Sarcoidosis with hepatic involvement in a 60-year-old patient

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ABSTRACT

Hepatic involvement of sarcoidosis is usually hard to detect on radiological imaging. We present a case of a 60-year-old female with symptoms of pulmonary sarcoidosis. Subsequent imaging work-up showed diffuse hepatic granulomas consistent with abdominal involvement of sarcoidosis. A literature review regarding hepatic sarcoidosis is provided and radiological appearances as well as considerations for differential diagnosis are described.

CASE REPORT

CASE REPORT

A 60-year-old female with a history of cough, dyspnea and fatigue was referred to our radiology department for chest X-ray evaluation. The patient complained about progressive sputum production and some weight loss since the last few weeks. Antibiotics had been prescribed by her general practitioner, without improvement of symptoms. Conventional imaging of her lungs revealed a small left perihilar consolidation along with multiple fine reticulations in both upper lobes (Fig. 1). Because of her prolonged symptoms and abnormal radiological findings the patient was referred to a pulmonologist. Pulmonary function test by spirometry showed reversible forced expiratory volume (FEV) after inhaling a bronchodilator. Beclometasone with formoterol inhaler was therefore prescribed and two weeks later a contrast enhanced computed tomography (CECT) scan of the thorax and upper abdomen was performed for further evaluation (Fig. 2 and 3). There was bilateral hilar and mediastinal lymphadenopathy. Some of the lymph nodes were partially calcified (Fig. 2a, b). The prior mentioned consolidation was seen in the posterior aspect of the left upper lobe (Fig. 2c – f). In addition, some smaller consolidations were seen in the apical left lower lobe. There were multiple fine nodules with upper and middle zone predominance along the subpleural surfaces and fissures and along the interlobular septa and peribronchovascular bundles, consistent with a perilymphatic distribution pattern. Some of the nodules scattered around the area of consolidations were distributed more randomly. There were no signs of pulmonary fibrosis. The upper abdomen showed extensive perihepatic lymphadenopathy and to a lesser extent peri-splenic and peri-aortic lymphadenopathy (Fig 3a). There was significant enlargement of the liver, measuring up to 18.5 cm in craniocaudal length. The liver parenchyma was characterized by diffuse inhomogeneous enhancement caused by multiple hardly distinctive and partially confluent hypoattenuating nodules, ranging in size from 1-10 mm (Fig 3b-d). The same pattern of fine nodules could be identified in the slightly enlarged spleen. Although the combination of findings were mostly in favor of sarcoidosis, our differential diagnosis included lymphoma or metastasis. Additional laboratory test showed elevated angiotensin converting enzyme (ACE) of 99 U/L (normally between 6-56 U/L). Alkaline phosphatase (AF), gamma glutamyltranspeptidase (GGT), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were normal. To exclude the possibility of infection a bronchoalveolar lavage (BAL) was performed, testing negatively for basal pathogens. Bronchoscopic aided biopsy

and cytology showed signs of chronic inflammation, but were insufficient for confirming sarcoidosis. Finally, ultrasound guided biopsy of the liver revealed the presence of portal and lobular aggregates of epithelioid histiocytes and multinucleated giant cells with formation of granulomas (Fig. 4 and 5). Along with the absence of necrosis and malignancy the pathological image was consistent with sarcoidosis.

DISCUSSION

Etiology & Demographics:

Sarcoidosis is defined as a multisystemic inflammatory disease characterized by noncaseating granulomas [1]. It has been estimated that the worldwide prevalence of sarcoidosis is 2–60 per 100,000 people [2, table 1]. Sarcoidosis is mostly seen around the age of 20-40 years, although a second age peak (> 50 years) has also been described [3]. Women are more often affected than men. The exact cause of the disease is not entirely understood, but there is a strong indication for multifactorial contribution involving immunological, genetic and environmental factors [4]. Although the lungs and the lymphoid system are the most commonly involved sites, every organ can be affected in sarcoidosis. Involvement of the abdomen is seen in 50 - 80 percent of the cases [5], with higher rates obtained in studies performing autopsy or random liver biopsy. Although uncommon, abdominal sarcoidosis can occur in the absence of lymphatic or pulmonary disease [6].

Clinical Features:

The majority of patients with abdominal involvement of sarcoidosis are clinically asymptomatic or present with mild symptoms [7]. When symptomatic, patients usually report complains of nonspecific fatigue, fever, weight loss and abdominal pain [8]. Abdominal pain has previously been described to occur in about 15% of patients with sarcoidosis and is most likely caused by stretching of Glisson's capsule [9]. Processes like local inflammation and extrinsic compression by granulomas in patients with liver sarcoidosis have been associated with hepatocellular dysfunction, cholestasis and vascular complications [10]. Vascular complications include portal vein thrombosis and Budd-Chiari syndrome [11, 12]. Portal flow obstruction secondary to hepatic granulomas may develop into presinusoidal portal hypertension [13]. Long-standing disease has been reported to result in such portal hypertension in roughly 3–18% of patients [14], with variceal bleeding being the most severe complication. Only a small proportion (6–8%) may develop progressive cirrhosis, which can ultimately lead to end stage liver failure requiring liver transplantation [8, 15]. In up to 35% of patients, mild liver function abnormalities may indicate abdominal involvement of sarcoidosis [16]. The degree of AF and/or GGT elevation have been correlated with cholestasis and extent of intrahepatic granulomatous inflammation. Measurement of serum angiotensin converting enzyme (ACE) levels can be useful, as they have been reported to be elevated in roughly 60% of patients with active sarcoidosis [17, 18]. These laboratory tests however lack sensitivity and specificity and normal test results can be seen in patients with chronic forms and in patients who have been treated with corticosteroids [17]. Negative lab results may therefore not be sufficient to rule out hepatic sarcoidosis.

Histopathological Findings:

Histologically, hepatic sarcoidosis is characterized by numerous well-formed noncaseating granulomas. Although favoring a periportal distribution pattern, lesions are generally dispersed throughout the liver parenchyma [19]. Granulomas in sarcoidosis appear as focal aggregates of epithelioid cells, which fuse together to form multinucleated giant cells. These aggregates are typically surrounded by a rim of inflammatory cells (mainly consisting of lymphocytes) and fibrin deposits [20]. Inclusions of so called asteroid (stellate eosinophilic inclusions made up of complex lipids) and Schaumann bodies (round or oval inclusions consisting of laminated calcium oxalate) may provide a useful clue to diagnosis [21, fig. 6]. Large confluent granulomas may eventually lead to extensive scar formation with histological signs of liver cirrhosis [22].

Radiological Findings:

Upper abdominal lymphadenopathy, hepatomegaly and splenomegaly are some of the most commonly reported findings in abdominal sarcoidosis [23, 24]. Detection of organomegaly was reported in about 40 % of the cases [25]. The small size of hepatic or splenic sarcoid nodules (usually between 1-5 mm) making visualization of these abnormalities difficult on all imaging modalities. The occurrence of multiple hepatic nodules can be easily confused with liver metastasis, although the presence of concomitant splenic granulomas may help point towards the diagnosis of sarcoidosis.

On ultrasound findings include hepato- and splenomegaly, lymphadenopathy around the porta hepatis and coeliac axis, increased parenchymal echogenicity and coarsening of the parenchymal appearance with or without discrete nodules [26]. When nodules are present, they most likely appear as hypoechoic foci, although they may also be hyperechoic depending on the degree of fibrosis present in the granuloma. Additionally, involvement of intrahepatic and/or extrahepatic biliary ducts by way of dilatation may be detected on ultrasound [26, 27].

CECT gives a better overview of the extent and distribution of abdominal lymphadenopathy. While more sensitive than ultrasound, only 10-15% of patients with abdominal sarcoidosis show hypoattenuating liver and/or spleen nodules on CECT [28]. CECT may also be useful in detecting sub-capsular fibrosis, which reflects loss of hepatocytes and replacement with fibrosis as seen in liver cirrhosis [29].

On magnetic resonance imaging (MRI) the sarcoid granulomas are normally hypointense on all sequences [26]. They can be most easily identified on T2-weighted fat saturated images and post-gadolinium T1-weighted images. The low T2 signal intensity of sarcoid nodules can be used to distinguish hepatic sarcoidosis from infectious and neoplastic focal lesions, which are usually hyperintense on T2-weighted images [23, 29]. On gadolinium-enhanced T1-weighted images the lesions enhance less than the background. MRI may also show high periportal signal intensity [26,30] and irregularity of intrahepatic vessels, probably due to the presence of granulomas in vessel walls and/or external compression of hepatic nodules [26].

Nuclear imaging with F-18 fluordeoxyglucose (FDG) positron emission tomography (PET) scanning and Gallium-67 citrate scintigraphic scanning have been shown to indicate disease activity in patients with extrapulmonary sarcoidosis [31]. Findings however are not diagnostic because positive results may just as well be seen in malignancy or infectious diseases. Furthermore, normal intense uptake of FDG and 67Ga in the liver and spleen limits the assessment of these organs [32].

Differential Diagnosis:

The diagnosis of hepatic sarcoidosis requires careful evaluation to exclude other pathologies that can mimic radiological and histological findings [table 2]. Primary biliary sclerosis (PBS) is the most important diagnosis to differentiate from [33]. Being the leading cause of hepatic granulomas in most histopathological studies (up to 24–55%), PBS is also characterized by noncaseating granulomas within portal tracts [34]. Such findings alone are therefore insufficient to differentiate PBS from sarcoidosis on imaging. However, the presence of pulmonary involvement with hilar lymphadenopathy may help point towards sarcoidosis, since it is not a feature in PBS. Positive antimitochondrial antibodies are found in most patients with PBS and may therefore be essential for definite diagnosis. Another immunological mediated entity that may mimic hepatic sarcoidosis is primary sclerosing cholangitis (PSC), as it can give the histologically appearance of periductal fibrosis. Although the absence of inflammatory bowel disease and/ or positive anti-neutrophil cytoplasmic antibody (ANCA) are mostly in favor of hepatic sarcoidosis, additional magnetic resonance cholangiopancreaticography (MRCP) may be important to definitely rule out PSC. In both PBS and PSC immunologic attack on the intra-or extrahepathic bile ducts can eventually lead to chronic cholestasis with extensive scar formation, cirrhosis and liver failure [35]. Hodgkin lymphoma, and to a lesser extent non-Hodgkin lymphoma have also been associated with hepatic granulomas and lymphadenopathy [36]. These entities however are histologically associated with presence of fibrin-ring granulomas, in which epithelioid cells surround a vacuole that often has an encircling fibrin ring. Diffuse metastasis can mimic hepatic sarcoidosis by presence of diffuse intrahepatic nodules. They should be excluded by careful evaluation of a primary malignancy. Peripheral enhancement of intrahepatic nodules typically is not seen in hepatic sarcoidosis [37] and can help distinguishing them from metastases (e.g. colorectal or pancreatic adenocarcinoma) in some cases. Although less common in developed countries, infectious diseases like tuberculosis, acquired immunodeficiency syndrome (AIDS)-related infectious diseases (e.g. Mycobacterium avium complex (MAC), cryptococcal infections) and fungal infection, such as disseminated histoplasmosis and coccidioidomycosis should also be considered in the presence of hepatic granulomas. Some drugs such as allopurinol, carbamazepine, chlorpropamide and others may cause noncaseating liver granulomas involving portal tracts and hepatic lobules. Careful medication history is therefore essential during initial workup [38].

Treatment & Prognosis:

As most patients with hepatic sarcoidosis have asymptomatic liver disease and normal or mild elevations of serum liver enzymes, most do not require medical therapy. It has been noted that in some asymptomatic patients, abnormal serum liver tests can resolve spontaneously or remain stable for many years [39]. Pharmacological therapy should be considered when symptoms of liver involvement are present or when there is evidence of cholestasis [40]. Patients who are at high risk for developing hepatic complications should also be treated. Pharmacological agents that have been described for treatment of hepatic sarcoidosis consist mainly of corticosteroids and ursodeoxycholic acid (UDCA). Corticosteroids decrease the number of hepatic granulomas by suppression of the inflammatory response and reduce liver size [41]. When they are insufficient, other agents like azathioprine, methotrexate, cyclosporine, cyclophosphamide, thalidomide and infliximab may be considered [42, 43]. When decompensated liver cirrhosis is present in advanced disease, transplantation is the only therapeutic option available [38].The mortality rate of sarcoidosis is about 1–5% [44]. Death usually occurs from severe pulmonary, cardiac, and central nervous system disease rather than hepatic involvement.

TEACHING POINT

In patients with sarcoidosis, hepatic involvement is an important manifestation that should be recognized in the early stages of disease, since its association with hepatocellular dysfunction, cholestasis and vascular complications. Radiological imaging may help differentiate hepatic sarcoidosis from other pathologies that should also be considered in the presence of hepatic granulomas but may require different types of treatment.

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FIGURES

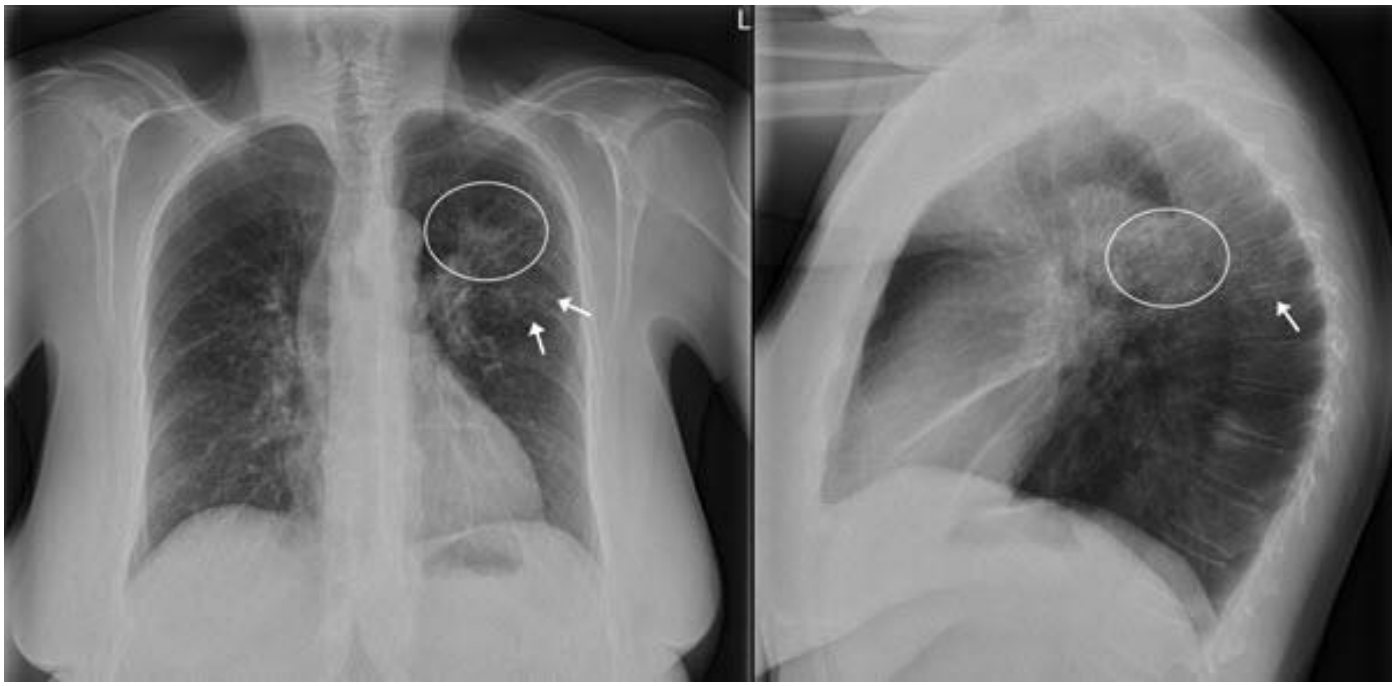

Figure 1: 60-year-old female with pulmonary abnormalities due to sarcoidosis.

TECHNIQUE: X-thorax, PA and lateral view. (General Electric (GE), PA: 125 kV, 2.6 mAs. Lateral: 125 kV, 4.5 mAs).

FINDINGS: There is a small left perihilar consolidation (circles) along with multiple fine reticulations in both upper lobes (arrow).

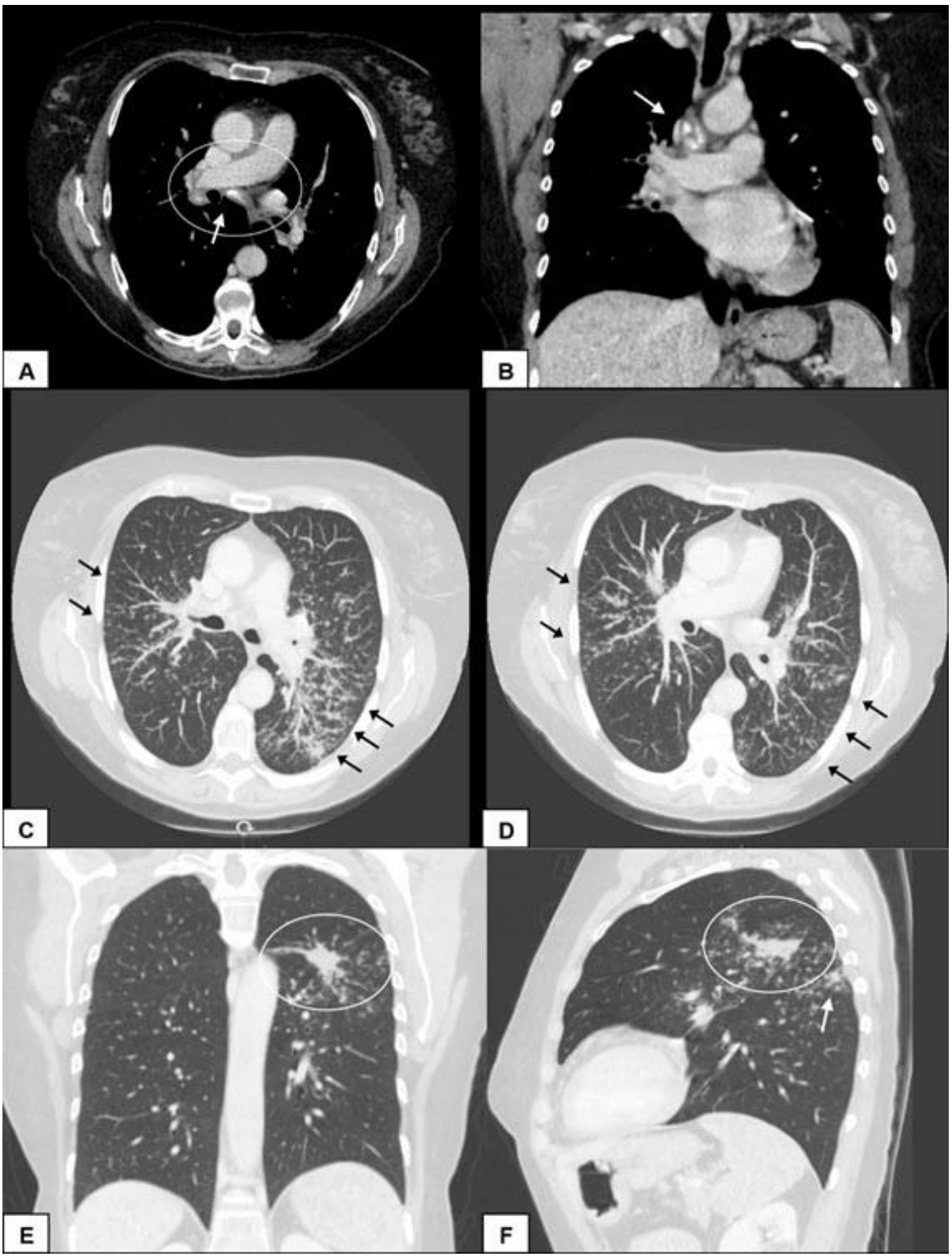

Figure 2: 60-year-old female with lymphatic and pulmonary abnormalities due to sarcoidosis.

TECHNIQUE: Contrast enhanced computed tomography (CECT) scan of the thorax/abdomen (only thorax shown in this figure). (General Electric (GE), 120 kV, CTDIvol: 3.44 mGy, DLP: 152 mGy*cm. 1 mm slice thickness, 90 cc visipaque 320).

FINDINGS: A and B) Axial and coronal images of the mediastinum showing bilateral hilar and mediastinal lymphadenopathy (circle). Some of the lymph nodes were partially calcified (arrows). C and D) Axial images in maximum intensity projection (MIP) setting showing multiple fine nodules along the subpleural surfaces and fissures and along the interlobular septa and peribronchovascular bundles (arrows), consistent with a perilymphatic distribution pattern. E and F) Coronal and sagittal images showing a consolidation in the posterior aspect of the left upper lobe and some smaller consolidations in the apical left lower lobe (arrow).

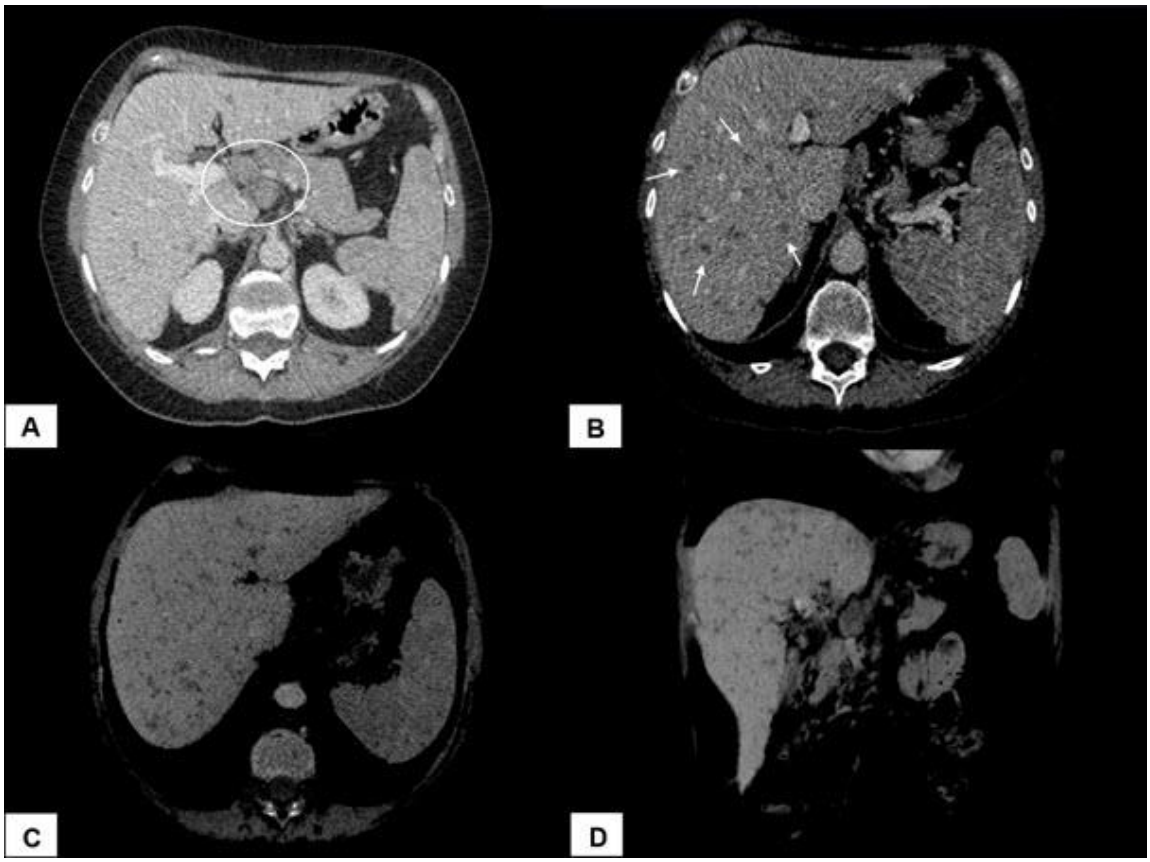

Figure 3: 60-year-old female with hepatic and splenic granulomas and perihepatic lymphadenopathy due to abdominal involvement of sarcoidosis.

TECHNIQUE: Contrast enhanced computed tomography (CECT) scan of the thorax/abdomen (only upper abdomen shown in this figure). (General Electric (GE), 120 kV, CTDIvol: 3.44 mGy, DLP: 152 mGy*cm. 1 mm slice thickness, 90 cc visipaque 320).

FINDINGS: A) Axial image showing extensive lymphadenopathy in the porta hepatis (circle). B) Axial image showing significant enlargement of the liver. The liver parenchyma is characterized by diffuse inhomogeneous enhancement caused by multiple hardly distinctive and partially confluent hypoattenuating nodules, ranging in size from 1-10 mm (arrows). C and D) The dispersed distribution of hepatic nodules is better seen in minimum intensity projection (Min-IP) setting. The same pattern of fine nodules could be identified in the slightly enlarged spleen.

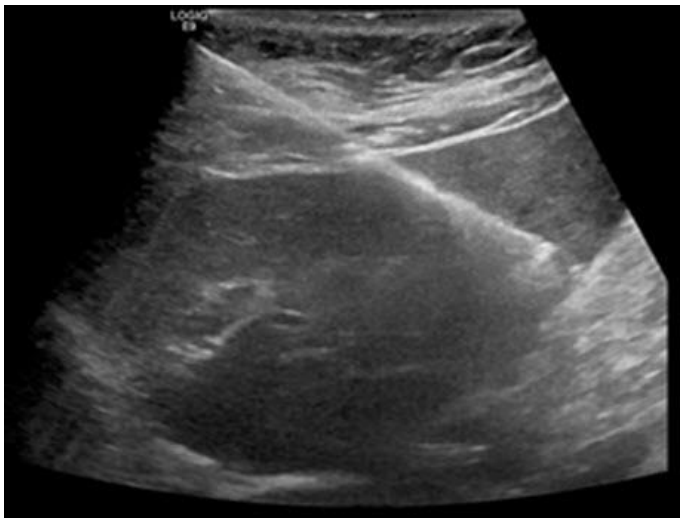

Figure 4 (right): 60-year-old female with hepatic involvement of sarcoidosis.

TECHNIQUE: Standard ultrasound procedure (General Electric (GE)), with ultrasound guided biopsy of the liver.

FINDINGS: There is subtle coarsening of the liver parenchymal appearance without discrete nodules. Biopsy was performed in liver segment II/ III.

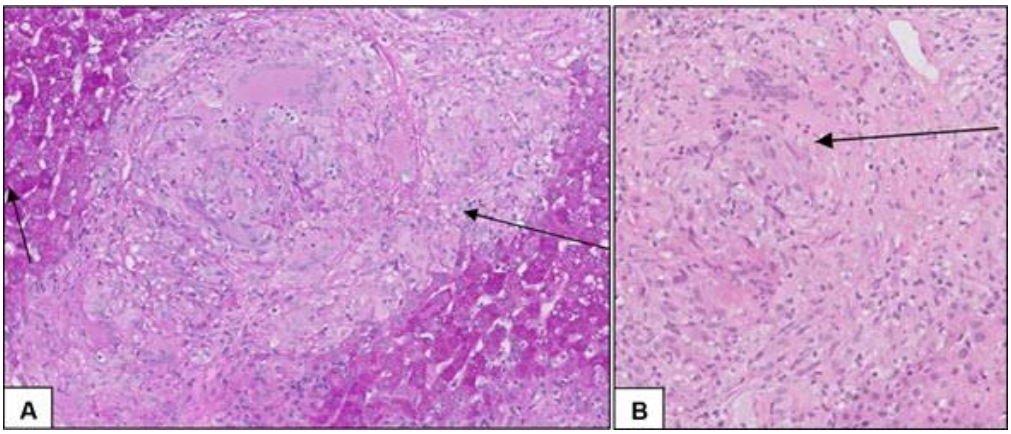

Figure 5: Liver biopsy specimen of a 60-year-old female with hepatic involvement of sarcoidosis.

TECHNIQUE: Microscopic image after Periodic acid-Schiff (PAS) staining.

FINDINGS: A) Aggregates of epithelioid histiocytes with regular margins forming multiple non-caseating granulomas within the portal tract as well as in the periportal areas of the liver. Short arrow: normal liver tissue. Long arrow: granuloma. B) Close view of a granuloma: aggregates of epithelioid cells, which fuse together to form multinucleated giant cells (long arrow).

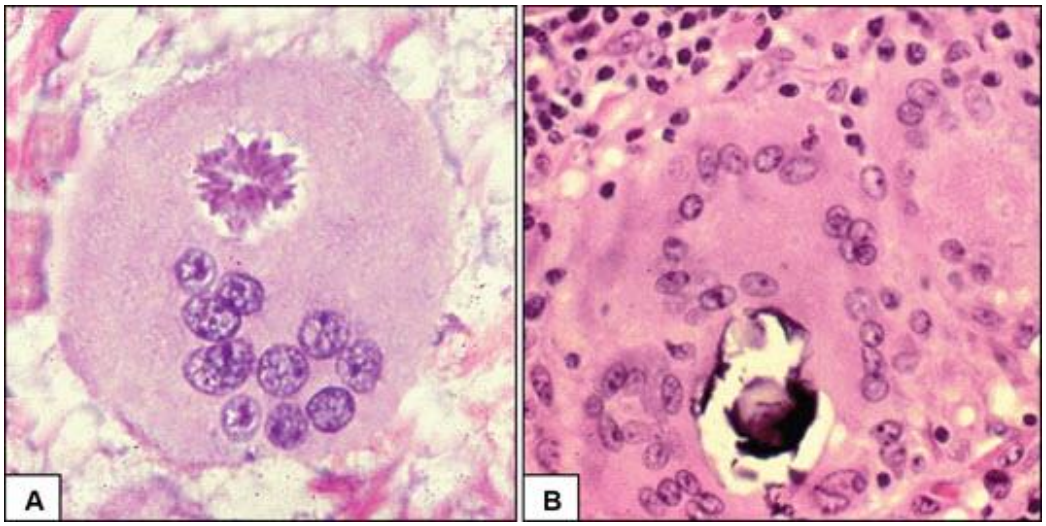

Figure 6: Histopathological findings in sarcoidosis. A) Sarcoid granuloma with an asteroid body. B) Well-formed sarcoid granuloma with multinucleated giant cells and a Schaumann body.

Source: Laga AC, Allen TC, Bedrossian C, et al. Noncellular structures. In: Color Atlas and Text of Pulmonary Pathology, 2nd Edition, Cagle PT, Allen TC, Barrios R, et al (Eds), Philadelphia: Lippincott Williams & Wilkins, 2008.

Clinical characteristics of abdominal sarcoidosis	
Etiology	Remains unknown. Believed to be multifactorial, including immunologic, genetic and environmental factors.
Incidence	50–80% of patients with systemic sarcoidosis, with higher rates obtained in studies performing autopsy or random liver biopsy.
Gender ratio	females > males across all ages and ethnicities
Age predilection	Peak of 20–40 years, although a second age peak (>50 years) has also been described.
Imaging findings	• Lymphadenopathy, hepatomegaly and/or splenomegaly (up to 40%) • hypoattenuating/hypointense liver and/or spleen nodules ranging in size, usually from 1-5 mm that correspond with coalescing granulomas • hypoattenuating/ hypointense on post-contrast CT / MR respectively
Complications	• Portal hypertension • Portal vein thrombosis • Budd-Chiari syndrome • Progression to cirrhosis with liver failure (rare)
Treatment	• First line agents: corticosteroids and ursodeoxycholic acid (UDCA) • Alternatives: azathioprine, methotrexate, cyclosporine, cyclophosphamide, thalidomide and infliximab.
Prognosis	• Mortality rate about 1–5% • Mainly caused by severe pulmonary, cardiac, and central nervous system disease rather than hepatic involvement.

Table 1: Summary table of abdominal sarcoidosis.

Differential diagnosis for hepatic sarcoidosis			
	CT	**MRI**	**Histology**
Sarcoidosis	•Mediastinal/ hilar lymphadenopathy •Pulmonary interstitial disease (including signs of pulmonary fibrosis)	•Low T2 signal intensity of sarcoid nodules •Absence of peripheral enhancement after gadolinium •Cardiac and neurological manifestations	•Well-differentiated noncaseating granulomas
Autoimmune disorders PBC, PSC, granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis), polymyalgia rheumatica, Crohn's disease.	•PBC and PSC: mainly to exclude pulmonary involvement and mediastinal/ hilar lymphadenopathy •PSC: liver contour abnormalities and atrophy	•PBC: parenchymal lace-like fibrosis and periportal halo sign on T2-weigted images •PSC: segmental strictures with proximal dilation and sacculation of the bile ducts ("beaded" appearance)	•PBC: Poorly-differentiated noncaseating granulomas •PSC: ''onion'' ring periductal fibrosis
Malignancy Hodgkin lymphoma and to a lesser extent non-Hodgkin lymphoma. Diffuse metastasis (lung or breast cancer, gastro-intestinal cancer, melanoma).	•Nodule/ mass •Consolidation •Linear densities •Presence of a primary tumor (lung, breast, gastro-intestinal, skin).	•Peripheral enhancement after gadolinium •Hyperintense on T2-weigted images	•Presence of neoplastic cells
Systemic infection Tuberculosis, AIDS-related infectious diseases (e.g. Mycobacterium avium complex (MAC), cryptococcal infections), fungal infections (disseminated histoplasmosis and coccidioidomycosis). Schistosomiasis, leprosy, brucellosis, Lyme disease, Q fever.	•Signs of abscess (layered wall appearance, enhancement that persists in delayed phases) •Pulmonary involvement (multifocal consolidations and ground-glass, cavitating lesions, bronchiolitis)	•Peripheral enhancement after gadolinium •Hyperintense on T2-weigted images •Restrictive diffusion on DWI (in case of an abscess)	•Positive blood cultures or PCR
Drugs allopurinol, carbamazepine, chlorpropamide, diltiazem, nitrofurantoin, quinidine	•Variable	•Variable	•Variable, depending on drug; presence of eosinophils in granulomas

Table 2: Differential diagnosis table for hepatic sarcoidosis.

ABBREVIATIONS

ACE = angiotensin converting enzyme
AF = alkaline phosphatase
AIDS = acquired immunodeficiency syndrome
ALT = alanine aminotransferase
ANCA = anti-neutrophil cytoplastmatic antibody
AST = aspartate aminotransferase
BAL = bronchoalveolar lavage
CECT = contrast enhanced computed tomography
FDG = F-18 fluordeoxyglucose
FEV = forced expiratory volume
GGT = gamma glutamyltranspeptidase
MAC = mycobacterium avium complex
Min-IP = minimum intensity projection
MIP = maximum intensity projection
MRCP = magnetic resonance cholangiopancreaticography
MRI = magnetic resonance imaging
PBS = primary biliary sclerosis
PET = positron emission tomography
PSC = primary sclerosing cholangitis
UDCA = ursodeoxycholic acid

KEYWORDS

Sarcoidosis; Hepatic sarcoidosis; Abdominal sarcoidosis; Hepatic granulomas; Computed tomography