



# Epithelioid Hemangioendothelioma and Angiosarcoma – Is there something in between? A Case Report of Malignant Epithelioid Hemangioendothelioma Diagnosed on Fine-Needle Aspiration and Core Biopsy

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## Abstract

Epithelioid hemangioendothelioma and epithelioid angiosarcoma are both rare malignancies of endothelial origin. Differentiation of these two diagnoses remains difficult due to their heterogeneous presentation and overlapping morphological features. Here we report a case of a 58-year-old female clinically presenting with primary hepatic vascular neoplasm. She was finally diagnosed with Epithelioid Hemangioendothelioma (EHE) based on cytology sampling and core biopsy. The immunohistochemical (IHC) studies and morphological features of this case may be suggestive of a continuum with Epithelioid Angiosarcoma (EAS). Given the mixed findings exhibited, a plausible intermediate diagnostic entity may be proposed, and further studies are warranted to investigate this possible intermediate variant with optimal management and follow up.

**Keywords:** Epithelioid; Hemangioendothelioma; Angiosarcoma; Hemangioma

## Abbreviations

HE: Hemangioendothelioma; EHE: Epithelioid Hemangioendothelioma; EAS: Epithelioid Angiosarcoma; IHC: Immunohistochemical; MEHE: Malignant Epithelioid Hemangioendothelioma; FNA: Fine Needle Aspiration; HPF: High-Power Field

## Introduction

Weiss and Enzinger first described Epithelioid Hemangioendothelioma (EHE) in 1982 [1]. It was first proposed as an intermediate diagnosis between hemangioma and angiosarcoma. Since then, fusion genes have been identified showing EHE to not be a true intermediate diagnosis, but a pathophysiologically different disease all together. Discernment

between EHE and epithelioid angiosarcoma (EAS) still remains problematic however due to significant cytological, immunohistochemical (IHC), and clinical overlap.

The term hemangioendothelioma (HE) is a non-specific general term describing several types of vascular neoplasms and includes both benign and malignant growths.

On account of the lack of unique defining features separating EHE from EAS, most diagnoses were based off the overall severity of the cytological and clinical presentation before molecular testing became available. Such criteria included a higher age of onset, more aggressive progression, and more severe cytological findings being more common but not specific to EAS. Differentiation continues to remain difficult when molecular testing is unavailable. Here we present a rare case of malignant vascular neoplasm with final diagnosis of EHE that presented with clinical features more consistent with EAS. This case raises the question, "Is there something in between these two entities of EHE and EAS?" If so, is it possible that there is an intermediate variant? Could malignant epithelioid hemangioendothelioma be the entity in between? We hope that by reporting this case we alert clinicians and pathologists to the possibility of this variant. By reporting additional cases, which include molecular testing findings, we may eventually reach the ultimate goal of definitive diagnosis so as to provide the optimal management for each entity.

## Case Presentation

A 58-year-old woman with a history of prior surgical removal of hepatic hemangioma presented with multiple liver lesions ranging from 0.8-4.2 cm. Before presentation,

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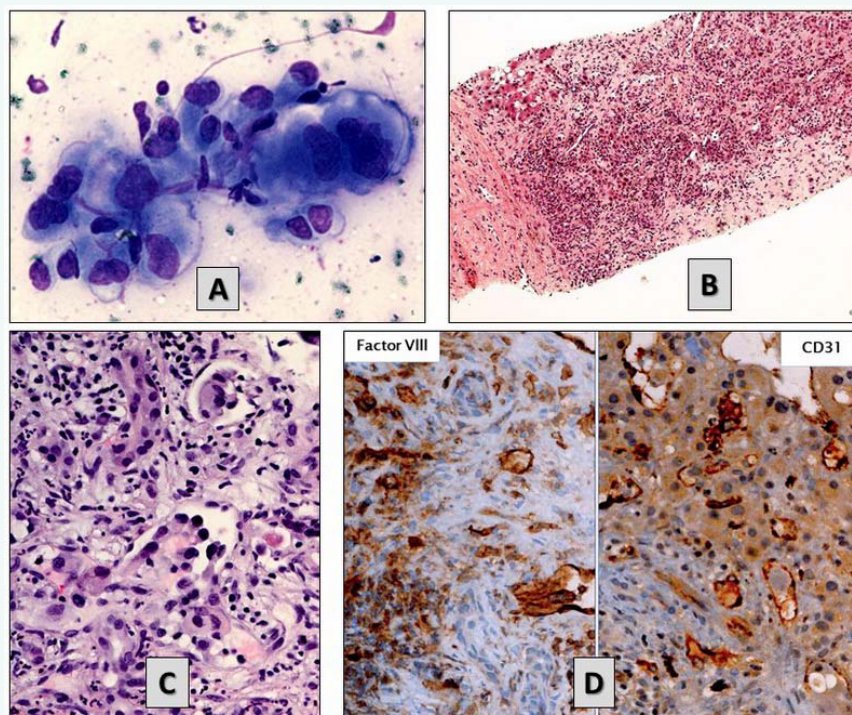


the patient experienced 2 months of low-grade fever as well as generalized fatigue and body aches. The patient's primary medical doctor referred her for a magnetic resonance imaging scan, which revealed multiple lesions in the liver. Radiologically, these lesions were consistent with malignant neoplasm, likely metastatic. Radiologically guided fine-needle aspiration (FNA) was performed. Cytology slides showed limited but diagnostic material (Figure 1, A). The concurrent core biopsy showed an infiltrating tumor displaying short cords and small nests, with some foci showing well-demarcated nodules infiltrating the preexisting hepatocytes and bile ducts (Figure 1, B and C). The tumor cells showed abundant eosinophilic cytoplasm with focal cytoplasmic vacuolization. The cells showed marked nuclear atypia, mitotic activity, 3 mitoses per 10 high-power fields, and focal spindling of cells. A characteristic intracellular lamina with some containing red blood cells was noted along with mixed epithelioid and dendritic tumor cells by S-100 in the myxohyaline stroma. Necrosis could not be evaluated in the limited core biopsy sample, which certainly may not be fully representative of the entire lesions. All hepatic and epithelial markers were negative (Hep-Par1, TTF-1, AE1.3, CK7, CAM 5.2, EMA), while mesenchymal and vascular markers were strongly positive (vimentin, CD31, CD34, factor VIII) (Figure 1, D). The morphologic and IHC features prompted the diagnosis of malignant epithelioid hemangioendothelioma (MEHE).

Further clinical evaluation revealed involvement of the liver, lung, and abdominal cavity. Due to widespread hepatic involvement and multiple metastasis, surgical management was not an option. The patient was treated with Thalidomide and chemo, which stabilized the disease for a few months before progression resumed. Palliative radiation and continued transcatheter arterial chemoembolization was given until the patient expired 13 months later due to multiple organ failure. This diagnosis may represent a morphologic continuum with EAS.

## Discussion

Due to the heterogeneous progression of EHE and the aggressive progression of EAS, accurate diagnosis is vital. The highly unpredictable prognosis of EHE may be suggestive of possible subtypes that if identified could permit tailored therapy. Hepatic EHE has been misdiagnosed in approximately 60 to 80% of cases [2,3]. This type of tumor has been histologically mistaken for metastatic carcinoma, angiosarcoma, hepatocellular carcinoma and cholangiosarcoma [3]. This potential misdiagnosis should be considered and evaluated by clinicians and pathologists when a patient is presented with a hepatic mass. Definitive diagnosis is made by biopsy with IHC staining. A review of literature shows the presence of factor VIII-related antigen, CD34, and CD31 in almost all patients, 94%, and 86% respectively [2]. FLI-1 has



**Figure 1** A: Fine needle aspiration of one of the liver lesions. Three-dimensional cluster of highly malignant cells showing enlarged irregular nuclei and moderate pleomorphism. (DQ stain, x100)  
B: Core biopsy of liver mass, low power view showing an infiltrating tumor displaying short cords and small nests, with some foci showing well-demarcated nodules infiltrating the preexisting hepatocytes and bile ducts. (H&E, x20)  
C: Core biopsy of liver mass, high power view showing marked nuclear atypia, mitotic activity, three mitoses per 10 high-power fields with focal spindling, the tumor cells showing abundant eosinophilic cytoplasm with focal cytoplasmic vacuolization (H&E, x40)  
D: Strongly positive Factor VIII and CD31 endothelial vascular markers..



proven to be another useful marker for detecting EHE with two studies having shown 100% sensitivity, however the marker lacks specificity against Ewing sarcoma, malignant melanoma, and various carcinomas [4,5]. These results emphasize the importance of using multiple markers for accurate diagnosis.

EHE is morphologically described as having rounded to slightly spindled eosinophilic endothelial cells that grow in small nests or cords with prominent cytoplasmic vacuolization and rounded nuclei [1,6]. Detailed morphologic characteristics were described in a review of 39 cases of EHE, which found 15 with ischemic necrosis and 4 with more than 3 mitosis/50 high-power field (HPF) with the two largest having 12 and 22/50 HPF [6]. Additional morphologic features were reported in another review of 25 patients which showed half of EHE cases containing nuclear grooves and cytoplasmic granules with cells found as fragments, clusters, or individual cells [7]. Clinically EHE usually appears in middle-aged patients as a low to intermediate grade malignancy. A 10% reoccurrence, 25% metastasis, and >10% mortality rate reveals the highly unpredictable clinical course of this disease [7]. A recent study of primary EHE lesions from varying sites in 33 people exhibited 1, 3, and 5-year survival rates of 96.2%, 87%, and 75.3% respectively [8]. Another study reports 1 and 5-year overall survival rate of 90% and 73% respectively, however the prognosis decreases to 53% and 24% respectively when the disease has progressed [9]. This reveals the importance of metastasis on mortality. There is also disparity among sites with soft tissues, liver and lung having a mortality of 13%, 35%, and 65% respectively [9]. Overall, the heterogeneous nature of EHE demonstrates highly specific findings with poor sensitivity, while frequently appreciated findings have poor specificity [1,6,7].

EAS is a rare tumor comprising less than 1% of all soft tissue sarcomas [10]. Cytologically EAS has more pleomorphism, atypia, mitotic activity, and causes more parenchymal destruction than EHE while causing less sclerosis [11]. Pale eosinophilic cytoplasm, spindle cells, hyperchromatic nuclei with atypia and high mitotic activity are common but not exclusive to EAS. Cells also usually presents as fragments, clusters, and individual cells in soft tissue with a higher incidence of single cells than seen in EHE [7]. A higher prevalence of prominent nucleoli is also seen in EAS with a high proliferation index and necrosis [7]. EAS is usually seen in patients between 50-70 years old. Patients with hepatic EAS usually present clinically with abdominal pain, weakness, fatigue w/ jaundice, hepatomegaly, and ascites [11]. Due to its more aggressive course and high metastatic potential EAS has a mean survival ranging between 6-16 months [7,9,10]. IHC studies are sensitive to endothelial markers with low specificity due to overlap of EAS with EHE as well as with other vascular endothelial neoplasms.

A more recent focus in molecular diagnosis has identified common fusion genes in EHE. Although the CAMTA1 gene which is a tumor suppressor on chromosome 1p36.23 and the WWTR1 gene which restricts proliferation and promotes apoptosis on chromosome 3q25 have been implicated in many types of cancers, only in EHE have they been found as a unique translocation fusion gene [11,12]. This translocation is also found to be absent in epithelioid hemangioma emphasizing its importance in

prognosis [11]. A study by Antonescu et al., revealed a subset of EHE cases presenting with a YAP1-TFE3 fusion that was absent in all controls [13]. As more subsets and possible intermediates are discovered, more accurate prognoses and treatment may become possible.

Because the prediction of hepatic EHE behavior and prognosis is difficult, establishing the best therapeutic algorithm for each patient is a challenging task. The therapeutic modalities for patients with hepatic EHE include liver resection, liver transplantation, systemic or locoregional radiation therapy, percutaneous ablative techniques such as radiofrequency ablation, systemic chemotherapy (anti-angiogenic or anti-tumor pharmacological treatment), locoregional chemotherapy such as transarterial chemoembolization, hormonal therapy, immunotherapy or only surveillance [14]. A review of treatment for 286 patients with primary hepatic EHE showed 44.8% received liver transplant, 24.8% no treatment, 21% chemo/radiotherapy, and 9.4% liver resection [2]. Although the treatment of choice for hepatic EHE was resection, multifocal nodules usually made the procedure contraindicated. A wait-and-see approach to treatment also shows merit as one review showed two patients who lived 10 years and 27 years post onset without progression and one patient had spontaneous regression [2]. Another died after two weeks emphasizing the variability of presentation which would allow a provider to determine if a wait and see is justified if subtypes are identified [2]. Five-year survival for conventional treatment of hepatic EHE include 54.5% for liver transplant, 30% for chemo-radiotherapy, 75% for liver resection and 4.5% for no therapy [2]. Another study by Mascarelli et al., identified EHE patients with concurrent chronic Bartonella infections suggestive of treatment for the infection as a way to possibly manage progression [15].

The case presented here raises the possibility of the presence of an intermediate malignancy that does not necessarily fall under EHE or EAS since EHE is considered a low to intermediate grade malignancy while EAS is known to follow a much more aggressive course. The biopsy contained morphologic features suggestive of a more aggressive EHE with moderate atypia, but the defining characteristics of angiosarcoma were not present. Our case showed predominantly low proliferation (10% nuclear staining with proliferation index Ki-67), with focal nodular areas showing higher proliferation. Angiosarcoma also expresses endothelial markers, but it is more destructive and often has a greater degree of nuclear atypia, mitosis, and necrosis. This diagnosis may represent a morphologic continuum with EAS. Clinically, however, the tumor presented characteristics more similar to the aggressive nature of EAS. The tumor followed an aggressive course with patient expiring within 13 months.

To improve the patient outcome and efficacy of novel treatments, there is an imperative need for better insight into the pathology, molecular biology and genetics of hepatic EHE, to improve the identification of tumors with aggressive behavior and to personalize treatment [14]. Currently, there is no consensus treatment protocol for hepatic EHE and we know that hepatic angiosarcomas are rarer and have a worse prognosis [16]. It is our hope that this report raises awareness of what remains an



unmet need in definitive diagnosis and management of various endothelial vascular diseases and that continued investigation drives further development of efficacious diagnosis and safe treatments for improving patient outcomes.

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