Radiologic-Pathologic Correlation: Metastatic Pulmonary Epithelioid Hemangioendothelioma of Bone Primary

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ABSTRACT

Epithelioid hemangioendothelioma is a rare vascular malignancy often characterized by a clinically indolent course and delayed diagnosis. The authors present the radiologic and pathologic features of a case of pulmonary epithelioid hemangioendothelioma which was initially thought to be calcified granulomas.

Key words: Calcified pulmonary nodules, epithelioid hemangioendothelioma, epithelioid vascular tumors, intravascular bronchioloalveolar tumors

INTRODUCTION

Epithelioid hemangioendothelioma (EHE) is a rare low-to-intermediate grade vascular malignancy that occurs in multiple organs and tissues with a predilection for soft tissue of the extremities, bone, liver, and lung. It can be considered part of the morphologic spectrum of epithelioid vascular tumors, encompassing benign epithelioid hemangioma, low-to-intermediate grade EHE, and high-grade epithelioid angiosarcoma, with EHE being histologically distinct.[1] The primary sites observed in a recent cohort of 39 EHE cases included lung in 18%, bone in 15%, liver in 5%, and the remainder in other soft tissue sites, with about 21% localized to the head and neck.[2] Pulmonary EHE is rare with small-numbered case series in the literature[3-5] since its first description as “intravascular bronchioloalveolar tumors” nearly 40 years ago.[6] It has no characteristic presentation, but a predilection for middle-aged females (mean age of 40.1 ± 17.5 years).

Although the biological behavior of EHE is typically more indolent than angiosarcoma, metastases occur in 20–30% of cases and the 5-year survival approaches 60%.[7] Significant independent risk factors in patients with pulmonary EHE include pleural effusion, pulmonary symptoms, weight loss, and anemia, with significantly worse survival in patients with hemorrhagic symptoms such as hemoptysis and hemorrhagic pleural effusions.

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Given its rarity, relatively slow growth, and nonspecific clinical and radiologic findings, EHE requires confirmatory tissue diagnosis. Typical clinical presentation is an indolent course with delayed diagnosis and several non-definitive intervening diagnostic tests. Treatment of pulmonary EHE is on a case-by-case basis with considerations of surgical resection, chemotherapy including hormonal therapy, radiotherapy, and lung transplantation.

A 61-year-old woman presented to our institution for definitive treatment of recently biopsy-proven EHE of the vertebral bodies and ribs. This patient is a lifelong nonsmoker who lives in an area where sequelae of prior granulomatous disease of the lungs are relatively common. Her clinical history started 6 years ago with empiric treatment for progressive thoracic back pain suspected to be neuropathic in origin. Her symptoms persisted and further work-up 3 years later revealed radiographic and computed tomography (CT) abnormalities in the left posterior 8th and 9th ribs; bilateral pulmonary nodules were described as bilateral calcified granulomas. Biopsy of the 9th rib showed Streptococcus bovis osteomyelitis, for which she was treated with surgical debridement and antimicrobial therapy. Over the last year, her pain worsened in the same region, and imaging revealed a soft tissue mass at the T7–T10 vertebral bodies and extending to the ribs; this was biopsied and pathology showed EHE. On presentation to our institution, additional imaging was performed to re-evaluate and determine if surgical resection with perioperative radiotherapy for local control was a viable option. This article focuses on the pulmonary radiologic and pathologic findings which ultimately determined clinical management.

**RADIOLOGIC FEATURES**

A non-contrast enhanced CT revealed multiple bilateral lobulated variable-sized pulmonary nodules, many with coarse calcifications [Figure 1a]. The largest nodule measured about 14 mm in the left upper lobe and showed very minimal enlargement compared to prior CT. Positron emission tomography/computed tomography (PET/CT) demonstrated minimal, if any, fluorodeoxyglucose (FDG) uptake of the pulmonary nodules [Figure 1b] and moderate FDG uptake of the rib lesions.

A literature review of 93 cases of pulmonary EHE described the usual radiologic feature of pulmonary EHE as bilateral pulmonary nodules of variable size ranging from 5 to 15 mm, but generally less than 20 mm.[21] A study evaluating CT features of 178 nodules or masses in six patients with pulmonary EHE showed a subpleural (93% within 2 cm from the pleura) and perivascular (100%) predilection, with typical pulmonary EHE appearing as multiple irregular nodules with punctate calcifications (90% were <10 mm in diameter with the largest nodule or mass in each patient having a mean size of 27 mm).[21]

Multiple calcified pulmonary nodules most commonly arise as sequelae of prior granulomatous diseases, such as histoplasmosis, and less often from healed varicella pneumonia and tuberculosis. Other differential considerations of calcified pulmonary nodules with variability in distribution, occurrence, and association with calcified lymph nodes include pneumoconioses such as coal workers’ pneumoconiosis and silicosis, secondary hyperparathyroidism, hamartomas, and metastatic diseases such as those from osteosarcoma, colon cancer, or those in association with chronic renal failure, hyperparathyroidism, sarcoidosis, and multiple myeloma.

Radiologic clues that may favor etiologies other than infectious or inflammatory include the irregular morphology of the soft tissue component of the pulmonary nodules as well as their distribution. In this case, the distribution was predominantly subpleural and perivascular. The pattern of solitary pulmonary nodule calcifications can be useful in refining the differential diagnosis with “popcorn”, “central”, “concentric”, or “homogeneous or diffuse” patterns of calcifications being classically benign. Other patterns of calcifications are more indeterminate and raise the suspicion for malignancy. The largely eccentric pattern of calcifications in the larger nodules in this case could represent engulfed adjacent calcified granulomas; however, this was not observed in the biopsy material.

Associated non-pulmonary findings such as the expansile lytic lesions in the left posterior 8th and 9th ribs [Figure 2] and the incidentally detected hepatic mass [Figure 3] in this case may provide additional clues to consider another differential diagnosis. While the generally nonspecific
imaging features of EHE in the lungs are also true in the bone and in the liver, the multi-system distribution of the disease would be consistent with a vascular process.

**PATHOLOGIC FEATURES**

Review of prior rib biopsies concurred with nonspecific chronic inflammation. A CT-guided biopsy of the largest pulmonary nodule demonstrated a predominantly myxohyaline matrix with embedded bland epithelioid tumor cells arranged in short cords. The neoplastic cells contained occasional intracytoplasmic vacuoles with fragmented red blood cells and intranuclear cytoplasmic inclusions. The neoplastic cells were strongly positive for the vascular markers CD31 and Fli-1, and weakly positive for keratin AE1/AE3 [Figure 4].

Microscopically on low power, the growth pattern of EHE often correlates with the lesions seen on chest imaging studies. The tumor frequently forms multiple pulmonary nodules, growing in a “lymphangitic” pattern in close proximity to bronchovascular bundles, interlobular septa, and the pleural surface. Intravascular growth is also common. The tumor nodules are often hyalinized and less cellular centrally. The EHE cells are typically embedded in a characteristic myxohyaline or myxochondroid matrix and are arranged in short cords. Although EHE is a vascular neoplasm, the cells do not form extracellular vascular structures. Instead, some EHE cells have a single intracytoplasmic vacuole that represents an intracytoplasmic vascular lumen. Occasionally, a fragmented red blood cell will be observed within the vacuole. In the lungs, a micropolypoid growth pattern may be observed at the periphery of the tumor nodules, in which plugs of tumor protrude into the adjacent alveolar spaces and bronchioles. The majority of EHE cases have bland nuclei with occasional intranuclear cytoplasmic inclusions; however, intermediate-grade tumors will display increased cellularity, necrosis, and increased nuclear pleomorphism.

Upon immunohistochemistry, the cells of EHE typically express vascular markers such as CD31, Friend Leukemia Integration 1 (Fli1), Ets Related Gene (ERG), and CD34, and up to 40% of the cells express low-molecular-weight cytokeratin or Epithelial Membrane Antigen (EMA).
Recently, a subset of both low- and intermediate-grade EHEs has been shown to harbor t(1;3)(p36;q23-25) resulting in the WWTR1–CAMTA1 fusion gene (WW Domain Containing Transcription Regulator 1 and Calmodulin Binding Transcription Activator 1, respectively). This recurrent genetic finding may be useful in differentiating EHE from other entities in the differential diagnosis, since it seems to be specific for EHE based on early studies.\textsuperscript{[10]} [Figure 4].

The histopathologic differential diagnosis of EHE is broad. Granulomatous inflammation is often considered because of the central hyalinization and occasional necrosis seen in EHE, and also because EHE cells may resemble epithelioid histiocytes. Another common pitfall is the expression of keratin by EHE, which may lead to consideration of metastatic carcinoma if a lymphangitic or intravascular growth pattern is observed, or consideration of malignant mesothelioma if pleural growth is prominent.\textsuperscript{[10]} EHE can be differentiated from these entities morphologically by careful attention to the characteristic extracellular matrix and intracytoplasmic vacuoles, and strong expression of vascular markers by immunohistochemistry. Finally, epithelioid angiosarcoma should be considered in the differential diagnosis when nuclear atypia, necrosis, and increased mitotic activity are observed. Identification of the characteristic matrix and intracytoplasmic lumen formation favors the diagnosis of EHE, while formation of extracellular vascular structures, papillary growth, blood lakes, and prominent nucleoli favors epithelioid angiosarcoma.\textsuperscript{[10]}

In difficult cases, testing for the WWTR1–CAMTA1 fusion may be helpful in differentiating EHE from epithelioid angiosarcoma, which can be performed by Reverse Transcription Polymerase Chain Reaction (RT-PCR) or Fluorescence In Situ Hybridization (FISH).

**DISCUSSION**

In isolation, the clinical and radiologic features of EHE are nonspecific; however, multi-system involvement can provide a clue to a vascular etiology. This case reflects the usual indolent course of EHE with delayed diagnosis confounded here by the diagnosis of osteomyelitis in the ribs and the initial radiologic interpretation of bilateral calcified granulomas in the lungs. The distinction between pulmonary calcified granulomas and metastatic pulmonary EHE can be radiologically challenging and tissue diagnosis may be needed, as was the case here. Here, osteomyelitis was almost certainly a false-positive in the setting of a pre-existing EHE. To our knowledge, there are no reports describing EHE arising from sites of treated osteomyelitis.

**CONCLUSION**

In this patient, tentative management of the osseous lesions was initially surgical excision with high probability of significant morbidity, followed by local radiation therapy. After the diagnosis of metastatic pulmonary EHE, however, the treatment approach was changed. She instead underwent local radiation to her ribs with concurrent Taxol treatment. Four-month follow-up PET/CT showed reduced metabolic activity in the left posterior thoracic...
hemangioendothelioma; the multiple lung nodules previously associated with minimal metabolic activity were relatively unchanged; and there were no new lesions identified.

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Conflicts of interest
There are no conflicts of interest.

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