CASE REPORT

Sarcomatous Hepatocellular Carcinoma
with Remittent Fever

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Abstract

We herein report a rare case of hepatocellular carcinoma (HCC) with sarcomatous changes. A 66-year-old man was admitted to our hospital with a high fever and upper abdominal pain. Initially, he was diagnosed as having a liver abscess; however, antibiotic treatment and drainage were ineffective. Further imaging studies revealed the typical appearance of HCC: the tumor had invaded the hepatic and portal veins. Surgical resection of the tumor was performed. A pathological examination demonstrated the presence of a sarcomatous hepatocellular carcinoma. Sarcomatous hepatocellular carcinoma with remittent fever is a rare disease entity.

Key words: sarcomatous hepatocellular carcinoma, remittent fever, paraneoplastic syndrome

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Introduction

Generally, hepatocellular carcinoma (HCC) is asymptomatic. Fatigue, abdominal distention and low-grade fevers are sometimes observed with HCC due to a deterioration of the liver function. Fever as a primary symptom of HCC is very rare. We herein report a case of HCC involving a high fever and a high C-reactive protein (CRP) level that was initially diagnosed as a liver abscess.

Case Report

A 66-year-old Japanese man whose hepatitis C virus had been curatively treated was admitted to our hospital due to epigastralgia and a fever of two weeks’ duration. On examination, the patient was found to be 171 cm tall and weighed 75 kg. His temperature fluctuated between 36.4°C and 38.4°C.

Table shows the laboratory data obtained on admission. A hypoechoic tumor measuring 4.4 cm in diameter was detected in two segments of the liver using ultrasonography. Contrast-enhanced computed tomography (CT) revealed an irregularly demarcated mass with a maximum diameter of 55 mm in the S2 lobe with slight peripheral enhancement. The patient was diagnosed as having a liver abscess due to the high fever and elevated CRP level, although the CT findings did not have a distinctive pattern. First, therapy with intravenous antibiotics was initiated. Then, percutaneous drainage was performed; however there was no exudate. The patient remained febrile, even after undergoing these treatments. Meropenem was then administered intra-arterially, and intravenous or intra-arterial antibiotics were administered for three weeks total; however, the fever continued and the CRP level rose to 18 mg/dL.

Therefore, further evaluations were conducted. The levels of tumor markers at that time were as follows: alfa fetoprotein (AFP): 559 ng/mL, AFP-L3 fraction: 51.3% and protein induced by vitamin K absence or antagonist II (PIVKA II): 78 mAU/mL. A needle biopsy was performed; however the tissue was found to be necrotic. Sonazoid-enhanced ultrasonography detected a vessel flowing in the tumor in the early phase that was not enhanced in the late phase (Fig. 1). Angiography and CT under angiography revealed a large he-
The patient died of rupture of the para-esophageal lymph node metastasis. Paraesophageal lymph node metastasis of sarcomatous HCC was diagnosed using endoscopic ultrasonography-guided fine-needle aspiration. Chemotherapy with tegafur/gimeracil/oteracil potassium (S-1) and radiotherapy were administered; however the lymphadenopathy progressed. The chemotherapy regimen was then changed from S-1 to sorafenib. The progression of the lymphadenopathy continued; therefore, lymphadenectomy of the paraesophageal and retroperitoneal lymph nodes was performed 19 months after hepatectomy. The resected lymph nodes exhibited the same histologic characteristics as the liver tumor described above. The patient died of rupture of the para-esophageal lymph node into the esophagus 26 months after undergoing hepatectomy.

Table. Laboratory Data on Admission

<table>
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<tr>
<th>WBC</th>
<th>8200</th>
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<th>γ-GTP</th>
<th>37</th>
<th>IU/L</th>
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<td>/mm&lt;sup&gt;3&lt;/sup&gt;</td>
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<td>52</td>
<td>IU/L</td>
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<td>Cr</td>
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<td>%</td>
<td>BUN</td>
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<tr>
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<td>12.5×10&lt;sup&gt;12&lt;/sup&gt;</td>
<td>/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>CRP</td>
<td>12.5</td>
<td>mg/dl</td>
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<tr>
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<td>%</td>
<td>GHu</td>
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<td>HbAg</td>
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<td>mg/dl</td>
<td>HCVRNA</td>
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<tr>
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Discussion

Fever has long been recognized to be a symptom of malignant disease. Malignant diseases with pyrexia include malignant lymphoma, acute leukemia, sarcoma and renal cell carcinoma. Generally, HCC is often asymptomatic. Fatigue, abdominal distention and low-grade fever are sometimes observed with HCC due to a deterioration of the liver function. A high-grade fever as a primary symptom of HCC is extremely rare.

Okuda et al. (1) reported the cases of five patients with HCC who presented with pyrexia and leukocytosis that mimicked liver abscesses and concluded that the fevers could have been caused by a pyrogen produced by malignant cells or macrophages in response to necrosis. Yeh et al. (2) reported that HCC is a pyogenic liver abscess, and suggested that the pathogenesis of HCC involves either spontaneous liquefied necrosis of the tumor interior or biliary obstruction caused by tumor fragments. Masaki et al. (3) reported a similar case of HCC involving central necrosis due to rapid growth that had impaired the intrahepatic biliary duct and resulted in an infection of the tumor.

Fever is the most common symptom of paraneoplastic syndrome. The pathophysiology of paraneoplastic syndrome is complex and intriguing. Antibodies to tumor cells may cause a paraneoplastic disorder. In other cases, paraneoplastic syndrome results from humoral factors produced by cancer cells. Interleukin-8 (IL-8), interleukin-6 (IL-6) and granulocyte-colony stimulating factor (G-CSF) have been reported to be humoral factors related to fevers associated with HCC.

Akiba et al. (4) reported the expression of IL-8 in HCC to be accompanied by rapid tumor growth and a poor prognosis. Wigmore et al. (5) reported that the presence of IL-8 results in dose-dependent increases in the CRP level. HCC patients with a high IL-8 expression have a significantly higher frequency of venous invasion, portal vein invasion and bile duct invasion than HCC patients with a low IL-8 expression (4). Patients with G-CSF-producing HCC commonly have a very poor prognosis with rapid tumor growth and a high probability of distant metastasis (6-8). It has been reported that coproduction of G-CSF and IL-6 is associated with the production of IL-1, a known inflammatory cytokine, in G-CSF-producing cancer cell lines (9). IL-6 is considered to act as an endogenous pyrogen (10, 11) that regulates the synthesis of acute phase proteins, including CRP (12). HCC that produces humoral factors exhibits more rapid tumor growth and has a higher probability of distant metastasis.

A small number of cases of sarcomatous HCC with concomitant pyrexia have so far been reported (1, 13). The incidence of accompanying sarcomatous changes in HCC is relatively low: in one study of 350 HCC autopsies, sarcomatous changes were found in only 3.9% of these cases (14). In most cases of HCC with a sarcomatous appearance, the
serum AFP levels have been reported to be low or negative and the incidence of extrahepatic metastasis has been reported to be higher than that observed in usual HCC (14-17). Sarcomatous HCC reportedly shows invasive and sinusoidal growth patterns without fibrous capsules (14). This could be a reason for the high incidence of extrahepatic metastases in cases of sarcomatous HCC. Sarcomatous HCC is known to exhibit central necrosis and hemorrhage.

Figure 1. Sonazoid-enhanced ultrasonography. a) The inflowing artery in the early vascular phase (arrow). b) The tumor was not enhanced in the post-vascular phase.

Figure 2. Angiographic findings and computed tomography (CT) under angiography. a) No tumor stains were observed. b) CT under superior mesenteric artery (SMA) angiography revealed a lack of left portal vein enhancement. c) CT under hepatic angiography revealed marginal, irregular, low-intensity enhancement of the tumor and a tumor thrombus from the left hepatic vein to the inferior vena cava.

Figure 3. Microscopic findings of the resected specimen. a) Hematoxylin and Eosin (H&E) staining, ×100 magnification. b) H&E staining, ×400 magnification. A poorly differentiated, compact type, sarcomatoid hepatocellular carcinoma.
more frequently than the more common types of HCC. Since sarcomatous HCC consists of very poorly differentiated cells and grows rapidly, it is conceivable that the neo-
vasculature cannot adequately nourish the fast-growing ma-
lignant cells, which leads to necrosis (1). This feature has
been clearly demonstrated on CT. In the present case, the
periphery of the tumor exhibited ring-like enhancement and
was shown to consist of viable cancerous tissue with a fi-
brous stroma. The imaging findings of the internal unen-
hanced region corresponded primarily with coagulation ne-
crosis and hemorrhage. Such enhancement patterns on en-
hanced CT can represent metastases, intrahepatic cholangio-
carcinomas or liver abscesses. In this case, the patient had
a high fever and elevated CRP levels, and a hypovascular re-
gion was observed on enhanced CT. Therefore, a liver ab-
scess was initially diagnosed. However, it is possible that G-
CSF or one of the other humoral factors described above
was produced by the tumor and caused the fever and eleva-
tion of the CRP level observed in the present case, although
this was not revealed on immunohistochemistry or by meas-
uring the serum cytokine levels.

For treating sarcomatous HCC, a surgical resection should
be considered because this type of tumor is resistant to
transarterial embolization therapy (16). This type of tumor
is also associated with a very poor prognosis due to its rapid
growth and quite low resectability (18). Kakizoe et al. (14)
reported that the mean survival time from the appearance of
initial symptoms is 4.7 months. Regarding the surgical prog-
nosis, Maeda et al. (19) reported that eight of 13 patients
with surgically resected cases of sarcomatous HCC died of
the disease within one year of undergoing surgery. The ef-
effects of chemotherapy on sarcomatous HCC remain uncer-
tain. The SHARP Investigators Study Group (20) showed
that treatment with sorafenib prolongs the median survival
time and the time to progression by nearly three months in
patients with advanced HCC. In the present case, chemo-
therapy with sorafenib was administered.

The present patient survived for more than two years
from the initial appearance of symptoms. The relatively long
survival time could have occurred, because the tumor was
completely resected with no intrahepatic or distant metasta-
ses. In addition, the patient received multidisciplinary ther-
apy (chemotherapy, radiotherapy, and lymphoadenectomy)
after the recurrence of the sarcomatous HCC. In conclusion,
we herein described a case of sarcomatous HCC involving
remittent fever that was initially diagnosed as a liver ab-
scess.

The authors state that they have no Conflict of Interest (COI).

References
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