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*Case Report*

# Sarcoidosis-Associated Hepatocellular Carcinoma

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**Sarcoidosis is a systemic granulomatous inflammation of unknown etiology, and seems to involve the liver parenchyma in most cases. However, sarcoidosis-associated hepatocellular carcinoma is rare. We report here a case in which a hepatocellular carcinoma occurred within the liver, which was probably involved as a result of systemic sarcoidosis. A 57–year-old Japanese man had been followed up for 2 years because of diabetic nephropathy and sarcoidosis. On admission for pneumonia, imaging studies revealed an unexpected hepatic tumor. Histology revealed a hepatocellular carcinoma accompanied by T–lymphocytic infiltration and marked granulomatous inflammation, which was surrounding some tumor nodules. The background liver parenchyma exhibited a moderate degree of fibrosis with granulomatous inflammation. The patient had no other apparent liver disease such as viral hepatitis, steatohepatitis, or primary biliary cirrhosis. Therefore, in the present case, sarcoidosis may be considered the probable background etiology for hepatocarcinogenesis.**

**Key words**: granuloma, hepatocellular carcinoma, lymphocytic infiltration, sarcoidosis

Sarcoidosis is a multisystem disease with granulomatous inflammation, and after lung and lymph nodes the liver is considered one of the organs likely to be most involved by sarcoidosis [1, 2]. However, cases of sarcoidosis-associated hepatocellular carcinoma (HCC) are believed to be rare. Here, we present such a case in a Japanese man and discuss sarcoid liver disease and hepatocarcinogenesis.

## Case Report

A 57–year-old, diabetic Japanese man was admitted to the National Defense Medical College Hospital (Tokorozawa, Japan) because of nephrotic syndrome. He had routinely drunk approximately 60 g of alcohol daily for 30 years, but had abstained for the last 2 years. Upon examination for nephrotic syndrome, he had been found to have swelling of the bilateral lung hilar and abdominal paraaortic lymph nodes, accompanied by elevations in the serum value for interleukin–2 receptor and in the uptake of radioisotopes in gallium scintigraphy. To rule out malignancies, biopsy of an abdominal paraaortic lymph node had been performed, and histology had identified a granulomatous lymphadenitis without necrosis or acid-fast bacilli. An accompanying renal biopsy had revealed the existence of diabetic nephropathy. A negative tuberculin skin (Mantoux) test and elevations in both the value for angiotensin-converting enzyme and the CD4/8 ratio in bronchoalveolar fluid had supported the diagnosis of

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sarcoidosis. No uveitis was evident on slit-lamp examination.

The patient was followed up in the outpatient office for a 2-year symptom-stable period, but he then complained of respiratory distress after flu-like symptoms. Imaging studies on admission revealed bilateral pulmonary infiltrates with a ground-glass appearance. Uremic lung or pneumonia and adult respiratory distress syndrome were considered, and both his symptoms and the radiologic infiltrates were resolved by treatment with antibiotics and corticosteroids. However, on the follow-up chest computed tomogram (CT), an unexpected hepatic tumor was found (Fig. 1). Laboratory data revealed him to be low in hemoglobin, platelet number, and serum albumin, and also revealed high serum values for blood urea nitrogen, creatinine, and protein induced by vitamin K absence or antagonist-II (PIVKA-II). Serum hepatitis B surface antigen and hepatitis C virus antibody were negative, and transaminases, angiotensin-converting enzyme, and alpha feto-protein values were each within the normal range. The retention of indocyanine green at 15 min after its injection was 7.5%. The liver tumor was suspected to be a HCC, although a sarcoid nodule could not be ruled out because he had sarcoidosis.

HCC was diagnosed by pathology using a specimen obtained in a needle-biopsy examination, and a subsequent partial liver resection was performed. A simple nodular-type tumor, sized $32 \times 25 \times 24$ mm, was found within the resected specimen. Histology revealed a thin-trabecular and pseudo-glandular proliferation of tumor cells (Fig. 2A). These tumor cells possessed rounded nuclei with distinct nucleoli and an eosinophilic polygonal cytoplasm, and some displayed fatty degeneration (Fig. 2B). The tumor was diagnosed as a grade 2 HCC. Interestingly, the tumor was associated with marked granulomatous inflammation and lymphocytic infiltration. These non-caseating granulomas were found circumferentially in the tumor capsule and septa (Fig. 2C, E), and were highlighted by the histiocytic marker CD68 (clone KP-1; Dako, Glostrup, Denmark; Fig. 2D, F). The accompanying lymphocytes were predominantly immunoreactive for

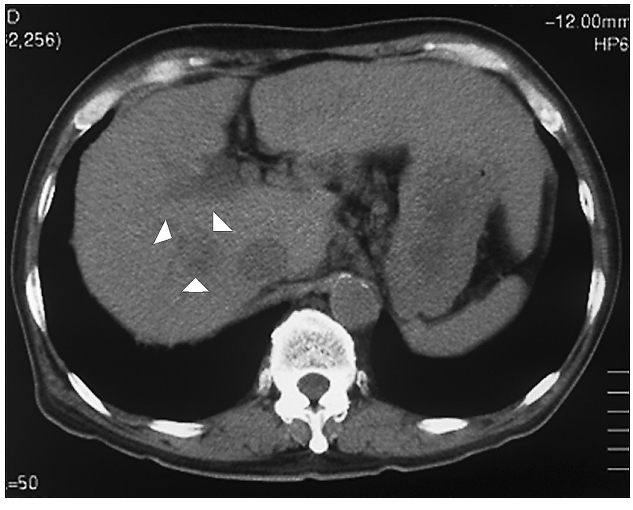


Fig. 1 A low-density mass (arrowheads) was incidentally found in the right lobe of the liver on the plain chest computed tomogram. Scale divisions represent 1 cm each.

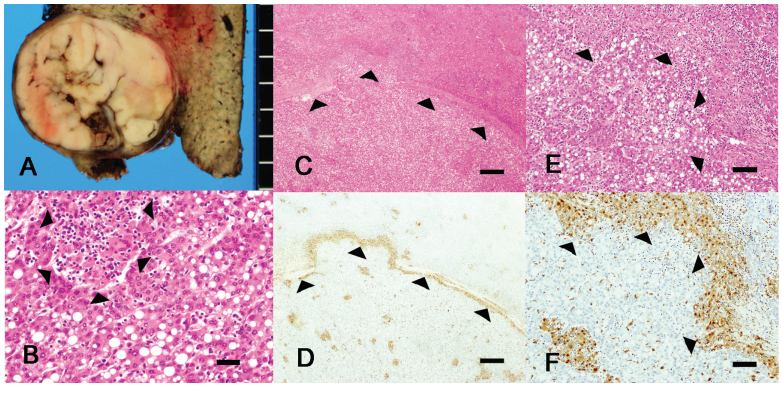


Fig. 2 A, Cut surface of the hepatic mass exhibited a whitish expanding tumor with a fibrous capsule. A nodule-in-nodule appearance was vaguely recognized. Scale divisions represent 5 mm each; B, Histologically, the tumor cells displayed fatty degeneration and were accompanied by non-caseating granulomas (arrowheads) and small lymphocytes (hematoxylin-eosin; scale bar indicates 50 $\mu$m); C-F, Tumor-cell nests were surrounded by granulomatous inflammation (arrowheads), which was highlighted by the histiocytic marker KP-1 (C, E: hematoxylin-eosin; D, F: diaminobenzidine; scale bars indicate 500 $\mu$m in C, D, and 100 $\mu$m in E, F).

the T-cell marker CD45RO (clone UCHL-1; Dako). No vessel permeation or intrahepatic metastases by tumor cells was observed. The background hepatic parenchyma contained non-caseating granulomas to a lesser degree than the tumor itself, and fibrosis was predominantly seen connecting among portal areas. No apparent features of steatohepatitis, primary biliary cirrhosis, or any other liver disease were observed. These findings are compatible with liver involvement by sarcoidosis. The post-operative period was uneventful, and the patient has been followed up for 2 years since the operation, without any recurrence of the liver tumor.

## Discussion

Sarcoidosis is a systemic granulomatous inflammation with an unknown etiology. In some studies of patients with sarcoidosis, hepatic granulomas have been found in as many as 70% of autopsy cases [3] and in 50-65% of liver biopsy cases [1]. Conversely, in a recent large-scale study, only 3.6% of liver biopsy samples included granulomas, with almost half of the samples with granulomas being diagnosed as primary biliary cirrhosis and approximately 8% as sarcoidosis [4]. Most patients with hepatic sarcoidosis are asymptomatic and have normal liver enzyme tests. Abnormalities in liver function tests are recognized in 20-40% of sarcoid patients [1], and liver enlargement can be found on ultrasound or CT in up to 50% of cases. On CT, the liver appears homogenous in the cases with organomegaly. In 5-15% of cases, sarcoid liver disease manifests itself as multiple, small (<1 cm) nodules [1, 5, 6]. However, as they increase in size, malignancy or other infectious causes should be included in the differential diagnosis. The precise frequency with which sarcoid liver is detected on magnetic resonance imaging remains unclear, despite the publication of reports describing the findings of such imaging [7, 8]. Rarely, sarcoid liver disease can cause cirrhosis and portal hypertension [9].

Among patients with sarcoidosis, an increasing risk of cancer is indicated by reports from Japan [10] and from Sweden [11]. In the former, death by lung cancer associated with sarcoidosis was high, while in the latter, lung cancer, non-Hodgkin's lymphoma, skin cancers, and furthermore liver cancer occurred even more frequently. Therefore, the Swedish authors proposed chronic inflammation as a putative mediator of carcinogenic risk [11]. In general, chronic inflammation is associated with an increased risk of cancers in the affected tissues [12]. Specifically, repeated tissue damage and regeneration of tissue, in the presence of the highly reactive nitrogen and oxygen species released from inflammatory cells, interacts with DNA in the proliferating epithelium, resulting in permanent genomic alterations such as point mutations, deletions, or rearrangements. On the basis of the above findings, hepatocellular damage and regeneration caused by inflammation may be considered to be an essential step in the carcinogenesis of sarcoidosis-associated HCC, as in the carcinogenesis associated with viral hepatitis [13]. Actually, cases of HCC in sarcoidosis are extremely rare [11, 14, 15], and one of these reported cases was complicated by cirrhosis [15]. Such a rare association of sarcoidosis with HCC may reflect the presence of relatively weak inflammation or weak hepatocytic regeneration in sarcoid liver disease. However, even if this is a rare association, clinicians should include primary liver cancer in the list used for the differential diagnosis of a liver mass in sarcoidosis patients. For differential diagnosis, both the increase in the serum values of tumor-marker proteins and the needle-biopsy procedure were useful.

In the present case, granulomatous inflammation with associated T-cell infiltration was observed in the liver, and this inflammation was present more strongly in the tumor itself than in the background liver parenchyma. This granulomatous reaction in the tumor may be similar to the so-called sarcoid-like reaction, which is frequently observed in the lymph nodes draining a metastatic tumor, and is considered to be an immunoreaction to the tumor [16]. A preponderance of granulomatous inflammation within the tumor, as observed in the present case, may be one of the characteristic features of sarcoidosis-associated cancers. Despite a favorable-looking suggesting host immunity against the tumor, its significance on prognosis is unclear because the so-called sarcoid-like reaction itself may not be significant as a positive influence on cancer-patient prognosis [16].

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