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Epithelioid hemangioendothelioma of the liver

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INTRODUCTION

Epithelioid hemangioendothelioma is an uncommon vascular tumor of intermediate malignant potential.[1-3] Hepatic epithelioid hemangioendothelioma (HEHE), a rare sarcoma of the liver, usually appears as multiple nodules involving both hepatic lobes, and can be misdiagnosed as metastatic carcinoma on the basis of its radiologic manifestations. HEHE is composed of neoplastic endothelial cells that closely resemble epithelial cells, and shows a characteristic zoning phenomenon. At the periphery, the tumor cells infiltrate preexisting sinusoids and terminal hepatic venules. The center reveals a marked desmoplastic stromal reaction with dense sclerosis, and these findings may mimic those of cholangiocarcinoma. Therefore, confirming that the tumor is of vascular origin using immunohistochemical staining for endothelial cell markers is critical for accurately diagnosing HEHE. In this issue, we present a case of HEHE in a 44-year-old woman and discuss the histopathologic findings.

CASE SUMMARY

A hepatic nodule was incidentally detected in a 44-year-old woman during an abdominal ultrasonography (US) in 2010. During the follow-up period, this hepatic nodule had grown in diameter from 1.7 cm to 4.9 cm. Clinical examination was unremarkable, and routine hematological and biochemical test results were within normal limits. Abdominal US showed a solitary 4.9-cm sized hypoechoic hepatic nodule in the subcapsular area of segment 5. This lesion was hypodense on computed tomography (CT), hyperintense on T2-weighted magnetic resonance imaging (MRI) (Fig. 1A), and hypointense on T1-weighted MRI (Fig. 1B). The lesion displayed concentric alteration in signal intensity, possibly corresponding to regions of different histology. A positron emission tomography-computed tomography (PET-CT). image showed moderate fluorodeoxyglucose (FDG) uptake. A sectionectomy was therefore performed and no obvious tumor recurrence was detected post-operatively during the 12-month follow-up period.

PATHOLOGICAL FINDINGS

Gross examination revealed a yellowish-white nodule with moderately hard consistency. It was relatively well defined, but had irregular margins and central fibrosis (Fig. 2A). Histologically, the tumor consisted of neoplastic endothelial cells resembling epithelial cells and showed a characteristic zonal pattern. The peripheral tumor cells grew along preexisting sinusoids and terminal he-

Abbreviations:

CT, computed tomography; FDG, fluorodeoxyglucose; HEHE, hepatic epithelioid hemangioendothelioma; MRI, magnetic resonance imaging; PET-CT, positron emission tomography-computed tomography; US, ultrasonography

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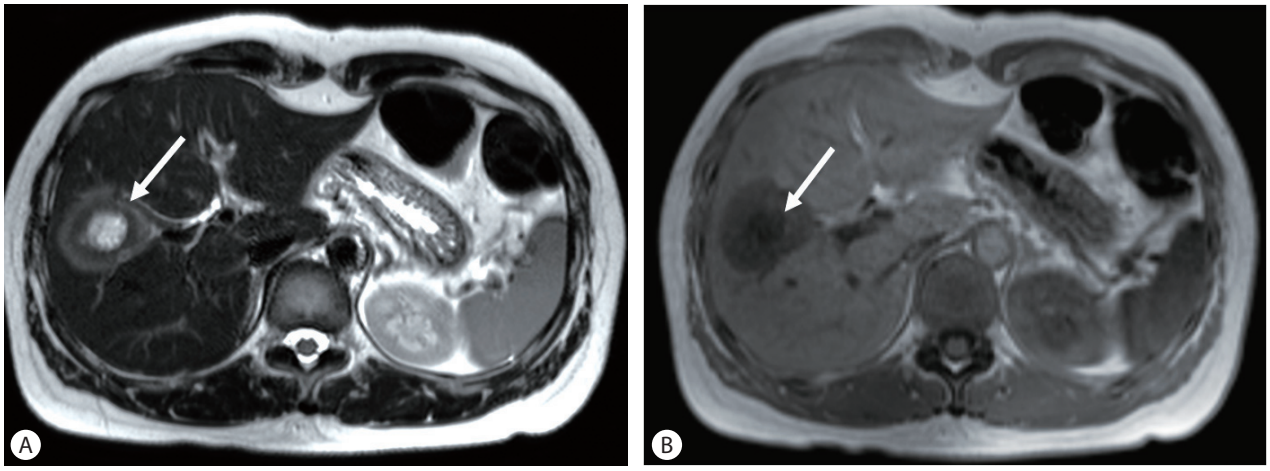

Figure 1. Magnetic resonance imaging findings. (A) Axial T2-weighted image shows high signal intensity in the central zone (arrow) and concentric alteration in signal intensity, corresponding to regions of different histology. (B) Axial T1-weighted image shows low signal intensity in the central sclerotic zone (arrow).

patic venules, and showed sinusoidal proliferation with polypoid or tuft-like projections (Fig. 2B, C). In contrast, the midzone demonstrated sinusoidal obliteration with marked atrophic hepatocyte plates in fibrous and myxochondroid stroma (Fig. 2B, D). The tumor cells were either epithelioid, dendritic, or intermediate. The epithelioid cells were rounded with abundant cytoplasm and atypical nuclei (Fig. 2C). The dendritic cells were irregular in shape with interdigitating processes, and some had intracytoplasmic vacuoles containing red blood cells, recapitulating primitive vascular channels (Fig. 2D). The intermediate cells were situated between the epithelioid and dendritic cell types. Immunohistochemically, the tumor cells expressed endothelial marers; factor VIII-related antigen, CD34 and CD31 (Fig. 3A, B). On the basis of these histological and immunohistochemical findings, the tumor was pathologically diagnosed as HEHE.

DISCUSSION

Epithelioid hemangioendothelioma is a distinctive vascular tumor occurring mostly in soft tissues of the extremities and various visceral organs. It was first described as a specific entity by Weiss and Enzinger in 1982.[4] Epithelioid hemangioendothelioma represents the most aggressive member of the hemangioendothelioma family of tumors, and is intermediate between hemangioma and angiosarcoma in terms of recurrence and metastatic potential.[5] Primary HEHE was first reported by Ishak et al in 1984.[1] A review of the literature for HEHE revealed less than 500 reported cases,[3] including about 20 cases from Korea. HEHE shows a slight female predominance (male-to-female ratio, 2:3), and usually occurs in middle-aged women (mean age, 41.7 years), as in our case,[3] but the causative factors are unknown. Some cases were associated with the use of oral contraceptive pills and these findings may explain the female predominance of HEHE; however, this relationship has not been validated.[3] Chronic liver disease is not considered a significant cause of HEHE. Clinically, 25% of the reported HEHE cases were asymptomatic and the most frequent symptoms were right upper quadrant abdominal pain, hepatomegaly, and weight loss.[3] Radiologically, HEHE presents with a multifocal nodular pattern in the early stage and the lesions coalesce and form an extensive mass in the advanced stage.[2,6] Most nodules are hypoechoic on US and hypodense on CT. These nodules appear hypointense on T1-weighted MRI images and hyperintense on T2-weighted MRI images, with a relatively hyperintense sclerotic zone. On PET-CT, HEHE shows moderate to intense FDG uptake.[7]

Macroscopically, HEHE lesions are usually multifocal with ill-defined nodules scattered throughout the liver. In the largest published case series, 87.3% of the HEHE cases were characterized by multiple lesions,[3] in contrast to our case, which had a solitary nodule. Most of the tumors are found in the subcapsular area and they may show typical central umbilication. HEHE acquired its name from tumor cells that consisted of endothelial cells resembling epithelial cells. Microscopically, the tumor cells grow along preexisting sinusoids with intervening collagenous fibrosis. They typically exhibit an intracytoplasmic lumina formation containing erythrocytes, which resembles signet ring-like structures, Howev-

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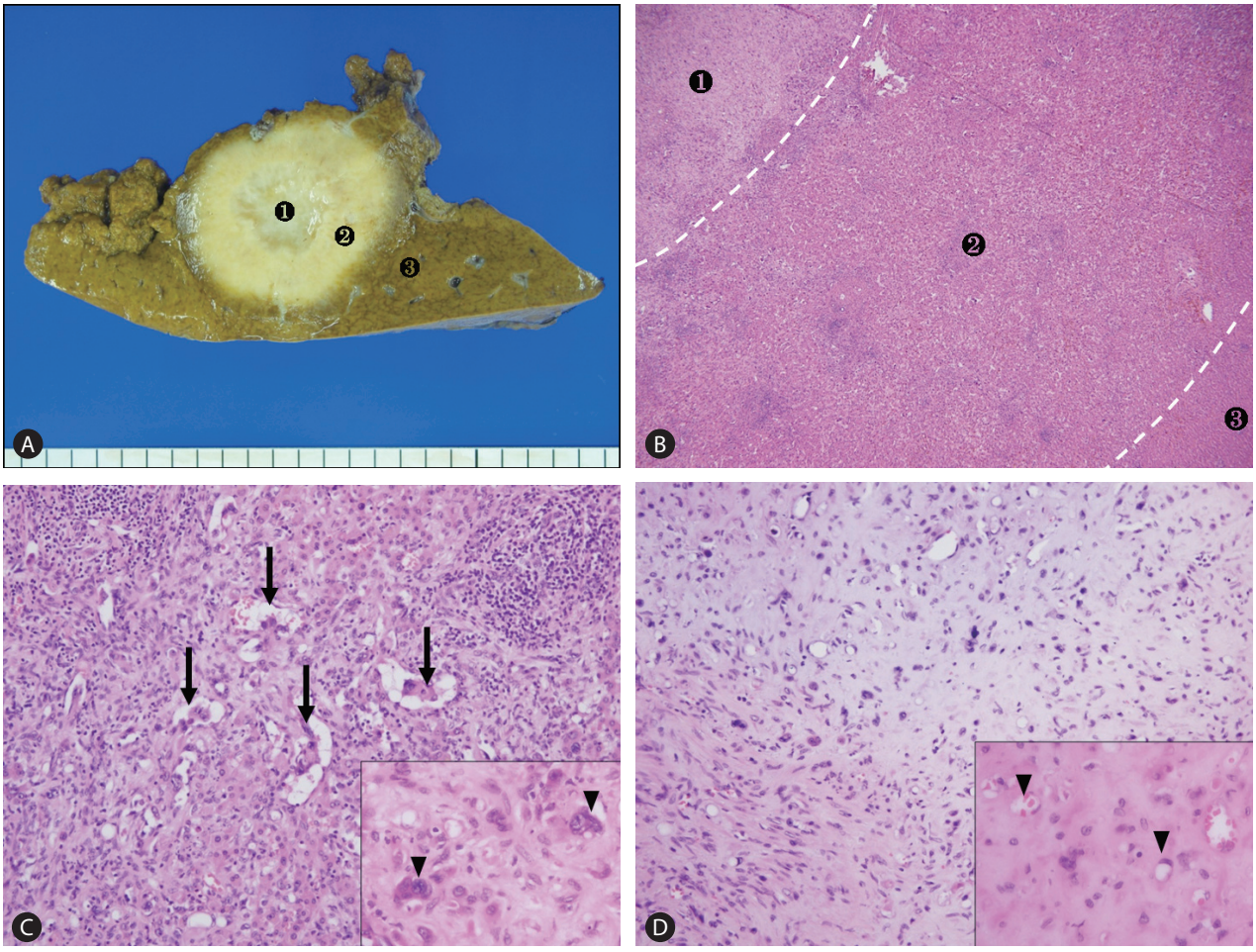

Figure 2. Macroscopic and histological examination. (A) The cut surface reveals a firm, yellowish-white mass with irregular margins and central fibrosis (No.1: central zone, No.2: peripheral zone, No.3: normal liver). (B) Histological findings correspond to the gross appearance of the tumor (No.1: central zone, No.2: peripheral zone, No.3: normal liver) (H&E, ×40). (C) At the peripheral zone, epithelioid tumor cells form polypoid projections (arrows) in dilated sinusoids, and epithelioid cells show atypical nuclei with prominent nucleoli (inlet, arrowheads) (H&E, ×200). (D) At the central zone, the dendritic tumor cells are embedded in myxochondroid and sclerotic stroma. Characteristically, the tumor cells have intracytoplasmic vacuoles containing red blood cells, which resemble signet ring-like structures (inlet, arrowhead) (H&E, ×200).

er, mucin staining always shows negative result. HEHE is comprised of 3 types of cells, namely, epithelioid, dendritic, or intermediate cells. Epithelioid cells are round with abundant eosinophilic cytoplasm and may contain atypical nuclei with prominent nucleoli. Dendritic cells are spindle shaped with multiple interdigitating processes and may also contain intracytoplasmic vacuoles, representing intracellular vascular lumens. The third cell type, intermediate cells, is morphologically intermediate between the other 2 cell types. HEHE sometimes shows a characteristic zonal patterning of histological changes, as in our case. The periphery shows sinusoidal proliferation with polypoid or tuft-like projections of epithelioid cells with moderate nuclear atypia. Central scars have sinusoidal obliteration with atrophic hepatocyte plates in sclerotic stroma and contain dendritic cells with slight nuclear atypia. The tumor sometimes reveals a marked desmoplastic stromal reaction with dense sclerosis and contains only scanty tumor cells. Needle biopsy specimens taken from such areas often pose the risk of misdiagnosis. The histopathological differential diagnosis includes angiosarcoma, cholangiocarcinoma, and signet ring cell carcinoma. Histologically, angiosarcoma is much more destructive than HEHE and obliterates acinar landmarks with extensive hemorrhage, although HEHE and angiosarcoma have similar immunoprofiles. Cholangiocarcinoma and signet ring cell carcinoma may mimic HEHE histologically, although these tumor cells express epithelial markers but not endothelial markers. The use of immunohistochemistry for endothelial markers

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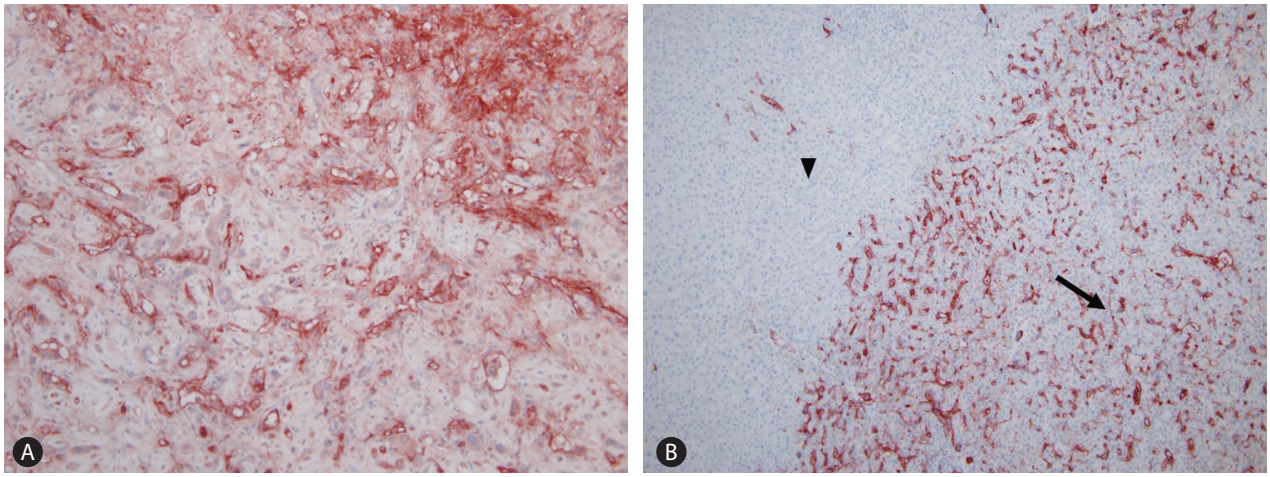

Figure 3. Immunohistochemical results. (A) The tumor cells synthesize factor VIII-related antigen (von Willebrand factor) in the cytoplasm and neoplastic vascular lumens. (B) The tumor cells with CD34 positivity (right arrow), in contrast to the neighboring normal hepatocytes, which show no immunoreactivity for CD34 (left arrowhead) and the immunoreactivity pattern for CD31 is identical to CD34 (figure not shown).

such as factor VIII-related antigen, CD34, CD31, podoplanin (D2-40 antibody),[8] and Fli-1 is helpful in making a definitive diagnosis.[9]

There is no standard therapeutic strategy for the treatment and follow-up of HEHE because of its rarity and variable clinical course. Currently, the treatments for HEHE include liver transplantation (44.8%), chemotherapy or radiotherapy (21%), liver resection (9.4%) and no treatment (24.8%).[3] Among them, the 5-year survival rate of liver resection (75%) or transplantation (54.8-75%) is significantly higher than the survival rate associated with other treatments (30%).[3,10] Although the liver resection is considered as the best therapeutic option it is not possible in the majority of the patients due to of the multicentric occurrence of the tumor. Orthotropic liver transplantation appears to be the only approach for patients with unresectable HEHE because the disease is poorly responsive to both chemotherapy and radiotherapy. Recently, a number of authors reported on a primary HEHE successfully treated with pegylated liposomal doxorubicin and a metastatic HEHE successfully treated with thalidomide.[11,12] Furthermore, the use of interferon alpha-2 in combination with surgical resection or transplantation in some patients was associated with successful metastasis prevention.[13] The prognostic factors of HEHE remain unclear, although some authors have reported that the presence of symptoms, older age, and elevated serum carbohydrate antigen 19-9 negatively affect outcome.[14]

Conflicts of Interest

The authors have no conflicts to disclose.

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