. Most of these lesions are usually asymptomatic, with only 5–30% presenting with atypical clinical signs and symptoms including nausea, vomiting, jaundice, abdominal pain and hepatosplenomegaly [2, 3], some of these signs are reported by our patients.

A small portion of hepatic sarcoidosis can be severe with the occurrence of complications such as cirrhosis, portal hypertension, chronic cholestasis and Budd-Chiari syndrome [2, 6]. The first report of portal hypertension associated with sarcoidosis was published in 1949 by Mino et al. [7], followed by Katskin in 1950 [8]. Since then, the incidence of sarcoidosis with portal hypertension and cirrhosis has gradually been increasingly reported [1]. Although half of patients with sarcoidosis may have portal hypertension without evidence of cirrhosis, early detection is crucial since the development of cirrhosis carries a poor prognosis [1]

The pathophysiology of portal hypertension may involve multiple mechanisms. It has been suggested that small arterio-venous shunts may form in the region of the granulomas, resulting in an elevated portal blood flow which subsequently increases intrahepatic resistance [1, 9, 10]. Others suggest that the granulomas in the portal areas may produce pressure and restrict its normal flow, causing a perisinusoidal block [1, 11]. Another theory suggests that cirrhosis and focal fibrosis are caused by ischemic changes brought about by primary granulomatous phlebitis of portal and hepatic veins, thereby increasing pre- and post-

sinusoidal resistance [1, 4]. The pathogenesis of chronic intrahepatic cholestasis in sarcoidosis is due to destruction of bile ducts by portal and periportal granulomas that can ultimately lead to biliary cirrhosis [1]

Although liver involvement is common in sarcoidosis, it rarely causes symptoms and may remain undiagnosed in many cases.

It has been suggested that the diagnosis is made by clinical and radiologic findings suggestive of sarcoidosis, supported by histopathologic findings of non-caseating granulomas on biopsy obtained from either the liver, after the exclusion of other causes of hepatic granuloma formation especially tuberculosis in our context. Nevertheless, in a minority of cases, hepatic sarcoidosis causes severe complications such as severe cholestatic jaundice, portal hypertension, cirrhosis and lead to end stage liver disease.

Hepatic sarcoidosis usually demonstrates abnormal liver-related tests in 20–50% of cases, with alkaline phosphatase being most commonly affected [3, 4]. Total bilirubin was normal in all cases (100 %), GGT and ALP were respectively elevated in 55.5 % and 44.4% of our patients. The degree of liver test abnormalities appears to be related to the degree of fibrosis and the degree of granulomatous inflammation [2]. ACE level elevation may be useful, 44.4 % of our patients had elevated ACE levels. Warshauer *et al* [12] report that ACE levels can correlate with the patient's abdominal involvement.

Radiographic evaluation of abdominal sarcoidosis includes US, CT and magnetic resonance imaging (MRI) [13, 14]. Imaging signs of abdominal sarcoidosis can be variable. Upper abdominal lymphadenopathy, hepatomegaly and splenomegaly are some of the most commonly reported findings. In fact, upper abdominal lymphadenopathy was seen in more than 50% of our subjects.

US does not usually show hepatic or splenic focal sarcoidosis lesions, but it can demonstrate a non-specific increase in heterogeneity or echogenicity with organ enlargement, as well as the degree of fibrosis present in the granuloma [13, 15]. In the majority of our patients, diffuse hepatic parenchymal heterogeneity was seen with both US and CT, and is likely due to innumerable microscopic granulomata surrounded by fibrous bands. MRI is considered superior to US and CT in the evaluation of abdominal sarcoidosis [13, 14].

Six of our Patients (66.6%) present with manifestations of portal hypertension. The average duration between diagnosis of liver disease and the development of portal hypertension was reported as 5.7 years [6].

Granulomatous necroinflammation, in combination with cholestasis and vascular disruption,

can lead to fibrosis deposition and nodular regeneration, or cirrhosis – a reported complication of sarcoidosis. None of our patients had developed cirrhosis.

The treatment of sarcoidosis with hepatic involvement remains controversial. The use of glucocorticoids may show some improvement of liver-related tests, but they do not alter the course and progression of the disease [1, 9, 16]. the most widely accepted approach in the treatment of hepatic sarcoidosis involves the use of glucocorticoids in patients with symptomatic sarcoidosis and evidence of cholestasis or elevated liver transaminases [9, 16]. No treatment is necessary in asymptomatic patients [9, 16].

Six Patients with active sarcoidosis were treated by corticosteroids. Specific treatment of esophageal varices was established in patients with hematemesis. With a mean follow-up of 5 years, patients showed a normalization of the liver tests and no one had developed cirrhosis, however some corticosteroids related complications were noticed.

Other alternate drugs reportedly being used in sarcoidosis include azathioprine, methotrexate, hydrochloroquine and infliximab [16]. No large randomized trials have been done to assess the efficacy of these drugs, which is most likely related to the rarity of the disease process. In advanced sarcoidosis of the liver, transplantation is the only option considered curative [16].

CONCLUSION

It is important to recognize that sarcoidosis can be a cause of unexplained liver dysfunction. Some patients may present with signs of chronic liver disease with portal hypertension signs without cirrhosis. We have shown that our patients had normalized their liver tests under treatment with no progression towards cirrhosis and no worsening of the portal hypertension signs.

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