Malignant epithelioid hemangioendothelioma is a rare hepatic tumor of vascular origin. It is most commonly found in young to middle-aged women, and the tumors vary in their reported potential for malignancy. The etiologic factors are not yet clear, and some investigators have suggested an association with oral contraceptives, whereas others have noted an association with exposure to vinyl chloride, asbestos, thorotrast, major trauma to the liver, viral hepatitis, primary biliary cirrhosis, and alcohol consumption. The clinical manifestations are nonspecific, and most are asymptomatic. Among symptomatic patients, the most common symptom is right upper quadrant pain, followed by jaundice, weight loss, fatigue, ascites, hepatomegaly, and fever. The only definitive diagnosis requires immunohistochemical evidence of endothelial differentiation, which is demonstrated by the presence of factor VIII-related antigen and cytokeratins. As with most mesenchymal tumors, surgical resection is the most effective means of controlling local disease and preventing distant metastasis, although adjuvant therapies have been offered for patients with unresectable tumors or who are not transplant candidates. We present the case of an elderly man with a hepatic malignant epithelioid hemangioendothelioma, and we reviewed the English-language literature. [International Journal of Gerontology 2009; 3(3): 188–191]

Key Words: epithelioid hemangioendothelioma, factor VIII-related antigen, liver neoplasms, liver transplantation, surgery

Introduction

Malignant hepatic tumors, including hepatocellular carcinoma, cholangiocarcinoma, metastatic carcinoma, often occur in the elderly population, and the mortality of the malignancy usually increases with age. However, one rare hepatic tumor, epithelioid hemangioendothelioma (EHE), is a malignant tumor which primarily affects middle-aged adults (30–40 years), predominantly women1. It is a neoplasm of vascular origin with unknown etiology and has a variable clinical course. Several cases have been reported in other organs such as lung, bone marrow, and head and neck, and have been described by various other names such as intravascular bronchiolar and alveolar tumor of the lung, sclerosing angiogenic tumor, sclerosing endothelial tumor, sclerosing interstitial vascular tumor, and sclerosing epithelioid angiosarcoma2–9. Here, we present an elderly male patient who was incidentally found to have this unusual hepatic tumor.

Case Report

A 66-year-old man was hospitalized with a hepatic tumor discovered incidentally from sonography, which revealed one hypoechoic lesion of about 3 cm in diameter at the
S6 segment of the liver. He had chronic hepatitis B without regular follow-up for 10 years. He denied fever, fatigue, jaundice, abdominal pain, or weight loss. Physical examination on admission revealed a flat, soft and non-tender abdomen without hepatosplenomegaly. Ascites and other stigmata of chronic liver disease were absent. His aspartate aminotransferase was 63 IU/L (normal, 5–35 IU/L), alanine aminotransferase 57 IU/L (normal, 5–30 IU/L), alkaline phosphatase 129 IU/L (normal, 40–120 IU/L), and total bilirubin 1.1 mg/dL (normal, 0.2–1.3 mg/dL). All other results, including complete blood cell counts, electrolyte concentrations, renal function and albumin concentration, were within normal limits. Tumor marker analysis revealed: CA 19-9, 12.18 U/mL (normal, < 30 U/mL); carcinoembryonic antigen, 1.0 ng/mL (normal, < 5 ng/mL); prostate specific antigen, 2.29 ng/mL (normal, < 5.36 ng/mL); and α-fetoprotein <2.76 ng/mL (normal <6 ng/mL). Abdominal computed tomography showed a hypoattenuating mass measuring 3 cm in diameter, localized in the S6 segment (Figure 1). It also showed low attenuation in the arterial, portal and late venous phases. Another small nodule was found in the right lower lung field. Chest computed tomography revealed multiple, small, well-defined nodules scattered throughout the periphery of both lungs (Figure 2). Echo-guided biopsy of the hepatic tumor revealed EHE in portal areas mixed with benign hepatocytes. The tumor cells revealed epithelioid pink cytoplasm and some contained cytoplasmic red blood cells (Figure 3). The tumor stains were positive for vimentin, CD34, CD31, and factor VIII related-antigen (Figure 4). Because of the diagnosis of hepatic EHE with pulmonary metastasis, the patient was started on combination chemotherapy comprising cisplatin (50 mg/m²), doxorubicin (50 mg/m²) and cyclophosphamide (500 mg/ m²), all given on day 1 and repeated every 21 days. A total of six cycles of chemotherapy was given, and repeated computed tomography of the thorax and whole abdomen showed no difference in the nodules. During the 17 months after the last course of chemotherapy, he did not suffer from any discomfort.

Discussion

The term epithelioid hemangioendothelioma was first described as a distinct entity by Weiss and Enzinger in 1982, for a group of 41 soft-tissue vascular tumors of endothelial origin, with unpredictable malignant
potential and intermediate histologic characteristics between hemangioma and angiosarcoma. However, primary malignant hepatic EHE is a rare tumor with an incidence of <0.1 per 100,000 population and was reported first in 1984 by Ishak et al. in a series of 32 patients. It has a variable natural course, ranging from a favorable disease with prolonged survival, even without therapy, to a rapidly progressive disease with a fatal outcome. In the largest reported series of 137 cases of liver EHE from the Armed Forces Institute of Pathology, the patients ranged in age from 12 to 86 years (median, 46 years) with 61% female and 39% male. In another review of published reports of 434 patients, the mean age was 41.7 years and female predominance (57.6%) was found. However, there was no significant difference in incidence between men (n = 16) and women (n = 18) of a 34-patient case study in Japan. This might be attributed to the increased use of oral contraceptives in other countries apart from Japan, which has governmental legal limitations on the use of such agents.

The clinical manifestations of hepatic EHE are nonspecific, and most are asymptomatic. Among symptomatic patients, the most common symptom was right upper quadrant pain. Other symptoms are uncommon and include jaundice, weight loss, fatigue, ascites, hepatomegaly, and fever. The etiologic factors are not yet clear, and some investigators have suggested an association with oral contraceptives, whereas others have noted an association with exposure to vinyl chloride, asbestos, thorotrast, major trauma to the liver, viral hepatitis, primary biliary cirrhosis, and alcohol consumption. However, hepatic EHE does not occur on a background of chronic liver disease or hepatitis, such as other types of tumors. In our patient, the only risk factor may be chronic hepatitis B, but it is an unclear one on current knowledge. In one reviewed report of 127 previously published cases, no positive correlation between EHE of the liver and any form of hepatitis could be confirmed. Only a few patients had positive results for hepatitis B surface antibody (5.6%), hepatitis B core antigen (11.5%), and hepatitis B surface antibody (11.5%). Two patients were found to have hepatitis C.

No reliable parameters, including tumor markers or imaging studies, have been identified to predict the biological behavior; therefore, the tumor is often misdiagnosed because of the pleomorphism of the tumor cells, together with the varied pattern of the tumors, as well as the parenchymal and stromal reactions. Approximately 60–80% of patients are initially misdiagnosed as having cholangiocarcinoma, angiosarcoma, hepatocellular carcinoma, metastatic carcinoma, or sclerosing hemangioma. In the 137-patient case series, most patients (82%) had multiple liver nodules generally in both lobes which differed greatly in size (0.2–14 cm). In a review of the literature of 434 patients, 87% presented with a multifocal tumor which involved both liver lobes, whereas only 13% had a unifocal tumor. The right lobe was affected more than the left lobe in both multifocal and unifocal presentations. Thus, the correct diagnosis can be signaled by certain features: the occurrence in young adults; the presence of numerous intrahepatic tumors, yet a good clinical condition; the slow course of the disease; and the presence of intratumoral calcifications, an inconsistent but suggestive feature. However, our patient did not have the above features.

There are several diagnostic difficulties. First, the presentation is nonspecific; second, liver function tests may not become abnormal until the disease is advanced; third, ultrasound scans of the liver can be inconclusive; and, finally, computed tomography may lead to a misdiagnosis of metastatic disease because of the tumor’s multifocal nature. So the definitive diagnosis requires immunohistochemical evidence of endothelial differentiation, which is demonstrated by the presence of factor VIII-related antigen and cytokeratins, as in our case. Microscopically, these tumors have central densely sclerotic, hypocellular myxoid areas or occasional necrosis and peripheral cellular regions of epithelioid and/or dendritic cells. The tumor may extend along the sinusoids and display papillary intravascular growth into portal and hepatic veins. The epithelioid cells may have eccentric nuclei with cytoplasmic lumina.

Figure 4. Tumor cells strongly immunostained with antibody to factor VIII-related antigen (40×).
Hepatic epithelioid hemangioendothelioma

The management of hepatic EHE has been liver resection, liver transplantation, no treatment, chemotherapy, radiotherapy, and transcatheter arterial embolization. Because of the rarity of this tumor and its unpredictable natural history, it is impossible to assess the effectiveness of these therapies. Only retrospective studies and a review of the literature offer adequate information. Among these therapeutic modalities, liver resection has been the treatment of choice in patients with resectable EHE, resulting in prolonged survival. However, surgical resection is often impossible, owing to the frequent multicentric origin of the tumor.

Orthotopic liver transplantation has been proposed as the treatment of choice because of the hepatic multicentricity of the tumor, especially because it affects young adults who are usually in good physical condition; this is also an acceptable option for patients who have extrahepatic manifestations. Some patients survive for a long time despite no treatment, as reported in a few reports. In addition, one 75-year-old woman had complete spontaneous regression of hepatic EHE within a 20-month period. However, it has been impossible to predict hepatic EHE reliably in patients with non-aggressive tumors until now and to consider them for "no treatment" and a "wait-and-see" strategy. Although chemotherapy and radiotherapy have been used, it is not possible to assess their effectiveness because of the variable natural history of hepatic EHE and lack of prospectively collected data. Thus, the role of different adjuvant therapies for patients remains to be determined.

Our patient was treated with doxorubicin, cisplatin and cyclophosphamide; he had stable disease all through follow-up, but this might be a result of the highly indolent course of the disease. Transcatheter arterial embolization was reported as having a short-term benefit in a few cases; however, the number of patients was too small to estimate the benefit of this form of treatment.

Hepatic EHE is a rare tumor which primarily affects middle-aged adults (30–40 years), especially women. A smattering of cases still occur in the elderly, and concurrent multiorgan involvement has been noted. It has a variable natural course and nonspecific clinical manifestations, which may mimic metastatic hepatic tumors. No reliable parameters, including tumor markers or imaging studies, have been identified. The only definitive diagnosis requires immunohistochemical evidence of endothelial differentiation, which is demonstrated by the presence of factor VIII-related antigen and cytokeratins. In addition, liver resection has been the treatment of choice in patients with resectable EHE, resulting in prolonged survival. Thus, this rare hepatic tumor should be considered in the differential diagnosis of hepatic tumors in the elderly.

References