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Hepatocellular carcinoma associated with sarcoidosis

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ABSTRACT

INTRODUCTION: The association of hepatic sarcoidosis with hepatocellular carcinoma (HCC) is considerably rare. Here we report a rare case of HCC associated with sarcoidosis.
PRESENTATION OF CASE: A 75-year-old male with no history of alcohol addiction or viral hepatitis was referred to our hospital because of an abnormal liver mass. Subsegmentectomy of the liver was performed for the diagnosis of HCC. A histopathological examination revealed small non-necrotizing granulomas with a tendency to coalesce that were scattered in and around the carcinoma. No features of cirrhosis, steatohepatitis, and any other liver diseases were observed. Furthermore, swelling of the bilateral lung hilar lymph nodes with uptake of 18F-fluorodeoxyglucose was found on positron emission tomography/computed tomography and the tuberculin reaction test results were negative. On the basis of these findings, the final diagnosis of HCC associated with sarcoidosis was confirmed.
DISCUSSION: By reviewing previous cases, we found only five cases that described patients diagnosed with HCC associated with sarcoidosis. Of these, four patients died within two years after diagnosis because of ruptures or inoperable huge tumors. In contrast, radical hepatectomy was performed at an earlier stage of disease in two patients, including ours, and both these patients have remained healthy with no recurrences or metastases at the latest follow-up visit.
CONCLUSION: Periodic checkups of the liver should be conducted for patients with systemic sarcoidosis, regardless of the presence of liver cirrhosis.

1. Introduction

Sarcoidosis is a multisystem disorder characterized by the presence of noncaseating granulomas in affected tissues.[1] The most commonly affected organs are the lungs and lymph nodes, followed by the liver, although several other organs can also be involved, including the liver, skin, eyes, heart, and brain.

Previous reports have documented evident liver involvement in approximately 50–80% of cases by biopsy and approximately 70% by autopsy.[2–4] However, the diagnosis of hepatic sarcoidosis is difficult because liver dysfunction is often mild and the condition is clinically silent in most cases.[5,6] Furthermore, hepatic sarcoidosis rarely causes severe complications such as jaundice, liver failure, cirrhosis, and portal hypertension, and the symptoms of cirrhosis or portal hypertension are reportedly present in ≤1% of the cases.[7] Granulomas may lead to chronic intrahepatic cholestasis with the loss of interlobular bile ducts, and these conditions may sequentially lead to the development of periportal fibrosis or micronodular cirrhosis.[8] In addition, the association of hepatic sarcoidosis with hepatocellular carcinoma (HCC) is thought to be considerably rare. Here we report a rare case of a 75-year-old male who was diagnosed with HCC associated with sarcoidosis and was treated by subsegmentectomy of the liver and cholecystectomy.

2. Presentation of case

A 75-year-old male was referred to our hospital for an abnormal liver mass detected on ultrasonography during a periodic medical checkup. He had no symptoms, although he had a medical history of arterial hypertension and type 2 diabetes mellitus that was controlled by an oral hypoglycemic agent for several years. He had no history of alcohol addiction and had never received a blood transfusion.

His preoperative laboratory data were as follows: platelet count, $193 \times 10^3/\mu L$ (normal, $120–330 \times 103/\mu L$); albumin, 3.3 g/dL (normal, 4.0–5.0 g/dL); total bilirubin, 0.3 mg/dL (normal, 0.2–1.0 mg/dL); aspartate aminotransferase, 53 IU/L (normal, 11–28 IU/L); alanine aminotransferase, 49 IU/L (normal, 6–30 IU/L); blood urea nitrogen, 24.2 mg/dL (normal, 8.0–21.0 mg/dL); creatinine, 1.60 mg/dL (normal, 0.63–1.05 mg/dL); prothrombin time

Abbreviations: HCC, hepatocellular carcinoma; CT, computed tomography; Gd-EOB-DTPA, gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid.

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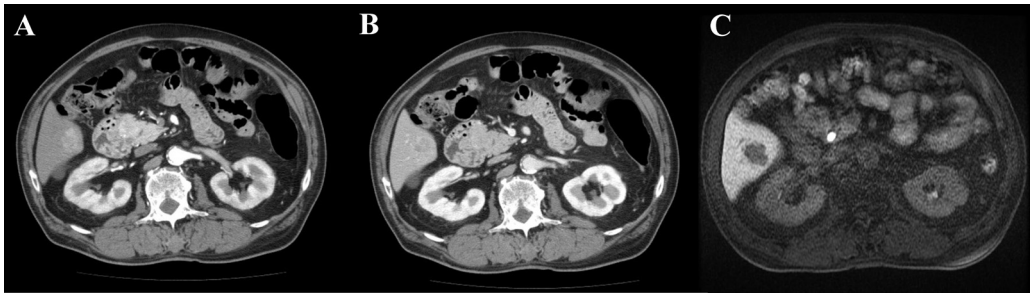

Fig. 1. (A, B) Abdominal computed tomography revealed a hypervascular tumor with washout of contrast-medium. A mass located in the right posterior section of the liver. (C) The tumor showed no gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB-DTPA) uptake on hepatocyte-phase images obtained by Gd-EOB-DTPA magnetic resonance imaging.

international normalized ratio, 0.98; and indocyanine green retension rate at 15 min, 6.6%. High serum levels of blood urea nitrogen and creatinine were evident, but urinary output was preserved and serum potassium level was not elevated. In addition, proteinuria (2.5 g/day) and hypoalbuminemia were observed. Judging from his medical history, diabetic nephropathy was thought to be responsible for these abnormal findings, although a renal biopsy for definitive diagnosis was not performed. Moreover, the elevation of the tumor markers such as serum alpha-fetoprotein (88.0 ng/mL; normal, 0.0–10.0 ng/mL) and des-gamma-carboxy prothrombin (76 mAU/mL; normal, 0.0–39.9 mAU/mL) was detected; however, test results for serum hepatitis B virus surface antigen, hepatitis B virus core antibodies, and hepatitis C virus antibodies were negative.

Abdominal computed tomography (CT) revealed a $3 \times 2\,cm^2$ hypervascular tumor with washout of contrast-medium located in the right posterior section of the liver (Fig. 1A and B). The tumor showed no gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB-DTPA) uptake and demonstrated hypointensity on hepatocyte-phase images obtained by Gd-EOB-DTPA magnetic resonance imaging (Fig. 1C). Subsequently, subsegmentectomy (segment VI) of the liver and cholecystectomy were performed for the diagnosis of HCC.

The resected solid encapsulated tumor measured $2.6 \times 2.3\,cm^2$, and contained a septum that was evident on macroscopic examination (Fig. 2A). A histopathological examination of the resected specimen revealed tumor cells that resembled hepatocytes and grew in cords of variable thicknesses with bile plugs. Small non-necrotizing granulomas with a tendency to coalesce were scattered in (Fig. 2B and C) and around (Fig. 2D and E) the carcinoma. No evidence of liver cirrhosis was found, but a slight degree of fibrosis was observed around the portal areas (Fig. 2F). In addition, vascular invasion and intrahepatic metastases were not apparent, and no features of steatohepatitis or any other liver diseases were observed. On the basis of these findings, a final diagnosis of HCC associated with sarcoidosis was confirmed.

We performed several additional examinations to arrive at a definitive postoperative diagnosis. Bilateral hilar lymphadenopathy with uptake of 18F-fluorodeoxyglucose was observed on positron emission tomography/CT (Fig. 3) and the results of tuberculin reaction test were negative. These findings confirmed systemic sarcoidosis. The patient remained healthy with no recurrences or metastases at 1 year after resection.

3. Discussion

The diagnosis of hepatic sarcoidosis is difficult, because liver dysfunction is usually mild and the condition is clinically silent in most cases.[5,6] Cirrhosis or portal hypertension has been reported in ≤1% of all sarcoidosis cases.[7] In other reports, 13% fo the patients with hepatic sarcoidosis exhibit liver involvement without lung disease and approximately 35–40% have abnormal liver

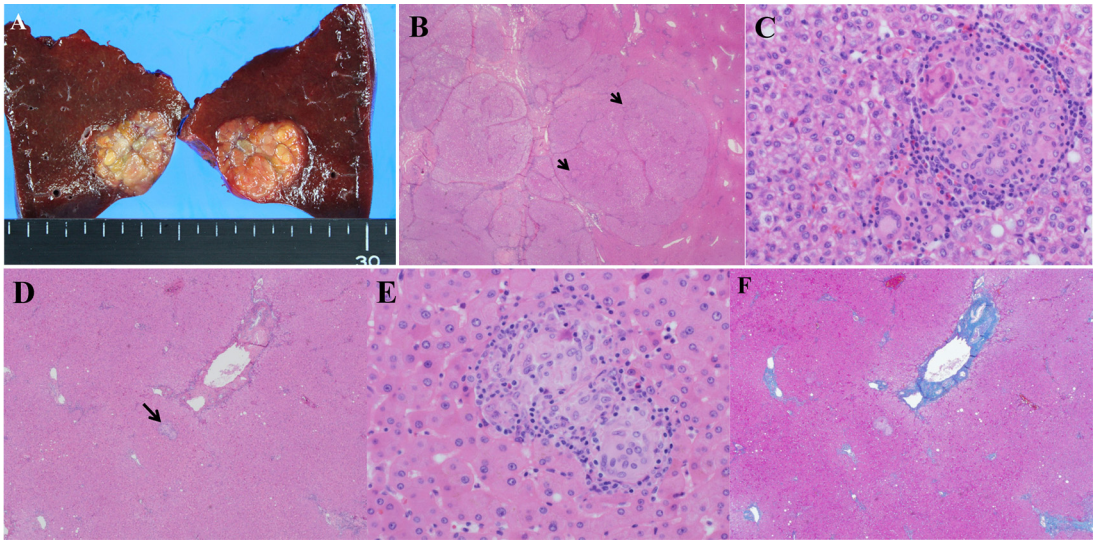

Fig. 2. (A) A resected solid encapsulated tumor is macroscopically evident. (B) Tumor cells grown in cords of variable thicknesses with bile plugs. Small non-necrotizing granulomas with a tendency to coalesce scattered in the carcinoma (arrow; H&E, ×4). (C) Small non-necrotizing granulomas in the carcinoma were observed at a higher magnification (H&E, ×40). (D) Small non-necrotizing granulomas were also observed in the background liver (arrow; H&E, ×4). (E) Small non-necrotizing granulomas in the background liver were observed at a higher magnification (H&E, ×40). (F) A slight degree of fibrosis can be seen around the portal areas (Azan stain, ×4).