Case Report

rare tumors

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An unusual case of aggressive malignant spread of epithelioid hemangioendothelioma

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Abstract

Epithelioid hemangioendothelioma (EHE) is a rare vascular neoplasm which typically originates from liver, lung, or bone. Due to the low incidence of disease, the most effective treatment is not easily studied and much of the information known about EHE has been learned through case reports and case series. In this case, we will present an uncommon form of primary soft tissue EHE with local recurrence, bone metastasis, and lymphangitic spread to the lungs leading to respiratory failure. Imaging of the chest was atypical for EHE with intraseptal thickening and hilar lymphadenopathy. Respiratory failure was progressive despite aggressive multimodal treatment. This case highlights an unusually aggressive recurrence and metastasis of primary soft tissue EHE with atypical pulmonary imaging findings.

Keywords

Sarcoma, epithelioid hemangioendothelioma, EHE, vascular neoplasm, lymphangitic spread, pulmonary epithelioid hemangioendothelioma, soft-tissue EHE

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Introduction

Epithelioid hemangioendothelioma (EHE) is a rare vascular neoplasm that was first identified in 1975 in patients presenting with slow growing pulmonary nodules.[1] According to the National Institutes of Health (NIH), it is suspected to affect 1 in 1 million people, with only 20 cases diagnosed in the United States each year. The median age at diagnosis is 30–50 years old with a female predominance.[2] EHE commonly presents in liver, liver and lung, lung, or bone. Diagnosis can be a challenge as it is asymptomatic in 50%–76% of cases.[3] Pathology is the gold standard for diagnosis, and tumor cells typically stain positive for CD31, CD34, Fli-1, and ERG.[3] Expression of CAMTA1 due to the *WWTR1-CAMTA1* fusion gene is a characteristic finding.[3]

The most effective systemic therapy for advanced stage disease remains unknown, although many experimental treatments have been proposed. Surgery is the mainstay for patients with localized disease. Patients with multifocal hepatic involvement may be candidates for liver transplantation even in the setting of extrahepatic involvement.[4] Traditional chemotherapy and radiation are not as effective due to the slow growth of the tumors. Experimental treatments include anti-angiogenics and steroids. The prognosis for local disease treated with surgery is favorable with 5 years cumulative survival incidence of 75.3%.[2] In Stage 1 soft tissue EHE, the National Comprehensive Cancer

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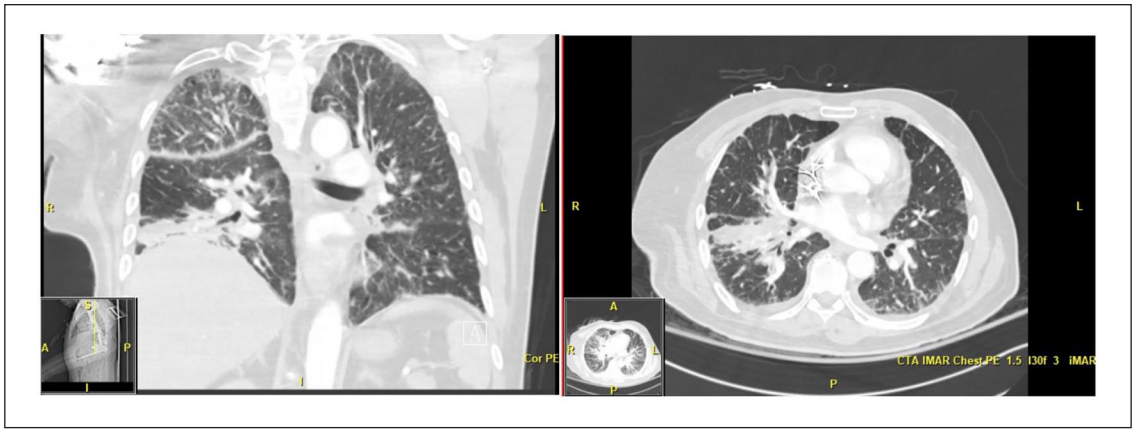

Figure 1. Coronal and transverse CT with contrast images of lung demonstrating subsegmental right lower lobe atelectasis with volume loss in the right hemithorax and asymmetric right greater than left diffuse interlobular septal thickening. Asymmetric lymphangitic carcinomatosis could present with a similar appearance.

Network guidelines recommend surveillance with MRI or CT imaging of the primary site and radiograph or CT imaging of the lungs every 6 months for 5 years. In this case, we will demonstrate an unusually aggressive recurrence and metastasis of primary soft tissue EHE with atypical imaging findings.

Case report

A 63 year old man with history of right median nerve EHE treated with wide local excision in 2013 presented to a primary care clinic 4 years later with pain along his right arm below his shoulder. He had received a radiograph of the right elbow and radiograph of the chest every 6 months for the past 4 years without evidence of recurrence. After history and physical examination of his arm, he was diagnosed with a benign muscular pathology potentially of the rotator cuff tendons. However, despite conservative treatments, the pain persisted and worsened. Although the pain was not in the same location as his previous tumor, his providers were concerned for tumor recurrence. He underwent CT scan of the right upper extremity in December of 2017, which showed post-surgical changes and no evidence of recurrence. The pain intensified, so in April of 2018, he had a PET-CT which showed abnormal uptake in the right forearm but no abnormal uptake in the area of pain and no evidence of metastatic disease. A biopsy was taken of the FDG avid area of the right forearm and interpreted as a traumatic neuroma. The patient was advised to continue conservative treatments. In February of 2019, due to intensifying pain, a radiograph of the right upper extremity showed an abnormality over the cortical surface of the distal aspect of the humeral shaft with a new lytic lesion. A repeat PET-CT in June of 2019 showed FDG avidity of the mid to distal right humeral shaft with associated periosteal changes and a medial soft tissue mass with two satellite nodules in the humeral neck area just above the elbow. A CT-guided biopsy of the right humeral mass confirmed recurrence of high-grade EHE. He was diagnosed with soft tissue recurrence and local bone metastasis of EHE. His case was discussed with a multidisciplinary team, who agreed to pursue surgical resection of his tumor.

Four days prior to surgery, he presented to a local emergency department with progressive dyspnea on exertion without hypoxia and lower extremity swelling. He reported "It is difficult to take a deep breath." CT imaging of the chest with angiography revealed new interstitial-nodular opacities suggestive of edema or infectious-inflammatory etiology and was negative for acute pulmonary embolism (PE). Cardiac work-up was also unremarkable. He did not have symptoms at rest and was discharged home. In the following days, he subjectively reported that his symptoms had improved and that he was no longer "huffing"; however, he continued to have dyspnea when climbing stairs. During pre-anesthesia medical evaluation it was noted that his lungs were clear to auscultation, he was able to lay flat without dyspnea, and his resting oxygen saturation was 96% on room air. However, a pre-procedure chest radiograph showed bilateral pulmonary opacities with predominantly interstitial/septal thickening and upper lung predominant fine reticulation/micronodularity.

He underwent surgical removal of his tumor. His pathology revealed high-grade EHE with nodal involvement and clear margins. In the post-operative period, the patient was successfully extubated; however, continued to require supplemental oxygen by nasal cannula. A chest CT angiogram with PE protocol showed a segmental PE associated with atelectasis, right diaphragm paralysis, and worsening interstitial-nodular opacities (Figure 1). This was suggestive of progression of his prior pulmonary edema but carcinomatosis could not be ruled out.

A transthoracic echocardiogram showed new severe right heart failure disproportionate to the degree of his PE. He was fully anticoagulated with heparin and received diuretics.

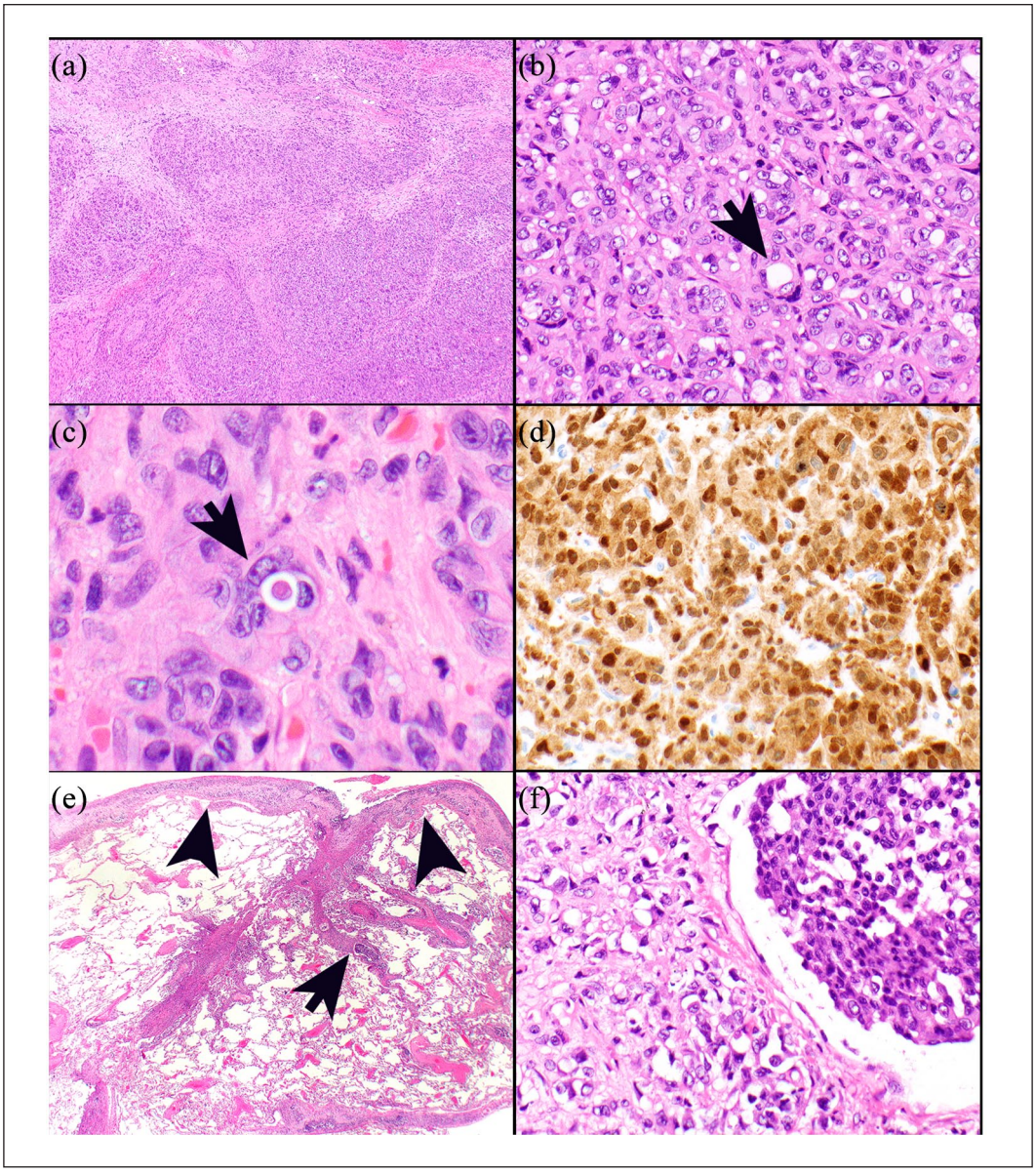

Figure 2. High-grade epithelioid hemangioendothelioma forming a 17.7 cm mass involving the humerus bone and adjacent soft tissue: (a) sheets of neoplastic cells in a fibrotic and desmoplastic background. (b and c) The neoplastic cells are of epithelioid cytology with many containing cytoplasmic vacuoles (arrows) which occasionally contain erythrocytes (arrow c). (d) The neoplastic cells are characteristically positive for CAMTA1. (e and f) Highgrade epithelioid hemangioendothelioma metastatic to lung (autopsy). (e) Lymphangitic distribution of tumor cells including subpleural (arrow heads) and interlobular septal (arrow) tumor spread. (f) The tumor cells are in interlobular septa (left hand side) and within lymphangitic spaces (right hand side). Magnification ×40 (a), ×400 (b, c-cropped, d, f), ×12.5 (e).

Over the next few days, his clinical status continued to decline. He ultimately developed respiratory failure and septic shock that required transfer to the intensive care unit (ICU) where he was intubated and treated with broad spectrum antibiotics. Bronchoscopy revealed bloody secretions with mildly edematous airway. No focal endobronchial abnormality or area of bleeding was identified. Bronchoalveolar lavage (BAL) was negative for malignancy. Chest imaging showed a diffuse alveolar filling process suspicious for alveolar hemorrhage, and he was treated empirically with high-dose steroids without response. Despite aggressive and comprehensive intervention, he ultimately succumbed to hypoxia without a unifying diagnosis for his rapid progressive illness. Autopsy revealed acute bronchopneumonia superimposed on organizing fibrinous pneumonia, right pulmonary artery thromboembolism, and EHE in a lymphangitic and intraparenchymal distribution (Figure 2).

Discussion

This case demonstrates a rare local recurrence of soft-tissue EHE with metastases to bone and lymphangitic spread to lungs 6 years after surgical removal of the primary tumor. The time to recurrence for bone EHE as seen in a few case reports was 12–18 months.[5,6] Multi-organ bone and lung involvement is felt to be rare in this disease estimated at 10% of metastatic cases.[7] Although the exact timing of pulmonary lymphangitic spread is unknown, the patient had no significant FDG uptake in the lungs on PET imaging 1 month prior to a CT scan showing interstitial-nodular opacities with possible carcinomatosis. Pulmonary EHE (pEHE) is heterogenous and diagnostically challenging as it ranges from radiographic signs with no clinical symptoms to those with clinical symptoms yet subtle radiographic signs. In a literature review of 93 cases of pEHE performed by Lee et al.,[8] typical radiologic findings of pEHE were described as bilateral pulmonary nodules less than 20 mm in diameter with an irregular morphology. A review of 20 cases of pEHE performed by Dail et al.,[9] identified cases with hilar lymphadenopathy, interlobular septal thickness, and pleural effusions. pEHE can mimic much more common conditions such as edema or infection. A few cases in the literature have described atypical CT findings including non-specific ground glass opacities, intralobular septal thickening, and airspace disease.[10–12] In our case, pEHE was concurrent with edema, infection, and arterial thrombus leading to a challenging diagnosis. Radiologic findings of lymphangitic spread can be interpreted as metastatic carcinoma and require a high index of suspicion.[13] As EHE can be an indolent tumor, PET imaging is not always positive for metastasis.[14] After treatment of EHE, the NCCN also recommends surveillance imaging of the chest with either radiograph or CT scan.

In our case, the screening chest radiographs and PET imaging were not suggestive of pulmonary lymphangitic spread, while a CT chest performed in the emergency department prior to surgery showed very subtle changes suggestive of edema or infectious/inflammtory changes. Mild changes were also see on the pre procedural chest radiograph. These changes were subtle and at the time were not attributed to lymphangitic spread. In one study comparing PET CT with high resolution CT imaging of the chest in the diagnosis of pulmonary lymphangitis carcinomatosis, both imaging modalities shared similar detection rates.[15] CT chest imaging could be considered to evaluate for pulmonary disease in EHE, particularly in high-grade subtypes.

In patients with pulmonary EHE, the most common cause of death is restrictive respiratory failure over years due to tumor burden or subacute alveolar hemorrhage. A few cases of more rapid decline have been described; however, these cases presented with pulmonary nodules with a discrete mass and a decline over months.[16] In contrast, our patient experienced progression over weeks with respiratory failure due to superimposed pneumonia and pulmonary artery thromboembolism. In this rare tumor type, lymphangitic spread is uncommon and not well studied. Corticosteroids have been proposed as a treatment option due to the tumor's occasional expression of glucocorticoid receptors; however, in this case, steroids were not effective.[7] Other case reports have suggested treatment of aggressive pleural EHE with carboplatin plus etoposide, interferon 2, azathioprine, and bevacizumab plus nab-paclitaxel. Traditional chemotherapeutic agents have been trialed without much success, and there are only a few examples of response.[17]

Due to the low incidence of EHE, little is known about the proper treatment, and clinical decision making still relies on case reports even 50 years after its discovery.[17] Based on our experience, we would recommend CT imaging of the chest when staging EHE, particularly in high-grade subtypes. Ongoing collaborative histology driven trials may advance our knowledge and understanding of this rare entity (NCT03331250, NCT03148275).[18,19]

Conclusion

This case illustrates an atypical and aggressive presentation of EHE that in a span of 1 month rapidly progressed to diffuse lung metastases complicated by multi-organ failure. The typical radiographic features of pulmonary nodules were not seen, and instead intraseptal thickening was noted in the radiology report. Radiograph and PET imaging were not suggestive of pulmonary involvement. CT imaging of the chest did show findings suggestive of lymphangitic spread. Corticosteroids have been suggested as a treatment option for EHE; however, they were not effective in this case. This case presentation is supported by a similar unique case in the literature and shows that regardless of the underlying histology any high-grade malignancy could lead to a fulminant course of systemic illness.

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Author contributions

ADH wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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Ethical approval

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Mayo Clinic Institutional Review Board.

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