



Navigating the Unconventional Liver Epithelioid Hemangioendothelioma Resection: A Case Study

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Introduction

Epithelioid Hemangioendothelioma (EHE)

Epithelioid hemangioendothelioma is an extremely rare, malignant vascular sarcoma that arises from the deep endothelial cells that line blood vessels.^{3,5,9} The suspected pathophysiology is driven by somatic genetic mutations with abnormal gene fusion, most commonly presenting as *WWTR1-CAMTA1* gene fusion, with the less common *YAP1-TEF3* gene fusion.^{3,7,9,10} There is little documented evidence in differing morbidity and mortality between both genetic mutations, with the overall risk of increased mortality being driven by the number and size of tumor deposits.^{3,9} Unifocal tumors have an almost 100% 5-year survival rate; larger and multifocal tumors pose a significant risk for systemic involvement and decreased survival by almost 50%.^{5,9}

These tumors most often arise within the liver, lungs, and bone, with a slight prevalence in women between 30-50 years old.⁹ Most EHE tumors have an asymptomatic presentation with no documented behavioral determinants; only about half of tumors that present with pain are those associated with close proximity to or involvement of intraparenchymal vasculature and lead to vascular occlusion.^{3,9}

Grossly, EHE may appear as a poorly circumscribed indurated mass with variable size.^{5,9} Microscopically the two genetic variants have unique presentations. The *WWTR1-CAMTA1* gene fusion histologically demonstrates endothelial cell cords and nests suspended within a myxohyaline stroma with vacuolization. The less common *YAP1-TEF3* gene fusion typically demonstrates as a more solid aggregate of epithelioid nests with rare vacuolization and fibrous stroma.⁹ Key endothelial-specific IHC markers to support the diagnosis of EHE include: *CD31*, *CD34*, *FLI-1*, and *ERG*; cytokeratin expression, including *CK7*, may also be observed in EHE, but should be interpreted cautiously.^{5,6,9} Notably, EHE typically lacks diffuse keratin expression.^{6,9} Immunostaining and molecular profiling are ideal for diagnosing EHE and differentiating between the two subtypes.⁹

Clinical History

The following case is that of a middle-aged woman who presented to the emergency room with sharp, intermittent right upper quadrant pain with an otherwise unremarkable history. Serial surveillance computed tomography (CT) and magnetic resonance imaging (MRI) demonstrated two distinct enlarging liver nodules in liver segments 6 and 7, measuring 0.9 cm and 2.7 cm in greatest dimension. An initial biopsy of the largest liver nodule revealed EHE with an elevated Ki-67 index, concerning for rapid growth. Ultimately a partial hepatectomy to include liver segments 6 and 7 with both nodules was performed.

Pathologic Findings

Macroscopic

- The partial hepatectomy specimen consisted of a 367 g (post-fixation), 12.7 cm (superior to inferior) x 8.4 cm (medial to lateral) x 5.1 cm (superficial to deep) excision of tan-brown well-vascularized liver parenchyma with a thin, smooth, glistening, and grossly unremarkable capsule.
 - The cut surface of the specimen exhibited 2 distinct fairly well-circumscribed, grossly unencapsulated white-gray, opaque, and fleshy tumor nodules measuring 0.9 x 0.8 x 0.6 cm (**Figure 1A**) and 2.7 x 2.7 x 2.2 cm (**Figure 1B**).
 - Both tumor nodules grossly abutted and focally surrounded the intraparenchymal vasculature.
 - The capsule and parenchymal margins appeared grossly free of tumor, absent of hemorrhage, necrosis, and/or calcifications.
 - No lymph nodes were isolated and no distant metastases could be assessed.
 - Key sections:
 - Entire smaller tumor nodule
 - Representative larger tumor nodule
 - Nearest capsule and margins
 - Uninvolved parenchyma between nodules and away from nodules



Figure 1: A) Cross section of the smaller bisected nodule (minimal fixation) shows a fairly well-circumscribed white-gray tumor. B) Cross section of the larger nodule (post-fixation) shows a fairly well-circumscribed white-gray tumor in relation to uninvolved liver parenchyma and branching vessels.

Histopathology

- Two distinct, infiltrative foci of EHE demonstrating cords and nests of epithelioid endothelial cells with abundant eosinophilic cytoplasm within a myxohyaline stroma and vacuolization (*WWTR1-CAMTA1*)
 - No psuedoalevolar formation or fibrous stroma
 - Negative for *TEF3* expression
- Negative surgical margins (>1 cm) were achieved
- Lymphovascular invasion and tumor cell necrosis were identified

Immunohistochemistry

- Positive IHC markers:** *ERG*, *CD31*, *CD34*, *CK7*, and *GATA3*
 - ERG* is a hallmark indicator of vascular angiosarcomatous tumors^{3,7}
 - CD31* is extremely sensitive for highlighting endothelial cells and vascularity⁵
- Negative IHC markers:** *CK20*, *CK5/6*, *CDX2*, *PAX8*, *ER/PR/HER2*, *p40*, *CA 19-9*, *TTF-1*, *HepPar1*, *mammaglobin*, *GCDFP-15*, and *SOX-10*
 - Keratin stains are often misleading and are normally a marker for epithelial cells to distinguish squamous cell carcinoma or metastatic carcinoma; some EHE tumor cells may focally express keratin^{4,5,6}

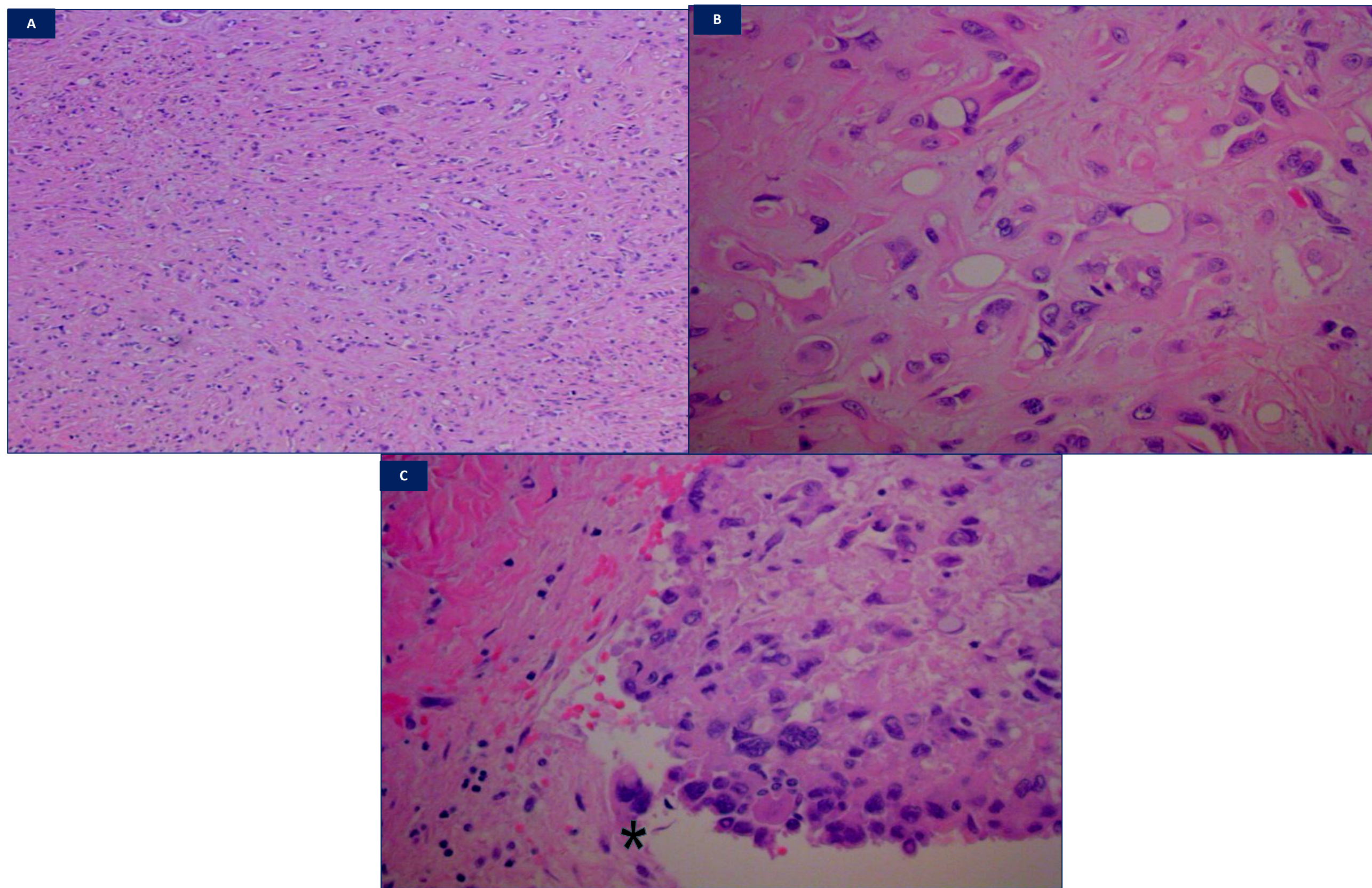


Figure 2: Larger liver nodule displaying tumor cells arranged in strands, cords, and small nests of epithelioid endothelial cells with abundant eosinophilic cytoplasm embedded within a myxohyaline stroma with abundant vacuolization; H&E stain. Magnification x10 (A) and x1000 (B). Larger liver nodule, tumor cells invading a medium-sized vessel (*) with marked nuclear atypia; H&E stain. Magnification x1000 (C).

Final Diagnosis

- Liver biopsy (2.7 cm nodule):** Epithelioid hemangioendothelioma with tumor necrosis and increased Ki-67 index
- Partial hepatectomy:** Infiltrative epithelioid hemangioendothelioma (2 foci)
 - Greatest tumor dimensions: 0.9 cm and 2.7 cm
 - Negative capsular involvement and surgical margins
 - Lymphovascular invasion (**Figure 2C**) and tumor necrosis present
 - WWTR1-CAMTA1* gene fusion
 - ERG*+, *CD31*+, *CD34*+, *CK7*+, *GATA3*+
 - CK20*-, *CK5/6*-

Discussion

Molecular Profiling Considerations

- Molecular confirmation of the type of gene fusion in EHE tumor resections is the gold standard in proper diagnosis.
 - The described liver nodules both demonstrated the more common *WWTR1-CAMTA1* gene fusion
 - Associated with dysregulation of the Hippo signaling pathway which normally acts a tumor suppressor¹⁰

Staging Considerations

The case was classified in concordance with the World Health Organization (WHO) Endocrine and Neuroendocrine Staging Protocols, 5th edition.

- EHE is a type of malignant mesenchymal tumor
- Presently no specific staging guidelines for EHE tumor resections
- Future management guidance for EHE includes: surgical resection, surveillance, ablation (typically reserved for poor surgical candidates)

Role of the Pathologists' Assistant (PA)

The PA should be mindful about selecting adequate tissue cores for biopsy specimens, based on size and color, for cassette submission. Increasing the number of cassettes is also encouraged given the increased demands for offsite molecular testing and potential for exhausting tissue cores. Correlation with prior radiology is also important for the PA when examining liver resections for tumor, making sure to correlate nodule sizes between radiology and the gross specimen, identifying the correct involved liver segment(s)/lobe(s), and documenting gross involvement of important structures and margins (i.e. in this particular case, documenting tumor involving the surrounding vessels).

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