

CASE REPORT

Multicentric epithelioid hemangioendothelioma; an entity with danger of misdiagnosis

ANILA KR¹, SAJEED A², LAKSHMI HARIDAS², ANITHA MATHEWS¹, JAYASREE K¹

¹Department of Pathology, ²Department of Radiation Oncology, Regional Cancer Centre, Thiruvananthapuram, Kerala, India

ABSTRACT

Epithelioid hemangioendothelioma (EH) is a rare neoplasm of vascular origin with uncertain malignant potential, known to involve many organs. In terms of behavior it is considered to be intermediate between angiomas at the benign end and angiosarcoma at the malignant end. The rarity of the condition, non-specific symptoms and lack of clinical experience can cause misdiagnosis. EH can present as a single organ disease or involve several organs, either as concurrent disease or as metastatic disease. The involvement of multiple organs can result in EH being mistaken for other conditions like metastatic carcinoma, granulomatous diseases etc, at the clinical and radiological level. We are presenting a case of EH with multiorgan involvement. With a clinical and radiological diagnosis of metastatic carcinoma a trucut biopsy was taken from liver. Diagnosis of EH was made based on histopathological and immunohistochemical findings. We are presenting this case to highlight the importance of knowing this entity so that diagnostic errors and subsequent treatment for unrelated conditions can be avoided.

Key words: epithelioid, hemangioendothelioma, multi-organ, vascular neoplasm.

INTRODUCTION

Epithelioid hemangioendothelioma is a distinctive vascular neoplasm with unpredictable malignant potential, first described by Weiss and Enzinger in 1982.¹ EH can involve many organs with predilection to skin, bone, liver and lungs. It usually manifests as multifocal nodules affecting a single organ. Synchronous multiorgan involvement of EH has been reported.² This leads to diagnostic dilemma both for clinician as well as for the pathologist. Patients usually present with non-specific symptoms. The differentials can range from wide spectrum of benign to malignant conditions, including granulomatous diseases, metastatic carcinomas, chondrosarcoma, chordoma etc. A high degree of suspicion and awareness of the varying clinical presentations of the condition is essential to clinch the diagnosis.

CASE REPORT

A 47-year-old man, a known diabetic presented with complaints of dry cough, evening rise of temperature, loss of appetite and weight loss of four months duration. Investigations for tuberculosis done at an outside centre turned out to be negative. Physical examination was unremarkable except for clubbing. Imaging studies done outside revealed multiple lesions involving liver and lung. With a clinical and radiological diagnosis of hepatocellular carcinoma/metastatic carcinoma, the patient was referred to our oncology outpatient clinic. As part of the workup ultrasound scan (USS) abdomen done at our centre picked up

a 7.5x5.3 cm irregular hypoechoic area with foci of calcification involving the right lobe of liver. Also seen were multiple tiny hypo echoic lesions ranging in size from six to eight millimeters involving both lobes. A radiological diagnosis of hepatic metastasis was considered. The serum AFP value was 2.9ng/ml. Serological tests for hepatitis B and C was negative. Hematological and biochemical investigations, including serum bilirubin, transaminases, alkaline phosphatase and proteins were within normal ranges. A computed tomography (CT) scan of thorax and abdomen done outside was also reviewed. The lesion in the right lobe of liver showed peripheral enhancement in the arterial phase and calcification (Fig. 1). Imaging studies also picked up multiple well defined small to medium sized nodules randomly distributed in both lungs (Fig. 1a). Periosteal reaction in the metadiaphyseal regions of multiple long bones were noted which was radiologically compatible with hypertrophic osteoarthropathy. USS of thyroid showed colloid nodule with features suggestive of thyroiditis. A guided biopsy was done from the liver lesion.

Histopathological evaluation of the hematoxylin and eosin sections showed liver tissue with a neoplasm composed of cords and loose cells in a myxohyaline stroma (Fig. 2a,2b). Immunolabelling showed negativity for cytokeratin, CEA, CK20 and Heppar-1 and positivity for CD 31 and CD34 (Fig. 3). A diagnosis of epithelioid hemangioendothelioma was made. Considering the multicentric nature of the disease and symptoms of the patient chemotherapy was given. He received the first course of chemotherapy with single agent Adriamycin at a dose of 75mg/m² every three weeks. He tolerated chemotherapy well and reassessment is planned after three courses.

Correspondence:

Anila KR

Department of Pathology, Regional Cancer Centre, Thiruvananthapuram, Kerala 695011, India.

Email: venuanila@yahoo.com

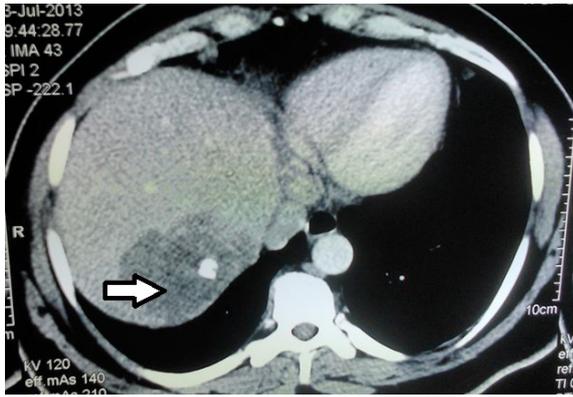


Figure 1, CT scan showing lesion right lobe of liver with calcification.

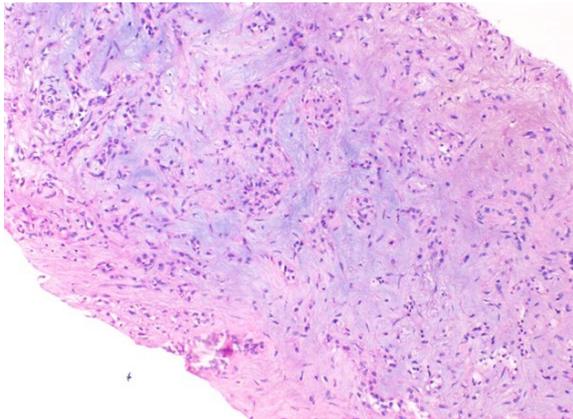


Figure 2a, A neoplasm composed of cords and loose cells in a myxohyaline stroma.(H&Ex100).

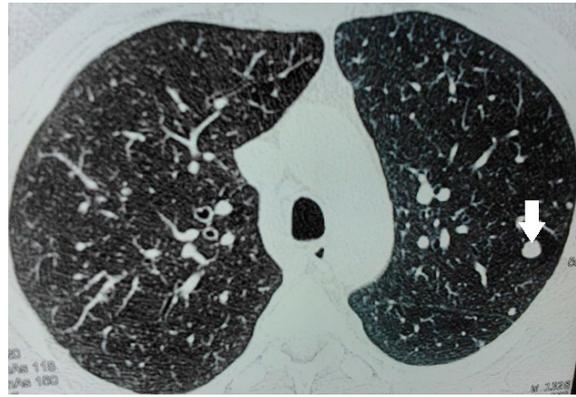


Figure 1a, MRI showing small to medium-size nodules randomly distributed in both lungs.

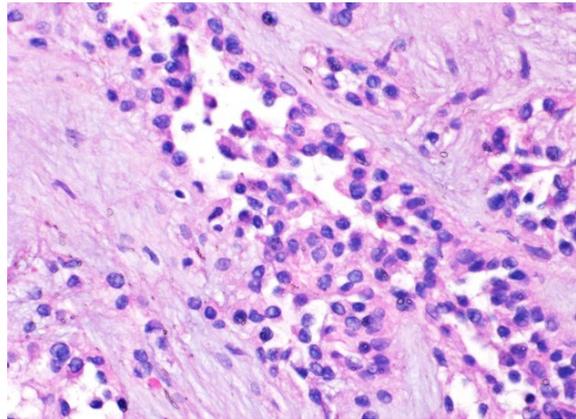


Figure 2b, Higher power view of the neoplasm (H&Ex400).

DISCUSSION

In terms of behavior, EH is considered to be intermediate in the spectrum of vascular tumors with angiomas at the benign end and angiosarcoma at the malignant end. The patients usually present with non-specific symptoms, mostly related to the organ which is most severely affected.

Our case of EH presented with concurrent involvement of liver and lung by multiple lesions. However EH can arise from single organ or involve multiple organs, including lungs, liver, bone, brain, colon, thyroid, lymph nodes, peritoneum and soft tissue. The multiorgan involvement can be either synchronous or in a sequential manner. When this occurs, it may be difficult to determine if the tumor is multicentric from the beginning or if there is a primary lesion with metastases to the other organs. There are case reports of multicentric EH in the literature. The most common organs to be involved in such reported cases were liver and lung.^{2,3} The multi-organ, multi-nodular involvement pattern of the neoplasm can result in it being misdiagnosed clinically as metastatic carcinoma or even as non-neoplastic conditions such as granulomatous disease.⁴ In our case also patient was initially investigated for tuberculosis and later diagnosed clinically and radiologically as hepatic metastatic disease.

There are reports suggesting an association be-

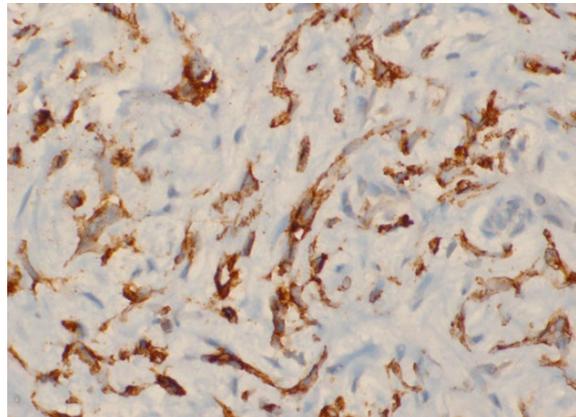


Figure 3, Tumor cells showing positivity for CD34(IH-Cx200).

tween vascular endothelial growth factor (VEGF) and EH. Also, VEGF blood levels were decreased after treatment of EH with Interferon-alpha.⁵ An association with oral contraceptives and vinyl chloride has also been reported.^{6,7}

CT is a sensitive imaging modality in the diagnosis of EH. Usual finding is multiple lesions with peripheral enhancement of tumor with contrast medium and evidence of calcification. 15-25% of hepatic EH may show parenchymal calcification which can be detected radiologically.⁸ However the definitive diagnosis is by histopathological examination. Cords and single epithelioid cells in a myxohyaline back-

ground are seen. The epithelioid appearance can lead to erroneous diagnosis of metastatic carcinoma. Because of the cord like arrangement of cells and myxoid stroma, depending on site of disease, EH can also be mistaken for myxoid chondrosarcoma or chordoma.² Immunohistochemistry helps to sort out the diagnostic dilemma. EH are positive for at least one endothelial marker CD31, CD34 or factor VIII related antigen. They are negative for epithelial marker cytokeratin (CK), which helps to rule out carcinoma. They are also negative for S100, which helps to exclude chondrosarcoma and chordoma. Though EH are usually negative for CK, they can sometimes express cytokeratin, because of the abundant intermediate filaments.⁹ This can sometimes cause diagnostic errors.

Several factors are involved in determining clinical outcome of patients with EH. In a study by Goodman et al of 60 cases of EH of liver they found that cellularity was the most important parameter in predicting behavior of hepatic EH.⁹ Kitaichi et al. in their study of pulmonary EH, observed that pleural effusion, pleuritis with extra pleural proliferation of tumor cells and spindle cell morphology were associated with unfavorable prognosis.¹⁰

Therapeutic options for EH are limited. Treatment has to be individualized for each patient depending on the clinical presentation.¹¹ Surgery is of limited value in case of multicentric disease. In solitary lesions surgery is the main line of management. Liver transplant is an option in case of multicentric hepatic EH. The efficacy of chemotherapy is also limited. Sangro et al reported a case of metastatic EH who had stable disease for 2 years on sorafenib a VEGF inhibitor.¹² Further studies on anti VEGF therapy may provide better treatment options for this rare disease. Asymptomatic patients can be kept on close follow-up without active intervention until development of symptoms.

CONCLUSION

This case is being presented to emphasize the need to include EH in the differential of any case presenting with multi-organ involvement in a multinodular pattern, especially when patient presents with non-specific symptoms. Awareness of this entity and its varying clinical patterns of presentation are essential to avoid diagnostic pitfalls and mismanagement of the patient.

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