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Hepatic sarcoidosis mimicking cholangiocellular carcinoma: A case report and literature review

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ABSTRACT

INTRODUCTION: Sarcoidosis is a multisystem disease characterized by the presence of non-caseating granulomas in affected organs. Almost 70% of patients with a sarcoidosis reaction have hepatic involvement. However, evidence-based clinical management or treatment strategies for hepatic sarcoidosis are poorly defined. Here, we present a case of a resected hepatic sarcoidosis patient. Additionally, we review the relevant hepatic sarcoidosis literature and discuss the clinical management of hepatic sarcoidosis.
PRESENTATION OF CASE: A 20-mm liver tumor of segment 8 was incidentally detected in a 64-year-old female. Radiological images resembled the enhancement pattern of cholangiocellular carcinoma. Thus, this lesion was assigned a preoperative classification of pT1N0M0 stage I according to the 7th Union for International Cancer Control guidelines. The patient underwent a partial liver resection. Histologically, the tumor contained sarcoidosis lesions indicated by a conglomerate of epithelioid granulomas with giant cells. These histopathological findings were consistent with the diagnosis of hepatic sarcoidosis.
DISCUSSION: Histopathological examination has been established as the definitive diagnostic tool for hepatic sarcoidosis. Therefore, liver biopsy or surgical resection of a liver tumor should be considered in cases that are difficult to preoperatively distinguish from malignant tumors.
CONCLUSION: We present the case of a patient with surgically resected hepatic sarcoidosis that was difficult to preoperatively distinguish from cholangiocellular carcinoma.

1. Introduction

Sarcoidosis is a multisystem disease characterized by the presence of non-caseating granulomas in affected organs [1]. The pulmonary system is the most common site of disease activity. Hepatic involvement is also common in sarcoidosis. In previous studies of patients with systemic sarcoidosis, hepatic involvement was observed in approximately 50–80% of patients with systemic sarcoidosis [2]. Evidence-based clinical management or treatment strategies of hepatic sarcoidosis remain poorly understood. Most patients with hepatic sarcoidosis are asymptomatic and do not require treatment. However, first-line pharmacological therapy such as corticosteroids or ursodeoxycholic acid can be considered for symptomatic patients with pain in the right upper quadrant, fatigue, pruritus, and jaundice. Furthermore, various immunosuppressant agents can be used as second-line treatments. Rarely, severe cases may require liver transplantation [3–5].

In terms of radiological studies on hepatic sarcoidosis, complicated presentations may be observed in ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) [6–10]. Therefore, preoperative differential diagnosis from malignant tumors, such as cholangiocellular carcinoma, hepatocellular carcinoma, and metastatic tumors from other organs, may be difficult.

In the present report, we present a case of a resected hepatic sarcoidosis patient in whom preoperative differentiation from cholangiocellular carcinoma was difficult. Additionally, we review the relevant hepatic sarcoidosis literature and discuss the clinical, biochemical, and therapeutic management of hepatic sarcoidosis, including its radiological features (Table 1).

2. Presentation of case

A liver tumor was incidentally detected in a 64-year-old female during a medical examination. The patient had no significant past medical history, drug history, family history, including any relevant genetic information, or psychosocial history. The results of a general physical examination were normal. No abnormal laboratory findings were observed. Serum carcinoembryonic antigen and carbohydrate antigen 19-9 were 4.0 ng/mL and 20.3 U/mL, respectively. These values were within the standard ranges. Abdominal ultrasonography revealed a 20-mm liver tumor of segment 8. CT

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Table 1
Clinical and histopathological features of hepatic sarcoidosis [12,13–18].

Symptoms	Elevated serum tests	Radiological finding	Histopathology	Medical management
Jaundice	Alkaline phosphatase	Hepatomegary	The granulomas are non-caseating and epithelioid.	Corticosteroids
Abdominal pain	Gamma-glutamyl transpeptidase	Multiple hypointense liver nodule	Macrophages that aggregate to form giant cells surrounded by fibrin rings.	Ursodeoxycholic acid
Cirrhosis	Aminotransferase	Multiple hypoattenuated liver nodule		Various immunosuppressant agents
Portal hypertension	Bilirubin	Splenomegary		Liver transplantation
Ascities	Antigen converting enzyme	Splenic garanuloma		
Organomegaly		Lymph nodes enlargement		
Budd-Chiari syndrome				

showed a 20-mm liver tumor of segment 8 with no enhancement in the early phase and very slight enhancement in the late phase (Fig. 1a and b). MRI with contrast revealed a 20-mm liver tumor of segment 8 with low signal intensity on T1-weighted images and slightly high signal intensity on T2-weighted images (Fig. 1c and d). The preoperative radiological findings were assumed to resemble the enhancement pattern of cholangiocellular carcinoma. Thus, this lesion was assigned a preoperative classification of pT1N0M0 stage I according to the 7th Union for International Cancer Control guidelines. Therefore, the patient underwent a partial liver resection of segment 8. This patient had good cardiopulmonary function and performance status in preoperative assessment. The operation was performed by R.M., who was a senior hepatobiliary pancreatic surgeon. The patient's postoperative recovery was uneventful, and she was discharged from the hospital after 10 days. At the time of publication, the patient exhibited no systemic sarcoidosis reaction, including in the liver. Therefore, the patient was observed without pharmacological therapy.

Histologically, the liver tumor was $20 \times 15 \times 14\,mm^3$ in volume (Fig. 2a). The tumor exhibited sarcoidosis lesions with a conglomerate of epithelioid granulomas with giant cells surrounded by a thin layer of lymphocytes (Fig. 2b and c). No histopathological findings indicated other granulomatous liver diseases, including *Mycobacterium tuberculosis* or mycosis.

3. Discussion

We present the case of a patient with surgically resected hepatic sarcoidosis that was difficult to preoperatively distinguish from cholangiocellular carcinoma. This case report was presented in line with the SCARE criteria [11]. The histological findings confirmed that the resected liver tumor contained sarcoidosis lesions, as indicated by a conglomerate of epithelioid granulomas with giant cells. The patient remained healthy after discharge and was symptom-free under observation without drugs during the postoperative follow-up period.

According to our review of previous reports, the clinical symptoms and radiological findings of hepatic sarcoidosis are non-specific. Among the more than 50% of patients with hepatic granulomas on liver biopsy, only 10–30% have elevated serum liver enzymes [12]. Furthermore, approximately 20% of these patients have palpable hepatomegaly or splenomegaly [13]. Previous stud-

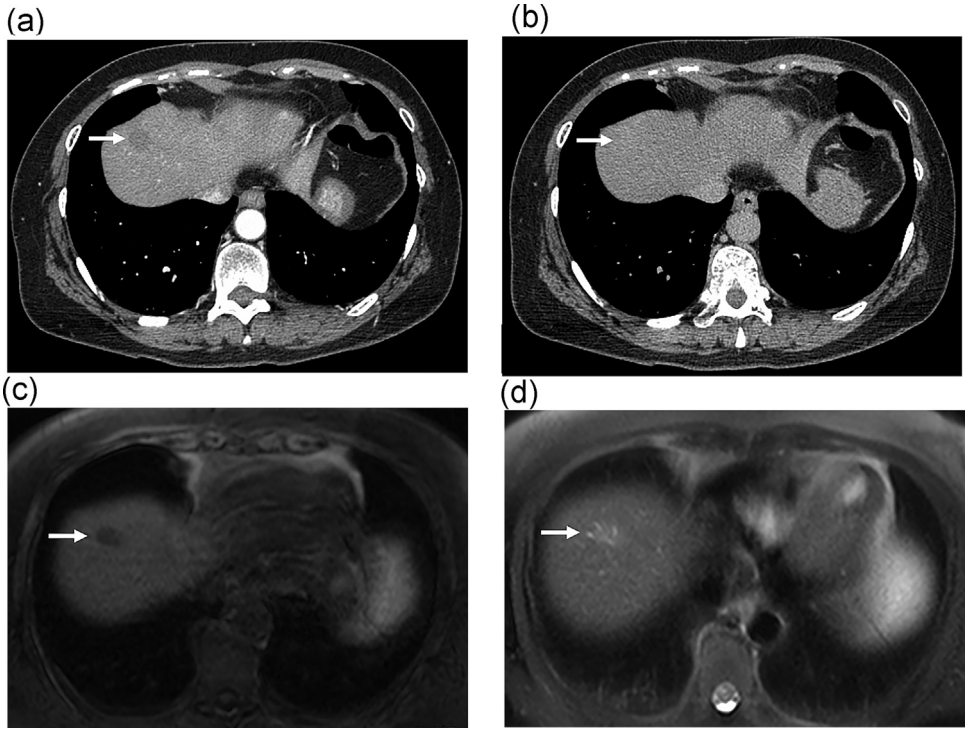

Fig. 1. Radiological findings of the liver tumor. **(a)** and **(b)** Computed tomography (CT) revealed a 20-mm liver tumor (arrow) of segment 8 with no enhancement in the early phase (a) and slight enhancement in the late phase (b). **(c)** and **(d)** Magnetic resonance imaging (MRI) with contrast revealed a 20-mm liver tumor (arrow) of segment 8 with low signal intensity on T1-weighted images (c) and slightly high signal intensity on T2-weighted images (d).

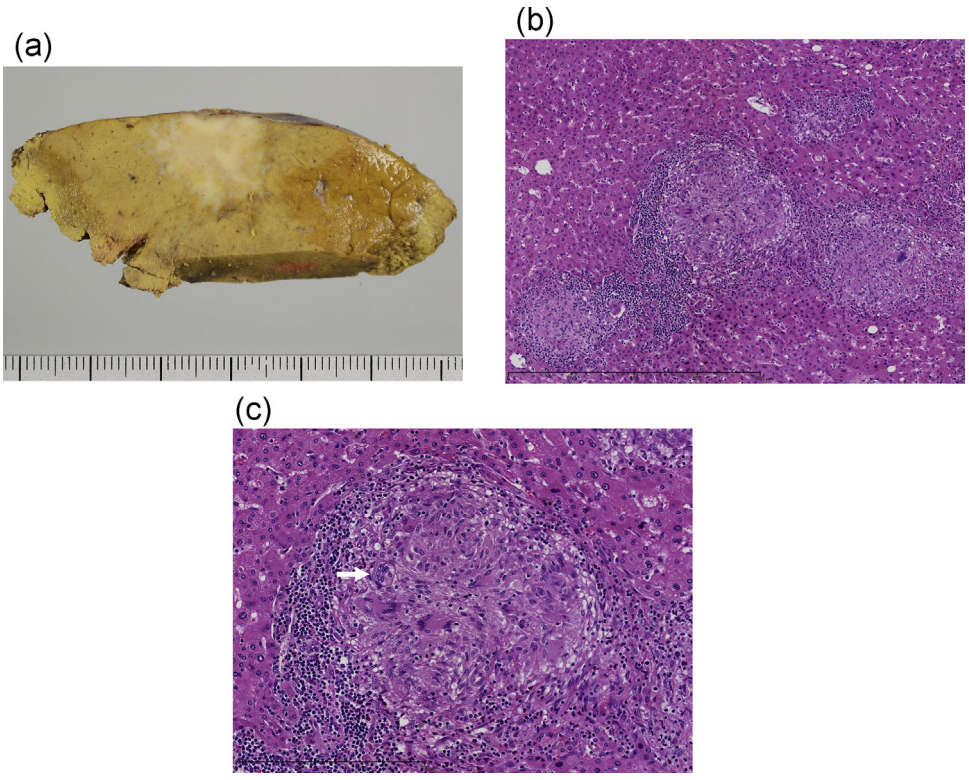

Fig. 2. Histopathological findings of the resected liver tumor. **(a)** Macroscopic view of the resected tumor mass. A $20 \times 15 \times 14\,mm^3$ liver tumor was observed. **(b)** and **(c)** The tumor exhibited sarcoidosis lesions, as evidenced by a conglomerate of epithelioid granulomas with giant cells (arrow) surrounded by a thin layer of lymphocytes. Hematoxylin and eosin staining, ×100 and ×200.

ies have recommended that a radiological examination, such as ultrasonography or CT, is useful to determine liver involvement and accurately evaluate organomegaly [3,13]. In fact, ultrasonography was useful for detecting the liver tumor in the present case. However, even in cases of radiological abnormalities or elevated serum liver enzymes, evidence of organ dysfunction is rare. Nevertheless, in a minority of patients, hepatic sarcoidosis causes severe complications, such as severe cholestatic jaundice, portal hypertension, Budd-Chiari syndrome, and cirrhosis, which lead to end-stage liver disease [14–17]. Therefore, it is important to provide an accurate description of the clinical presentation and biochemical and imaging findings of hepatic sarcoidosis to identify patients who require close monitoring and treatment.

According to previous reports, systematic liver function tests are recommended during the initial evaluation of hepatic sarcoidosis. Increased alkaline phosphatase, gamma-glutamyl transpeptidase, and aminotransferase are typical laboratory findings [18]. Measurement of serum angiotensin-converting enzyme has been useful in patients with active sarcoidosis [19]. In the present case, since we did not assume that this lesion was hepatic sarcoidosis, we did not measure serum ACE preoperatively. Serum ACE measured postoperatively was within the standard range. Liver biopsy is also recommended in cases in which the preoperative diagnosis is uncertain and treatment is considered. Previous reports recommend obtaining a liver biopsy if aminotransferase is elevated at least two-fold above the upper limit of normal [18,19]. However, in the present case, we employed surgical resection of the liver tumor for liver biopsy, due to potential dissemination, because preoperative differentiation with cholangiocellular carcinoma was difficult. In terms of the surgical procedure, anatomical liver resection with lymph node dissection was considered. However, we decided to perform a partial liver resection because we assumed this would secure the surgical margin sufficiently and because no swelling of regional lymph nodes was observed before or during the operation.

Histopathological examination has been established as the definitive diagnostic tool. In the present case, the histopathological findings were consistent with the diagnosis of hepatic sarcoidosis. Hepatic sarcoidosis should be differentiated from other autoimmune liver diseases, especially primary biliary cirrhosis and primary sclerosing cholangitis [17]. In hepatic sarcoidosis, granulomas are usually abundant and well formed in the periportal and portal regions. Typically, the granulomas are non-caseating and epithelioid. Sarcoid epithelioid granulomas are characterized by macrophages that aggregate to form giant cells surrounded by fibrin rings.

In terms of the medical management of hepatic sarcoidosis, evidence-based clinical management or treatment strategies remain poorly understood. Most patients with hepatic sarcoidosis are asymptomatic and do not require treatment. However, first-line pharmacological therapies such as corticosteroids (prednisone 0.5-1.0 mg/kg daily) or ursodeoxycholic acid (13–15 mg/kg daily) can be considered for symptomatic patients with pain in the right upper quadrant, fatigue, pruritus, and jaundice [3,20]. Various immunosuppressant agents can be used as second-line treatments. Rarely, severe cases may require liver transplantation. However, disease recurrence in the graft has been reported, and the survival rate has tended to be lower than that for patients who receive transplants for other diseases [17].

4. Conclusion

We presented a case report and reviewed previous studies concerning hepatic sarcoidosis. The clinical symptoms and radiological findings of hepatic sarcoidosis are non-specific. Histopathologi-

cal examination has been established as the definitive diagnostic tool. Therefore, in cases that are difficult to preoperatively distinguish from malignant tumors, surgical resection of liver tumors should be considered. Evidence-based clinical management and treatment strategies for hepatic sarcoidosis remain poorly understood. Although the overall prognosis is favorable, pharmacological therapy including corticosteroids or ursodeoxycholic acid should be considered for symptomatic patients.

Conflicts of interest

All authors have no potential conflicts of interest to disclose.

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Ethical approval

The present study was approved by the ethics committee of Tsukuba Medical Center Hospital.

Consent

Informed consent was obtained for the publication of this case from the patient concerned.

Authors' contribution

All authors participated in the treatment of this case.

All authors made substantial contributions to the acquisition, analysis, and interpretation of data and participated in writing the paper.

All authors read and approved the final manuscript.

Guarantor

The guarantor is Ryoichi Miyamoto.

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