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Epithelioid Hemangioendothelioma: An Approach to A Pleural Spindle Cell Sarcoma

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ABSTRACT

Epithelioid hemangioendothelioma (EHE) is a rare neoplasm of vascular endothelial origin. It can develop in any tissue, however, it occurs primarily in the soft tissue, liver, and rarely in the lung and pleura. Most cases of EHE are discovered incidentally. This current report represents a case of a 58-year–old male who presents with vague symptoms of back pain and decreased mobility. The patient was found to have an incidental epithelioid hemangioendothelioma of the pleura.

Keywords: *Pleural Epithelioid Hemangioendothelioma, Sarcomatoid Carcinoma, Solitary Fibrous Tumor, Malignant Mesothelioma, Desmoid Tumor*

Introduction

Epithelioid hemangioendothelioma (EHE) is a rare neoplasm of vascular endothelial origin. It can develop in any tissue, rarely seen in the pleura. Diagnosis of EHE is usually challenging, especially for those arising in the pleura. We report a case of EHE located in the pleura and an approach to such difficult cases.

Case Presentation

A 58-year-old male presented with lower back pain and decreased mobility for the past 4 years, and currently on a wheel chair. He was investigated and a computed tomography (CT) scan showed multiple lytic bone lesions and spinal stenosis. Incidentally, a well-defined right upper lobe pleural-based soft tissue lesion, measuring 2.0 x 3.0 cm was identified. The lesion was only found in the pleural cavity without pulmonary involvement. In addition, the patient was found to have hyperparathyroidism causing his lytic bone lesions. CT-guided core needle biopsy from the right pleural mass was performed.

Microscopic examination of the hematoxylin eosin-stained section from the tumor showed a proliferation of low-grade spindle cell neoplasm embedded within myxohyaline stroma. This morphology suggests the differential diagnosis of vascular neoplasm, Solitary fibrous tumor (SFT), Malignant mesothelioma (MM), and Sarcomatoid carcinoma (SC) (it will be discussed further later on). The following immunohistochemical (IHC) stains have been done showing the neoplasm to be positive only for ERG (ETS family transcription factor ERG) (Fig. 1). It is negative for Pancytokeratin (AE1/AE3), Factor VIII, CD34, CD31, CD68, CD163, Chromogranin A, S100 protein, HMB45, Desmin, Smooth muscle actin (SMA), Calretinin, TTF-1, and STAT6. The positivity of ERG antibody is suggestive of low-grade vaso-formative neoplasm, including the histomorphology of a low-grade spindle cell neoplasm embedded within myxohyaline stroma is consistent with epithelioid hemangioendothelioma. He underwent a video assisted thoracic surgery (VATS) and pleural mass resection, it further confirms the the diagnosis of Epithelioid Hemangioendothelioma (Fig. 2-3). The patient was admitted for the workup of malignancy under the care of oncology. Due to the patient's morbidities a constant follow up approach is taken instead of chemotherapeutic or radiotherapeutic modalities.

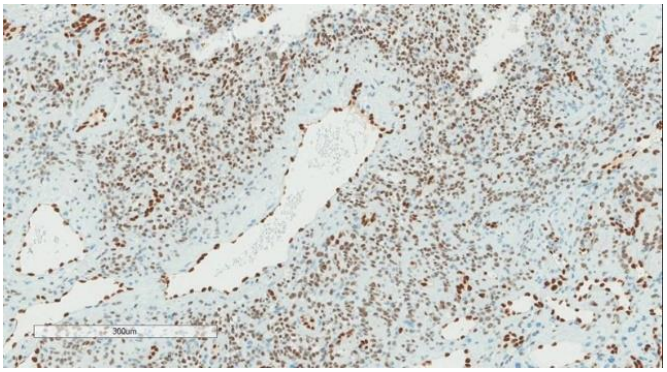

Figure 1: Low power immunohistochemical stain for ERG antibody is positive in the spindle cells and endothelial cells of the large vessels. This confirm vascular origin of the spindle cell lesion and supporting the diagnosis of epithelioid hemangioendothelioma X 400.

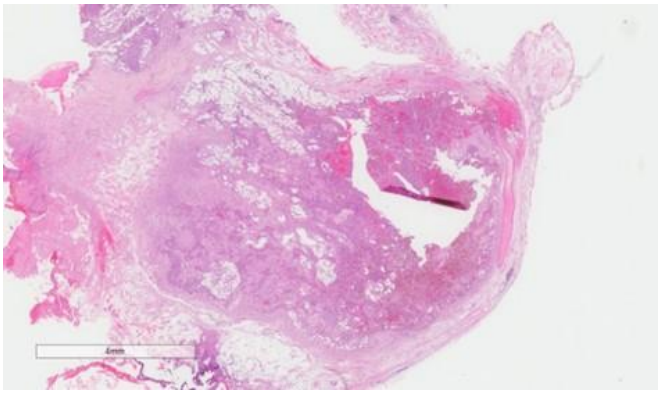

Figure 2: Low power hematoxylin eosin stained section show a well circumscribed nodule within the parietal pleura with dark and pale areas. X 200.

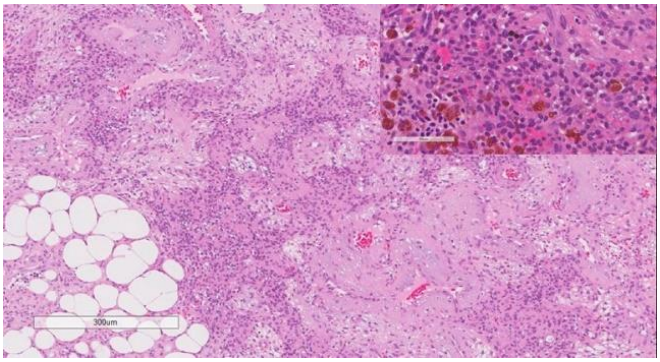

Figure 3: Low power hematoxylin eosin stained section, show thick walled vessels surrounded by a spindle cell proliferation, the inset confirm low grade nuclei with rare mitosis. Some of the cells show cytoplasmic clearing X 400.

Discussion

Epithelioid hemangioendothelioma (EHE) is a malignant endothelial neoplasm that most commonly involves soft tissue, bone, lung, skin, and liver; rarely in the pleura (Lazarus *et al*., 2011; Kim *et al*., 2011). To the best of our knowledge there are about 40 cases of pleural EHE (PEHE) have been reported in the English literature (Fan *et al*., 2016). The initial symptoms of PEHE are typically non-specific with chest pain, dyspnea, or persistent cough. On the other hand, similar to our case, it can be found incidentally (Salijevska *et al*., 2015).

Our case highlights how to reach a final diagnosis on limited tissue and broad differential diagnosis. The microscopical picture examination has its limitation due to the small size of the biopsy; nevertheless, the lesion is a low-grade, spindle cell neoplasm embedded within myxohyaline stroma. As the lesion has a myxohyaline stroma and the aforementioned single positivity for ERG IHC, the following differential diagnoses are thought of: Epithelioid hemangioendothelioma (EHE), Sarcomatoid carcinoma (SC), Solitary fibrous tumor (SFT), Malignant mesothelioma (MM) and Desmoid tumor (DT).

First, SFT has an indolent presentation. Microscopically it has a distinctive disorganized arrangement of low-grade looking spindle cells “patternless pattern” within a collagenized stroma. It is usually positive for STAT6, CD34, and BCL-2 (Ali *et al*., 2021); our case was negative for the aforementioned IHCs. These findings together with ERG positivity in our case has led us to remove SFT from the differential diagnosis. Further evaluation by molecular analysis of the NAB2-STAT6 gene fusion (Huang *et al*., 2016) has not been done due to limited tissue samples.

Second, MM, the sarcomatoid variant, has a somewhat similar microscopic picture; spindle cells embedded in collagenized/hyalinized stroma. However, MM differs by having intermediate to high cytological atypical spindle cells arranged in bundles to fascicles. Rare cases of MM have heterologous

elements (Hajj *et al*., 2021). MM is usually positive for Calretinin and Cytokeratin, although rare cases can be negative (Travis *et al*., 2010). Surprisingly, rare cases of MM can be positive for TTF-1 (Richter *et al*., 2016). Our case did not demonstrate reactivity to either of the aforementioned IHCs. Although, Sarcomatoid MM has a variable IHC staining pattern, nevertheless, the morphology of malignant epithelial cells is almost always present which led us to remove it from the list of differentials. MM has versatile genomic alteration (Hajj *et al*., 2021), which was not studied in our case.

Third, DT comprising intersecting fascicles of bland spindled fibroblastic cells interspersed with a loose fibrillar collagenous matrix, it has an infiltrative border to the surrounding tissue (Travis *et al*., 2010). Usually, it is positive for SMA, nevertheless, our case is negative. ERG is usually negative in DT. CTNNB1 Mutation is found in ~90% of cases.

Lastly, EHE, the classic WWTR1-CAMTA1 fusion morphology has epithelioid endothelial cells with abundant and eosinophilic, often vacuolated, cytoplasm. The nucleus is round, vesicular chromatin, and occasionally indented. Vascular lumina are present, most of them are small; some are located intracellularly and are responsible for the cytoplasmic vacuolation. Occasionally, containing red blood cells within the vascular lumina. YAP1-TFE3 fusion shows distinctive histological features. The tumor cells usually have eosinophilic cytoplasm with predominantly solid growth and often form vascular spaces. Mitoses, pleomorphism, and necrosis are variable, however, some areas show scanty or absence of the aforementioned features. An inflammatory infiltrate is often present at the periphery; this may contain well-formed germinal centers and/or a large number of eosinophils. The stroma may be scanty or have a prominent myxoid appearance. Osteoclast-like multinucleated giant cells may be present (Rosai J and Ackerman's Surgical Pathology, 2011).

Miettinen, *et al*. mentioned in their article that 42 out of 43 cases of EHE were positive for ERG IHC, as it is found in the majority of malignant vascular endothelial neoplasms (Miettinen *et al*., 2011).

Wu, *et al*. mentioned that they have studied 33 cases of EHE and found that 32 of the cases are positive for CD34 and CD31 IHC (97%) (Wu *et al*., 2019).

Also, Fujji, *et al*. mentioned primary liver EHE is CD31 positive in 8 cases out of 9 (89%) and CD34 positive in all 9 cases (100%) (Fujii *et al*., 2008).

The IHCs CD34 and CD31 are positive in the majority of EHE cases nonetheless there are rare occurrences where they are negative, as seen in our case. ERG IHC is more specific and sensitive for EHE compared to CD34 and CD31.

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According to Rosenbaum, *et al*. WWTR1-CAMTA1 fusion is present in most classic epithelioid hemangioendothelioma. A small subset of cases show distinct morphology and are characterized genetically by a YAP1-TFE3 fusion. Lastly, more than half of the tumors studied in their institute had a genetic alteration beyond the disease-defining gene fusion. Pleural EHE had an aggressive clinical course, with a 22% survival rate at 5 years (Rosenbaum *et al*., 2020).

Conclusion

Epithelioid hemangioendothelioma is a malignant endothelial neoplasm that has different clinical presentations. Two molecular variants with their respective histomorphology. It is positive for endothelial IHC markers. Has intermediate prognosis. There are different treatment modalities.

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