

Case Report

# A Case of Vanishing Metastatic Mass: Right Atrial Mass in the Setting of Primary Epithelioid Hemangioendothelioma of the Spine

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## Keywords

Epithelioid hemangioendothelioma · Right atrium · Spine

## Abstract

Epithelioid hemangioendothelioma (EHE) is a rare low-grade vascular neoplasm that is characterized as intermediate between benign hemangioma and high-grade angiosarcoma affecting 1 in 1,000,000 people worldwide. It has been described throughout the body with lung, liver, skin, and bone being the most frequent sites. Primary EHE of the spine has been reported in 56 cases so far with no correlation of age and sex. Our case highlights a rare clinical presentation, etiopathogenesis, diagnosis, and treatment of EHE of the spine with metastasis to the right atrium. This is the first documented case of EHE of the spine with metastatic spread to the heart treated with bevacizumab leading to resolution of the heart metastatic mass. Further studies are warranted to develop a treatment formula for this rare tumor, to consider combination chemotherapy and new adjuvant targeted immunotherapies to prevent progression of disease.

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## Introduction

Epithelioid hemangioendothelioma (EHE) is a very rare low-grade vascular neoplasm that is characterized as an intermediate between benign hemangioma and high-grade angiosarcoma affecting 1 in 1,000,000 people worldwide. It has been described throughout the body with lung, liver, skin, and bone being the most frequent sites. Primary EHE of the spine is extremely rare with only 56 cases reported in the literature to date. Primary bone EHE constitutes less than 1% of the malignant bone tumors with very few cases occurring in the spine [1]. Our case highlights a rare clinical presentation, etiopathogenesis, diagnosis and treatment of EHE of the spine with metastasis to the right atrium.

## Clinical Summary

A 49-year-old African American man with no past medical history presented to the emergency room with 1 month of worsening upper back pain and 1 week of increasing inability to ambulate with associated numbness at the level of the umbilicus and downwards. On examination, the patient had significant bilateral lower extremity weakness with decreased sensation. Furthermore, point tenderness was noted on palpation of T6 and T7 vertebrae. MRI of the thoracic spine revealed a 3.7 × 6.5 × 8.5 cm T6 mass with severe thoracic cord compression and loss of posterior bony elements (Fig. 1a, b). The patient was scheduled for emergent posterior decompressive laminectomy with resection. The mass was noted to be highly vascular with an estimated blood loss of 4,000 mL and he received 6 units of pRBCs as well as 4 units of FFP intraoperatively. Pathology was consistent with EHE with a Ki-67 proliferative index of 60–70% (Fig. 2a–d). He was transferred to acute rehabilitation postoperatively where his hospital course was complicated by a syncopal episode while participating with therapy. Transthoracic echocardiogram (TTE) performed at the time of admission and ECG at the time of the syncopal episode were unremarkable. The patient's syncopal episode was presumed to be neurocardiogenic in origin. He was eventually discharged home with close outpatient follow-up.

He returned on the same day of discharge due to a second syncopal event, which occurred while watching television. Repeat TTE was performed, 3 weeks after the initial study, showing a large, fixed mass, measuring 4 × 4 cm in the superior right atrial cavity. Transesophageal echocardiogram was subsequently performed revealing a large, multi-lobulated, echogenic mass, measuring 8 × 5 cm in the lateral right atrial cavity (Fig. 3a–c). There was partial uptake of contrast and the mass was not attached to the septum. The patient underwent a PET scan for further delineation showing increased uptake in the thoracic spine and right atrium. Deemed to not be a surgical candidate, he was started on chemotherapy with bevacizumab and radiation of the spine. He was followed up 1 month later after 1 cycle of bevacizumab with the third TTE showing dissolution of the mass (Fig. 3d). Though he had significant improvement within 1 month of receiving bevacizumab, he was later noted to have progression of disease elsewhere. Foundation cancer gene testing identified genomic alterations in telomerase reverse transcriptase (TERT) within promoter region –124 C>T, functional loss of TP53 and BRCA2 gene.

## Discussion

Primary EHE of the spine has previously been reported in 56 cases so far with no correlation of age and sex. The average age of onset for the 56 cases reported in literature as well as in our case was 39 years (range 16–74) with 32 of them being male and 25 female. Lesions were distributed in different levels of the spine with some of them having multiple levels of involvement, commonly presenting with bone pain [2].

The pathogenesis of EHE remains unknown. There have been multiple hypotheses regarding the possible pathogenesis. An *in vivo* murine model reported that monocyte chemoattractant protein-1 (MCP-1) is required for the proliferation of endothelial cells by stimulating angiogenic behavior with anti-MCP-1 therapy leading to failure of tumor development [3]. Boudousquie et al. [4] reported several complex clonal abnormalities, an unbalanced translocation of chromosome 7 and 22 having multiple breakpoints, a robertsonian translocation of chromosome 14, and loss of chromosome Y that could be involved in the pathogenesis. Errani et al. [5] concentrated on recurrent translocation t(1;3)(p36.23;q25.1) involving calmodulin-binding transcription activator 1 (CAMTA1) on chromosome 1p36.23 and WW domain-containing transcription activator 1 (WWTR1) on chromosome 3q25.1. Though this translocation has been involved in oncogenesis, it was found to be extremely important in ruling out morphologic mimics of EHE-like epithelial hemangioma and epithelioid sarcoma-like EHE, thus preventing overtreatment. Antonescu et al. [6] focused on WWTR1-CAMTA1 fusion gene negative subset, showing yes-associated protein 1 (YAP1)-transcription factor E3 (TFE3) fusion with similar morphological features of well-formed vascular channels in patients with a mean age of 30 years.

EHE is diagnosed based on unique histologic, immunohistochemical, and molecular characteristics [7]. EHE on histology consists of spindled endothelial cells arranged in nests and cords. Often, lesional cells contain intracytoplasmic vacuoles that occasionally compress the nucleus leading to a signet-ring-like appearance. Some lesions also induced a desmoplastic reaction [8, 9]. Immunohistochemistry is likewise useful in contributing to the diagnosis. The vascular nature of EHE is identified by Friend leukemia integration 1 transcription factor (Fli-1), which is a transcription factor, expressed in endothelial cells [10]. CD31, CD34, and ERG have also been evaluated. CD34 is expressed by more than 90% of vascular tumors, so while relatively sensitive is not very specific for EHE. In contrast, CD31 is a more specific vascular tumor marker, and as such, the combination of Fli-1 and CD31 has been suggested to identify EHE immunohistochemically [8, 10].

EHE remains a rare neoplasm of uncertain behavior. Hence, access to further large randomized data is not possible to understand and study optimal treatment strategies. Watchful waiting is advised as spontaneous regressions have been reported in asymptomatic patients with diffuse pulmonary lesions [11]. Treatment for metastatic disease has included cytotoxic chemotherapy, immunotherapy, and targeted therapies. An open-label, multicenter phase 2 study using bevacizumab for treatment of angiosarcoma and EHE showed that bevacizumab is effective and well-tolerated alone and should be considered for combination with other chemotherapeutic agents in the future as 17% of patients showed partial response and 50% showed stable disease with a mean progression of 26 weeks [12]. Analyzing gene expression might be a very important tool in guiding treatment in the future given the rarity of the condition. Theurillat et al. [13] reported the appearance of less differentiated EHE with accumulation of TP53 and Murine Double Minute-2 (MDM-2) protein, decreased Caveolin-1 (CAV-1) expression, and increased vascular endothelial growth factor expression.

Cardiac metastasis is very rare but the autopsy incidence has been increasing over the last few years. Though secondary metastasis to the heart is more common than primary tumors, they tend to be unrecognized because they are clinically silent [14]. Mesothelioma, melanoma, lung, and renal cancer are the most common primary tumors that metastasize to the heart [15]. To the best of our knowledge, only 1 reported case of metastatic EHE to the heart has been reported in the literature, which was pulmonary in origin and metastasized to the pericardium.

### Conclusion

Our case report highlights an extremely rare clinical presentation, etiopathogenesis, diagnosis, and treatment of EHE of the spine with metastasis to the right atrium. Further studies are warranted to develop a treatment formula for this very rare tumor and consider combination chemotherapy and new adjuvant targeted immunotherapies to prevent disease progression. This rare manifestation prompts the following questions: (1) Are genomic alterations in TERT, TP53, and BRCA2 responsible for tumorigenesis? (2) Will Poly ADP Ribose Polymerase (PARP) inhibitors be useful in treating BRCA2-positive EHE?

### Statement of Ethics

The authors have no ethical conflicts to declare.

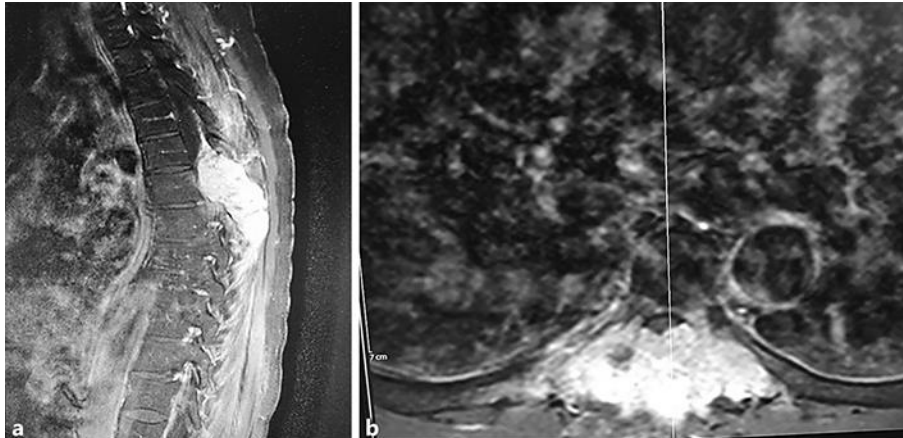
### Disclosure Statement

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this paper.

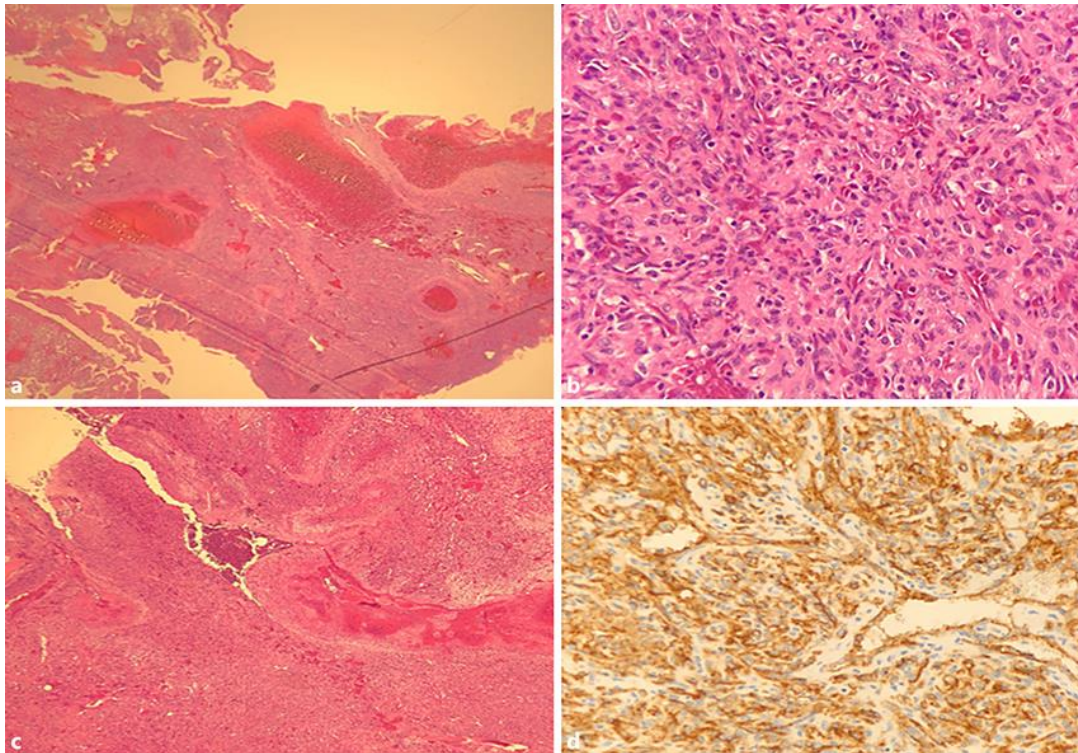
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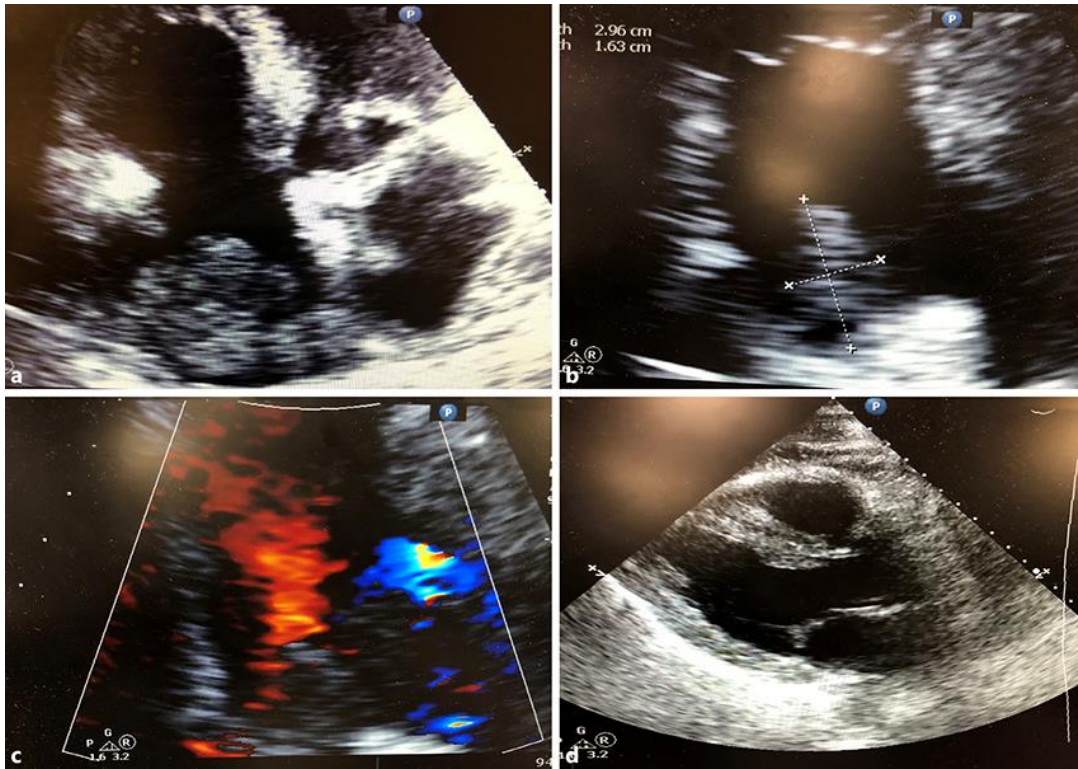
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**Fig. 1.** MRI of the thoracic spine: sagittal view (a) and axial view (b) showing a T6 mass measuring 3.7 × 6.5 × 8.5 cm leading to severe thoracic cord compression and loss of posterior bony elements.



**Fig. 2.** **a, b** Low-power HE-stained slides demonstrating ill-defined vascular channels. **c** High-power HE-stained slide demonstrating spindled epithelial cells. **d** Medium-power CD34 immunohistochemistry.



**Fig. 3.** a, b Initial Echo at the time of syncope showing a mass in the right atrium. c Initial Echo color Doppler showing reduced blood flow through the right atrium due to a mass lesion. d Repeat Echo after bevacizumab treatment showing no mass in the right atrium.