Case Report

Hepatic Sarcoidosis: Lesson Based on a Case Report

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Abstract

Sarcoidosis is a multisystemic disease of unknown etiology that can involve lungs, abdominal organs, and lymph nodes. The incidence of sarcoidosis is highest between the ages of 20 and 40 years, and it affects both sexes equally. The most frequent localization is in the lungs, and about half of the affected patients are generally asymptomatic but can involve in small percentages of various other parts such as the biliary tract, pancreas, stomach, and urinary tract. Hepatic and splenic localization is infrequent, and lesions are often mistaken for metastases due to their morphologic similarity. The histological lesion of sarcoidosis is a noncaseous granuloma always associated with high levels of angiotensin-converting enzyme, hypercalcemia, hypercalciuria, and, in a significant percentage of cases (35%–40%), liver enzyme alteration. The pathological evolution of granulomas is fibrosis, and the most severe cases of hepatic sarcoidosis can develop into cirrhosis or portal hypertension. Imaging is essential for lesion localization and is represented by ultrasound, computed tomography (CT), magnetic resonance imaging, and positron emission tomography/CT. The differential diagnosis is very difficult and is almost always histological. We describe a case of hepatic sarcoidosis in an asymptomatic patient with elevated liver enzymes.

Keywords: Computed tomography, hepatic sarcoidosis, magnetic resonance imaging, sarcoidosis, ultrasound

Introduction

Sarcoidosis is a multisystem disease of unknown etiology[1] that can involve lungs, abdominal organs, and lymph nodes and therefore shows many similarities with lymphomas. The incidence of sarcoidosis is highest between the ages of 20 and 40 years, and it affects both sexes equally. The most frequent localization is the lungs of around 90%,[2] and half of affected patients are generally asymptomatic, while symptomatic patients present with airway manifestations such as cough or dyspnea. The association between pulmonary and hepatic sarcoidosis is reported in only 13% of cases. The association between hepatic and splenic sarcoidosis is infrequent (5% and 15%).[3] Rare associations are also described with skin, lacrimal, and ocular gland manifestations as well as with rare syndromes such as Löfgren's[4] or Heerfordt's.[5] The disease can involve in minimal percentages of various other abdominal parts such as the intra- and extra-hepatic biliary tract with cholestatic jaundice;[6] even more rarely, the disease can affect the pancreas with episodes of nonspecific pancreatitis, the stomach with ulcer-like lesions or thickening of the mucous membrane, and the urinary tract with interstitial nephritis or with hydronephrosis from extrinsic compression caused by the lymph nodes. An association between hepatic sarcoidosis and Crohn's disease has also been described in the literature[7] which, although rare, further suggests the autoimmune origin of sarcoidosis.

The histological lesion of sarcoidosis is a noncaseous granuloma always associated with high levels of angiotensin-converting enzyme (ACE), hypercalcemia, and hypercalciuria and, in a significant percentage of cases (35%–40%), with liver enzymes alteration. These noncaseous granulomas are characterized by central accumulation of mononuclear cells, mainly macrophages, with a peripheral border of lymphocytes and fibroblasts.[8] The pathological evolution of granulomas is fibrosis, and the most severe cases of hepatic sarcoidosis can evolve into portal hypertension or cirrhosis and represent only 1%.[9] Acute granulomatous hepatitis in most cases presents with a syndromic triad with fever, hepatomegaly, and elevated

Received: 16-06-2022 **Revised:** 05-08-2022 **Accepted:** 18-08-2022 **Available Online:** 07-10-2022

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DOI: 10.4103/jmu.jmu_62_22

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How to cite this article: Farina R, Clemenza M, Borzì SR, Basile A. Hepatic sarcoidosis: Lesson based on a case report. J Med Ultrasound 2023;31:318-22.

alkaline phosphatase.[10] The diagnosis is multidisciplinary and includes instrumental and laboratory investigations. Imaging is essential for the lesion detection, and in most patients, it is done with X-ray or computed tomography (CT) of the chest which, upon finding typical pulmonary signs (hilar and mediastinal lymph adenomegaly associated with pulmonary micronodules), should be extended abdomen to assess the disease extent. Ultrasound (US) allows to highlight the hepatic and splenic lesions in most patients, but it only provides morphological information that is not sufficient for the diagnosis; more information may come from contrast enhancement US (CEUS) which shows the enhancement dynamics of the lesions.[11] Magnetic resonance imaging (MRI) and positron emission tomography (PET)/CT are very sensitive for disease detection; however, like CT, they often do not lead to a sure diagnosis of hepatic sarcoidosis, for which biopsy is almost always necessary. We describe a rare case of hepatic sarcoidosis in an asymptomatic patient.

Case Report

A 57-year-old female who came to our imaging department with suspected heterologous pancreatic mass found on a previous US examination. Her laboratory tests showed increased alkaline phosphatase: 275 IU/L) (normal range: 40–129 IU/L), gamma-glutamyl transpeptidase: 197 IU/L (normal range: 38 IU/L), calcemia: 15 mg/dl (normal range: 8.5–10.5 mg/dl), and ACE: 175 (normal range <40 nmol/ml/min.). The patient did not report any previous pathologies; she was of normal weight and asymptomatic. She underwent gray-scale US, color Doppler US, CEUS, CT, MRI, PET/CT, and liver biopsy. US was performed with a MyLab Nine device (Esaote Biomedica, Genoa) using a 3–8 MHz convex and 7–15 MHz linear probes. The gray-scale US excluded pancreatic diseases and revealed a peripancreatic lymph node adjacent to the cephalic portion of the pancreas; the liver was enlarged, with inhomogeneous structure and regular margins, with multiple not confluent, rounded subcentimeter hypoechoic lesions without clear margins, widespread in all hepatic segments [Figure 1a]. The spleen had increased in size, with homogeneous structure and some subcentimeter and rounded hypoechoic lesions without clear margin. Hepatic and splenic lesions did not show intralesional vascular signals. There were hilar hepatic, mesenteric, periaortic, and perirenal lymph nodes, with a maximum diameter of 25 mm. CEUS performed after intravenous administration of SonoVue (Bracco) confirmed hepatic [Figure 1b] and splenic [Figure 1c and Video 1] lesions which showed distinct margin than gray-scale US; with color Doppler US, the abdominal lymph nodes appeared highly vascularized [Figure 1d], while CEUS did not add further information [Figure 1e]. Subsequently, she underwent CT examination with Signa 64 multidetector device (GE, USA). CT confirmed the hepatic lesions detectable only in the venous phase after contrast medium administration [Figures 2a-d], the spleen lesions [Figure 3a], the peripancreatic lymph node [Figure 3b], and abdominal lymph nodes [Figure 3c]; in addition, CT excluded abdominal neoplastic masses. MRI performed immediately after abdominal CT confirmed liver lesions [Figure 3d] but did not add additional significant elements for the differential diagnosis. Chest CT showed some pulmonary micronodules (<3 mm) in the lower lobes and mediastinal lymph adenomegalies (maximum diameter 15 mm) [Figure 4a-d]. The patient then underwent a PET/CT scan, which revealed areas of hepatic, splenic, abdominal, and mediastinal accumulation. At the end of instrumental exames, she underwent a liver biopsy obtaining the diagnosis of noncaseous granuloma. The patient refused the treatment, and after 10 months, she underwent MRI, CEUS, and laboratory tests. MRI [Figure 5a] and CEUS [Figure 5b-d] showed the disappearance of hepatic [Videos 2 and 3] and splenic [Video 4] lesions and reduction of the abdominal lymph nodes.

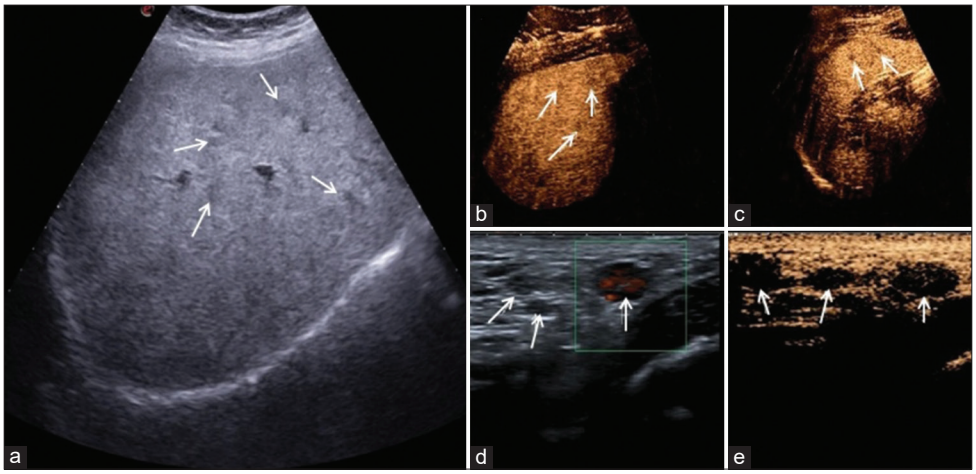

Figure 1: (a) Gray-scale ultrasound. The liver scans revealed blurred subcentimetric hypoechoic areas in all segments (arrows). (b) CEUS allows for better visualization of liver granulomas (arrows) that show sharper margins than grayscale examination. (c) CEUS shows granulomas with distinct margin in the spleen (arrows). (d) The gray-scale ultrasound shows enlarged mesenteric lymph nodes, some of which are highly vascularized. (e) CEUS allows for better detection of mesenteric lymph nodes that show sharper contours than gray-scale ultrasound, CEUS: Contrast enhancement ultrasound

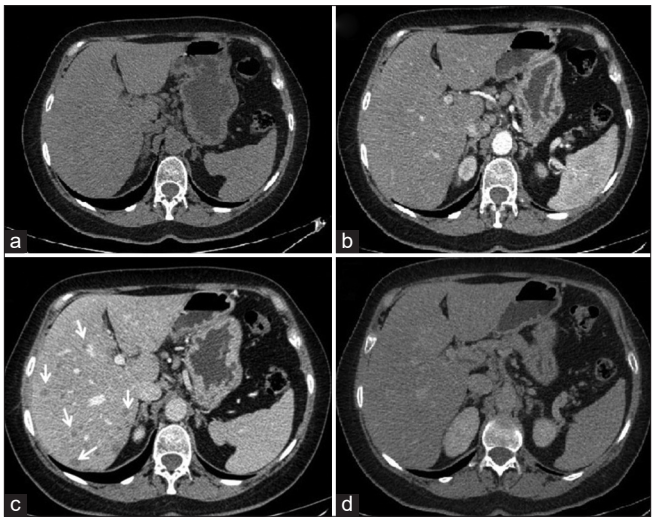

Figure 2: Abdominal CT. CT scans of the liver were performed before (a) and after contrast medium administration: in arterial phase (b), venous phase (c) and late phase (d), and show multiple hypodense subcentimetric lesions (arrows), with distinct margins, diffuse in all hepatic segments, detectable only in the venous phase (1 min after administration of contrast medium). CEUS: Contrast enhancement ultrasound, CT: Computed tomography

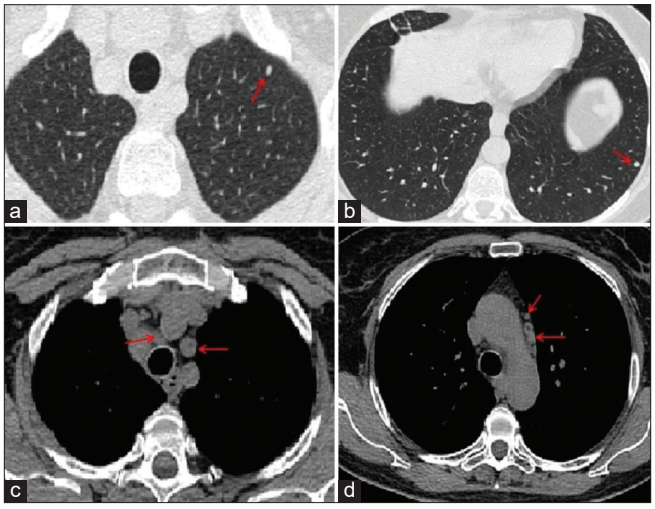

Figure 4: Chest CT. In the axial images, intraparenchymal lung micronodules (red arrows) (a and b) and mediastinal lymph nodes (red arrows) (c and d) are visible. CT: Computed tomography

Discussion

Most patients with hepatic sarcoidosis can remain asymptomatic for a long time, and the disease can even regress spontaneously without therapy. The asymptomaticity explains the often incidental discovery that generally occurs during routine checks for alteration of hepatic enzymes.[12] Differential diagnosis of hepatic sarcoidosis with imaging remains very difficult as the lesions show enhancement features similar to metastases. It is essential first of all to exclude neoplastic masses in other parts of the body, ascertain the negativity of tumor markers, and compare the instrumental data with

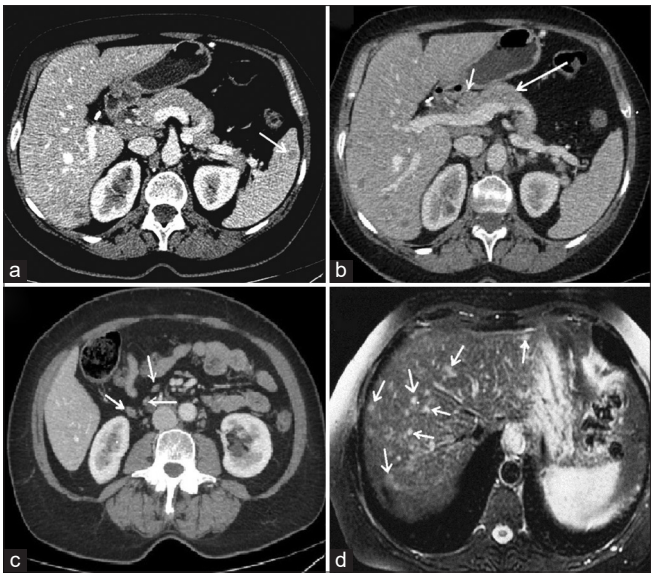

Figure 3: (a) In this CT scan, a hypodense lesion in the spleen is clearly evident (arrow). (b) This CT scan shows a lymph node resting on the cephalic portion of pancreas (short arrow). Pancreas (long arrow). (c) CT shows some perirenal and perivascular lymph nodes (arrows). (d) Abdominal MRI. Axial plane view shows hyperintense, subcentimetric liver lesions spread throughout the parenchyma (arrows). CEUS: Contrast enhancement ultrasound, CT: Computed tomography

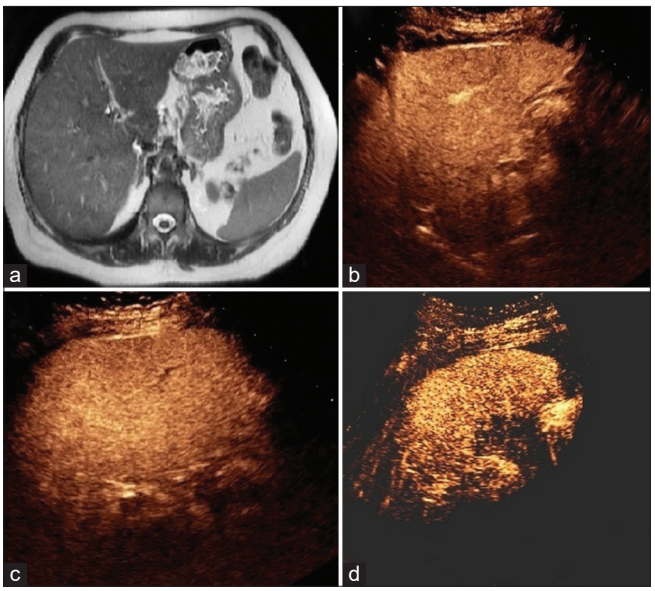

Figure 5: Check after 10 months. (a) MRI no longer shows focal liver and spleen lesions. CEUS confirms the absence of focal hepatic lesions in the left lobe (b) and right lobe (c), and absence of splenic lesions (d). MRI: Magnetic resonance imaging

those of the laboratory. Only with a multidisciplinary approach can the disease be reasonably suspected. In our case, the negativity of tumor markers (AFP, CA 19–9) and the absence of symptoms and familiarity for oncological diseases induced diagnostic suspicion. After excluding the oncological hypothesis, granulomatous pathologies of the liver and spleen such as tuberculosis, histoplasmosis, brucellosis,

schistosomiasis, viral hepatitis, drug-induced hepatitis, or the Hodgkin's lymphoma must be considered.[13] With gray-scale US, hepatic and splenic lesions appeared without clear margin and were not differentiable from metastases. With CEUS, all the lesions showed distinct margins and were more easily identifiable, but the most significant information concerned the enhancement; in fact, the lesions showed the same echogenicity in all phases of the study (parenchymal, venous, and late), unlike metastases that in the parenchymal phase they appear without enhancement. This behavior of sarcoid is likely due to a lack of vascularity and could be a characteristic of the lesions. The diagnostic suspicion got stronger after comparison with the data from the CT which highlighted the pulmonary micronodules and lymph adenomegalies typical of pulmonary sarcoidosis, but the most significant elements emerged from the morphology and enhancement of hepatic and splenic lesions which were subcentimeter and detectable only in the venous phase, after 1 min from the contrast medium administration; this behavior was in contrast to the characteristics of the metastases which are generally visible both in basal and in contrast phases, also almost always have different dimensions, and are often confluent. MRI was performed to get more information but did not add any further elements useful for the differential diagnosis. Because of the doubts remaining, PET/CT was performed which identified the areas of accumulation corresponding to hepatic, splenic, pulmonary, and lymph node lesions but did not clarify the doubts about the nature of the lesions. Ultimately, although highly suggestive of sarcoidosis, imaging did not avoid the use of liver biopsy which allowed the diagnosis. Among all the imaging methods used, in our opinion, CT is the most indicated in the suspicion of hepatic sarcoidosis on the basis of particular enhancement that the hepatic granulomas show evident only in the venous phase and equal size; this feature, if supported by large case history, could be a pathognomonic sign of hepatic sarcoidosis. MRI does not add more elements than CT and is more indicated in patients with allergy to radiological contrast media or with renal insufficiency. PET/CT is highly sensitive for the granulomas localization but has a low specificity and not clarify the lesions nature.[14] Management of patients with hepatic sarcoidosis is pharmacological and is based on long-term administration of corticosteroids with low daily doses (10–15 mg) of prednisolone which may increase in symptomatic patients with cholestasis or pruritus. In patients resistant to therapy, ursodeoxycholic acid at dose of 10–15 mg/kg/day can be used in combination.[15] There are still controversies on the management of patients with sarcoidosis; in fact, the mechanism and usefulness of corticosteroid therapy is not yet clear since about 50% of patients spontaneously regress in the absence of therapy;[16] moreover, according to some authors, corticosteroid therapy should be used only in presence of an impairment of the function of organs such as lungs, central nervous system, and eyes.[17] In a study conducted on patients with hepatic sarcoidosis, Kennedy *et al*.[18] found a complete regression of the disease in one-third of the selection, while in one-third of the patients, there was no response; therefore, on the basis of these results in two thirds of patients, corticosteroid therapy yields no results. In our opinion, however, one-third of positive response is a satisfactory result, and we therefore recommend that the treatment be administered to all patients diagnosed with hepatic sarcoidosis.

In our case, the patient refused to undergo drug treatment, and at control after about 10 months with laboratory tests, MRI, and CEUS [Figures 5a-c], complete remission of hepatic and splenic lesions was found with reduction of abdominal and thoracic lymphadenopathies and return to normal of the hepatic index.

Conclusions

The differential diagnosis of hepatic sarcoidosis with the metastases is very difficult; the rarity of the disease and nonspecificity of the symptoms contribute to further the diagnostic doubts. The instrumental tests are not sufficient to complete the diagnostic process, only the comparison with laboratory data (ACE, hypercalcemia, and hypercalciuria) can induce the suspicion of sarcoidosis, but biopsy is almost always inevitable. CT finding of diffuse, subcentimeter liver lesions evident only in the venous phase associated with abdominal lymph adenomegaly, elevated ACE levels, and negative tumor markers should lead to suspicion the sarcoidosis, especially in asymptomatic patients. Early treatment can significantly improve the course of the disease. These cases require periodic follow-up of liver injury and of response to therapy. Failure to diagnose and treat patients can expose them to serious consequences such as the evolution of the disease toward fibrosis and cirrhosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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