Malignant Hepatic Epithelioid Hemangioendothelioma with Abdominal Pain due to Rapid Progression

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Abstract

Hepatic epithelioid hemangioendothelioma (HEH) is a rare tumor. We report on a patient who underwent hepatectomy for malignant HEH associated with abdominal pain due to rapid progression. An 83-year-old man was admitted to Nippon Medical School Hospital because of acute, severe upper abdominal pain. Seven months before admission, a hepatic tumor, 3 cm in diameter, had been detected in the left lateral sector. The diagnosis was hepatic cavernous hemangioma. Abdominal ultrasonography revealed a heterogeneous hyperechoic tumor with a smooth border, 6 cm in diameter, in the left lateral sector (segment 3). Contrast-enhanced computed tomography of the abdomen showed that the tumor was enhanced from the early to the late phase. Abdominal angiography revealed a cotton wool-like appearance of the tumor. The diagnosis was hepatic cavernous hemangioma. A malignancy could not be ruled out because of the tumor’s rapid growth, which had caused abdominal pain. Left hepatectomy was performed. Histopathological examination showed necrosis throughout the tumor. Slightly pleomorphic neoplastic cells with rounded, spindle-like nuclei and scant cytoplasm were sporadically found in vascular channels. Intracytoplasmic lumina occasionally contained red cells. Neoplastic cells were positive for factor VIII-related antigen, CD31, and CD34. The Mib-1 index was high. The tumor was diagnosed as malignant HEH. The postsurgical course was uneventful, and the patient was discharged on postoperative day 11. After 3 months, multiple metastatic tumors appeared in right hepatic lobe. Transcatheter arterial chemoembolization was performed.
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Key words: epithelioid hemangioendothelioma, liver resection, recurrence
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Introduction

Epithelioid hemangioendothelioma, first reported by Weiss and Enzinger in 1982, is a rare borderline tumor composed of epithelioid, endothelial, or dendritic cells. Its estimated prevalence is 1 per 1,000,000 in the general population. Epithelioid hemangioendothelioma is not specific to soft tissue and has occurred in other organs, such as the lung, liver, bone, brain, heart, salivary gland, veins, and pleura. Hepatic epithelioid hemangioendothelioma (HEH) is a rare tumor that was first described by Ishak et al. in 1984. The most common symptoms of HEH are upper abdominal pain and weight loss, but in most patients HEH is asymptomatic and found incidentally.

We report on a patient who underwent hepatectomy for malignant HEH associated with abdominal pain due to rapid progression.

Case Report

An 83-year-old man was admitted to Nippon Medical School Hospital because of acute, severe upper abdominal pain. Seven months before admission, a hepatic tumor, 3 cm in diameter, had been detected in the left lateral sector. The diagnosis was hepatic cavernous hemangioma. The medical history was not relevant to the present disorder. Initial laboratory tests revealed a serum hemoglobin concentration of 11.7 g/dL (normal, 14 to 17 g/dL) and a serum platelet count of 10.4 × 10^4/μL (normal, 12 to 38 × 10^4/μL). The serum concentration of carcinoembryonic antigen was 0.6 ng/mL (normal, <2.5 ng/mL), that of PIVKA-2 was 18 mAU/mL (normal, <37 mAU/mL), and that of alpha-fetoprotein was 45.9 ng/mL (normal, <10 ng/mL). Serum surface antigens for hepatitis B and anti-hepatitis C virus antibodies were negative.

Abdominal ultrasonography revealed a heterogeneous hyperechoic tumor with a smooth border, 6 cm in diameter, in the left lateral sector (Segment 3) (Fig. 1). Contrast-enhanced computed tomography of the abdomen showed that the tumor was enhanced from the early to the late phase (Fig. 2).

![Fig. 1 An abdominal ultrasonographic image showing an nonhomogeneous tumor with a smooth border in the left hepatic lobe (segment 3). The tumor was 6.0 cm in diameter.](image)

![Fig. 2 A contrast-enhanced computed tomographic scan of the abdomen, showing that the tumor was enhanced from the early phase (a: arrow) to the late phase (b: arrow).](image)
Abdominal angiography revealed a cotton wool-like appearance in the tumor (Fig. 3). The tumor was diagnosed as malignant HEH. The postsurgical course was uneventful, and the patient was discharged on postoperative day 11. After 3 months, multiple metastatic tumors appeared in the right hepatic lobe. Transcatheter arterial chemoembolization was performed.

**Discussion**

HEH is a rare vascular tumor often mistaken for a carcinoma. The prevalence of HEH is unclear. HEH has been associated with oral contraceptives, vinyl chloride, polyurethane/silicone, the contrast agent Thorotrust, primary biliary cirrhosis, and hepatitis B virus, but the etiology of HEH remains uncertain. Although primary hepatic HEH is considered a low-grade malignant neoplasm, its clinical course is highly unpredictable; some patients die within weeks after diagnosis, whereas others survive for prolonged periods despite no active treatment.

HEH is usually detected incidentally and is asymptomatic in 22% to 25% of patients. The most frequent clinical manifestations are nonspecific and include abdominal pain, weight loss, epigastric mass, ascites, nausea, jaundice, liver failure, Budd-Chiari syndrome, and portal hypertension. At the time of diagnosis, most patients (87%) have bilarobar disease, and extrahepatic involvement is frequent (36.6%).

Our patient had acute severe upper abdominal pain due to rapid progression of the tumor, but only the left lobe was involved.

Imaging studies play an important role in the diagnosis of HEH. On ultrasonography, a hypoechoic pattern is found in the majority of cases (66.3%). A heterogeneous pattern accounts for 22.5% of HEHs, whereas a hyperechoic and isoechoic pattern with a hypoechoic rim is rare. On non-contrast-enhanced computed tomography, hepatic HEHs appear as solid, nonhomogenously hypodense nodules with a ring-like, low-density border and a lower-density center. After administration of a contrast agent, the lesions show no enhancement or slight peripheral enhancement during the arterial phase, but a halo sign appears during the portal venous phase. A “capsular retraction” sign can occur near the lesions. Magnetic resonance imaging shows nonhomogenously hypointense lesions on T1-weighted images and nonhomogenously hyperintense lesions on T2-weighted images. Lesions show peripheral ring-like enhancement during the arterial phase and stronger enhancement during the portal venous phase, with some lesions having a “halo” sign.

In our patient, abdominal ultrasonography revealed a heterogenously hyperechoic tumor with a smooth border. On contrast-enhanced computed tomography the tumor was enhanced from the early to the late phase. Abdominal angiography revealed a cotton wool-like appearance of the tumor. The tumor was diagnosed to be a hepatic cavernous hemangioma. A malignant nature could not be ruled out because the tumor grew rapidly, causing abdominal pain.

The diagnosis of HEH must be confirmed through microscopic examination of tissue. Typical early histopathological features of HEH include an infiltrative growth pattern with preservation of the...
Fig. 4 Histopathological examination showed necrosis throughout the tumor. Slightly pleomorphic neoplastic cells with rounded, spindle-like nuclei and scant cytoplasm were sporadically found in vascular channels. Intracytoplasmic lumina occasionally contained red cells (hematoxylin and eosin, ×600) (a). Neoplastic cells were positive for factor VIII-related antigen (×600) (b), CD31 (×600), and (c), CD34 (×600) (d). The Mib-1 index was high (×400) (e).

Liver acinar architecture and portal tracts. The tumor is composed of epithelioid, dendritic, or intermediate cells in a fibromyxoid stroma. The epithelioid cells are characterized by abundant eosinophilic cytoplasm and vesicular nuclei. Intracytoplasmic lumina, occasionally containing red cells, are common. The center of the tumor becomes sclerotic with neoplastic cells entrapped within regions of increased fibrosis. At the periphery, the tumor cells tend to infiltrate pre-existing sinusoids, terminal hepatic venules, and portal vein branches25. Endothelial differentiation was demonstrated by immunohistochemical staining for factor VIII-related antigen, CD34, and CD3125. In the present case, immunohistochemical staining for endothelial cell markers, such as factor VIII-related antigen, CD34,
and CD31, was consistently positive. In addition, the Mib-1 index exceeded 50%. Malignant HEH was therefore diagnosed.

There is no standard treatment for HEH, because of its rarity. Current treatments for HEH include liver transplantation (44.8%), chemotherapy or radiotherapy (21%), and liver resection (9.4%); 24.8% of patients with HEH receive no treatment\(^1\). Resection for localized lesions, even extended hepatic lobectomy, is generally accepted procedure\(^5\). For patients with no metastases, orthotopic liver transplantation may be justified as another potentially curative procedure\(^6\). Tumor resection is possible in only a limited number of cases because most HEHs are multiple and nodular or diffuse. In recent years, most cases have been treated with liver transplantation\(^7\). However, some patients have had rapid tumor recurrence in liver grafts after transplantation\(^8\). In our patient, the tumor was solitary and had not metastasized outside the liver. However, postoperative chemotherapy with such drugs as doxorubicin and 5-fluorouracil has been recommended for patients with extrahepatic disease\(^9\). We performed left hepatectomy, but after only 3 months, multiple metastatic tumors appeared in the right hepatic lobe, and transcatheter arterial chemoembolization was performed. The 5-year survival rates of patients who undergo liver resection (75%) or transplantation (54.8%~75%) are significantly higher than those of patients who received other treatments (30%). The 5-year survival rate of patients given no treatment was only 4.5% after a mean follow-up of 26 months\(^10\). Drugs such as interferon have been used in combination with hepatic resection or transplantation in some patients and have successfully prevented or reduced the rate of metastasis\(^11\).

The clinical outcomes of HEH are unpredictable\(^12\). The prognosis of HEH ranges from favorable with prolonged survival, even without therapy, to rapid progression with a fatal outcome\(^12\). In patients who have received no treatment or have undergone orthotopic liver transplantation with positive lymph nodes or vascular invasion\(^13\), long-term survival and even spontaneous regression of the lesions have been reported\(^14\). In contrast, the tumor may rapidly progress, leading to liver failure and death\(^15\). The prognosis of HEH usually is much more favorable than that of angiosarcoma: prolonged survival (5~28 years) has been reported after surgical resection or liver transplantation. Makhlouf et al have reported that in a series of 60 patients with HEH, the rate of metastasis was 27%. Survival ranged from 4 months to 28 years; 43% of their patients (26 of 60 patients) survived for more than 5 years\(^16\). Due to the rarity and the unpredictable course of HEH, early diagnosis and curative therapy are imperative. In conclusion, malignant HEH should be suspected when a hepatic tumor resembling a cavernous hemangioma progresses rapidly.

**References**

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