Malignant Hepatic Epithelioid Hemangioendothelioma with Villaret Syndrome

Hanchanale Pavan, Joy Varghese, Kavya Harika, Mukul Vij, Venkataraman Jayanthi, Mohamed Rela

Institute of Liver Disease & Transplantation, Department of Pathology, Global Health City, Chennai, India

Malignant hepatic epithelioid hemangioendothelioma is a rare, vascular tumor of the liver with peak incidence in the middle age with a female preponderance and of unknown etiology. Majority of the tumors are asymptomatic. The gold standard for diagnosis of the tumor is liver histology showing presence of epithelioid tumor cells on a background of a hyaline stroma. Immunohistochemical positivity for CD31, CD34, Factor VIII, and Podoplanin (D2-40) is confirmatory. The treatment of choice is liver transplantation. (J CLIN EXP HEPATOL 2017;7:68–70)

A 26-year-old woman was referred to our institution with a histopathological diagnosis of focal nodular hyperplasia for a space occupying lesion in the liver. The patient had a history of abdominal discomfort localized to the right upper quadrant with significant anorexia and weight loss of 8 kg over a period of 3 months. On examination of the abdomen, at admission, the liver was enlarged (span of 20 cm) and firm in consistency with a smooth surface and regular margin. Spleen was not palpable and there was no free fluid. Other system examinations were normal.

The following laboratory investigations were investigated: Hemoglobin—11.9 g/dL, white blood cell count—8100 cells/mm³ (neutrophils 72%, lymphocytes 17%, monocytes 07%, and eosinophil 04%), ESR—36 mm per h, and platelet count—259 × 10⁵/mm³. Blood sugar, and serum creatinine were normal. The following liver function tests were conducted: serum total bilirubin 1.23 mg/dL, direct—0.35 mg/dL, serum aspartate amino transferase—37 U/L, serum alanine amino transferase—37 U/L, serum alkaline phosphatase—430 U/L, and serum gamma glutamyl transpeptidase—123 U/L. International Normalized Ratio was 1.21.

Ultrasound of the abdomen done elsewhere showed normal liver echotexture, with regular margins and multiple hypoechoic lesions in the right lobe, suggestive of hepatocellular carcinoma. Portal, hepatic veins, and suprahepatic inferior vena cava were normal. There was no free

fluid. Ultrasound-guided fine needle aspiration of the lesion revealed focal nodular hyperplasia.

Contrast-enhanced computed tomography (CECT) done at our institution showed multiple hypoattenuating lesions in both lobes of the liver with conglomeration of lesions in the right lobe. Differentials included multicentric hepatocellular carcinoma and malignant epithelioid hemangioendothelioma (Figure 1). A repeat ultrasound-guided biopsy was done, which showed spindle to epithelioid tumor cells embedded in myxoid background and cytoplasmic lumina (vacuole inside their cytoplasm corresponding to a vascular lumen) (Figure 2). Immunohistochemistry showed a diffuse positivity for CD 34 (Figure 3) and focal positivity for CD 31 (Figure 3) suggestive of malignant hepatic epithelioid hemangioendothelioma (HEH).

Liver transplant was recommended, which she denied. She reported 7 months later with hoarseness of voice, dysphagia, and nasal regurgitation. Neurological examination revealed left IX, X, XI, XII cranial nerve palsy, and ipsilateral Horner's syndrome. Magnetic resonance imaging of the brain confirmed bone metastases including involvement of the jugular foramen. The constellation of cranial nerve palsy with ipsilateral Horner syndrome due to lesion in jugular foramen is referred to as Villaret syndrome.¹ Supportive treatment alone was recommended as she now had widespread metastases.

The following are the final diagnoses: Malignant HEH with Villaret syndrome.

DISCUSSION

HEH is a rare tumor that has histological appearance and behavior simulating both hemangioma and hemangiosarcoma.² It is often reported in women between 30 and 40 years. Da Ines reported a similar case in an 11-year-old boy with metastasis to the lymph nodes.³

The etiology remains unknown. Speculated risk factors include use of oral contraceptives, exposure to vinyl chloride, and hepatitis B virus infection.⁴ A genetic basis of the tumor has also been reported.⁵

Keywords: epithelioid hemangioendothelioma, hepatic epithelioid hemangioendothelioma, malignant hepatic epithelioid hemangioendothelioma, Villaret syndrome

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Address for correspondence: Kavya Harika, Department of Hepatology, Institute of Liver Disease & Transplantation, Global Health City, 439, Cheran Nagar, Perumbakkam, Chennai 600100, India.

E-mail: drkavya85@gmail.com

Abbreviations: CECT: contrast-enhanced computed tomography; EHE: epithelioid hemangioma; HEHE: hepatic epithelioid hemangioendothelioma

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Figure 1 CECT showing large hypoechoic lesion in right lobe of liver with satellite lesions in the left lobe.

In contrast to most primary hepatocellular carcinoma, malignant HEH occurs in a normal noncirrhotic liver. It has been described in other organs like the spleen, bone, brain, meninges, breast, heart, head, neck, stomach, lymph nodes, and soft tissue.⁶

Grossly, the tumor is hard and white, with a well-defined periphery, often multifocal (>70%) with variable-sized nodules ranging from a few to several centimeters, with widespread dissemination in the liver parenchyma.

Morphologically, there are 2 types of malignant HEH; the nodular type is seen in the early stage and the diffuse

type corresponds to an advanced stage of the disease. The increase in size with coalescence of the hepatic lesions is often associated with vascular invasion. The peripheral lesions have a tendency to extend into the liver capsule resulting in flattening or retraction or “umbilication” of the liver capsule due to fibrosis and compensatory hypertrophy of the unaffected liver.⁷ Histology shows epithelioid tumor cells, isolated or in small groups, scattered throughout an abundant fibrous, and a hyalinized stroma. Another classical histological feature is the presence of a vacuole inside the cytoplasm.⁶ This was typically seen in our patient.

Immunohistochemistry for endothelial markers when positive for CD31, CD34, and Factor VIII are diagnostic of malignant HEH. Podoplanin (D2-40) when expressed in tumoral cells has a sensitivity of 78% and specificity of 100%. Our patient was positive for CD 31 and 34.

Clinical findings are nonspecific and include localized pain to the right hypochondrium, anorexia and weight loss, fulminant hepatic failure, and Budd-Chiari syndrome.⁸ Common metastatic sites include abdominal lymph nodes, peritoneum, lungs, and bones.⁷

On investigating, laboratory investigations (hemogram and biochemistry), tumor markers, and ultrasound are nonspecific for malignant HEH. Liver function tests may show mild derangement; tumor markers like alpha-fetoprotein and cancer antigen 19-9 levels are normal. Carcinoembryonic antigen may be elevated. Ultrasound shows the hepatic lesions to be either isoechoic, hyperechoic, or heterogenous.

CECT is diagnostic. Typically, there are multiple hypoattenuating lesions in both lobes of the liver that coalesce to form larger confluent lesions in the periphery or

Figure 2 Spindle to epithelioid tumor cells embedded in myxoid background, demonstrating cytoplasmic lumina (arrow).

Figure 3 Immunohistochemistry showing focal CD 31 positive lesions and diffuse CD34 positive stain. (a) IHC focal CD31 positive. (b) IHC showing diffuse positivity for CD34.

subcapsular region. The smaller lesions show a halo while the larger ones have target pattern of enhancement. Typically, the subcapsular lesions show capsular retraction.⁹ In our patient, though we did see a coalescing lesion, the typical retraction of the capsule was not seen.

Biological behavior of the tumor is variable. While some patients succumb within months after diagnosis, there are others with milder course who survive for longer periods of time.

Surgical treatment includes either nodulectomy (nodular pattern) or liver transplantation (diffuse involvement). The latter is acceptable even in metastatic disease.¹⁰

In conclusion, malignant HEH is a rare hepatic tumor with overlapping features of hemangioma and hemangiosarcoma, with poor prognosis. On computed tomography, coalescing hypoattenuating lesions with capsular retraction is diagnostic. Histological studies with immunohistochemistry is necessary for confirming the diagnosis. Coexisting Villaret syndrome suggested metastases at jugular foramen, one of the jugular foramen syndromes.

CONFLICTS OF INTEREST

The authors have none to declare.

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