Hepatic Epithelioid Hemangioendothelioma with Cecal Metastasis in a Natural Course: A Case Report

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Abstract

Epithelioid hemangioendothelioma (EHE) is a rare vascular tumor of low malignant potential that occurs mostly in soft tissue. So far, only two cases of EHE involving the intestine have been recorded. Here, we describe a rare case of cecal EHE due to a subsequent metastasis from the primary liver tumor three years after initial diagnosis. A 74-year-old man had sudden onset of epigastralgia for 24 hours. The abdominal CT revealed an ileocecal mass with a small bowel obstruction, and extensive tumor involvement in the liver was noted. He received an emergent right hemicolecetomy for relief of the ileus. Unfortunately, he expired four days later due to septic shock. The pathologic diagnosis of EHE prompted a molecular study for a WWTR1-CAMTA1 fusion. The Sanger sequencing results showed the fusion involved exon 4 of WWTR1 with exon 8 of CAMTA1. There is no standard treatment for hepatic EHE because of its rarity and variable clinical outcome. The decision on a treatment strategy should be individualized for each patient. Since the patient received supportive care only for the liver tumor, this case demonstrated a natural course of hepatic EHE with a survival of more than 3.3 years.

Keywords: Cecal tumor; Epithelioid hemangioendothelioma; Liver; Metastasis; WWTR1-CAMTA1 gene fusion

Introduction

Epithelioid hemangioendothelioma (EHE) is an uncommon vascular tumor of low malignant potential and occurs mostly in soft tissue. In the literature, only two cases of EHE involving the intestine have been recorded [1,2]. Here, we report a rare case of cecal EHE, which represents a subsequent metastasis from the primary liver tumor, three years after the liver tumor diagnosis. Notably, since the patient received supportive care only for the liver tumor, this case demonstrated a natural course of hepatic EHE with a survival of more than 3.3 years.

Case Report

A 74-year-old man had a liver tumor diagnosed at a different hospital facility not related to NCKUH in April 2010. The patient presented with multiple hepatic masses and metastatic nodules in the lung at that time of initial diagnosis. The patient and his family refused aggressive treatment and chose to receive supportive care only. The follow-up images showed progression of hepatic and pulmonary tumors with metastasis to mediastinal and paracaval lymph nodes. On August 12, 2013 the patient presented to our emergency medicine department complaining of sudden onset epigastralgia for the previous 24 hours. An elevated alkaline phosphatase level (187 U/L, normal range, 30-100) with normal aminotransaminase liver enzyme profile was detected. Abdominal Computed Tomography (CT) revealed an ileocecal mass, measuring 4.0x3.3 cm with a small bowel obstruction (Figure 1A arrow).

![Figure 1: Clinicopathologic features of hepatic epithelioid hemangioendothelioma with cecal metastasis.](image-url)

(A) Abdominal CT reveals an ileocecal mass (arrow), measuring 4.0x3.3 cm with small bowel obstruction. (B) Microscopically, the tumor infiltrates the colonic wall with a focal mucosal involvement (H&E, 20X), and is composed of cords or nests of epithelioid cells with characteristic intracytoplasmic vacuoles in a myxohyaline stroma (inset, H&E, 400X). (C) Extensive tumor emboli are found in the sample (H&E, 100X). (D) Immunohistochemically, the tumor cells are positive for CD34 (left panel) and CD31 (right panel).
In addition, extensive tumor involvement in the liver was also noted (Figure 1A inset). For relief of the ileus, he received an emergent right hemicolectomy. Unfortunately, the post-operative course was complicated by septic shock with adult respiratory distress syndrome. The patient expired four days later.

Grossly, the specimen was a segment of the right side colon (37 cm in length) containing a cecal mass (3x3x2 cm). The tissue sample was fixed in 10% neutral buffered formalin for 24 hours at room temperature and paraffin-embedded using standard procedures. Tissue sections were cut at 4 µm and stained with hematoxylin and eosin (H&E). Two independent pathologists interpreted the slides and described their findings. Microscopically, the tumor mainly infiltrated into the colonic wall and peri-colonic tissue with focal mucosal involvement (Figure 1B). It was composed of cords and nests of epithelioid tumor cells with characteristic intracytoplasmic vacuoles in a myxohyaline stroma (Figure 1B inset).

**Figure 2:** Molecular studies of the WWTR1-CAMTA1 gene fusion. Paraffin-embedded tumor tissues were used for RT-PCR to test for the WWTR1-CAMTA1 fusion transcript with six pairs of primers as listed. The positive results are labeled in red (upper right panel). Because the RNA molecules were fragmented in paraffin tissue, expected products more than 400 bp were unamenable for detection (upper left panel lanes 2, 3 and 6). The lower bands in lanes 4 and 6 indicate non-specific PCR products. The fusion involves exon 4 of WWTR1 with exon 8 of CAMTA1 as detected by Sanger sequencing (lower panel).

Mitotic figures and necrotic foci were occasionally found. Extensive tumor emboli were discerned (Figure 1C), consistent with a metastatic nature. Since the tumor cells were epithelioid, the differential diagnosis may include carcinoma and epithelioid mesenchymal sarcoma, especially vascular tumors. The bland nuclear features, a low mitotic activity, and a slow progressive course would collectively argue against aggressive carcinoma or angiosarcoma. Utilizing a tissue autostainer (Bond-Max autostainer; Leica Biosystems Newcastle Ltd, Australia), immunohistochemical staining was performed on 4-µm-thick sections after tissues were deparaffinized with xylene and pre-treated with either Epitope Retrieval Solution 2 (EDTA, pH 9.0) or 10 mM sodium citrate buffer (pH 6.0). Hematoxylin was used as a counterstain. The primary antibodies were as follows: CD31 (JC70A, 1:100, Dako, Glostrup, Denmark), CD34 (QBEnd-10, 1:50, Dako), pan cytokeratin (AE1/AE3, 1:200, Dako), and D2-40 (D2-40, 1:25, MyBiosource, San Diego, CA, USA). Appropriate positive and negative controls were used. Immunohistochemically, the tumor cells were positive for CD34 (Figure 1D left panel), CD31 (Figure 1D right panel) and D2-40, but negative for pan cytokeratin stain. Under the impression of EHE, a molecular study by reverse transcriptase polymerase chain reaction (RT-PCR) confirmed the WWTR1-CAMTA1 gene fusion in paraffin-embedded tumor tissue (Figure 2). After reviewing the liver tumor pathology, it showed similar morphology as the metastasis. Taken together with the clinical history, the diagnosis of hepatic EHE with cecal metastasis was made, an extremely rare case.
Discussion

Hepatic EHE is a rare vascular tumor, which originates from endothelial cells with an incidence of <0.1 per 100,000 population. It appears more often in women with a male-to-female ratio of 2:3 and a peak incidence in the 3rd to 4th decade of life [3]. Histologically, EHE appears as nests or cords of epithelioid endothelial cells with characteristic intracellular vascular lumina which sometimes contains red blood cells. Immunoreactivity for CD31, CD34, D2-40 and Factor VIII-related antigen provides further evidence of endothelial differentiation. EHE carries a disease-defining genetic mutation of t (1;3)(p36.3;q25) involving a fusion transcript where exon 4 of WWTR1 is fused in frame with either exon 8 or exon 9 of CAMTA1 [4]. An alternative fusion transcript of YAP1-TFE3 or novel WWTR1-CAMTA1 fusion variants have also been observed and may bear significance on clinical behavior and variant morphology [5,6]. CAMTA1 is a transcription factor and putative tumor suppressor [7]. One of this WC fusion protein subsequently leads to oncogenic transformation and resistance to anoikis (anchorage-dependent cell death) [7]. Molecular genetic methods, for example RT-PCR or fluorescent in situ hybridization (FISH), are the gold standard for detection of tumor-specific genetic alterations. Recently, nuclear CAMTA1 expression has been found to be a useful immunohistochemical marker and can distinguish EHE from its histologic mimics [8,9]. Up to one-half of EHE cases show multifocal presentation even in different locations [10]. Utilizing molecular analysis to understand disease progression, multifocal EHEs probably represent metastatic implants of the primary tumor rather than synchronous multiple tumor clones [10]. Consistent with the above concept, the cecal tumor in our case was considered to be secondary to the hepatic EHE, although the primary tumor tissue was unavailable for molecular analysis.

There is no standard treatment for hepatic EHE because of its rarity and variable clinical outcome. The decision on a treatment strategy should be individualized for each patient. Surgical resection is the treatment of choice for localized liver involvement, and liver transplantation is reasonable when the liver parenchyma is diffusely involved. Adjuvant chemotherapy is considered when extrahepatic involvement occurs [11]. An optional choice is trans-arterial chemoembolization with chemotherapy and/or radiotherapy, although EHE may be poorly responsive to both therapies. Palliative resection is not advocated because the tumor behaves aggressively after liver resection [11]. Recently, a novel alternative therapy targeting angiogenesis, for e.g. thalidomide or metronomic cyclophosphamide, has been found to be promising [12-14]. The 5-year survival rates for hepatic EHE patients with liver resection, chemotherapy or radiotherapy, and no treatment are 75%, 30% and 5% respectively [11]. Liver transplantation for multicentric liver tumors yields a 5-year survival rate of 55% [11]. The overall 5-year survival rate of EHE is 41%. Our case demonstrated a natural disease course of hepatic EHE with a survival of more than 3.3 years.

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References