CASE REPORTS

MULTIFOCAL PULMONARY EPITHELIOID HEMANGIOENDOTHELIOMA: A METASTATIC DISEASE MIMICKER

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Abstract

We present the case of a 79-year-old woman with multiple bilateral pulmonary nodules identified during an investigation for abdominal pain, initially suspected to represent metastatic disease. Extensive clinical, laboratory, and imaging workup failed to reveal a primary origin. After two non-diagnostic transthoracic lung biopsies, the patient underwent single-port video-assisted thoracoscopic surgery (VATS) with excision of two nodules from the upper and lower lobes of the right lung. Histopathological examination revealed an epithelioid hemangioendothelioma (EHE), a rare vascular neoplasm. This case illustrates the diagnostic process and pathological features of pulmonary EHE, with a brief clinical overview.

Keywords: *Hemangioendothelioma, Epithelioid; Lung; Thoracic Surgery; Pulmonary Medicine; Pathology*

INTRODUCTION

Epithelioid hemangioendothelioma (EHE) is a rare, low-grade malignant vascular neoplasm that can arise in various organs, including the liver, lung, and bone. In the lung, it typically presents as multiple bilateral nodules.[1] Histopathology plays a central role in diagnosis due to the lack of specific clinical manifestations.

CLINICAL CASE

A 79-year-old woman underwent abdominal and pelvic computed tomography (CT) due to abdominal pain, which revealed multiple bilateral pulmonary nodules. Given the suspicion of pulmonary metastases from an unknown primary, she was referred for further etiologic investigation. A comprehensive diagnostic workup was performed, including PET-CT, thoracoabdominal-pelvic CT, thyroid ultrasound with fine-needle aspiration of a benign nodule, mammography, colonoscopy, upper endoscopy, and full laboratory evaluation, none of which identified a primary neoplasm. The lung lesions demonstrated mild growth and significant 18F-FDG uptake.

Two percutaneous transthoracic biopsies were inconclusive. Due to lesion persistence and lack of diagnosis, surgical biopsy was proposed. The patient underwent uniportal VATS with wedge resection of nodules in the upper and lower lobes of the right lung, without complications.

Intraoperative inspection revealed mild anthracosis and two subpleural nodular lesions, one in the upper lobe with pleural retraction, and one in the lower lobe, and both were excised.

Histological examination revealed well-circumscribed nodular lesions composed of a central hypocellular, hyalinized to myxohyaline stroma, with a relatively more cellular peripheral component. Tumor cells were predominantly arranged singly, in cords and small nests, embedded within the myxohyaline matrix. The neoplastic cells were epithelioid, with abundant eosinophilic cytoplasm and round to oval nuclei with inconspicuous nucleoli. Characteristic intracytoplasmic vacuoles, occasionally suggestive of primitive vascular lumina, were identified. No significant cytological atypia was observed. Mitotic figures were absent, and there was no necrosis. The lesions showed a non-destructive growth pattern, with preservation of the surrounding lung parenchyma and no evidence of an infiltrative architecture.

Immunohistochemical analysis showed positivity for CD31, ERG, and CAMTA1. Tumor cells were negative for S100, AE1/AE3, TTF-1, Desmin, DOG1, and TFE3. The proliferative index (Ki-67) was low (<5%).

Overall, the morphological and immunohistochemical findings were consistent with pulmonary epithelioid hemangioendothelioma. Figure 1 illustrates the main morphological and immunohistochemical features of the tumor.

Following surgery, the patient remained asymptomatic. Given the low-grade histology, multifocality, and absence of symptoms, a surveillance strategy was adopted. The patient is currently under active surveillance by Pulmonology and Thoracic Surgery.

DISCUSSION

EHE is a rare tumor, classified among low-grade malignant vascular neoplasms. It is more common in females and, while it can occur at any age, it is usually diagnosed between the third and fifth decades of life [2], making this case particularly unusual due to the patient's advanced age. Nevertheless, its often indolent clinical course may allow lesions to remain clinically silent for prolonged periods, which may account for diagnosis at an advanced age, as observed in the present case.

Its typical presentation with bilateral pulmonary nodules can closely mimic metastatic disease, often

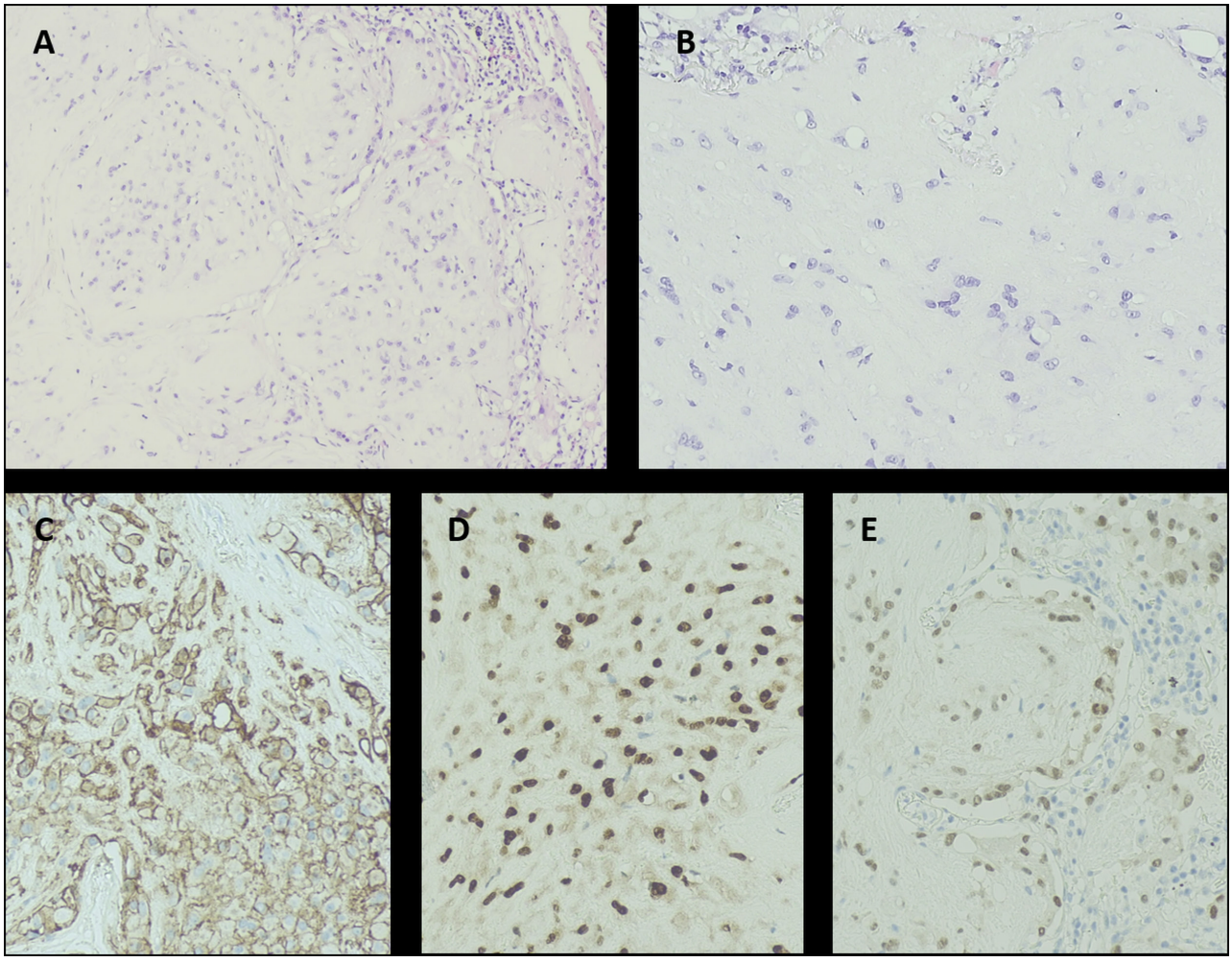

Figure 1

Pulmonary Epithelioid Hemangioendothelioma.
A) Hematoxylin–eosin (HE), 40×: well-circumscribed pulmonary lesion composed of a sclerotic to myxohyaline stroma with cords and nests of epithelioid tumor cells.
B) HE, 200×: detail showing epithelioid cells with round to oval nuclei and characteristic intracytoplasmic vacuoles, suggestive of primitive vascular lumina; no significant cytological atypia or mitotic activity is identified.
C) CD31, 200×: diffuse membranous and cytoplasmic positivity in tumor cells, confirming endothelial differentiation.
D) ERG, 200×: diffuse nuclear expression supporting endothelial differentiation.
E) CAMTA1, 200×: nuclear positivity, used as a surrogate marker for the WWTR1–CAMTA1 gene fusion in epithelioid hemangioendothelioma.

prompting extensive diagnostic workup as in this case.[3,4] Despite its low proliferative activity, increased FDG uptake on PET imaging has been described in pulmonary EHE and may further contribute to diagnostic confusion, particularly in asymptomatic patients. [5]

Histological diagnosis may be challenging due to the tumor's rarity and variable cellularity, especially in older individuals. While endothelial markers such as CD31 and ERG are essential to establish vascular differentiation, definitive classification relies on careful evaluation of morphological features and, when available, molecular findings. The differential diagnosis of pulmonary epithelioid hemangioendothelioma includes both metastatic epithelial malignancies and other epithelioid vascular neoplasms. In this context, integration of histological architecture, cytological features and clinical presentation is fundamental.

Among vascular neoplasms, epithelioid angiosarcoma represents the most relevant differential diagnosis. It is characterized by an aggressive and destructive growth pattern, with poorly demarcated, highly infiltrative lesions composed of irregularly shaped anastomosing vascular channels or sheet-like growth, marked cytological atypia, frequent mitotic activity and necrosis. In contrast, the present case showed well-formed cords and nests of epithelioid cells embedded in a myxohyaline stroma, with characteristic intracytoplasmic vacuoles and a low proliferative index, features that are typical of pulmonary epithelioid hemangioendothelioma.

At the molecular level, identification of the WWTR1–CAMTA1 gene fusion is considered the diagnostic gold standard for EHE. Nuclear CAMTA1 immunohistochemical expression has been shown to be a highly sensitive and specific surrogate marker for this translocation and was demonstrated in the present case.[6] Approximately 10% of EHEs harbor an alternative YAP1–TFE3 fusion; accordingly, negative CAMTA1 expression does not exclude the diagnosis, and immunohistochemical staining for TFE3 may be useful in selected cases. [7] In our case, TFE3 immunostaining was negative, consistent with a non–YAP1–TFE3 fusion epithelioid hemangioendothelioma.

Prognosis in pulmonary epithelioid hemangioendothelioma is variable and influenced by several factors, including symptomatic presentation, pleural involvement, tumor burden, and extrapulmonary dissemination.[8,9] In asymptomatic patients with low-grade histological features and stable disease, a conservative management strategy is generally appropriate. In the present case, the absence of symptoms, low-grade histological features and lack of disease progression supported an approach based on active surveillance. Surgery is mainly indicated for diagnostic purposes or local control, whereas systemic therapies are reserved for cases with symptomatic progression or organ dysfunction.[8]

CONCLUSION

This case highlights the importance of a multidisciplinary approach in the evaluation of multiple pulmonary nodules of unknown origin. EHE, although rare, should be considered in the differential diagnosis, particularly in multifocal presentations with no evident primary tumor. Histopathology and immunohistochemistry remain essential for accurate diagnosis.

Conflict of interest

The authors declare no conflicts of interest.

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