Review Article

Hepatic Sarcoidosis

Micheal Tadros[1], Faripour Forouhar[2] and George Y. Wu[1]

[1]*Department of Medicine, Division of Gastroenterology-Hepatology, University of Connecticut Health Center, Farmington, CT, USA;* [2]*Department of Anatomic Pathology, University of Connecticut Health Center, Farmington, CT, USA*

Abstract

Sarcoidosis is a multisystem disease characterized by the presence of non-caseating granulomas in affected organs. Pulmonary involvement is the most common site of disease activity. However, hepatic involvement is also common in sarcoidosis, occurring in up to 70% of patients. Most patients with liver involvement are asymptomatic. Therefore, the majority of cases are discovered incidentally, frequently by the finding of elevated liver enzymes. Pain in the right upper quadrant of the abdomen, fatigue, pruritus, and jaundice may be associated with liver involvement. Portal hypertension and cirrhosis are complications linked to long-standing hepatic sarcoidosis. Liver biopsy is usually required to confirm the diagnosis. It is important to differentiate hepatic sarcoidosis from other autoimmune and granulomatous liver diseases. Not all cases of hepatic sarcoidosis require treatment. For symptomatic patients, the first line treatment includes corticosteroids or ursodeoxycholic acid. Various immunosuppressant agents can be used as second line agents. Rarely, severe cases require liver transplantation.

Introduction

Sarcoidosis is an inflammatory disorder of unknown etiology categorized by the presence of non-caseating granulomas, which can involve multiple organs of the body,[1] in the absence of infections, other autoimmune diseases, and exposure to foreign agents. It has been estimated that the worldwide prevalence of sarcoidosis is 2–60 per 100,000 people.[2] Sarcoidosis affects all ethnicities with higher prevalence rates described in patients of Scandinavian descent.[2] In contrast, sarcoidosis has been only rarely reported in patients of Chinese and Taiwanese origin.[3,4] In the USA, African Americans have been reported to have a three times higher age-adjusted incidence of the disease.[1,5] Sarcoidosis affects females more often than males across all ages and ethnicities,[6] with an age peak of 20–40 years.[6] A second age peak (>50 years) has also been described.[6]

The hallmark of sarcoidosis is the formation of epithelioid granulomas that are typically non-caseating, in the absence of tuberculosis, fungal infection, malignancy, or other causes of granulomatous reactions.[7] The pulmonary system is the most common site of involvement, and is affected in about 90% of cases.[6] Extra-thoracic sarcoidosis occurs in 40–50% of patients.[8] Sites affected include peripheral lymph nodes (30%), the hepatic system, the spleen, stomach, small bowel, bone, and skin. Involvement of the solid organs can present as organ enlargement. Dermatological sarcoidosis may present as erythema nodosum or lupus pernio. Myopathy, uveitis, granulomatous meningitis, facial nerve palsy, cardiomyopathy, and parotid enlargement have been reported less commonly.

There are two classic syndromes described for sarcoidosis. The first is Löfgren syndrome, which is characterized by hilar lymphadenopathy, erythema nodosum, arthritis and fever.[6] The second is Heerfordton syndrome, which is characterized by uveitis, swelling of the parotid gland, fever, and facial palsy.[9]

The pathogenesis of sarcoidosis is still not completely understood, but it is thought to be multifactorial, involving the interplay of immunological, genetic, and environmental factors.[1,6] It has been theorized that an environmental trigger initiates a specific immune reaction in a genetically predisposed individual. The immunological response in sarcoidosis includes T helper 1 (Th1) cells triggered by an antigen, leading to cytokine production, mainly tumor necrosis factor alpha[10] which in turn, leads to macrophage aggregation with subsequent granuloma formation.[11] Certain histocompatibility antigens have been associated with sarcoidosis such as human leukocyte antigen-A1 (HLA-A1), B8, DRB1, DQB1, and DRB3.[12] This suggests a genetic susceptibility and familial clustering of the disease. Some of the possible postulated triggers of environmental antigens include reactive oxygen species, and viruses (herpes simplex virus, cytomegalovirus, retroviruses) and bacteria (*Borrelia burgdorferi*, mycobacteria).[2,6]

Epidemiology of hepatic sarcoidosis

In biopsy and autopsy studies of patients with systemic sarcoidosis, liver involvement was found in about 50–80%,[17] whereas only 10–30% of patients presented with abnormal liver enzymes during laboratory testing.[2,18] The majority of patients with hepatic sarcoidosis are asymptomatic, despite the presence of granulomas on biopsy, abnormal liver enzymes, or radiological evidence of disease.[14] It has been reported that the percentage of patients with clinically

Keywords: Sarcoid; Granuloma; Epitheloid.

Abbreviations: ACE, serum angiotensin converting enzyme; AFB, acid-fast bacteria; AMA, anti-mitochondrial antibody; ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; p-ANCA, peripheral anti-neutrophil cytoplasmic antibody; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

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Correspondence to: George Y. Wu, Department of Medicine, Division of Gastroenterology-Hepatology, University of Connecticut Health Center, Farmington, CT 06030, USA. E-mail: wu@nso.uchc.edu

significant disease is less than 20%.[19] Risk factors associated with hepatic sarcoidosis include African American ethnicity, prior exposure to pegylated interferon, and the presence of splenomegaly.[13,14,20] Reports on the differences in prevalence based on gender have been contradictory. In studies containing hundreds of patients, one study reported liver disease to be more common in women,[21] whereas the other showed the opposite.[22]

Spectrum of hepatic sarcoidosis

There is a spectrum of clinical presentations of liver involvement in sarcoidosis. Of the more than 50% of patients who have hepatic granulomas on liver biopsy, only 10–30% have elevated serum liver enzymes.[2,18] About 20% of patients have palpable hepatomegaly or splenomegaly. Radiological examination (ultrasound or computed tomography) is accurate in the detection of organomegaly, demonstrating this feature in about 40% of cases.[13,17] However, even in cases of elevated serum liver enzymes or radiological abnormalities, evidence of organ dysfunction is rare.

Some clinical symptoms and signs suggest liver involvement, and may warrant a liver biopsy. Systemic symptoms such as fatigue, fever, and arthralgias are non-specific, but are present in the majority of patients with active liver sarcoidosis.[23,24] More specific symptoms include jaundice and pruritus, mostly from chronic cholestasis.[25,26] Right upper quadrant abdominal pain, in theory, results from stretching of the Glisson's capsule by hepatomegaly as a consequence of the increasing intrahepatic volume occupied by the developing hepatic granulomas. Abdominal pain has been reported to occur in 15% of patients with sarcoidosis, and jaundice in less than 5%.[19]

Long-standing disease has been reported to result in portal hypertension in 3–18% of patients.[16] This may be due initially to compression of portal venules by granulomas, and can result in variceal bleeding. A small proportion (6–8%) of patients can develop portal hypertension because of progression to cirrhosis. Indeed, some patients can develop end-stage liver disease and require liver transplantation.[26–28] These account for about 0.012% of the total number of liver transplantation cases in the USA. Unfortunately, they often have a worse prognosis than patients with other cholestastic liver diseases such as primary biliary cirrhosis and primary sclerosingcholangitis.[29] Some case reports have linked sarcoidosis with an increased risk of developing Budd-Chiari[30] syndrome, hepatopulmonary syndrome,[28] hepatocellular carcinoma,[31,32] and biliary sarcoid mimicking cholangiocarcinoma. Table 1 lists postulated mechanisms of liver injury in hepatic sarcoidosis. Table 2 summarizes the clinical spectrum of the disease.

Investigations

Elevations of alkaline phosphatase and/or gamma glutamyltranspeptidase have been correlated with cholestasis and liver involvement.[25,34] Alkaline phosphatase of hepatobiliary origin can be elevated 5–10 times the upper limit of normal. Aminotransferase elevations are usually mild and less frequent compared with elevations in alkaline phosphatase.[19] The severity of liver test abnormalities was shown to be associated with the extent of granulomatous inflammation.[33] Hyperglobulinema may be seen. Measurement of the serum angiotensin converting enzyme (ACE) levels can be useful; they have been reported to be elevated in about 60% of patients with active sarcoidosis.[35–37] However, the test lacks sensitivity and specificity, with low positive and negative predictive values (84 and 74%, respectively).[38] Normal levels can be seen in chronic forms and in patients who have been on corticosteroids. Therefore, a normal ACE level does not rule out sarcoidosis, but an elevated level may help distinguish sarcoidosis from other granulomatous disease. Elevated ACE levels can also be present in patients with inflammatory bowel disease.[36]

Radiological studies[39] such as ultrasonography,[40] computed tomography (CT)[41] or magnetic resonance imaging (MRI)[42,43] may show hepatomegaly or multiple hypointense or hypoattenuated liver nodules. The occurrence of such multiple nodules can be confused with liver metastasis or other granulomatous diseases. The presence of concomitant splenic granulomas may help point towards a diagnosis of sarcoidosis.

Table 1. Postulated mechanisms of liver injury in hepatic sarcoidosis

Liver injury	Possible mechanism
Jaundice[13,14]	Chronic cholestasis from hepatic fibrosis, bile duct strictures (mimics cholangiocarcinoma) Obstruction of small bile ductules External compression from a sarcoid mass at the pancreatic head, or porta-hepatis adenopathy Hepatocellular carcinoma
Cirrhosis[13,15]	Granuloma formation with subsequent hepatic fibrosis, with or without granulomatous phlebitis and thrombosis Secondary biliary cirrhosis
Portal hypertension[16,17]	Intrahepatic pre-sinusoidal obstruction secondary to granulomas or sinusoidal obstruction from biliary fibrosis or cirrhosis Pre-hepatic obstruction from portal vein thrombosis Post-hepatic (hepatic vein thrombosis); Budd-Chiari syndrome Portal hypertension can occur without cirrhosis
Ascites[17]	Cirrhosis and portal hypertension Cor pulmonale Hypoalbuminemia Peritoneal sarcoidosis Chylous ascites (sarcoid lymphadenopathy)

Table 2. The clinical spectrum of hepatic sarcoidosis[17,19,33]

Feature	Presentation (%)
Asymptomatic	50–80%
Abnormal liver profile	30% 10–15% patients are symptomatic, and 85% are symptomatic.
Organomegaly (Liver or spleen)	50% detected on radiological exam, < 15–20% detected clinically
Clinical hepatitis	Abdominal pain 15%, pruritus and jaundice < 5%
Cirrhosis	6–8%
Portal hypertension	3–18%
Liver failure requiring liver transplantation	0.012% of all liver transplants in the USA

Liver biopsy should be considered if the diagnosis is uncertain and treatment is considered. Some authors recommend obtaining a liver biopsy if aminotransferase levels are elevated at least two-fold above the upper limit of normal. Histopathological examination is the definitive diagnostic tool. In sarcoidosis, granulomas are usually abundant and well-formed in the periportal and the portal regions. Typically, the granulomas are non-caseating and epithelioid (Fig. 1). There is scant lymphocytic inflammatory infiltration. Occasionally, fibrinoid necrosis, prominent fibrosis, and multinucleated giant cells can be seen. Staining for acid-fast mycobacteria, and for fungi should be negative. Progression of the disease can result in micronodular cirrhosis.[27]

Differential diagnosis

Hepatic sarcoidosis needs to be differentiated from other (autoimmune) liver diseases, especially primary biliary cirrhosis and primary sclerosing cholangitis[44,45] (Table 3).

The differential diagnosis of granulomatous liver disease can be separated into four main categories based on the type of granulomas present:[7] epithelioid, foreign body, lipogranulomatous, and lymphohistiocytic. Sarcoid epithelioid granulomas are characterized by macrophages that aggregate to form giant cells surrounded by fibrin rings. Table 4 includes some of these etiologies, and their differentiating characteristics. In the setting of post-transplant granulomas, it is important to remember that the treatment itself can lead to granulomas from drug reaction, and predispose patients to develop opportunistic infections that can cause liver granulomas.[7,46,47] In cases of sarcoidosis co-existing with hepatitis C, granulomas may be due to hepatitis C, or may have been induced by prior exposure to interferon therapy for hepatitis C.[48]

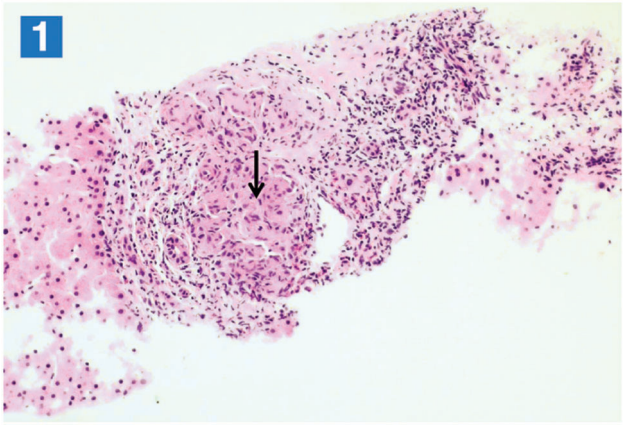

Fig. 1. A liver biopsy specimen showing a single portal epithelioid granuloma (arrow) surrounded by a thin cuff of lymphocytes. H&E, ×100.

Management

When evaluating patients with hepatic sarcoidosis for treatment, consultation with other specialists involved in the patient's care is recommended to ensure that other organ systems that may be involved with sarcoidosis such as the pulmonary system, central nervous system and/or ocular systems are treated adequately.[49]

Observation without medical management

Observation alone is indicated for patients with asymptomatic liver disease or mild elevations of serum liver enzymes, and normal synthetic liver function without evidence of cholestasis.[17,19,49] Hepatomegaly alone noted on physical examination and/or radiographic investigation in the absence of symptoms does not qualify as an indication for treatment. It has been noted that in some asymptomatic patients, abnormal serum liver tests can resolve spontaneously or remain stable for many years.[25,34]

Medical treatment

For patients who have symptoms of liver involvement, and have biochemical evidence of cholestasis or who are at high risk for developing hepatic complications, pharmacological therapy should be considered.[17,19,49] The first line agents that have been studied include corticosteroids and ursodeoxycholic acid.

Steroids

It has been shown that corticosteroids can decrease the number of hepatic granulomas by suppression of the inflammatory response,[50] and reduce liver size[25] which may be helpful for patients with persistent abdominal pain due to hepatomegaly. In addition, steroids are recommended for patients with constitutional symptoms such as fever, fatigue, pruritus, and weight loss. Low-dose prednisone (10–20 mg/daily) may be sufficient for those with mild symptoms, while a higher dose of prednisone (20–40 mg/daily) is warranted for

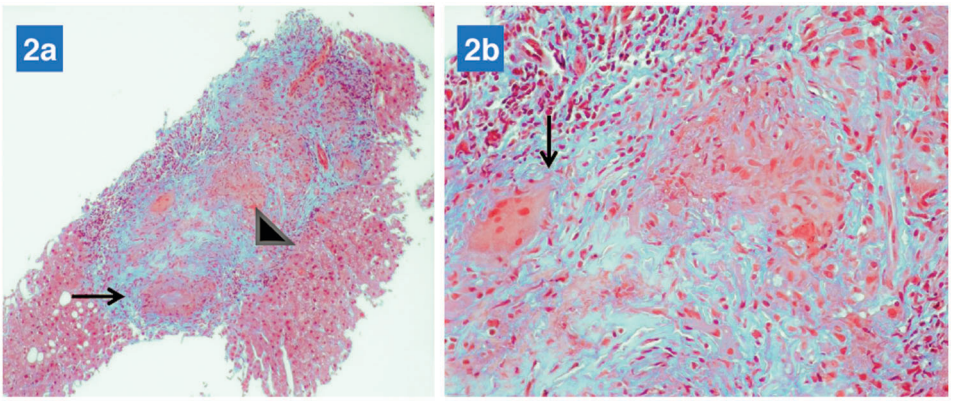

Fig. 2. A liver biopsy specimen showing: a, a conglomerate of granulomatous reaction (arrow) with significant fibrosis (arrow head); b, significant as well conglomerate of epithelioid granulomas with giant cells (arrow), but without necrosis. Trichrome, ×400.

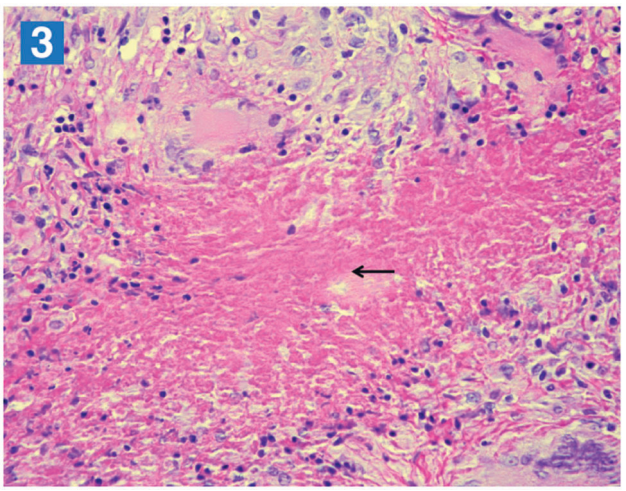

Fig. 3. A liver biopsy specimen showing a sarcoid granuloma in liver with central fibrinoid necrosis (arrow). H&E, ×400.

those with severe symptoms.[17,51] Prednisone can also be considered for patients with significant adenopathy in the porta hepatis.

Treatment duration should be determined by clinical and laboratory response. Some authors recommend 12 months of therapy before tapering the dose.[52] Relapsing symptoms may require long-term therapy or steroid-sparing agents. Side effects of long-term steroid use (including ostopenia, bone fractures, avascular hip necrosis, hyperglycemia, cataracts, and hypertension) should be considered.[52] No studies have reported on the use of oral budesonide (a systemic steroid eliminated on first pass through the liver) in the treatment of hepatic sarcoidosis.

The benefit of steroids in patients at the extremes of the clinical spectrum (that is, asymptomatic individuals or patients with cirrhosis and portal hypertension) is questionable. Steroids can help in the normalization of these laboratory abnormalities in asymptomatic patients with elevated aminotransferases.[14,34] However, it is important to consider that serum liver tests can normalize

Table 3. List of features that distinguish hepatic sarcoid from primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC)

	PBC	Sarcoidosis	PSC[44]
Histology	Granulomas - usually few, poorly defined and located in the portal tract along damaged bile ducts, with eosinophils. Florid ductal lesions present in early disease	Granulomas: many, well-formed and usually periportal. Prominent fibrosis and multi-nucleated giant cells. Less prominent biliary injury.	Concentric prominent periductal fibrosis: "onion skin" fibrosis. No granulomas.
Serum Tests	Anti-mitochondrial antibody (AMA)	Serum angiotensin converting enzyme (ACE)	Peripheral anti-neutrophil cytoplasmic antibody (p-ANCA)
Imaging	—	—	Magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP): generalized beading of the biliary tree
Extra-hepatic disease	Rare	Pulmonary nodules, hilar lymphadenopathy	Ulcerative colitis

Table 4. List of features of various granulomatous liver diseases (adapted from Coash et al.[7])

Mycobacterium tuberculosis	Acid-fast bacteria (AFB) inside epithelioid granulomas and giant cells, often with a ring of lymphocytes and histiocytes
M aviumin tracellulare	Aggregates of foamy macrophages in parenchyma and portal triads with positive AFB staining
M leprae	Foamy histiocytes in portal tracts and lobules with multiple AFB found
Brucella	Non-caseating granulomas
Rickettsia	Fibrin rings surrounding vesicles of fat
Francisella	Suppurative microabscesses with surrounding macrophages
Listeria	Microabscesses with small granulomas
Bartonella henselae	Stellate abscesses with three distinct zones
Tropheryma whipplei	Epithelioid granulomas
Histoplasma	Macrophages and lymphocytes with histoplasma and epithelioid cells in the center
Schistosoma	Eosinophils with fibrosis and collagen deposition in peri-portal and peri-sinusoidal areas, often with eggs in the center
Leishmania	Fibrin ring or epithelioid granulomas
Hepatitis C	Epithelioid granulomas
Drugs and chemicals	Granulomas with eosinophils
Malignancy	Non-necrotic granulomas

spontaneously.[25,34] Because there is a lack of long-term studies, it is unclear if steroids prevent liver damage or halt the progression of the disease. In patients with progressive disease (significant fibrosis, chronic cholestasis, and portal hypertension), steroid treatment has not been shown to have beneficial effects.[16]

Ursodeoxycholic acid

Ursodeoxycholic acid decreases biliary secretion of cholic and chenodeoxycholic acid, and inhibits the intestinal absorption of bile salt. It also helps to modulate the immune response by decreasing HLA class I and class II antigens on the cell membranes of the hepatic and bile duct epithelial cells, respectively.[53] Recent studies have shown a beneficial effect of this agent in the treatment of hepatic sarcoidosis, especially when patients with cholestasis are symptomatic with pruritus.[49] It has the potential effect of delaying the progression of the disease. Given its relative safety compared to steroids, some authors recommend starting with ursodeoxycholic acid before prednisone. In a recent retrospective study of 17 patients comparing placebo vs. prednisone vs. ursodeoxycholic acid,[54] ursodeoxycholic acid was found to be superior in improving aminotransferase levels, pruritus, and fatigue.[54] The usual dose is 13–15 mg/kg orally per day.[55]

Second-line and third-line agents

These agents may be useful for patients for whom prednisone fails or patients who are deemed to be steroid dependent. Azathioprine has been reported to normalize aminotransferases, but can also cause acute hepatitis.[49] Methotrexate, glutathione, chlorambucil, cyclosporine, cyclophosphamide, thalidomide, pentoxifylline, and infliximab[56,57] have been reported to be beneficial. However, there is inadequate evidence to support the use of these agents.[49]

Treatment of advanced liver disease

Portal hypertension and decompensated cirrhosis should be managed by standard measures. Steroids may not be beneficial, and liver transplantation may be required. Reported rates of graft and patient survival for hepatic sarcoidosis are 78% at 1 year, 66–67% at 3 years, and 60–61% at 5 years.[29] Recurrence of disease in the graft has been reported.[58]

Prognosis

The mortality rate of sarcoidosis is about 1–5%.[59,60] Death usually occurs from severe pulmonary, cardiac, and central nervous system disease rather than hepatic involvement. These survival rates are comparable to other causes of transplantation, except for PBC and PSC.[29,61,62]

Conclusions

Hepatic sarcoidosis is a granulomatous disease of unknown etiology. Around 70% of patients have epithelioid non-caseating granulomas on liver biopsy; 20–40% of patients have hepatomegaly or elevated liver enzymes. Most of the cases with liver involvement are asymptomatic and do not require treatment. Pain in the right upper quadrant of the abdomen, fatigue, pruritus, and jaundice are the most commonly associated symptoms. For symptomatic patients, prednisone and/or ursodeoxcholic acid may be considered. Those patients who do not respond to steroids and/or ursodeoxcholic acid may require other immunosuppressive agents. Portal hypertension and cirrhosis are possible complications from long-standing hepatic sarcoidosis. Patients may require liver transplantation, but disease recurrence in the graft has been reported, and survival rates tend to be lower than those for patients transplanted for other diseases.

Conflict of interest

None

Author contributions

Writing the medical text (MT), writing the pathology section (FF), organizing and editing the manuscript (GYW).

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