Malignant Hepatic Epithelioid Hemangioendothelioma with Rapid Progression and Fatal Outcome

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Abstract

A 46-year-old woman was admitted to our hospital because of pain in the right upper quadrant and dyspnea. Abdominal and chest computed tomography (CT) scans revealed areas of low attenuation in both hepatic lobes, left pleural effusion, and multiple nodules in both lungs. Laboratory data indicated disseminated intravascular coagulation. She developed rapidly progressive respiratory and hepatic failure despite intensive treatment including mechanical ventilation and died of respiratory failure 3 weeks after admission. Immunohistochemical analysis of liver necropsy and cytology of the left pleural effusion stained positive for factor VIII-related antigen and CD31. Based on these observations, a diagnosis of hemangioendothelioma (EHE), a rare vascular tumor, was made. A rapid clinical course and fatal outcome, as in the present case, are rare clinical manifestations in EHE.

Key words: hepatic epithelioid hemangioendothelioma, pulmonary metastasis, disseminated intravascular coagulation, acute respiratory distress syndrome, vascular tumor

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Introduction

Epithelioid hemangioendothelioma (EHE) is a rare vascular tumor of intermediate behavior that can arise from various sites, including the liver, spleen, bone, soft tissue, and lungs (1-7). EHE usually affects adult women, and its malignant potential ranges between benign hemangioma and obviously malignant hemangioendotheliosarcoma (5-7). The clinical progression of EHE is usually slow. Here, we report a patient with rapidly progressive disease involving the liver and lungs with fatal outcome 4 months after symptom onset.

Case Report

A 46-year-old woman was admitted to hospital with a 3-month history of gradually increasing general fatigue and pain in the right upper quadrant. She had undergone a hysterectomy due to uterine myoma at 45 years of age, but had no other history of abnormal laboratory or chest X-ray findings. Laboratory examinations on admission revealed liver dysfunction and chest X-ray showed pleural effusion on the left side (Fig. 1). A few days after admission, she developed dyspnea with hypoxemia and a diagnosis of acute respiratory failure was made. The patient was then transferred to Shinshu University Hospital for further examination and treatment.

Her vital signs upon admission were: body temperature, 38.3°C; pulse rate, 120 beats/min; blood pressure, 142/68 mmHg; SpO₂, 86% during breathing oxygen at 10 L/min. Physical examination revealed reduced breath sounds in the lower left lung and hepatomegaly with tenderness (3 finger widths below the right costal margin with a firm and irregular surface). Chest X-ray showed increased left pleural effu-
sion compared with the findings at the hospital she initially attended seven days previously (Fig. 2a). Chest computed tomography (CT) revealed multiple nodules with diameters ranging from 3 to 20 mm with ground-glass opacity in both lung fields suggesting the presence of pulmonary edema (Fig. 2b). In addition, increased left pleural effusion was observed (Fig. 2c). Abdominal CT confirmed hepatomegaly and revealed areas of low density in the right anterior segment of the liver (Fig. 3). The tumor area revealed relatively low density compared with the normal area of liver in all phases. Laboratory findings were as follows: white blood cell count, 19,120/dL; hemoglobin, 9.7 g/dL; platelet count, 5.0×10⁴/dL; C-reactive protein, 10.83 mg/dL; total protein, 6.0 g/dL; total bilirubin, 1.84 mg/dL; lactate dehydrogenase, 438 U/L; aspartate aminotransferase, 167 U/L; alanine aminotransferase, 270 U/L; blood urea nitrogen, 21 mg/dL; and creatinine, 0.26 mg/dL. Coagulation examination revealed disseminated intravascular coagulation (DIC): prothrombin time, 17.8 s; activated partial thromboplastin time, 28.5 s; fibrinogen, 329 mg/dL; and fibrinogen degradation product D dimer 12.0 μg/mL. Serum tumor markers were normal. Arterial partial oxygen tension was 42.0 torr while breathing using an oxygen mask at 10 L/min.

The patient was treated immediately with mechanical ventilation and intravenous sivelestat sodium hydrate for acute respiratory failure. In addition, continuous infusion of ga-

![Figure 1](image1.png)

**Figure 1.** Chest X-ray showed slight pleural effusion on the left side.

![Figure 2](image2.png)

**Figure 2.** Chest X-ray showed increased left pleural effusion compared with that detected in the first hospital and infiltrative shadow in both lower lung fields (a). Chest CT scan showing multiple and nodules with diameters ranging from 3 to 20 mm in both lungs (b) and pleural effusion on the left side (c).

![Figure 3](image3.png)

**Figure 3.** Abdominal CT scan showed hepatomegaly and a diffusely expanded low-density area in right anterior segment of the liver.
Figure 4. Pathological findings from open liver necropsy. (a) Microscopy showed slightly pleomorphic neoplastic cells with rounded nuclei and scant cytoplasm occasionally arranged in vascular channels. The cytoplasm included many vacuoles containing erythrocytes (Hematoxylin and Eosin staining; ×400). (b) Partial necrosis of the tumor (Hematoxylin and Eosin staining, ×200). (c) Tumor cells immunostained with antibody to factor VIII-related antigen (factor VIII-related antigen; ×100) and (d) CD31 (×100).

Figure 5. Malignant cells in pleural effusion immunostained with antibody to CD31 (×60).

bexanemesylate and heparin was also started for DIC. Left pleurocentesis showed bloody and exudative effusion and cytological analysis revealed malignant cells. However, the origin was still unknown. The respiratory and hepatic failure progressed despite intensive therapy and the patient died of respiratory failure on the 21st hospital day after admission to our institution.

Liver necropsy was performed with written informed consent from the patient’s family. We cut an opening of about 3×3×2 cm from the right lobe of the liver. Microscopy showed slightly pleomorphic neoplastic cells with rounded nuclei and scant cytoplasm occasionally arranged in vascular channels, and several intracytoplasmic vacuoles containing erythrocytes. Necrosis and inflammatory cell infiltration were present to some extent (Fig. 4a and b). Histological and immunohistochemical staining showed that the tumor cells were positive for the endothelial marker factor VIII-related antigen and CD31 (Fig. 4c and d, factor VIII-related antigen and CD31, respectively). A diagnosis of EHE was made based on these findings. In addition, malignant cells in the pleural effusion were also positive for CD31 (Fig. 5). These findings indicated that the patient died as a result of EHE involving the liver and pleura.

Discussion

We described a case of hepatic EHE with rapid progression and fatal outcome. In this case, multiple pulmonary metastasis and DIC were associated with the initial clinical presentation. Weiss and Enzinger proposed the term EHE in 1982 to describe a group of 41 soft tissue vascular tumors of endothelial origin (1). The clinical course of the disease was highly variable and intermediate between benign hemangioma and angiosarcoma (1). The liver is an important site of EHE, but EHE has also been identified in other sites,
Hepatic EHE was first reported in 1984 by Ishak et al (2) in a series of 32 cases, which was followed by several review articles (6, 7). Hepatic EHE develops mainly in adults, with a higher prevalence in women (woman : man ratio, 1.6-2.0: 1) (6, 7). The main clinical symptoms are right upper quadrant pain (45%-48.6%) or weight loss, but the clinical manifestations are usually nonspecific and asymptomatic (2, 6, 7). The patient described here, a woman, initially presented with pain in the right upper quadrant, consistent with other reports (2, 6, 7).

The radiological features of hepatic EHE have been discussed in several reviews (8, 9). The tumor begins as hepatic nodules that grow and coalesce, forming large confluent masses preferentially involving the liver periphery. Extensive hepatic involvement is associated with enlargement of uninvolved portions of the liver and splenomegaly (8). Furui et al suggested that nodular lesions may be an earlier form of hepatic EHE, as they gradually become diffuse (9). Mehrabi et al reported that the majority of patients had enhancement, whereas no enhancement and irregular enhancement were the other reported patterns (7). In addition, the metastatic rate during the clinical course of hepatic EHE is 27% (6). The most frequent site is the lung at a rate of 81%, followed by abdominal lymph nodes (39%), omentum and mesentery (31%) in patients with EHE (6). The most characteristic feature in metastatic pulmonary lesions on chest radiograph or CT images is the presence of multiple nodules with well- or ill-defined margins ranging up to 2 cm in diameter (9, 10). The radiographic findings in both liver and lungs in the present case were compatible with hepatic EHE and multiple pulmonary metastases. Although the histological diagnosis of intrapulmonary metastasis was not definitive, pleural involvement was confirmed in the present case. Based on these histological and radiographic findings, the present case had primary hepatic EHE and metastatic intrapulmonary and pleural dissemination.

The clinical course in hepatic EHE reported in the literature is quite variable. In general, the progression of hepatic EHE is slow and surgical resection or liver transplantation is recommended if possible. The 5-year overall survival rate of patients with hepatic EHE varies from 43%-55%, which is significantly better than those for other hepatic malignancies (5, 6). However, the progression of hepatic EHE is unpredictable. Makhlouf et al reviewed 60 cases of hepatic EHE available for analysis of follow-up data after diagnosis and reported a median survival period of 51 months ranging from 4 months to 336 months after diagnosis (6). In the literature, a detailed clinical course in a patient with the minimum survival period of 4 months was not reported. Several case reports have described a rapid course and fatal outcome after onset of symptoms in hepatic EHE (11-13). Dean et al reported a 43-year-old woman with fulminant abdominal pain who died within one month after the clinical inset (11). Terg et al also reported a 28-year-old man with abdominal pain and cholestasis who died within 6 months of symptom onset (12). Thus, the clinical course and prognosis of hepatic EHE are quite variable. The patient described here died within 4 months of the onset of symptoms, which is an extremely rare clinical course in hepatic EHE. In particular, the initial clinical manifestation was associated with DIC. Imanishi et al described a fatal case of relapsed hepatic EHE after resection associated with thrombocytopenia and consumption coagulopathy (14). However, the frequency of DIC complications during the clinical course of EHE remains unclear. It is well known that the existence of DIC contributes to the development of acute respiratory failure as well as multiple pulmonary metastasis (15). Thus, we feel that the development of DIC contributed to the fatal outcome in the present case.

The definitive diagnosis of EHE is determined by histological staining. Some vascular tumors are unique in that they are composed of large endothelial cells with abundant eosinophilic cytoplasm and well-defined margins that mimic epithelial cells. These cells form large groups within small veins and sinusoids and can also develop a vascular lumen in their cytoplasm in which red blood cells become lodged. Hepatic or tumoral tissue around the affected vessels can show atrophic changes. The rest of the hepatocytes can take the form of nests, cords, or even tubular structures. These neoplastic cells express normal endothelial cell markers, typically the factor VIII-related antigen, CD31, and/or CD34 (6). Neoplastic cells obtained from the present patient were obviously positive for factor VIII-related antigen and CD31.

In summary, we described a case of hepatic EHE initially presenting with multiple pulmonary metastasis and DIC. The overall clinical course after the onset of symptoms was about 4 months, which was an extremely rapid and fatal outcome. We emphasize the possibility of disseminated and rapid clinical manifestations of hepatic EHE.

References

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