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CASE REPORT

Ductopenia related liver sarcoidosis

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Abstract

Sarcoidosis is a systemic granulomatous disease which may involve many organs. In approximately 95% of patients there is liver involvement, with noncaseating hepatic granulomas occurring in 21 to 99% of patients with sarcoidosis. Liver involvement is usually asymptomatic and limited to mild to moderate abnormalities in liver biochemistry. The occurrence of jaundice in sarcoidosis is rare; extensive imaging procedures and the examination of liver biopsies permit a precise diagnostic. Ductopenia associated with sarcoidosis has been reported in less than 20 cases and can lead to biliary cirrhosis and liver- related death. We report here on a case of ductopenia-related sarcoidosis in which primary biliary cirrhosis and extrahepatic cholestasis have been carefully excluded. The patient follow up was 8 years. Although ursodesoxycholic acid appears to improve liver biochemistry it does not preclude the rapid occurrence of extensive fibrosis. A review of the literature of reported cases of ductopenia related to sarcoidosis is provided.

Key words: Sarcoidosis; Cholestasis ductopenia; Ursodeoxycholic acid

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INTRODUCTION

Sarcoidosis is a systemic granulomatous disease which may involve many organs, although the lungs remain the most frequent and specific localization[1]. An incidence rate of 71/100 000 and prevalence of 2.0% was reported in a large recent study performed in black American women[2]. Asymptomatic liver involvement may be present in up to 95% of the patients and is usually limited to liver test abnormalities The most common histological lesions are noncaseating hepatic granulomas[3]. The occurrence of jaundice in sarcoidosis is rare. Imaging procedures and liver biopsy are clues to the pathogenesis of jaundice. Ductopenia associated with sarcoidosis has been reported in less than 15 cases and can progress to biliary cirrhosis and liver-related death.

CASE REPORT

A 54-year-old Caucasian woman was admitted in our hospital on June 2nd 1996 with abdominal pain, fever, jaundice,

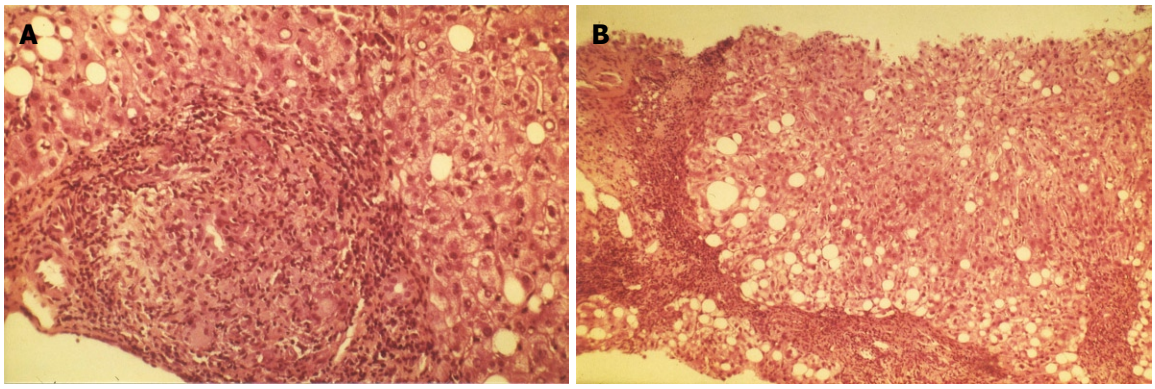

Figure 1 Hematoxilin Eosin Safran staining. A: × 40, non caseating granulomas with giant and epithelioid cells associated with periportal fibrosis and lobular chronic inflammatory cells are seen, as well as moderate steatosis (< 20%) without signs of steatohepatitis. There is no evidence of cirrhosis; B: × 20, distortion of the normal liver architecture, with bridging and annular fibrosis containing noncaseating granulomas including giant and epithelioid cells with significantly diminution in number of interlobular bile ducts are seen.

night sweats and weight loss that began in April. She was born in France and had never left that country. Her medical history was remarkable for obesity (body index: BMI 35kg/m^2), arterial hypertension and type 2 diabetes mellitus treated for several years with metformin(850 mg bid). In 1988, she underwent a cholecystectomy for (histologically proven) calculus cholecystitis. Liver biopsy was not performed at that time. There was no history of alcoholism, viral hepatitis exposure or blood transfusion. She has no risk factors for tuberculosis. Physical examination on admission showed a body temperature of 40°C and moderate scleral icterus. The abdomen was soft, without tenderness, there was no cutaneous rash, or flitting arthalgia. There was no hepatomegaly, splenomegaly, ascites or collateral venous circulation. Laboratory values on admission showed normal complete blood count and C-reactive protein 28, 9 mg/L [N < 10]. Bacteriological examination of blood, urine and stools was negative. Prothrombin index was 98%. Results of liver tests were as follows: total bilirubin, 63 μmol/L [N = 5-20](conjugated 50); gamma-glutamyl-transpeptidases, 52 times upper limit of normal (ULN) [N = 5-45]; alkaline phosphatases, 5 ULN L [N = 30-100 UI/L]; aspartate aminotransferases, 1.1 ULN [N = 6-40]; and alanine aminotransferases, 3 ULN [N = 6-45]. Protidogram showed a mild decrease in albumin levels (36 g/L; 37-42) and increased beta-globulins (16 g/L; 5-8); IgM was below 2 g/L. Stools were beige and the urine dark. Serologic tests for hepatitis A, B and C were negative. Screening for antinuclear antibodies, anti-smooth muscle antibodies and antimitochondrial antibodies was negative. The tuberculin test was mildly positive. Serum angiotensin converting enzyme was elevated, 60 U/mL [N = 20-40]. Abdominal ultrasonography showed homogeneous hepatomegaly without splenomegaly, ascites, or biliary tract dilatation.

Chest x-ray studies showed no pneumonia, and revealed bilateral hilar adenopathies. Thoracic computed tomography showed bilateral hilar adenopathies without lobar or interstitial pneumonia. Abdominal tomodensitometry showed moderate hepatomegaly without splenomegaly, no biliary tract dilatation, and no pancretic abnormality. Biliary tract endosonography did not show biliary tract abnormalities but revealed calcified mediastinal adenopathies. Biliary MRI scans were normal as were upper gastrointestinal endoscopy and colonoscopy. There was no improvement in liver biochemistry or physical condition in spite of parenteral administration of antibiotics. The transbronchial biopsy (June 10th 1996) showed multiple epithelioid granulomas in the bronchial mucosa with normal pulmonary parenchyma. A large transparietal liver biopsy with 10 to 12 portal tracts (June 15th 1996) revealed diffuse noncaseating granulomas including giant and epithelioid cells within the portal tracts and within the lobules, associated with periportal fibrosis without bridging, as well as lobular chronic inflammatory cells. These granulomas were not aggressive against the bile ducts. There was moderate pure macrovacuolar steatosis (< 20%) without signs of steatohepatitis or cholangitis. There was no cirrhosis (Figure 1A). The number of bile ducts was significantly reduced, suggesting ductopenia (between 30 to 50 % of the portal tracts did not contain bile ducts). This liver histological pattern, associated with the presence of multiple epithelioid granulomas in the bronchial mucosa, was compatible with the diagnosis of hepatic sarcoidosis rather than of primary biliary cirrhosis.

Therapy with an oral steroid (prednisolone), the standard treatment for sarcoidosis, was started at a dose of 0.5 mg/kg per day on June 17th. After one month of treatment, the fever had disappeared and the patient's condition had markedly improved. However, the initial abnormalities in liver biochemistry persisted. Ursodesoxycholic acid was added to the treatment on July 15th at a daily dose of 13 mg/kg, and induced a progressive improvement in liver function tests (Table 1). Prednisolone treatment was maintained a 7 mg per day. A subsequent liver biopsy performed after 16 mo (January 1998) of ursodiol treatment revealed noncaseating granulomas including giant and epithelioid cells, and progressive diminution in the number of interlobular bile ducts. Marked steatosis (> 50%) was noted, in part related to a 10 kg increase in body weight. Fibrosis in portal and periportal areas was present, but there was no pericellular fibrosis destroying bile ducts, through bridging and loss of lobular architecture. There was

Table 1 Clinical course and laboratory Findings after treatment with ursodeoxycholic acid in our patient

Treatment with UDCA	ALP UI/L (N+ 30 - 100)	GGT UI/L (N + 5 - 45)	ALT UI/L (N + 6 - 45)	AST UI/L (N + 6 - 40)	Jaundice[a]
1996-07-15	520	1210	150	48	+++
1996-09-24	370	966	89	26	+++
1996-12-23	226	249	29	21	++
1997-02-21	123	215	31	22	0
1997-04-22	113	210	27	43	0
1997-07-08	134	235	26	17	0
1999-04-16	143	258	47	34	0
2000-05-05	103	152	40	29	0
2001-01-10	113	167	35	31	0
2002-12-05	88	170	30	36	0
2003-06-19	92	181	23	29	0

[a]Degree of change: 0: Absent; ++: Moderate; +++: Marked; N: Value of laboratory; Abbreviations: ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transpeptidase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; UDCA: Ursodeoxycholic acid.

no balloon degeneration or Mallory bodies present. This process may eventually lead to secondary biliary cirrhosis (Figure 1B). At final follow up in November 2004, liver tests were normal, no GP 210 antibodieswere found, and abdominal ultrasonography showed moderate hepatomegaly.

DISCUSSION

In this report, the diagnosis of sarcoidosis was supported by abnormalities found in chest x-ray studies and the presence of multiple noncaseating granulomas in the liver. Diagnosis of hepatic sarcoidosis with ductopenia was based on liver histology and normal findingd on biliary tract endosonography and biliary MRI; thereby excluding common bile duct stone or primary sclerosing cholangitis.

Sepsis was unlikely to be the cause of cholestasis since there was no improvement in liver biochemistry or physical condition despite intravenous antibiotic treatment. The presence of a systemic disease was confirmed, with bilateral hilar adenopathies and bronchial involvement, and subsequent liver histology showing numerous and well-defined granulomas, suggesting sarcoidosis rather than primary biliary cirrhosis. The immunological features and the results of liver biopsy allowed us to exclude primary biliary cirrhosis,the main possible differential diagnosis.

Sarcoidosis is a multisystem disease of unknown etiology. The disease, more common in blacks than whites, is characterized pathologically by diffuse noncaseating granulomatous lesions[1,5]. Usual sites of disease are the lungs and the mediastinum, although the liver seems to be frequently involved[5]. Clinical signs of hepatic involvement may range from asymptomatic forms to chronic cholestasis portal hypertension[6,7,8] and signs of hepatic vein obstruction (Budd-Chiari syndrome[8]). Jaundice, however is very rare[9,10].

Hepatic sarcoidosis may resemble primary biliary cirrhosis, as both diseases can lead to chronic cholestasis and to biliary cirrhosis. Thus, it may be very difficult to distinguish between these two entities. Primary biliary cirrhosis characteristically affects women of middle age, but sarcoidosis particularly affects black males under 40 years[6]. Hepatomegaly has been reported in 2%-21% of patients with sarcoidosis[11,12]. These are often incidental findings, but abdominal pain, dizziness may suggest hepatic involvement[13]. The frequency of abnormal findings in liver function tests in patients with sarcoidosis is highly variable, ranging from 2%-60%[14]. Elevation in alkaline phosphatase activities is the most common laboratory indicator, being detected in up to one third of patients[10, 14]. Anti-mitochondrial antibodies are detected in primary biliary cirrhosis, but are absent in sarcoidosis[15].

In seronegative primary biliary cirrhosis, anti GP 210 antibodies are found in 47% of patients without anti-mitochondrial antibodies[16] but were absent from the serum of our patient. Absence of anti GP 210 antibodies was an additional surrogate marker against PBC diagnosis. Elevated serum angiotensin-converting enzyme levels (observed in our patient) favoured of the diagnosis of sarcoidosis[17], although elevated levels have been observed in patients with hepato-cellular diseases of varied aetiologies[17,18].

Despite a mild increase in ACE, tuberculosis was excluded by clinical, radiological, pathological data as well as by the outcome.

Histological features of liver sarcoidosis usually consist of well defined and abundant confluent noncaseating granulomas, predominantly in the portal and periportal areas, as well as mononuclear cell infiltration, hepatocyte injury, and foci of fibrosis or cirrhosis[19]. Severe intrahepatic cholestasis and bile ductopenia only occur in a subset of patients with advanced disease[4,14]. In a study of 100 patients with sarcoidosis and abnormal liver function tests, liver biopsies showed cholestasis in 58%, a necroticoinflammatory process in 41%, and vascular changes in 20% of the patients[3]. In the cholestatic group, 19% of the patients had bile lesions similar to those of primary biliary cirrhosis. An additional 13% of the patients had a dense periductal fibrosis without accompanying inflammation, similar to that usually seen in primary sclerosing

Table 2 Epidemiological, clinical features and outcome of reported cases with hepatic sarcoidosis and ductopenia

Ref.	Age (Year)/Sex/Race	Jaundice	Maximum ALP	Maximun AST	Clinical outcome
[4]	29/M/Black	Yes	10 X	1 X	Died 9 years after diagnosis
	31/M/Black	Yes	14 X	5 X	Died 11 years after diagnosis
	23/M/Black	Yes	30 X	13 X	Alive, portal hypertension
	20/M/Black	Yes	35 x	9 X	Died 10 years after first seen
	33/M/Black	Yes	30 X	6 X	Died 18 years after first seen
[20]	56/M/White	Yes	3 X	4 X	Alive, no symptoms
[21]	50/F/Black	Yes	6 X	2 X	Alive, portal hypertension
	46/M/Black	Yes	3 X	2 X	Alive, portal hypertension
[15]	-/M/	Yes	9 X	4 X	Alive, no symptoms
[22]	62/F/-	No	10 X	2 X	Alive, cirrhosis
[23]	38/F/White	Yes	12 X	3 X	Died 26 years after diagnosis
	40/M/-	Yes	10 X	4 X	Died 10 years after diagnosis
[5]	27/M/Black	Yes	10 X	3 X	Alive, portal hypertension
	28/M/Black	No	9 X	2 X	alive, disabled
	44/M/Black	No	7 X	2 X	Alive, well
	24/F/Black	Yes	7 X	1 X	Alive, well
[24]	52/M/Black	No	8 X	1 X	Died, 4 years after diagnosis
[25]	44/M/-	No	4 X	1, 5 X	Alive, cirrhosis
[26]	62/M/-	No	1, 8 X	ND	Died, 3 years after diagnosis
Present case	54/F/White	Yes	5 X	1 X	Alive, cirrhosis

X: Upper limit of normal; ND: Not done; Ref: Reference; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase.

cholangitis. A decreased number of interlobular bile ducts were noted in 37%[3] of liver specimens. The female gender of our patient, the absence of inflammatory bowel disease , the course of the disease , the normality of Biliary MRI and of liver the histological specimens, ruled out a primary or secondary biliary sclerosing cholangitis in our patient. The liver biopsy did not show florid lesions of bile ducts or disruption of the biliary epithelium although parenchyma granulomas, paucity of bile ducts, and intense fibrosis did resemble primary sclerosing chlolangitis. The syndrome of disappearing intrahepatic bile ducts or "ductopenia" associated with sarcoidosis has, to our knowledge, previously been reported in 19 patients[4,5,21-26].

Epidemiological and clinical features of theses cases are summarized in Table 2. The majority of patients were black men and their ages ranged from 20 to 62 years. Jaundice was present in 13 of 19 the patients (70%). Liver biopsies showed noncaseating granulomas, bile duct depletion and cholestasis in all of these patients.

The clinical outcome was poor with death occurring in 9 patients, chronic sequelae consisting of severe liver disease in 6 others, and four patients who were free of symptoms. In our case, the second liver histological examination showed portal and periportal fibrosis destroying bile ducts and causing ductopenia, which may lead to secondary biliary cirrhosis. The intrahepatic bile ducts are open to several form of attack. The mechanisms of destruction may be immunological, vascular, infective or chemical[27]. Among possible immunological causes of of destruction are PBC, graft-versus-host disease and sarcoidosis. PSC is usually associated with immunological features, but the hepatic histology is not that of an immunological disease[27]. Among possible chemical casues, a variety of therapeutic drugs have occasionally been associated with bile duct destruction and loss. These may include chlorpromazine, prochlorperazin, organic arsenicals and tolbutamid[28, 29].

Diseases with disappearing bile ducts have a long natural history and hepatocellular failure usually occurs late in the process. At this stage, hepatic transplantation may give good results[27,30,31]. Treatment of patients with hepatic sarcoidosis is difficult to evaluate due to the variable clinical course of the disease, the variable timing of therapy and the possibility of sampling error in flow-up liver biopsies[23]. Steroids could improve clinical symptoms, but Valla *et al* showed that they were ineffective in improving liver function tests[6]. In addition, they did not prevent the development of portal hypertension[6]. Murphy *et al*, reported on 2 patients with symptoms of small-duct sarcoid biliary disease who showed biochemical- but not histological- improvement under steroid therapy[5]. In our patient, the clinical symptoms improved, but biochemical changes persisted despite steroid treatment. When ursodiol was added, a decrease in jaundice and cholestasis were observed. However, the liver histological findings did not improve. In end-stage liver sarcoidosis, there orthotopic liver transplantation is indicated[32], although recurrent sarcoidosis has been reported in such cases[33].

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