Case Report

Pleural epitheliod hemangioendothelioma: What started as a liver fluke and ended up being almost mistaken for malignant mesothelioma

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Abstract:

Epitheliod hemangioendothelioma (EHE) is a rare tumor of vascular origin. The pleural variant has only been reported around 20 times in English literature. It commonly occurs in older men and carries a poor prognosis with average survival lasting from a few weeks to months. Pleural EHE (PEHE) can be a diagnostic challenge due to its rarity as well as similarities to other pleural and vascular tumors. There is currently no standard treatment for EHE. Due to the rarity of this disease, reaching a final diagnosis is challenging. It's clinical, radiological, and pathological resemblance to malignant mesothelioma can cause a delay in diagnosis. Special stains such as CD31, CD34, and factor VIII related antigen can help differentiate between the two. Ordering appropriate stains in a timely manner can help avoid misdiagnosing PEHE.

Key words:

Epitheliod hemangioendothelioma, mesothelioma, pleural epitheliod hemangioendothelioma

Epitheliod hemangioendothelioma (EHE) is a rare tumor of vascular origin.[1] Dail *et al*. described the first case of EHE in 1975 and named it "intravascular bronchi alveolar tumor" believing it to be an aggressive form of bronchi alveolar cell carcinoma.[2] The term EHE was coined by Weiss and Enzinger in 1982 after histological studies demonstrated the endothelial origin of the tumor.[3]

Pleural EHE (PEHE) has been reported around 20 times.[4] It is highly aggressive with no defined treatment.[5,6] We report a unique presentation of the youngest case of PEHE to date.

Case Report

A 24-year-old Middle Eastern male presented in the clinic with abdominal pain. Initial diagnostic studies suggested *Echinococcus* infection in the liver. The patient had moved to the US along with his family, from Iraqi Kurdistan, at the age of two. After being prescribed albendazole, the patient returned with persistent nausea, vomiting, chest pain, abdominal pain, shortness of breath, and a 40 pound weight loss a few weeks later.

Further imaging revealed a liver lesions characteristic of *Echinococcus* and a right sided pleural effusion. Thoracentesis revealed a *Klebsiella* infection with negative cytology. After failing antibiotics, an exploratory laparotomy was performed for hepatic marsupialization of the cysts. Intraoperatively, the cysts could not be aspirated, and biopsy results were negative for malignancy. The patient was discharged postoperatively.

The patient presented with worsening symptoms including hemoptysis only 2 weeks later. Repeat imaging revealed a pleural effusion on the same side. With no diagnosis after another thoracentesis and bronchoscopy, a video-assisted thoracic surgery was performed. The intraoperative findings of significant

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pleural thickening suggested mesothelioma. Frozen sections initially showed malignant neoplasia of the pleura favoring mesothelioma was made [Figure 1]. The final stains, performed at University of Michigan, were strongly positive for CD31 and negative for MOC-31, Ber-Ep4, p63, OCT-4, and alpha-fetoprotein. Based on these results a final diagnosis of PEHE was made.

The patient's condition deteriorated quickly. A computerized tomography scan revealed peritoneal nodularity most consistent with peritoneal carcinomatosis. He did not tolerate a trial of carboplatin and paclitaxel and died due to respiratory failure within 2 months.

Discussion

EHE is a low-grade vascular tumor representing only 1% of all vascular tumors. It can occur in variable locations such as the lung, liver, skin, bone, and gastrointestinal tract.[4]

The exact etiology of EHE is unclear. Theories regarding angiogenesis stimulation and endothelial proliferation due to biological substances or genetic disorders have been postulated.[4,7] Although there are no strong genetic links, Woelfel *et al*. was able to detect a recurrent break in the chromosomal region 1p36.3 in 5 out of eight cases. This chromosomal aberration had previously been described in two independent cases suggesting it as a unique molecular cause for the development of EHE.[8] PEHE, in particular, has been related to asbestos and radiation exposure.[7] Our patient did not have a history of radiation or asbestos exposure while living in the US. However, he was unsure of exposure to asbestos in Kurdistan. He only visited 4 times with each visit lasting 3-4 weeks, a period not long enough to be associated with asbestos-related pleural disease.

PEHE more commonly targets older men with the average age at diagnosis being 62.3 years.[4] Clinical manifestations of PEHE may include nonspecific pulmonary complaints such as cough, pleuritic chest pain, dyspnea, and sputum production. More than half of the patients, however, are asymptomatic with an incidental radio-graphic finding.[4,7]

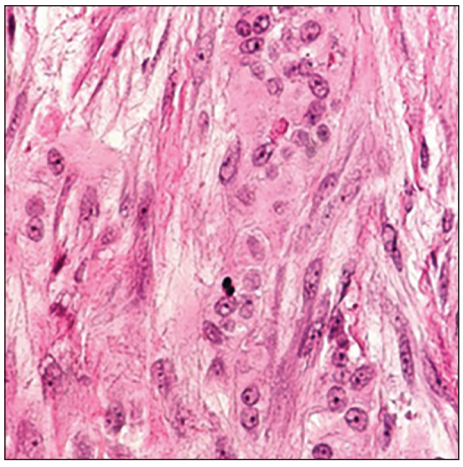

Figure 1: Histological staining of pleural biopsy with atypical cells initially favoring mesothelioma

PEHE is diagnosed based on histopathological examination along with immunohistochemical staining. However, diagnosing PEHE can be a challenge at times due to its low incidence and difficulty to differentiate from other pleural and vascular tumors. It's clinical, radio-graphical and histological mimicry of malignant pleural mesothelioma, another rare tumor, has often led to the initial misdiagnosis of PEHE.[8,9] Endothelial markers such as CD31, CD34, factor VIII related antigen, Fli-1, and BNH9 can help distinguish between the two as malignant mesothelioma does not demonstrate vascular differentiation.[1,4] Recently, WWTR1/CAMTA1 gene fusion has been reported as a genetic abnormality, which may help in distinguishing PEHE from other vascular tumors such as epitheliod hemangioma and epitheliod angiosarcoma, especially on small biopsy samples. However, its sensitivity and specificity has not yet been defined.[1,8] Due to the rarity of PEHE as well as the unavailability of some of these differentiating tests at most institutes, the diagnosis of PEHE is difficult. Therefore, it is imperative to include PEHE as a differential on the list of pleural tumors and order appropriate tests to confirm the diagnosis early on.

PEHE is a highly aggressive tumor with a mean survival time of 10-12 months. Currently, there is no standard treatment for PEHE. Surgical resection is considered for locally extended PEHE but firm adherence to the lung, chest wall or diaphragm is a contraindication. Cases that cannot be surgically resected die within a few weeks secondary to worsening respiratory compromise.[5,6]

EHEs are chemo and radio-resistant tumors. Radiation is reserved as a palliative measure for rare cases with bone involvement and when chemotherapy does not obtain a complete response. The combination of six cycles of carboplatin and etoposide resulted in a complete response in one case whereas the combination of cisplatin and etoposide resulted in a partial response in another.[4,10] A Korean case of PEHE with bone involvement treated with palliative radiation followed by three cycles of tri-weekly adriamycin and sequential mesna, doxorubicin, ifosfamide, and dacarbazine (MAID) resulted in 10 months survival, when response to MAID had previously been incomplete in pulmonary EHE.[5] Other drugs targeting the vascular origin of PEHE such a bevacizumab, retinoids, and interleukin-2 have all shown a low rate of response.[4]

We highlight the importance of adding PEHE to the list of differentials for pleural tumors and being able to distinguish it from other pleural and vascular tumors in order to avoid misdiagnosing it initially.

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Conflicts of interest
There are no conflicts of interest.

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