Epithelioid hemangioendothelioma (EHAE) is a vascular tumor which, due to its rarity, is often misdiagnosed as other hepatic tumors based on radiological characteristics. We herein report a case of EHAE in the liver and the mesentery of the small intestine. A 64-year-old asymptomatic woman was admitted to the hospital due to a hepatic tumor identified using computed tomography (CT). An enhanced CT scan revealed multiple tumors in the liver and a tumor in the mesentery. One of the hepatic tumors and the mesenteric tumor were resected and histologically examined. The two tumors exhibited similar histological characteristics and were diagnosed as EHAE. When multiple tumors are found in the liver, EHAE should be included in the differential diagnosis, as the prognosis of EHAE differs from that of carcinoma or benign tumors.

Introduction

Epithelioid hemangioendothelioma (EHAE) is a rare low-to-intermediate-grade malignant vascular tumor derived from endothelial cells (1,2). EHAE was first described in 1975 by Dail and Liebow as an aggressive bronchoalveolar cell carcinoma (3). The term epithelioid hemangioendothelioma was introduced in 1982 by Weiss and Enzinger, who described the tumor as originating from blood vessels (1). The estimated incidence of EHAE is <1/million, with a female:male ratio of 3:2 (4). Primary hepatic EHAE is an extremely rare occurrence and was first reported in 1984 by Ishak et al (5).

The aim of the present study was to report a case of EHAE presenting with multiple lesions in the liver and a lesion in the mesentery of the small intestine.

Case report

A 64-year-old woman was admitted to the Toyooka Hospital (Toyooka, Japan) in November 2013 with elevated levels of serum aspartate aminotransferase and alanine aminotransferase and due to tumors in the liver, which were identified on a computed tomography (CT) scan. The patient did not report any noticeable symptoms related to the tumor; she had diabetes mellitus and hypertension, and she was receiving treatment with estradiol dipropionate and dydrogesterone for climacteric symptoms. The patient's family cancer history was significant: Her father had been diagnosed with gastric and lung cancer, her mother had been diagnosed with pancreatic cancer, her older brother had been diagnosed with cancer of the urinary bladder, her older sister had been diagnosed with ovarian cancer, and her younger sister had been diagnosed with breast cancer.

An enhanced CT scan revealed multiple low-density tumors in the liver and a 30-mm irregular tumor in the mesentery (Fig. 1). Ethoxybenzyl-magnetic resonance imaging revealed that the tumor had high signal intensity on T2-weighted images (Fig. 2A), low signal intensity in T1-weighted images (Fig. 2B) and high signal intensity on diffusion-weighted images (Fig. 2C). These tumors also presented as hot spots on positron emission tomography/CT scan (Fig. 3). Blood tests revealed normal levels of carcinoembryonic antigen, α-fetoprotein and carbohydrate antigen 19-9. There were no abnormalities noted on the upper or lower gastrointestinal endoscopic examinations.

On laparoscopic observation, several whitish tumors were identified on the bilateral lobes of the liver and on the mesentery of the small intestine. It was impossible to resect all the tumors, since multiple lesions were present in both the left
and right lobes of the liver. As we were unable to determine whether the hepatic and mesenteric tumors were of the same type by diagnostic imaging alone, resection of the mesenteric tumor and one of the hepatic tumors was attempted and the resected specimens were sent for histological examination.

The size of the mesenteric and hepatic tumors was 33x28x25 and 25x25x10 mm, respectively (Fig. 4). The tumors were hard and whitish on cross-section, and they were relatively well-defined, with irregular margins. Histologically, the two tumors exhibited similar characteristics, such as epithelioid and dendritic cells with abundant cytoplasm and atypical nuclei (Fig. 5). In the periphery of the tumor, the tumor cells proliferated along pre-existing sinusoids. In the center of the tumor, the myxomatous stroma was conspicuous and contained tumor cells that were present either as single cells or in small groups. Some tumor cells were arranged in a trabecular pattern.

Immunohistologically, the tumor was positive for vimentin and vascular endothelial growth factor receptor (VEGFR)2,
partially positive for CD31, CD34 and factor VIII, and negative for cytokeratin AE1/AE3, hepatocyte-specific antigen, c-Kit, α-smooth muscle actin and S-100, suggesting that the tumor was derived from the endothelial cells of the blood vessels (Fig. 5 and data not shown). Moreover, the tumor was partially positive for CAM5.2.

Based on the macroscopic and microscopic characteristics, as well as the results of the immunohistological examination, the tumor was diagnosed as EHAE originating in the liver with metastasis to the mesentery.

As the residual hepatic tumors were multiple and were present in both the left and right lobes of the liver, they could not all be resected. Therefore, radiofrequency ablation was performed for the hepatic lesions and the patient was treated with pazopanib, which is a potent and selective multi-targeted receptor tyrosine kinase inhibitor that blocks tumor growth and inhibits angiogenesis, as EHAE expresses VEGFR2 (Flk-1) and platelet-derived growth factor receptor β. Approximately 3 years and 7 months after the first hospital visit, the patient maintains stable disease under pazopanib treatment (the hepatic tumors have not grown and there are no additional metastatic lesions). The patient's last follow-up was in June 2017.

Discussion

We herein described a case of EHAE arising in a 64-year-old woman presenting as multiple lesions in the liver and a single lesion in the mesentery.
It has been reported that EHAE is a rare tumor, and that its most common site of origin is the liver (4). However, some cases of EHAE originating in the mesentery or peritoneum have been reported. It is conceivable that, in the present case, the EHAE first developed in the liver and then metastasized to other sites inside the liver and to the mesentery, based on the most common EHAE site of origin and the distribution and number of the lesions.

A case of hepatic EHAE metastasizing to the mesentery was previously reported (6). In that case, there were multiple EHAE lesions in the liver and the EHAE had also metastasized to the peritoneum, omentum and mesentery, resulting in multiple organ dysfunction syndrome. In the present case, several lesions were identified in the liver but the only metastatic lesion was observed in the mesentery. The mesenteric lesion and one of the hepatic lesions were resected. As there were multiple hepatic lesions in both the left and right lobes of the liver, the resection of all the tumors was not feasible.

Epidemiologically, the estimated prevalence of EHAE is <1/million (4). EHAEs present mainly in the liver alone (21%), in the liver and the lung (18%), in the lung alone (12%), or in the bone alone (14%) (7). Mehrabi et al reviewed 434 cases of primary hepatic EHAE (8). The age of the patients ranged from 3 to 86 years, with a mean age of 41.7 years, and the male:female ratio was 2:3. The major symptoms of hepatic EHAE were upper abdominal pain, hepatomegaly and weight loss, although the majority of the patients were asymptomatic at the time of diagnosis. Of the hepatic EHAE patients, 87% exhibited multifocal tumors that involved the bilateral liver lobes.

The patient presented herein was female, asymptomatic, and had multifocal hepatic tumors with metastasis to the mesentery. It has been reported that extrahepatic involvement at the time of diagnosis is observed in 36.6% of hepatic EHAE patients, and that the lung (8.5%), regional lymph nodes (8.5%), peritoneum (6.1%), bone (4.9%), spleen (3.2%) and diaphragm (1.6%) are the most common sites of extrahepatic involvement (8).

In the present case, extrahepatic involvement of the mesentery was observed. These results suggest that hepatic EHAE may easily metastasize to other sites of the liver, but do not readily metastasize to other organs.

The patient was receiving estradiol dipropionate and dydrogesterone for climacteric symptoms. Factors possibly involved in the etiology of EHAE include oral contraceptives (9), vinyl chloride (10), asbestos (11), thorotast (12), liver trauma (13), viral hepatitis (14), primary biliary cirrhosis (15) and alcohol-related hepatic disorders (6). These findings suggest that inflammation or female hormones may be associated with the development of EHAE. It has been also reported that long-term administration of female hormones, such as oral contraceptive pills, is associated with the development of liver tumors (16).

Chromosomal and genetic abnormalities have also been reported to be associated with EHAE (17-19). Errani et al reported that the WWWTR1-CAMTA1 fusion gene was present in EHAE, and that the same pattern of WWWTR1-CAMTA1 fusion genes occurred in each tumor of each patient with multiple EHEAs (18,19). These results suggest that the WWWTR1-CAMTA1 fusion gene may be associated with the development of EHEA, and that multiple EHAE lesions may originate from a single lesion. Further research on the association between EHAE and genetic abnormalities, as well as other contributing factors, is required to optimize treatment.

In conclusion, we herein present a case of EHAE that presented as multiple lesions in the liver and a lesion in the mesentery, in a woman who had been receiving estradiol dipropionate and dydrogesterone for several years. Approximately 3 years and 7 months have passed since the patient's first hospital visit; she remains alive and the EHEA has not progressed. More effective therapeutic options must be developed for EHAE in the future. This case report was approved by the Ethics Committee of Toyooka Hospital and the patient consented to the publication of the case details and associated images.

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