

Hepatic sarcoidosis

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Abstract

Sarcoidosis is a multisystem disease of unknown aetiology. Histological evidence of non-caseating granulomas represents the main finding. It affects mostly young people, targeting primary the lung and hilar lymph nodes although liver involvement is often encountered. Hepatic sarcoidosis covers a broad spectrum from asymptomatic hepatic granulomas formation and slightly deranged liver function tests to clinically evident disease with cholestasis or, in advanced cases, cirrhosis and portal hypertension. Other granulomatous diseases (mainly systemic infections like tuberculosis) should be excluded prior to treatment, as longstanding corticosteroid administration is the main stem of therapy. In advanced cases, liver transplantation represents the ultimate therapeutic option.

Key words: Liver granuloma, idiopathic granulomatous hepatitis, cholestasis, hepatic sarcoidosis, liver sarcoid.

Introduction - Epidemiology

Sarcoidosis is a systemic disorder of unknown origin. It is characterized by non-caseating epithelioid granulomas disrupting normal tissue histology. Current theory suggests that sarcoidosis results from exposure to an antigen (infectious agent, aerosols, etc.) in genetically predisposed individuals.

Prevalence is estimated at 1-40:100,000 and young people (10-40 years of age) are most often affected. The disorder is more often observed in northern European countries (Scandinavian countries), the United States and

Japan. US Afro-Americans have a three-fold increased lifetime risk of developing sarcoidosis compared to the white population.¹⁻³ In the ACCESS study (a case-control aetiological study of sarcoidosis), the relative risk for disease development in first or second degree relatives was 4.7 after adjustment (age, sex, socio-economic class, shared environment). Although familial clustering has been described, screening of asymptomatic family members is not generally necessary.⁴

Sarcoidosis primarily affects the lung and hilar lymph nodes. Liver, spleen, heart, bone marrow and less often eye, skin and salivary glands are common extrapulmonary sites of disease manifestation.¹⁻³

Based on the existing literature, this review will focus on histopathologic features, clinical presentation, differential diagnosis and treatment options available in hepatic sarcoidosis.

Histopathology

Granulomas are the main histological feature of sarcoidosis. These lesions consist mainly of aggregated epithelioid histiocytes and multinucleated giant cells. Lymphocytes and fibrin deposits are often present at the periphery of the lesions and seldom in the center. Necrosis is absent in typical cases although it presents centrally in atypical ones. Giant cell inclusions are sometimes observed. They consist of asteroid bodies, Schaumann bodies, centrospheres and calcium oxalate crystals but are not pathognomonic.^{5,6}

Granulomatous lesions in hepatic sarcoidosis are very small in size and almost always present in liver biopsy. They typically occur in the portal and periportal zones of hepatic sinuses, are many in number, evenly distributed in the liver parenchyma and demonstrate an identical stage of maturation. The turnover rate of the granuloma cells is very high and large confluent granulomas may ultimately lead to hyalinized scar formation.⁷⁻⁹

Granulomatous lesions are not the only histological feature of hepatic sarcoidosis. Intrahepatic cholestasis is found in up to half of biopsy specimens. One of the many contributing factors seems to be the progressive interlobular bile duct injury due to inflammatory infiltration of basement membranes and portal granuloma formation. It has been proposed that the latter results in fibrosis of portal tracts, "lacking" (vanishing) bile ducts and ultimately

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ductopenia. This so-called “granulomatous cholangitis” is often seen in Afro-Americans and Jamaicans. Excluding the granuloma formation this histological picture resembles primary biliary cirrhosis from which it is sometimes difficult to differentiate from.^{5,10}

Devaney et al,⁵ found cirrhosis in a small number of patients with hepatic sarcoidosis. This may be the result of chronic cholestasis and possible coexistence of other liver-injuring diseases or the outcome of vascular injury, scar formation by granulomatous phlebitis and thrombosis of terminal venule (hepatic or portal) branches. Once cirrhosis establishes, the clinical manifestations of portal hypertension appear.^{5,11}

Clinical presentation and laboratory findings

Involvement of the liver is very common in patients with sarcoidosis. The diagnosis depends on the methodology and the diagnostic procedure followed. In autopsy series hepatic granulomas are found in as much as 70% of cases with sarcoidosis.¹² When liver biopsy is employed, “involvement” ranges from 50 to 65%.^{7,10,13} Abnormalities in liver function tests (LFTs) are encountered in 20-40% of patients but clinical expression of hepatic disease is not commonly observed. Most patients with hepatic sarcoidosis are asymptomatic and have normal liver enzyme tests. Hepatosplenomegaly (15-40%) and abdominal pain (5-15%) are the commonest clinical findings. In some patients with systemic sarcoidosis (5%) constitutional symptoms such as weight loss, night sweats and fever dominate the clinical picture and suggest hepatic involvement.^{5,6,10,14} In one report 60% of patients with hepatic sarcoidosis had fever and arthralgias in contrast to patients without liver disease.⁷

Jaundice, pruritus, liver failure, ascites and hepatic encephalopathy are rare unless the disease is advanced or complicated. Clinical aspects such as cholestasis, portal hypertension and Budd-Chiari syndrome are further analyzed below.

Depending on disease activity hyperglobulinaemia, increased serum alkaline phosphatase (ALP), •-GT, bilirubin (usually < 5 mg/dL) and slightly elevated transaminase levels are typical laboratory findings. Increased ALP can be found in as much as 90% of patients with signs and symptoms of hepatic disease but only in 10-15% of cases with only histological evidence.^{5,6,10,14}

Serum angiotensin converting enzyme (SACE) is usually elevated but not pathognomonic. Serial measurements are implemented to monitor disease activity, response to treatment and ongoing relapse. Increased levels of calcium (10-20% of patients) due to overproduction of 1, 25-dihydroxycholecalciferol from activated macrophages, as well as elevated levels of Ca19-9 in cholestasis can be encountered.^{5,6,14}

Cholestasis

As mentioned above intrahepatic cholestasis is a central finding in hepatic sarcoidosis. Devaney et al⁵ found intrahepatic cholestasis in 58 out of 100 patients. Beside the described “granulomatous cholangitis”, alternative mechanisms of cholestasis include the following:^{5,8,9}

- Sarcoidosis of extrahepatic bile ducts
- Common bile duct compression by enlarged perihilar lymph nodes or involvement of the pancreas
- Associated primary biliary cirrhosis and primary sclerosing cholangitis

These alternative mechanisms need to be analyzed further.

Sarcoidosis can be seen in association with primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). Expression of sarcoidosis can precede or follow PBC for many years, a situation encountered in less than 1% of patients with PBC.¹⁵ Differentiation of (chronic) cholestasis due to sarcoidosis or PBC can be challenging. Although on histology PBC is typically characterized by chronic non-suppurative destructive cholangitis, in atypical cases findings are obscured or overlap. In these cases distinction is based on different patient features (usually middle-aged women with longstanding history of PBC) and selected clinico-laboratory findings (*Table I*). Sometimes, differential diagnosis is quite impossible and patients have clinico-histological findings attributed to both conditions and laboratory parameters (Kveim-Siltzbach test and mitochondrial antibodies) both either positive or negative.^{5,15,18,19}

PSC has a weaker association with sarcoidosis than PBC and coexistence of both diseases has been reported in only a few cases.^{20,21} Sarcoidosis can become clinically evident either before or after manifestation of PSC. It is remarkable that 7% of patients with PSC demonstrate granulomata on liver biopsy.²² Differentiation of intrahepatic cholestasis due to sarcoidosis from that of PSC requires combination of clinical, histological and laboratory parameters (*Table II*).

Budd-Chiari syndrome

There are few case reports of hepatic sarcoidosis complicated by hepatic vein thrombosis.^{23,24} Thrombosis may be the result of venous channels compression and stasis or expression of coexistent underlying thrombotic disorder. Large and medium sized intrahepatic veins can be narrowed either by granulomas-evolving from the vessel wall- or by extrinsic compression due to inflammation and oedema of sarcoid granulomata growing in hepatic parenchyma. Idiopathic granulomatous venulitis has been reported in few cases but it is unclear if it represents a variant of sarcoidosis.^{25,26}

Table I. Differential diagnosis of sarcoidosis and PBC.¹⁵⁻¹⁷

	Sarcoidosis	PBC
Kveim-Siltzbach skin test	Positive (can be negative in > 20% of acute cases)	Negative
Mitochondrial antibodies (AMA)	Absent	Present (> 90% of cases)
Histologic picture	Granulomata in portal and periportal areas	Infiltrates of plasma cells, lymphocytes and eosynophils in relation to damaged bile ducts. Few poorly defined granulomata
Extrahepatic granulomata	Present	Absent
SACE level	Elevated	Not elevated
IgM levels	Normal	Elevated
Response to corticosteroid	Rapid improvement	Slow response

Table II. Differential diagnosis of sarcoidosis and PSC.^{5,15,20}

	Sarcoidosis	PSC
Inflammatory bowel disease	Absent	Present
Narrowing of bile ducts	Restricted to a single biliary system area	Generalized
Histologic picture	Granulomata in portal and periportal areas	Chronic concentric periductal fibrosis
ANCA-antibodies	Absent	Present
IgM levels	Normal	Elevated
Response to corticosteroid	Rapid improvement	Slow response

Table III.

1. Systemic diseases
 - Granulomatoses
 - Sarcoidosis
 - Idiopathic hypogammaglobulinemia
 - Chronic granulomatous disease
 - Wegener's granulomatosis
 - Temporal arteritis
 - Polymyalgia rheumatica
 - Erythema nodosum
 - Allergic granulomatosis
 - Crohn's disease
 - Granulomatous lesions of unknown origin (GLUS)
 - Other systemic disorders
 - Systemic lupus erythematosus
 - Ulcerative colitis
 - AIDS
 - Malignant diseases
 - Hodgkin's disease
 - Non-Hodgkin's lymphoma
 - Carcinoma
 - Melanoma
2. Infections
 - Mycobacteria
 - Tuberculosis
 - Atypical mycobacteria

Portal hypertension and cirrhosis

Portal hypertension is an uncommon finding in sarcoidosis and the mechanisms involved are not completely understood. Portal hypertension in hepatic sarcoidosis may or may not coexist with cirrhosis (macro- or micronodular). As mentioned above true cirrhosis was noted in only 6% of patients with sarcoidosis reported by Dev-

aney et al,⁵ and appears to be the result of chronic cholestasis, associated PBC, PSC or other underlying coincidental hepatic disease (hepatitis C, alcohol etc). In the same report 3% of cases had portal hypertension.

Beside cirrhosis other possible causes of increased portal blood flow include the newformation of arteriovenous shunts in areas of liver and spleen granulomas, the extensive cirrhotic scar formation caused by large confluent granulomas with resultant healing fibrosis and the extrinsic compression of portal vein by enlarged perihilar lymph nodes.^{15,27} There is evidence to ground the theory of pre-sinusoidal portal hypertension attributed to portal area granulomas,²⁸ and even that of an ischemic cause due to granulomatous venulitis of portal and hepatic vein branches.¹¹

Hepatic sarcoidosis on imaging studies

Liver enlargement is found on ultrasound (US) or computerized tomography (CT) scan in up to 50% of cases.²⁹⁻³¹ It is the commonest CT finding, often accompanied by splenomegaly and (less often) abdominal lymph node enlargement. Hepatic granulomas are found on CT in only few cases (< 5% of patients). They are typically visualized as multiple, discrete, low-attenuating, non-enhancing (after contrast injection) nodules of variable size (0.5-0.8 cm). As they increase in size, they tend to become confluent and have to be differentiated from various infectious and neoplastic conditions (eg. liver metastases, lymphoma and angiosarcoma).³⁰⁻³²

Hepatic nodules are also encountered on magnetic resonance imaging (MRI). They present as hypodense le-

sions on T1- and T2- weighted sequences without enhancement after gadolinium injection, with progressive loss of conspicuity on successive images and intact surrounding vascular architecture. Based on these MRI findings, sarcoid nodules can be differentiated from metastatic disease but not from regenerative nodules of cirrhotic liver or other infectious lesions.³³

Diagnosis and differential diagnosis

Sarcoidosis is a multisystem disease and diagnosis must be made on clinico-laboratory findings combined with histological evidence of non-caseating granulomas. Granulomas are generally found in 5-15% of all liver biopsy specimens. In Western countries a large portion is attributed to PBC (up to 55% of cases) and sarcoidosis (15-30%) but infective causes, like tuberculosis and brucellosis, should always be kept in mind during initial investigation.^{7,34,35} Usual causes of hepatic granulomas are shown in *Table III*. Therefore evaluating hepatic granulomas should therefore include a detailed medical and drug history followed by extensive laboratory testing. The liver biopsy specimens should be stained for acid-fast bacilli, fungi (silver stain), spirochetes (Whartin-Starry stain), and examined for eggs, foreign bodies, eosinophils, lipid vacuoles and fibrin (Q fever). Evidence of various pathogens should be sought through liver specimen culture and specific PCR genome amplification.

Hepatic granulomas of unknown cause in the absence of extrahepatic involvement have been outlined as idiopathic granulomatous reactions restricted to the liver (idiopathic granulomatous hepatitis). This situation is encountered in 3-37% of cases and it is uncertain if at the end should be considered as a variant of hepatic sarcoidosis.^{35,37,38} It is necessary to distinguish this condition from true hepatic sarcoidosis; therefore an additional extrahepatic organ involvement has to be documented. On the basis of this consideration the ACCESS instrument was proposed.

Second organ involvement can be specified on sufficient clinical evidence (e.g. positive Kveim test) and exclusion of other causes making histological confirmation of the second organ involvement unnecessary. The ACCESS instrument also defines hepatic involvement in extrahepatic sarcoidosis without the need for liver biopsy. It has been suggested that hepatic sarcoidosis can be diagnosed if serum liver function tests are elevated more than three times the upper limit of normal, provided that there is no other clinical explanation for this abnormality and biopsy of an extrahepatic organ shows non-caseating granulomas. Diagnosis of hepatic sarcoidosis is probable if a CT scan reveals abnormalities consistent with sarcoidosis or the serum alkaline phosphatase is elevated, provided that there is no other clinical explanation for this abnormality.^{4,39}

Another mentionable condition, possibly of extra pulmonary sarcoidosis with documented hepatic granulo-

mas, is the granulomatous lesions of unknown significance (GLUS) syndrome. Characterized by prolonged fever and tendency for recurrence, it should be differentiated based on the lack of hypocalcaemia, normal SACE levels, and negative Kveim-Siltzbach test and -in contrast to sarcoidosis- different T-cells immunotyping involved in granuloma formation.^{40,41}

Other diseases with overlapping clinico-histological features, like PBC and PSC, have been mentioned above and the differential diagnosis is summarized in *Tables I and II*.

Therapy

The treatment of hepatic sarcoidosis is dependent on clinical and laboratory disease manifestation.

No treatment is required when only histological appearance of non-caseating granulomas is encountered without clinical or biochemical liver disease or dysfunction. In cases of liver function test abnormalities -without other clinical or laboratory evidence of systemic sarcoid involvement- treatment (agent, start, dose and duration) is still a controversial issue because, even untreated patients demonstrate "spontaneous" LFTs improvement. Since chronic use of corticosteroids is the main stem of therapy in systemic sarcoidosis, it seems prudent to observe (with serial liver function test) those patients who are asymptomatic or have only mild disease that may spontaneously remit.^{1,3,14,42}

There are no large controlled trials evaluating the efficacy of corticosteroids in hepatic sarcoidosis. Because of slow and diachronic disease evolution our knowledge is based on few small trials, retrospective studies and case reports. It has been noted that improvement of liver function tests after corticosteroid administration may not indicate improvement in liver histology and therefore; progression to cirrhosis may eventually occur. In the same way early corticosteroid administration does not preclude the appearance of cholestasis or that of portal hypertension. Beside serial LFTs monitoring, liver biopsy remains substantial not only in diagnosis but also in disease follow-up.^{14,42}

When systemic symptoms of fever, abdominal pain and weight loss develop steroids are essential. Many patients require a daily low dose of 10-15 mg prednisolone, often continued for several years. Higher corticosteroid doses (30-60 mg/d) are needed in case of clinical evident chronic cholestasis with jaundice and pruritus. Clinical and laboratory improvement is often observed, but histological changes ultimately progress and portal hypertension develops. Corticosteroids do not show any benefit once bile duct depletion and fibrosis have occurred.^{42,43}

Alternative pharmacological options include several drugs with varying treatment efficacy. They have been mostly used as steroid-sparing agents in order prevention in order to prevent the side effects from chronic corticoids

teroid administration. Chlorambucil and methotrexate have been used despite their malignant and hepatotoxic potential. Chloroquine seems to improve liver enzyme abnormalities in asymptomatic patients but is ineffective in chronic cholestasis. Cyclosporine has been used with success only in regard to immunosuppression offered after liver transplantation in patients with end-stage disease. Ursodeoxycholic acid (UDCA) seems to be effective in the chronic cholestatic syndrome of hepatic sarcoidosis. At a daily dose of 10 mg/kg it appears to improve clinical symptoms and liver function test abnormalities. Beside the inhibitory effect on intestinal bile salt absorption, UDCA also seems to improve cholestasis through an immune-modulating pathway. Other systemic acting agents as azathioprine, cyclophosphamide, pentoxifylline, thalidomide and infliximab are mentioned in the international literature. Their use as steroid-sparing agents is scrutable but their effectiveness and usefulness in hepatic sarcoidosis remains unsolved.⁴²⁻⁴⁵

Portal hypertension and the Budd-Chiari syndrome implicating hepatic sarcoidosis are managed in a similar way as from other causes with liver transplantation representing the ultimate treatment alternative in refractory cases. Ideal patients for liver transplantation should have minimal extrahepatic organ involvement and survival seems to be equivalent to other transplant recipients with end-stage liver disease although sarcoidosis may ultimately recur in the allo-graft.⁴⁶⁻⁴⁸

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