



## A RARE CASE REPORT: HEPATIC EPITHELIOID HEMANGIOENDOTHELIOMA.

### Oncopathology

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### ABSTRACT

**Background:** Epithelioid hemangioendothelioma (EH) is a malignant endothelial neoplasm composed of epithelioid cells in a myxohyaline or fibrous stroma, most commonly with a WWTR1-CAMTA1 fusion gene or YAP1-TFE3 fuse gene. Epithelioid hemangioendothelioma is rare. Epithelioid hemangioendothelioma is sporadic. It is most commonly characterized as multifocal is identified in >75% of patients, involving the right and left lobes. **Case Presentation:** A39-year-old female patient presented to our institute with a complaint of dull abdominal pain for 2 months. Hematological investigations and tumor markers were within normal limits. HBsAg and HCV Ag were negative. Abdominal ultrasound revealed hepatomegaly with multiple heterogeneously hypoechoic and mildly hyperechoic lesions of varying sizes in both lobes of the liver. Patient underwent CT guided core biopsy which showed features suggestive of epithelioid hemangioendothelioma. **Conclusion:** Hepatic Epithelioid hemangioendothelioma is a rare tumor. It should be considered in the differential diagnosis list of intrahepatic lesions manifesting as solitary or diffuse nodular lesions. Epithelioid Hemangioendothelioma is sporadic. The diagnosis only can be confirmed by awareness of entity.

### KEYWORDS

Epithelioid hemangioendothelioma, endothelial neoplasm, ERG

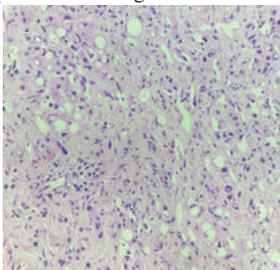
### INTRODUCTION

Epithelioid hemangioendothelioma is a malignant endothelial neoplasm composed of epithelioid cells in the background of myxohyaline or fibrous stroma. Epithelioid hemangioendothelioma (EH) has a reported incidence of <0.1 per 1 lac population.<sup>2</sup> Ishak et al. first described Epithelioid endothelioma as multiple nodular lesions in the liver in the year 1984.<sup>3</sup> There is no specific etiology of Hepatic epithelioid hemangioendothelioma (HEHE). Various pathogenic and risk factors have been found such as exposure to polyurethane, chloroethylene, or silica; exposure to asbestos and alcohol use; oral contraceptive use; viral hepatitis and primary biliary cirrhosis.<sup>4,5</sup> Patient presents with non-specific clinical signs and symptoms which include right hypochondriac pain, jaundice, weight loss, anorexia, and, in advanced cases, ascites. Approximately 25% of cases are asymptomatic. Radiological findings are variable; 30% of cases show a targetoid appearance on MRI. Hepatic epithelioid hemangioendothelioma can be characterized as single, multifocal, or diffuse and the multifocal form is the most common. It is a low-to-intermediate grade of malignant tumor.<sup>4</sup>

### Case Report

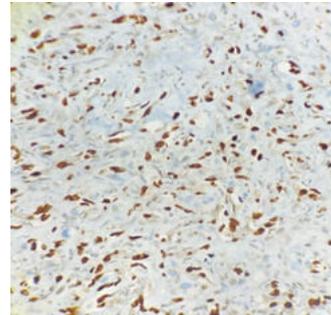
A39-year-old female patient presented to our institute with a complaint of dull abdominal pain for 2 months. It was not associated with fever, yellowish discoloration of skin, or vomiting. Clinical examination revealed a palpable mass with tenderness in the epigastric region. Patient was non-alcoholic. Hematological investigations like alkaline phosphatase, (serum glutamic pyruvic transaminase SGPT), (serum glutamic oxaloacetic transaminase) SGOT, alpha fetoprotein, carcinoembryonic antigen (CEA) and Cancer antigen 19.9 were within normal limits. HBsAg and HCV Ag were negative. Abdominal ultrasound revealed hepatomegaly with multiple heterogeneously hypoechoic and mildly hyperechoic lesions of varying sizes in both lobes of the liver. Patient was further advised CT guided biopsy from liver lesion for further evaluation.

On evaluation, it demonstrated cores of liver parenchyma with an epithelioid to spindle cell tumor. The tumor cells have intracytoplasmic lumina and myxohyaline stroma. The tumor cells express CD31, ERG and Pancytokeratin and negative for Desmin, EMA, CEA and S100. The features favor an epithelioid hemangioendothelioma.

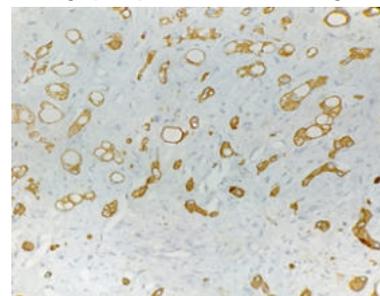


**Figure 1 :** H&E image (400x) : Composed of cords of epithelioid cells

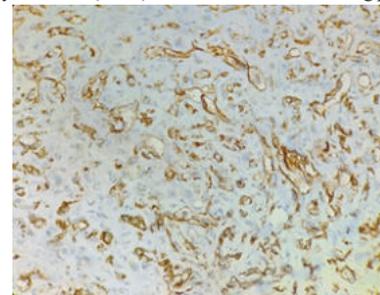
embedded within a hyaline stroma. There is myxohyaline stroma and prominent cytoplasmic vacuoles present



**Figure 2:** ERG image (400x) : Nuclear ERG staining in the tumor cell.



**Figure 3:** Cytokeratin (400x) : Membranous ck staining present.



**Figure 4:** CD31 (400x) : Diffuse cytoplasmic CD31 staining in the tumor.

### DISCUSSION

Epithelioid hemangioendothelioma (EH) is a rare low-grade vascular malignant tumor that may originate in the soft tissue, brain, lung, liver, bone, and small intestine.<sup>7</sup> Liver Involvement may be seen as a

metastasis or rarely as a primary tumor.<sup>1</sup> Clinical manifestations are nonspecific. Diagnosing hepatic EH is fairly difficult for the radiologist because of its findings are variable; 30% of cases show a targetoid appearance on MRI with peripheral high signal intensity on T1-weighted images and low signal intensity on T2-weighted images, referred to as the bright dark ring sign.

In the absence of classic radiologic features, pathologic examination is the diagnostic modality of choice of this rare tumor.<sup>1</sup> In the present case, the diagnosis of hepatic epithelioid hemangioendothelioma was made on core biopsy assisted by immunohistochemistry staining. In the histopathologic appearance, tumours are composed of epithelioid, stellate, and spindle cells with fine chromatin, small nucleoli, and eosinophilic cytoplasm, including occasional intracytoplasmic vacuoles, arranged in cords or as single cells. Invasion of sinusoids and portal and hepatic veins is a frequent feature, sometimes associated with necrosis. The fibrous stroma with lacunae is characteristic and may be useful to suggest epithelioid hemangioendothelioma (but is also seen in cholangiocarcinoma). Occasional tumors show nuclear atypia and variability, including pleomorphic and multinucleated cells. The mitotic rate is highly variable; many tumors contain rare mitotic figures.<sup>1</sup>

Epithelioid hemangioendothelioma with YAP1-TFE3 fusion shows distinctive histological features. The tumor cells usually have brightly eosinophilic cytoplasm and are more likely to have solid growth and often form vascular spaces; the latter feature is generally not seen in the classic form of epithelioid hemangioendothelioma. A small subset (<10%) of epithelioid hemangioendotheliomas have atypical histological features, including nuclear pleomorphism, solid sheet-like growth, increased mitotic activity and necrosis.

Epithelioid hemangioendothelioma tumor cells express the endothelial markers CD34, podoplanin (D2-40), CD31, FLI1, and ERG. Epithelial antigens are expressed in as many as 40% of cases (CK7, CK18, CK8, pan-keratin), but expression of EMA is unusual.<sup>1</sup>

The microscopic differential diagnosis of epithelioid hemangioendothelioma takes Carcinoma, Melanoma, Epithelioid sarcoma, Epithelioid angiosarcoma, Malignant mesothelioma, Epithelioid hemangioma, Pseudo myogenic hemangioendothelioma and Epithelioid malignant peripheral nerve sheath tumor into consideration.<sup>8</sup> Few cases of Epithelioid hemangioendothelioma may show high cellularity and mitotic activity which may be confused with carcinoma. But Positive staining with endothelial markers such as CD31, CD34, and Factor VIII helps in differentiating epithelioid hemangioendothelioma from carcinoma. Negative staining with S100 ruled out melanoma.<sup>5</sup> In addition, cytokeratin is strongly positive in almost all carcinomas as well as epithelioid angiosarcomas and epithelioid sarcomas. Epithelioid hemangioendotheliomas are cytokeratin positive but EMA negative, but carcinoma, epithelioid sarcoma and malignant mesothelioma react for cytokeratin and EMA. Carcinoma and malignant mesothelioma are negative for vascular marker. Epithelioid angiosarcoma shows more cytological atypia and mitotic activity than EHE, lack myxohyaline background and CAMTA1 is negative in epithelioid angiosarcoma.<sup>9</sup>

EHE is driven by WWTR1-CAMTA1 or YAP1-TFE3 fusion genes. EHEs that occur due to WWTR1-CAMTA1 fusion gene with t(1,3)(p36;q25) translocation express CAMTA1 while those occurring due to YAP1-TFE3 fuse gene express TFE3 (less specifically).<sup>1</sup> WWTR1-CAMTA1 fusion is positive in 90% of hemangioendothelioma cases.<sup>10</sup> The treatment of choice for epithelioid hemangioendothelioma of stable/slowly progressing unifocal or limited locoregional tumor that is technically resectable is surgical resection with the goal of complete tumor resection with R0 margins. Liver transplantation for unresectable hepatic EHE and no extrahepatic disease provides comparable outcomes to patients with other indications. Stereotactic body RT (SBRT), radiofrequency ablation (RFA) and microwave ablation (MWA) are other therapeutic modalities for patients with unifocal disease who are not fit for surgery and for patients with recurrence of tumor after liver resection or liver transplant and/or as a bridge to Liver Transplant.<sup>11</sup> Epithelioid hemangioendothelioma of the liver pursues a variable clinical course; some patients have progressive disease, whereas others have indolent, stable disease. The distant metastatic rate is 20-30%.<sup>1</sup> Histological features do not reliably predict outcome.<sup>1</sup>

## CONCLUSION

Hepatic Epithelioid hemangioendothelioma is a rare tumor. It should

be considered in the differential diagnosis list of intrahepatic lesions manifesting as solitary or diffuse nodular lesions. Epithelioid Hemangioendothelioma is sporadic. The diagnosis only can be confirmed by awareness of entity.

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