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Particularities of Hepatic Sarcoidosis

Laura Iliescu and Letitia Toma

Abstract

Liver sarcoidosis is usually an underdiagnosed disease, which can have severe implications in the evolution of a patient. Due to the fact that sarcoidosis is a disease based on immunological disorders, it is only natural that the liver should be one of the first organs to be affected. The imaging of liver sarcoidosis is of marked importance, especially in the differential diagnosis of the disease. While the histology aspect of sarcoidosis is relatively clear and should prompt a positive diagnosis, finding a liver granuloma in ultrasonography raises a multitude of questions and implies extensive testing for diagnosis. Furthermore, treatment of liver sarcoidosis is controversial, taking into account the possibility of developing end-stage liver disease in patients with a long history of sarcoidosis. This chapter aims to review diagnostic and treatment options for liver sarcoidosis and to determine the best management of these patients.

Keywords: liver granuloma, sarcoidosis, cholestasis, abdominal ultrasonography, liver transplant

1. Introduction

Liver granulomas may appear as either a primary condition or secondary to systemic disease [1]. They consist of modified macrophages and other inflammatory cells that adhere due to antigenic stimulation. If there is liver inflammation within or surrounding these granulomas, the term used is granulomatous hepatitis.

The prevalence of liver granulomas is as high as 15% in biopsy specimens in the general population [2], with a higher frequency (up to 75%) in special populations like HIV-infected patients and patients with prolonged fever of unknown etiology [3].

Common causes of liver granulomas include primary biliary cirrhosis, sarcoidosis, infectious diseases (*Mycobacterium tuberculosis*, Listeria, Histoplasma, Schistosoma and hepatitis C virus), drugs and malignancies [1]. However, up to 36% of all liver granulomas are of unknown etiology [4].

Granuloma formation takes place during a chronic inflammation reaction, involving epithelioid cells, lymphocytes, monocytes and plasma cells, recruited under the influence of T-cell interleukins [1]. The reaction is consistent with a delayed hypersensitivity cellular immune response to pathogenic material.

2. Etiology and histology of hepatic sarcoidosis

Sarcoidosis is a non-caseating granulomatous disease, of unknown etiology, affecting primarily mediastinum lymph nodes and the lungs. Its diagnosis is mainly an exclusion one, requiring elimination of all infectious and antigen-producing diseases [5]. The pathognomonic histological aspect is of non-caseating granulomas containing epithelioid cells [6]. Typically, sarcoidosis affects the lungs in over 90% of the cases, but several other organs may be involved, including the liver, the skin, the central nervous system, the heart and the eyes [7, 8]. The main peak of incidence is described for the age group 20–39 years for both genders, with women having a second incidence peak at the ages of 65–69 [9].

The main pathophysiological process in sarcoidosis is the immune paradox, with exaggerated inflammation at disease sites and relative anergy in the unaffected regions [10]. Several theories have been suggested as explanation for this paradox [11]. First, there may be an imbalance between regulatory and effector T-cell lymphocytes that accumulate in the periphery of the granuloma and exert inhibiting effects on naïve T cells. Second, the intense immune stimulation at the disease sites causes lymphocytes to converge in these sites and produces a relative peripheral leukopenia. Third, subsequent to disease chronicity, immunosuppressive T cells are more abundant in the peripheral blood, producing anergy to other antigen stimulations.

The result of this immune imbalance is the non-caseous granuloma, probably containing a partially degraded antigen surrounded by macrophages and T-helper cells. [11]. These macrophages will in turn differentiate into epithelioid cells that will eventually fuse to form multinucleate giant cells. The periphery of the granuloma contains CD8+ T cells, regulatory T cells, fibroblasts and B cells.

As mentioned before, a large percentage of patients with sarcoidosis present with typical signs of the disease in liver biopsy specimens, while only 10–30% have abnormal liver tests [12]. Risk factors associated with liver involvement in sarcoidosis include African-American ethnicity, exposure to pegylated interferon and splenomegaly [13].

The histology aspect of liver sarcoidosis is defined by the presence of epithelioid granulomas in both the portal tracts and hepatic lobules [14]. About 30% of patients with liver sarcoidosis have histological chances similar to those in primary biliary cirrhosis or primary sclerosing cholangitis [15]. However, typical granulomas in sarcoidosis are larger, better defined and associated with multinucleate giant cells. Occasionally, the granulomas may conflate resulting in large masses, which can be misdiagnosed for liver tumors on abdominal imaging [15]. Furthermore, granulomas from primary biliary cirrhosis are portal based and are associated with bile duct destruction, unlike sarcoidosis. In sarcoidosis, there are other signs of organ involvement, as it is a systemic disease, and anti-mitochondrial antibodies are always negative. The histological differential diagnosis between liver sarcoidosis and drug-induced liver injury (DILI) takes into account the fact that DILI manifests as granulomatous hepatitis, with small intralobular granulomas with periportal inflammation [16].

The most important aspect of differentiation between sarcoidosis and infectious granulomas is the presence of caseous necrosis, typical for infectious granulomas [17]. As such, caseating granulomas with central necrosis must be considered infections, until serious evidence eliminates the diagnosis. However, histochemical stains have a low sensitivity for infections, and false-negative results are frequent.

The histology aspect of sarcoidosis may vary, thus explaining the differences in symptomatology and evolution [15]. In a report of 100 cases with sarcoidosis and liver biopsy due to abnormal liver test results, all patients presented with liver

granulomas, 99% non-caseating, frequently located in the periportal region. None of the patients had serology or cultures suggestive for infectious granulomas. Three types of histologic alterations were encountered: most patients had cholestatic changes (58%), while 41% presented with necroinflammatory changes and 20% presented with vascular alterations. Patients with cholestasis presented with histology aspects similar to those encountered in primary biliary cirrhosis (19 patients with bile duct lesions) or primary sclerosing cholangitis (13 patients with periductal fibrosis). Biliary ductopenia was noted in 37 out of 58 patients with cholestasis. Twelve patients presented with acute cholangitis without signs of biliary obstruction. Necroinflammatory changes consisted of spotty necrosis and chronic portal inflammation, suggesting hepatitis of various etiologies (viral or drug-induced). Vascular alterations encountered in these patients were sinusoidal dilatation and nodular regenerative hyperplasia. Fibrosis was present in 21 patients overall: 13 patients with periportal fibrosis, 2 patients with bridging fibrosis and 6 patients with cirrhosis.

3. Clinical aspects of hepatic sarcoidosis

The spectrum of liver damage in sarcoidosis varies greatly from asymptomatic patients to end-stage liver disease [12]. Commonly, mild liver cytolysis can be observed (in about 30% of patients with positive biopsies for sarcoidosis) [12]. Abdominal imaging reveals hepatomegaly in less than 50% of the cases [18].

Non-specific symptoms are frequently encountered in patients with sarcoidosis, including malaise, fatigue, arthralgias and fever [19]. Symptoms suggesting liver involvement are jaundice, pruritus and abdominal pain in the upper right quadrant, due to chronic cholestasis and distension of the Glisson capsule by hepatomegaly containing granulomas [19, 20]. One report even describes fever and arthralgias in 70% of patients with liver sarcoidosis, as opposed to those without liver involvement [21].

Rarely, the chronic evolution of liver sarcoidosis can lead to portal hypertension and in a minority of cases, end-stage liver disease with the need for liver transplantation [19]. Also, few cases of association between liver sarcoidosis and Budd-Chiari syndrome have been reported [22]. In a report published in 2006 [23], out of 180 patients, 50% had altered liver function associated with sarcoidosis, while 13% of the patients had liver affection without lung sarcoidosis. Fourteen patients presented with liver cirrhosis from the diagnosis of liver involvement, while two patients developed cirrhosis in the course of the disease, despite corticoid therapy. Six patients underwent liver transplantation, and recurrence of liver sarcoidosis was reported in one patient after transplantation.

Case reports of liver sarcoidosis show either non-specific general symptomatology or altered liver enzymes at the time of diagnosis. For example, liver sarcoidosis was diagnosed in a 41-year-old patient with a known history of ocular and lung sarcoidosis for 6 years, who presented with an increase in liver enzymes during periodic follow-up [24]. Final diagnosis was based on positron emission tomography and subsequent liver biopsy.

Liver sarcoidosis may also appear in association with cutaneous sarcoidosis. In a report of 40 cases of patients with cutaneous sarcoidosis (with positive histology) monitored for a mean period of 9 years, 32 patients developed lung and thoracic lymph node disease; 1 patient developed liver sarcoidosis [25].

A recent case series of 7 patients with liver sarcoidosis found that the liver was affected in the evolution of known sarcoidosis in 2 cases, while the other 5 had liver involvement at the time of diagnosis [26]. Four patients presented with upper right

quadrant abdominal pain and one patient had incidentally discovered altered liver enzymes on routine evaluation. One patient also presented with cutaneous sarcoidosis (erythematous lesions on the scalp), one patient had ocular involvement (Sicca syndrome), while one patient had both skin and ocular manifestations (uveitis and sarcoid nodules). Notably, hepatomegaly was observed in all 7 patients, with 2 patients presenting with concomitant splenomegaly. One of these patients was found to have primary Budd-Chiari syndrome.

Another case report presents the diagnosis of liver sarcoidosis in an asymptomatic 66-year-old woman with abnormal liver function test on routine evaluation [27], requiring extensive evaluation by tomography and magnetic resonance imaging and ultimately liver biopsy for diagnostic confirmation.

In rare instances, necrosis of the sarcoid granulomas may appear [28]. The case of a 37-year-old woman with sudden onset of fever and right abdominal pain is reported. Initially, the patient was treated for suspicion of intra-abdominal infection. The presence of liver and splenic lesions on abdominal CT scan prompted the need for liver biopsy, showing necrotizing granulomas negative for infection, with remission of symptoms after corticoid therapy.

Few cases of typical sarcoidosis have been described under the age of 20 years [29]. One case report [30] presents the diagnosis of pediatric-onset adult sarcoidosis, with lung, liver and lymph nodes involvement. The 9-year-old patient presented with asthenia, weight loss, hepatosplenomegaly and 2 palpable lymph nodes (supraclavicular and inguinal). The major aspect of this case is the emphasis on the differential diagnosis from lymphoproliferative diseases in patients with abdominal organomegaly.

Furthermore, liver sarcoidosis may evolve silently with the development of cirrhosis and portal hypertension. Such a case was reported in 2012 [31] in a 48-year-old patient, complaining of abdominal pain. CT scan in this patient revealed hepatosplenomegaly and increased diameter of portal and splenic vein, suggestive of portal hypertension. In the absence of autoimmune and viral markers, the patient underwent liver biopsy with a positive diagnosis of liver sarcoidosis. Repeated thorax CT scans did not reveal pulmonary or lymph nodes involvement. Splenectomy was required due to severe pancytopenia. The patient's evolution was complicated with the development of ascites; the authors note the absence of esophageal or gastric varices as a sign of portal hypertension in this patient.

A review of 37 patients with sarcoidosis and portal hypertension [20] found a predominance of female patients. All patients presented with hepatosplenomegaly and esophageal varices in different degrees. Direct measurement of pressure in the portal vein was performed in 18 patients, with an average portal pressure of 24.6 mmHg. The authors emphasize the different physiopathological aspects of portal hypertension in sarcoidosis: healing fibrosis, large sarcoid granulomas and small perigranular arteriovenous shunts may increase sinusoidal resistance leading to portal hypertension. A presinusoidal blockage may occur by the direct pressure of the sarcoid granulomas in the portal areas. Another possible explanation is ischemia-induced fibrosis and cirrhosis in the setting of primary granulomatous phlebitis of the portal and hepatic veins [32].

Liver sarcoidosis can be associated with chronic cholestasis, either intrahepatic (mimicking primary biliary cirrhosis or primary sclerosing cholangitis) or extrahepatic (by hilar or ductal compression by adenopathies) [20]. Clinical manifestations of intrahepatic cholestasis reported in 31 patients were pruritus, jaundice and right quadrant abdominal pain. Extrahepatic cholestasis is far rarer [33], and CT scan and endoscopic retrograde cholangiopancreatography are required for the diagnosis.

Acute sarcoidosis rarely presents with liver involvement [20]. Usually, the clinical presentation is dominated by pulmonary symptoms (cough, dyspnea and
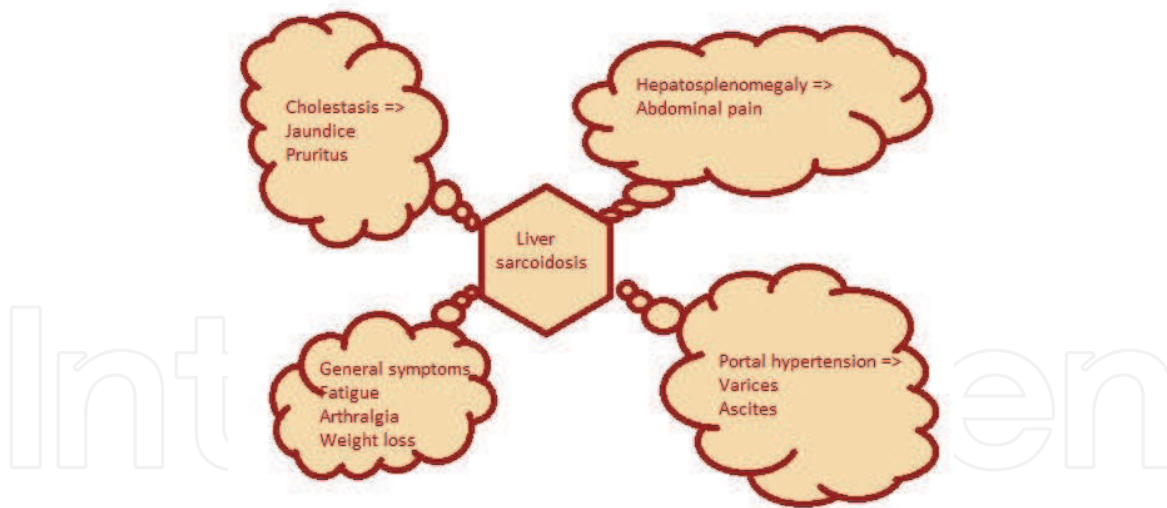
Figure 1.
Summary of clinical aspects encountered in liver sarcoidosis.

chest discomfort) and constitutional symptoms (fever, fatigue, malaise and weight loss). Liver involvement may be suspected in the presence of jaundice, pruritus or abnormal liver function tests.

Figure 1 summarizes possible clinical aspects of liver sarcoidosis.

4. Laboratory findings in liver sarcoidosis

Both cholestasis and hepatocytolysis can appear in liver sarcoidosis. Abnormal liver tests are found in up to 40% of patients with sarcoidosis, with a predominance of cholestasis (increased alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (γGT) and minor increases in bilirubin levels) [34]. ALP can be increased in up to 90% of the patients with symptoms of hepatic disease, up to 10 times the upper normal limit [19]; by contrast, increases in transaminases are mild and less frequent. The severity of the cholestasis is associated with the degree of granulomatous inflammation [35].

Peripheral lymphopenia, especially noted in CD4+ positive cells, can be useful in suspecting sarcoidosis [31]. Hypercalcemia and hypercalciuria can also be found, but unrelated to liver involvement.

In cases with portal hypertension, frequent findings are pancytopenia [20, 31] with the predominance of thrombocytopenia. Hypoalbuminemia can also be encountered as a sign of liver disease.

Most laboratory determinations are aimed at excluding other causes of liver disease. Most commonly used are viral serology markers for hepatitis B and C infection, serum markers for Wilson's disease and hemochromatosis (especially in young patients), autoantibody determinations for celiac disease, primary biliary cirrhosis and autoimmune hepatitis. **Table 1** summarizes the main serum determinations to exclude other etiologies of liver disease [36].

Patients with active disease may present with increased levels of serum inflammation markers (such as erythrocyte sedimentation rate and C-reactive protein), regardless of the organs involved [37]. CRP may also be associated with fatigue in sarcoidosis. However, these tests are not specific in any way to sarcoidosis.

There are yet no serum markers for the clear diagnosis of sarcoidosis. High serum levels of angiotensin-converting enzyme have been associated with sarcoidosis and are present in about 60% of patients with active disease [19]. Nevertheless, the test is far from pathognomonic, with low positive and negative predicting values

Determination	Result	Diagnosis	Comments
HBs antigen	Positive	Hepatitis B infection	Determine HBV-DNA Search for HDV co-infection
HCV antibodies	Positive	Possible hepatitis C infection	Confirm infection with HCV- RNA
IgM antibodies for cytomegalovirus	Positive	Possible CMV hepatitis	Determine viremia
Ceruloplasmin	Low values	Possible Wilson's disease	Confirm with genetic testing
Serum copper	High values		
Urinary copper	High values		
Serum ferritin	High values	Possible hemochromatosis	Confirm with genetic testing/liver biopsy
Transferrin levels	High values		
Antinuclear antibodies	Positive	Possible autoimmune hepatitis	Search for concurrent abnormal tests and/or other organ involved
Antismooth muscle antibodies (SMA)	Positive	Possible autoimmune hepatitis	
Antiliver kidney muscle antibodies (LKM-1)	Positive	Possible autoimmune hepatitis	
Antimitochondrial antibodies	Positive	Possible primary biliary cirrhosis	
Antineutrophil cytoplasmic antibodies	Positive	Possible Wegener's disease, other vasculitis	
Anti-*Saccharomyces cerevisiae*	Positive	Possible inflammatory bowel disease, associated with primary biliary cirrhosis	
Antitissue transglutaminase	Positive	Possible celiac disease	

Table 1.
Biological parameters required in the etiology of liver disease (adapted from [36]).

(84% and 74%, respectively). Normal ACE levels should not be used for exclusion of sarcoidosis-they can be encountered in patients with chronic disease or patients under corticoid therapy. High values are indicative of sarcoidosis and can be used in excluding other granulomatous diseases. However, inflammatory bowel disease can also manifest with high level of ACE, and the differential diagnosis is difficult, especially when primary biliary cirrhosis is associated. Increased levels of ACE can also be found in pulmonary silicosis, asbestosis, military tuberculosis, diabetes mellitus and hyperthyroidism [38].

5. Imaging in liver sarcoidosis

In asymptomatic patients, a routine laboratory testing or abdominal ultrasound can raise suspicion of liver disease, especially in the setting of a known history of sarcoidosis. In fact, some authors recommend routine testing for liver sarcoidosis in the course of the disease [19].

Abdominal ultrasonography frequently reveals hepatomegaly, possibly associated with splenomegaly in the case of splenic involvement or portal hypertension. One review found that 8% of patients with liver sarcoidosis had marked hepatomegaly, with an anteroposterior diameter of over 25 cm [39]. The general aspect of

the liver is of increased echogenicity, either homogenous or diffusely heterogeneous [40] (**Figure 2**). The aspect sometimes may resemble fatty liver disease [41].

Focal liver nodules may appear on ultrasonography in the case when sarcoid granulomas conflate and form macroscopic masses. Such nodules have been described in up to 19% of patients [40]. Typically, there are innumerous round nodules, diffusely distributed, with size ranging from 1 to 2 mm to centimeters [39]. Color Doppler ultrasonography reveals hypovascularization of the nodules.

Splenomegaly is also reported in almost 60% of patients with liver sarcoidosis [40], with markedly increased dimensions (over 18 cm) in 6% of the cases. In 15% of cases, splenomegaly is associated with hypoechoic splenic nodules. The frequency of nodules appears to vary according to geographical distribution and ethnic characteristics [40]. They are distributed diffusely within the splenic parenchyma, with a medium size of 1 cm [42]; they demonstrate hypovascularization on Doppler analysis. Isolated splenic nodules are more frequent than isolated hepatomegaly or liver nodules in sarcoidosis.

Up to 76% of patients with liver and splenic nodules also associate with enlarged abdominal lymph nodes [43], with infrequent punctate calcifications. Adenopathies are usually found periportal, celiac, paracaval and para-aortic, with dimensions ranging from 1 cm to 4–6 cm [44, 45]. Larger perihepatic lymph nodes can be associated with advanced liver disease. They raise the need for differential diagnosis to malignant conditions (primarily lymphoproliferative disorders), intra-abdominal infections and benign conditions such as primary biliary cirrhosis or chronic hepatitis C.

Contrast-enhanced ultrasonography (CEUS) has emerged as a new, reliable and non-invasive means of evaluation of liver disease [45]. CEUS has proven its greatest utility in differentiating between benign and malignant liver and splenic nodules, with sensitivity and specificity similar to those of CT scans. The use of CEUS in abdominal sarcoidosis has been evaluated in small case series or case reports [45], due to the scarcity of the cases and also to the fact that patients with hepatosplenic sarcoidosis rarely present with focal lesions, making them difficult candidates for CEUS (**Figure 3**).

If hypoechoic liver lesions appear on conventional ultrasonography, they have variable arterial enhancement with progressive washout in the portal and late phases [45].
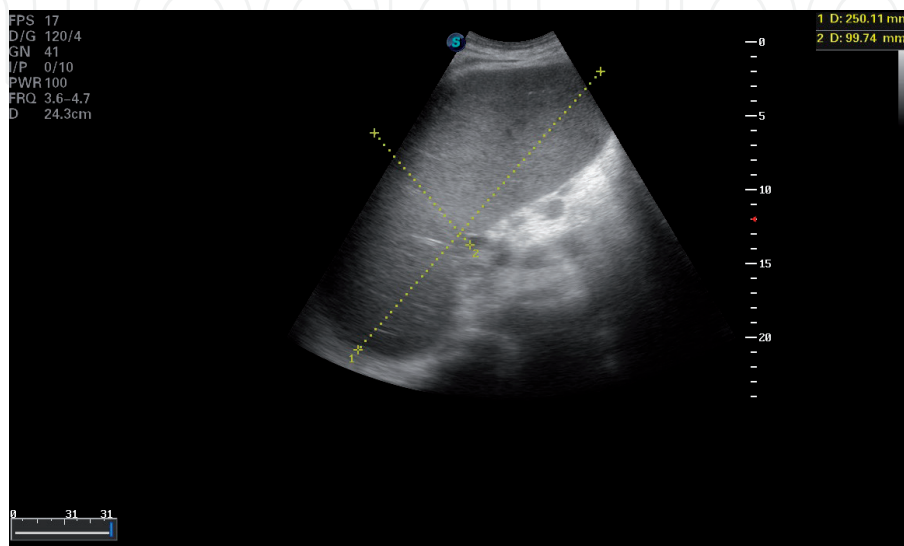

Figure 2.
Abdominal ultrasonography revealing diffusely heterogeneous hepatomegaly in a patient with liver sarcoidosis.
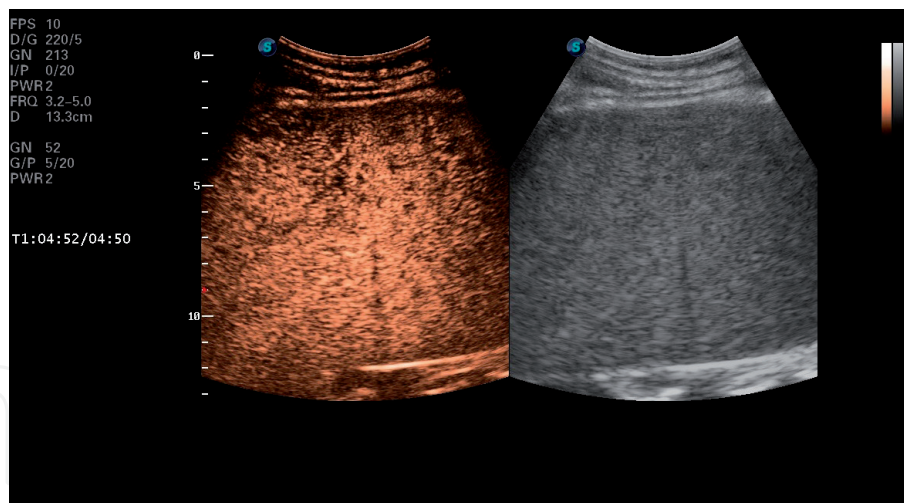
Figure 3.
CEUS in a patient with liver sarcoidosis—diffuse disease, without focal lesions (late phase).

Regarding hypoechoic splenic nodules, on CEUS, they appear as progressive hypoenhancing nodules in the arterial and parenchymal phases. As the investigation progresses into the parenchymal phase, the lesion-to-parenchyma contrast diffusion is increased. The mild enhancement in the arterial phase can be homogenous or diffusely heterogeneous, while in the parenchymal phase, it may be homogenous or with a dotted pattern. Sometimes, peripheral blood vessels may be visible and have an irregular aspect. These characteristics may be compatible with malignant conditions; therefore, biopsy is mandatory for a clear diagnosis.

A study performed in 2013 evaluated the efficacy of CEUS in diagnostic abdominal disease in 21 patients with pulmonary sarcoidosis [46]. Eighteen patients had no hepatosplenic disease, one patient had splenic nodules and two patients had liver lesions. CEUS as well as CT scan and abdominal MRI gave concordant results. The authors underline the importance of CEUS in the evaluation of these patients, as it offers the same information without any contraindications that CT or MRI might have including allergy to contrast, contrast-induced nephropathy or the presence of pacemakers or metallic devices. It is also suggested that CEUS should be used in the first evaluation of patients with pulmonary sarcoidosis and in their monitorization during treatment.

The latest review on the importance of CEUS in the evaluation of abdominal involvement in sarcoidosis describes the following characteristics [47]:

- Liver aspect on CEUS: variable nodular enhancement in the arterial phase, progressive hypoenhancement in the portal and late phases.

- Splenic aspect on CEUS: progressive hypoenhancement in the arterial and parenchymal phase. Possible patterns: rim-like, homogenous, dotted.

Endoscopic ultrasound elastography could also be used to characterize liver sarcoidosis [47]. The lesions may appear as single masses with blue hard patterns within and around.

However, the lack of sufficient data especially from clinical trials or large studies makes it impossible to establish clear recommendations on the use of CEUS in liver sarcoidosis; therefore, other imagistic methods are required for a complete positive diagnosis.

CT scans in liver sarcoidosis may reveal homogenous hepatomegaly (with possible low-density intrahepatic septa) [40] (**Figure 4**). Liver nodules appear as hypoenhanced masses as opposed to the adjacent normal liver parenchyma. There is
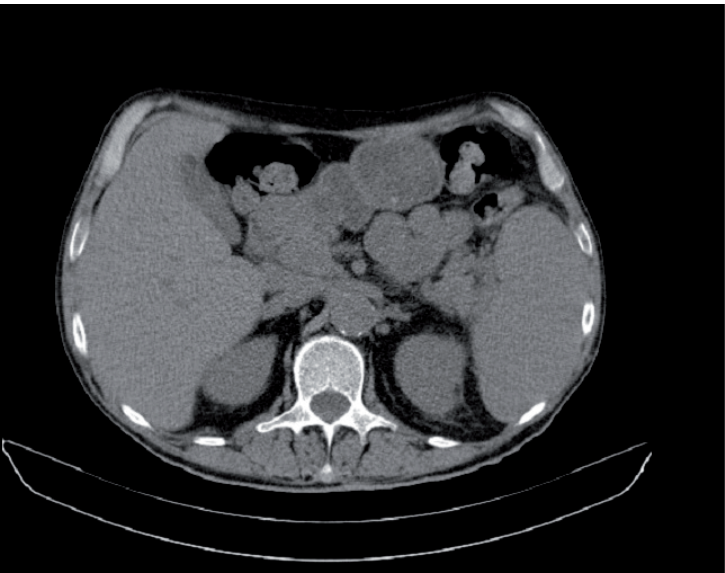
Figure 4.
Abdominal CT scan of a patient with liver sarcoidosis showing homogeneous hepatomegaly and splenomegaly.

no visible peripheral enhancement. Typically, the nodules have no mass effect. Sometimes, these numerous hypodense nodules with variable dimensions warrant differential diagnosis to metastatic disease of the liver, but also miliary liver tuberculosis, fungal infections or Langerhans cell histiocytosis [48].

CT scan is useful in the diagnosis of liver cirrhosis and portal hypertension subsequent to sarcoidosis [49], as rare as they appear. Typical aspects include hypertrophy of the caudate lobe, dilatation of the portal and splenic veins, irregular liver contour, collateral circulation vessels around the digestive tract as well as ascites.

MRI evaluation of liver sarcoidosis may reveal hypointense and hypoenhancing nodules relative to the adjacent liver parenchyma [40] (**Figures 5** and **6**). Still, the particularity of the imaging is the lack of mass effect or any impact of the nodules on the surrounding parenchyma or adjacent vessels.

T2-weighted fat-saturated images are the most conclusive in diagnosing hypointense nodules in liver sarcoidosis. This is an important part in the differential diagnosis from malignancies, as these appear most frequently as hyperintense. Other signs suggestive of sarcoidosis are irregular contour of the liver and high periportal
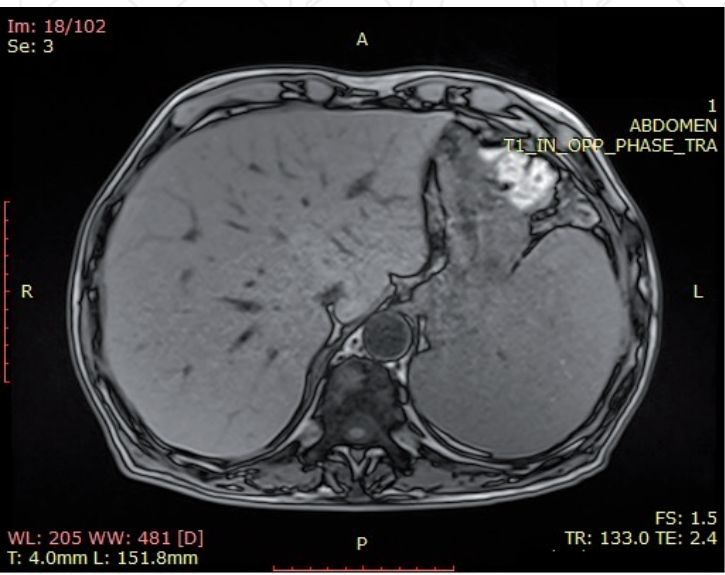

Figure 5.
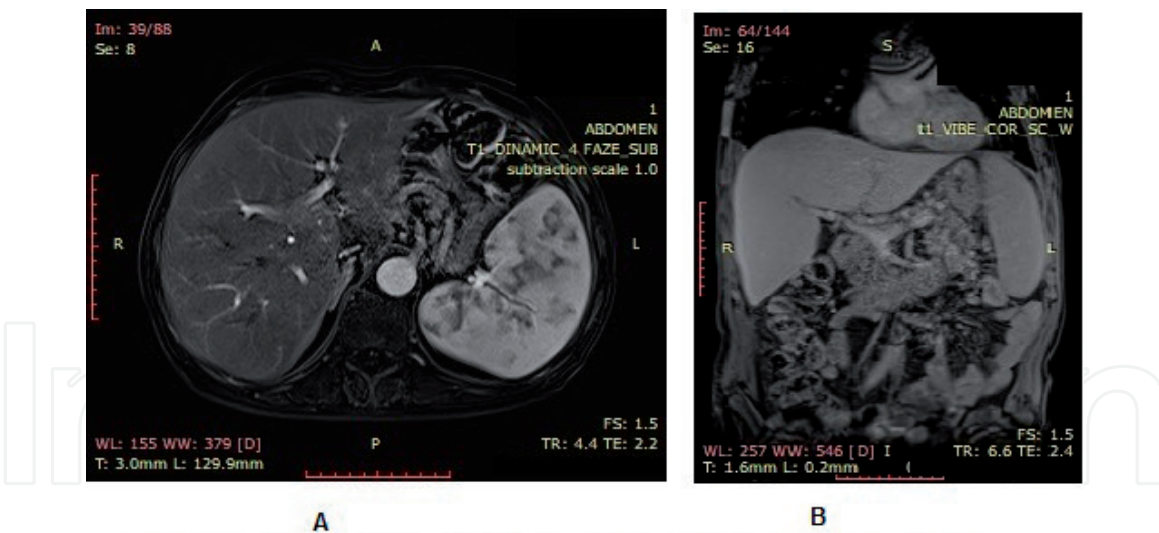*MRI of a patient with diffuse liver sarcoidosis.*

Figure 6.
MRI in a patient with liver and splenic sarcoidosis demonstrating hypoattenuation of splenic lesions (A). MRI in the same patient demonstrating hepatosplenomegaly (B).

signal intensity [50]. However, cases have been described where masses with T2 hyperintensity have proven to be liver sarcoidosis in histology examination [51].

Nodules located in the hilar area need to be differentiated from cholangiocarcinomas. In cases thus located or in the case of hilum adenopathies and subsequent stenosis of biliary ducts, magnetic resonance cholangiopancreatography may reveal the stenosis with dilatation of intrahepatic bile ducts, similar to that in a Klatskin tumor [52]. In this case, the positive diagnosis is set by biopsy, usually obtained by ERCP.

6. Management of liver sarcoidosis

Guidelines for the management of sarcoidosis are relatively old and have little approach to the possibility of liver sarcoidosis [53]. Staging of sarcoidosis takes into account the pulmonary and mediastinal lymph node involvement, without considering systemic disease. Recommendations for monitoring are as follows:

• Surveillance for 2 years to determine the need for systemic therapy (taking into account the fact that many patients present spontaneous remission).

• Therapy should be initiated in patients with severe, active or progressive disease.

• Patients with remission after corticoid therapy should be more closely monitored as the relapse rate is higher than in patients with spontaneous remission.

Mild disease (including skin lesions, uveitis and respiratory symptoms) may be managed with topical steroids. Systemic or progressive disease can be managed with systemic corticotherapy, and if necessary cytotoxic therapy or antimalaric agents. Cardiac or neurologic involvement, hypercalcemia and ocular disease not responsive to topic therapy are clear indications for systemic therapy. Regarding pulmonary disease, the consensus is that progressive pulmonary infiltrates or progressive decrease in pulmonary function may require medical therapy. Recent reviews [5, 54] support the idea of initiating therapy in the case of systemic disease with potential of progression to permanent organ damage or life-threatening conditions (such as arrhythmias).

Data for the management of liver sarcoidosis is gathered from small trials and case reports. The following recommendations may be followed:

- In patients with asymptomatic liver disease or mildly elevated liver enzymes without cholestasis, observation is required. Incidentally discovered hepatomegaly falls under this category [55].

- In patients with symptomatic liver disease, cholestasis or risk for hepatic complications, medical treatment is required.

The first line of treatment includes steroids and ursodeoxycholic acid (UDCA). Alternatively, azathioprine, methotrexate, glutathione, cyclosporine, cyclophosphamide, thalidomide and infliximab have been studied in the management of liver sarcoidosis.

The beneficial effect of corticosteroids is based on their ability to suppress the inflammatory response, thus decreasing the number of liver granulomas and the liver size, as well as ameliorating constitutional symptoms. Low-dose prednisone (10–20 mg/day) is recommended for patients with mild disease, while higher doses can be required in patients with severe symptoms. Treatment duration varies according to clinical and laboratory response, with up to 1 year of treatment before tapering the doses [56]. However, steroids have not proven beneficial for asymptomatic patients or patients with advanced stages of liver disease, including cirrhosis and portal hypertension [19].

UDCA has proven effective especially in patients with liver sarcoidosis manifested by pruritus. Recent trials has also proven its effect on delaying disease progression. One study has even proved that UDCA is superior to prednisone in improving cytolysis syndrome, pruritus and fatigue [57]. The usual daily dose of UDCA is 13–15 mg/kg.

Table 2 summarizes case reports with unusual treatment and evolution of liver sarcoidosis.

Drug	Dosage	Time to improvement	Remarks	Reference
Infliximab	3 mg/kg at 8 weeks	6 weeks	A patient with cirrhosis, portal hypertension and refractory ascites	[58]
Azathioprine	50–150 mg/kg	8 weeks	4 patients	[23]
Methotrexate	10–15 mg/week	6 months	2 patients, with improvement in liver function tests	[59]
Leflunomide	20 mg/day	6 months	1 patient	[60]
Cyclosporine	20–200 mg/day	Mean treatment duration 4 years	9 patients after liver transplantation for sarcoidosis	[61]
Thalidomide	100–200 mg/kg	7–12 months	3 patients with concomitant skin lesions	[62]
Mycophenolate mofetil	250 mg/m^2 up to 1 g/m^2	1 month	1 patient with pediatric-onset adult sarcoidosis	[30]

Table 2.
Treatment options for liver sarcoidosis.

Nevertheless, it is essential to remember standard treatment measures in patients with advanced liver disease [19]. These patients may benefit from liver transplantation, with 60% survival at 5 years [63]. Careful monitoring is required as reports of sarcoidosis recurrence after transplantation have emerged.

7. Conclusions

Liver sarcoidosis is a frequent involvement in an otherwise rare disease. Having an incompletely elucidated etiology, its clinical and biological spectrum is extremely vast, and with few reports and no substantial clinical trials, its management is mainly patient-based. However, suspicion of systemic sarcoidosis in a patient should warrant extensive evaluation for associated liver disease, as this may impact the prognosis of the patient in the clinical history. The fact that this condition can progress to end-stage liver disease and can represent an indication for liver transplantation should set sarcoidosis among hepatopathies to be clearly diagnosed and monitored.

Acknowledgements

Conflict of interest

The authors declare no conflict of interest.

Author details

Laura Iliescu[1,2]* and Letitia Toma[1,2]

1 Fundeni Clinical Institute, Bucharest, Romania

2 "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

*Address all correspondence to: laura_ate@yahoo.com

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