Hepatocellular carcinoma associated with sarcoidosis

Takuma Arai a,*, Shingo Akita a, Masahiro Sakon a, Taishi Fujii a, Haruki Tanaka a, Keiko Ishi b, Shiro Miwa a

a Department of Surgery, Okaya Municipal Hospital, Hon-machi 4-11-33, Okaya 394-8512, Japan
b Department of Pathology, Okaya Municipal Hospital, Hon-machi 4-11-33, Okaya 394-8512, Japan

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 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.

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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; 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 × 10³/μL (normal, 120–330 × 10³/μL); 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.

* Corresponding author. Tel.: +81 266 23 8000; fax: +81 266 23 0818.
E-mail address: t-arai@gd5.so-net.ne.jp (T. Arai).

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international normalized ratio, 0.98; and indocyanine green retention 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 × 2 cm² 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 × 2.3 cm², 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.6,5 Cirrhosis or portal hypertension has been reported in <1% of all sarcoidosis cases.7 In other reports, 13% of the patients with hepatic sarcoidosis exhibit liver involvement without lung disease and approximately 35–40% have abnormal liver
function test results, which are most commonly indicated by alkaline phosphatase levels.\textsuperscript{3,10} Less frequently, multiple, tiny, low-density nodules are detected on abdominal CT and liver enlargement is observed in approximately 50% of patients with nodular hepatosplenic sarcoidosis.\textsuperscript{11}

The relationship between sarcoidosis and carcino genesis has not been fully elucidated. However, the lymph nodes and lungs are most commonly involved, followed by the liver, and hepatic sarcoidosis rarely causes severe complications such as jaundice, liver failure, cirrhosis, or portal hypertension. In addition, the association of hepatic sarcoidosis with HCC is thought to be considerably rare. Cirrhosis is an obvious risk factor for the development of HCC, but the mechanisms by which cirrhosis predisposes to carcinogenesis are poorly understood. Numerous studies have shown that chronic inflammation and oxidative stress increase the risk of carcinogenesis, and several recent studies have demonstrated that oxidative stress can enhance the malignant potential of HCC through telomerase activation.\textsuperscript{1,2} Chronic inflammation and oxidative stress because of sarcoidosis may be associated with an increased risk of the development of HCC. Our patient suffered from type 2 diabetes mellitus which is reportedly a potential risk factor for HCC.\textsuperscript{13,14} Therefore, additive or synergistic adverse effects to the liver because of both sarcoidosis and diabetes mellitus may promote the development of HCC. Previous studies have demonstrated an increased risk of HCC in patients with sarcoidosis; however, this result is thought to be controversial because there was no mention of hepatitis B or C infection, alcohol addiction, or autoimmune status of the patients.\textsuperscript{15} On the other hand, a direct causal link between HCC and sarcoidosis was not detected by reviewing this case. Although the coincidence of these two diseases may be possible, this potential comorbidity cannot be predicted by case series.

By reviewing previous cases, we found only five (four males and one female) that described patients diagnosed with HCC associated with sarcoidosis (Table 1).\textsuperscript{16–20} The mean age of the patients, including our patient, was 57.0 ± 12.5 years. Four patients (66.6%) had liver cirrhosis. Case 1 presented with incidental manifestation of sarcoidosis and HCC-associated liver cirrhosis, which terminated in a rupture into the peritoneal cavity. Cardiac involvement was considered as a cause of complete A-V block before death in this patient. Case 2 also developed tumor rupture, and cases 3 and 4 were inoperable because of large tumor size. Each of these patients died within 2 years after diagnosis. In contrast, radical hepatectomy was performed at an earlier stage of disease in case 5 and our patient, and both of these patients have remained healthy with no recurrences or metastases at the latest follow-up visit. These findings suggest that the outcomes of patients with HCC associated with sarcoidosis can be improved if surgery is performed at an earlier stage of disease.

### 4. Conclusion

Periodic checkups of the liver should be conducted in patients with systemic sarcoidosis, regardless of the presence of liver cirrhosis.

### Conflict of interest

The authors declare no conflicts of interest.

### Funding

None.

### Ethical approval

Written consent was obtained from the patient and a copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

### Author's contributions

Conception and design, Takuma Arai and Shiro Miwa; collection and assembly of data, Masahiro Sakon, Shingo Akita, Taishi Fujii, Haruki Tanaka, and Keiko Ishii; data analysis and interpretation, Takuma Arai; manuscript writing, Takuma Arai; final approval of manuscript, Takuma Arai, Masahiro Sakon, Shingo Akita, Taishi Fujii, Haruki Tanaka, Keiko Ishii, and Shiro Miwa.
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