



CASE REPORT

Orthotopic Liver Transplantation in a Case of Novel YAP1-TFE3 Hepatic Epithelioid Hemangioendothelioma [HEHE]; Case Report and Review of Literature

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Abstract

Epithelioid hemangioendothelioma is an extremely rare vascular neoplasm arising in soft-tissues and different visceral organs, with liver being the most commonly involved viscera. Hepatic epithelioid hemangioendothelioma (HEHE) is a malignant tumour with an indolent behaviour and unpredictable clinical course. It has a better prognosis among the malignant tumours of the liver, in spite of being a diffuse multifocal liver disease or metastatic at the time of presentation. HEHE is usually found to be noted in the fifth decade with slight female preponderance. No single treatment strategy has yet been established owing to its variable clinical course, ranging from an indolent tumour with prolonged survival to an aggressive, metastatic disease with a fatal outcome. Here, we present a case of a novel HEHE in a 25-year-old female who was treated successfully with orthotopic living donor liver transplantation and discuss the presentation, histopathology and management of this rare, fatal yet treatable malignant tumour.

Keywords: hepatic epithelioid hemangioendothelioma; vascular tumour

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Case Summary

A 25-year-old female presented with complaints of right-sided upper quadrant pain on and off for the last 1 year associated with significant weight loss. Her blood investigations were normal except for mild increase in transaminases

[SGOT & SGPT]. Rest of her liver function tests were within normal limits. Abdominal ultrasonogram followed by Doppler was done which showed a coarse echotexture of the liver with multiple heterochoic lesions with coalescence seen in periportal and sub-pleural regions, the largest

lesion measuring 10.7 × 14.4 cm. Portal and hepatic veins were patent. CT of the abdomen was done which revealed a liver with heterogeneous density and multifocal confluent hypodense areas along the subscapular region and along the portal vein branches. Lesions were seen predominantly in the right lobe and scattered across segments VIII, V, VII, IVA and IVB. The largest lesion in periportal region extending to left lobe measuring 9.8 × 6.9cm. Post-contrast study showed heterogeneous enhancement of lesions with no calcifications within [Figure 1]. Image-guided biopsy of the liver lesion was done which was suggestive of Hepatic Epithelioid Heman-gio Endothelioma [HEHE]. She was evaluated further and was advised to undergo liver transplantation. Her maternal uncle came forward to donate a part of his liver and after complete evaluation and risk assessment, he was cleared to donate his right lobe. Right lobe without middle hepatic vein was harvested from the donor. The anterior sector outflow was reconstructed using 10-mm PTFE [Poly Tetra Fluoro Ethylene] graft and the graft was implanted.

Her explant liver weighed 1356 g measuring 22 × 15 × 9 cm, with right lobe measuring 11 × 15 x 9 cm and left lobe 12 × 11 × 7 cm. On slicing, multifocal tumour involving both right and left lobe was identified with largest tumour in right lobe measuring 8 × 7 cm and largest in left lobe measuring 7 × 5 cm. Smaller tumour nodules were also noted [Figure 2]. The tumour was infiltrative, firm and greyish-white with indistinct margins and yellowish areas of necrosis. Non-tumoral liver showed patchy congestion. The tumour was involving vessels and was infiltrating hilar connective tissue grossly. The sections showed a multifocal diffusely infiltrating tumour with round to polygonal tumour embedded in

fibromyxoid stroma. The tumour cells are arranged singly, in cords and also in clusters and tuft in sinusoids and vessels. Multinucleation was noted. The tumour cells show high nucleocytoplasmic ratio and pleomorphic hyperchromatic nuclei with variable eosinophilic cytoplasm. Small nucleoli and cytoplasmic vacuolisation were noted. Areas of necrosis and admixed inflammation comprising of lymphocytes, his-tiocytes and polymorphs were present. Diffuse infiltration of hepatic vessels with luminal obliteration along with tumour infiltration in portal areas were seen. Entrapped nerve bundles were noted. There non-tumoral liver showed areas of sinusoidal dilatation, congestion and hepatocyte atrophy and hepatocyte dropout. Regenerative changes of hepatocyte plates are noted. The final impression was that of multifocal hepatic epithelioid hemangioendothelioma. Immunohisto-chemistry was done and cells were strongly positive for CD34 [Figure 3] with positive FLI1, D2-40 and patchy mild positive for PAN-CK. TFE-3 nuclear expression was suggestive of TF3-YAP1 fusion [Figure 4].

She recovered well and was discharged from the hospital on eighth post-operative day. She was started on tacrolimus, mycophenolate mofetil and steroids for immunosuppression titrated against the lower limit of the recommended tacrolimus trough levels, and has been on regular follow-up with no recurrence till date.

Introduction

Epithelioid hemangioendothelioma (EHE) was first described in soft tissues by Weiss and Enzinger about four decades ago. Since then, EHE has been reported in other organs such as

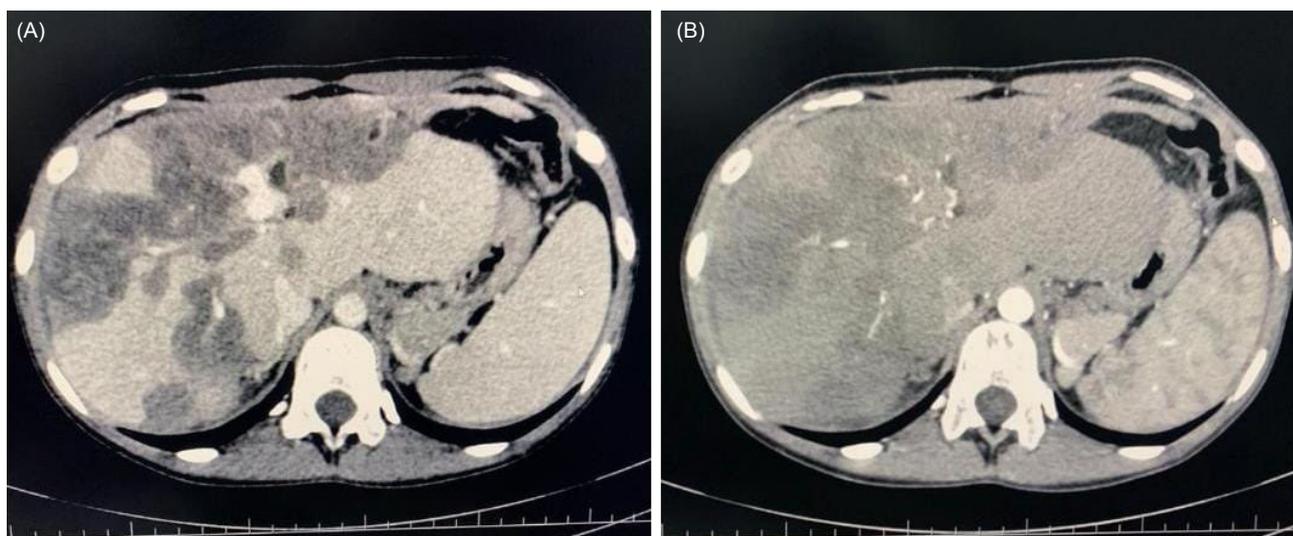


Figure 1: Post-contrast study showed heterogeneous enhancement of lesions with no calcifications.

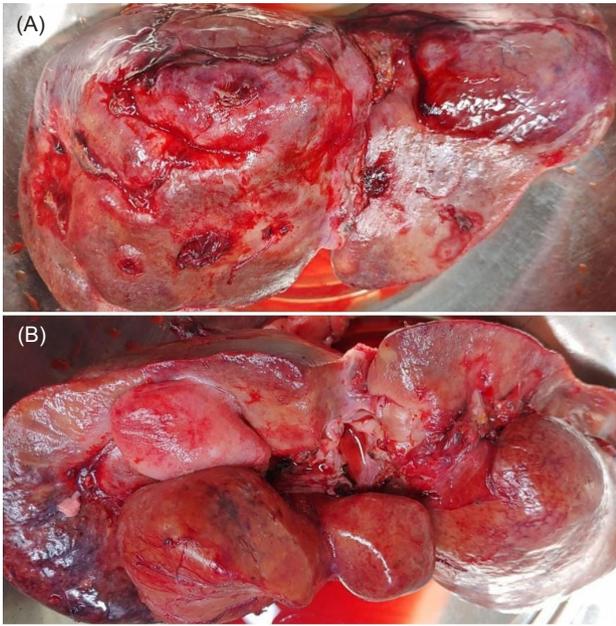


Figure 2: Smaller tumour nodules were also noted.

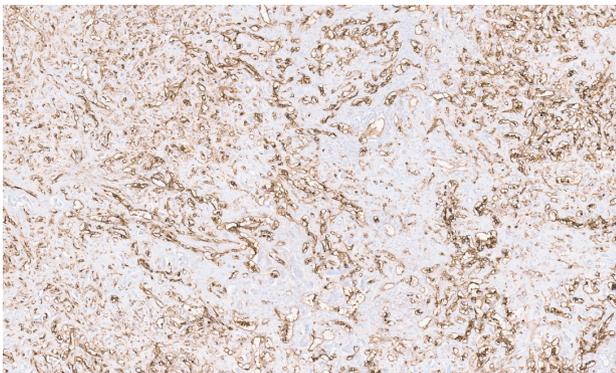


Figure 3: Immunohisto-chemistry showing cells strongly positive for CD34.

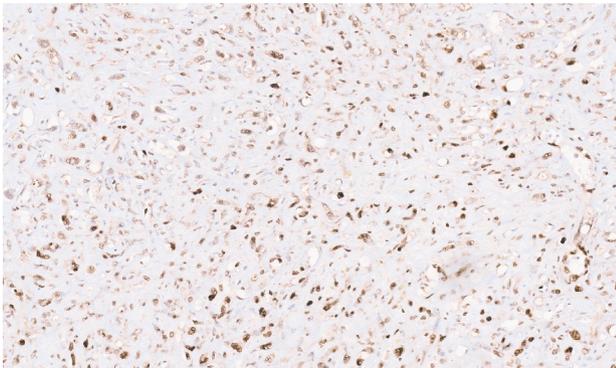


Figure 4: TFE-3 nuclear expression was suggestive of TF3-YAP1 fusion.

lungs, liver, mediastinum and bone (1). Ishak reported the first Hepatic epitheloid hemangioendothelioma (HEHE) in 1984, while he was studying the clinical and morphologic features of HEHE in a series evaluating 32 patients. HEHE is a rare vascular tumour with an incidence rate of 1 in 100,000 originating from endothelial cells; however, it resembles an epithelioid neoplasm. Usually noted in the fifth decade with slight female preponderance with a female-to-male ratio of 3:2 (2). Factors predisposing to HEHE have not been well-defined; however, prolonged usage of oral contraceptive pills, hepatitis B infection, alcohol abuse, primary biliary cirrhosis and exposure to vinyl chloride, polyurethane, silicone, asbestos and thorotrast are postulated to be the possible risk factors (3).

Usually detected incidentally on imaging studies, since the presenting clinical symptoms, signs and laboratory findings are non-specific (4). The most common presenting features among symptomatic patients are right upper quadrant pain, hepatomegaly and weight loss. These features are more pronounced when they develop features of portal hypertension, Budd–Chiari syndrome or hepatic failure (5).

All the routine tumour markers namely carcinoembryonic antigen (CEA), CA19-9 and alpha-fetoprotein are usually not elevated (6). Rarely, it can be solitary, but majority cases are multicentric with bilobar involvement of both liver lobes (3). The lesions start as small discrete nodules commonly located at the periphery and invades the capsule. These nodules gradually grow in size, coalesce to form complex confluent masses. Contrast-enhanced CT shows lesions with a low attenuating centre surrounded by a peripheral rim of enhancement. MRI shows similar features (7). Retraction or flattening of the liver capsule secondary to fibrosis is a characteristic finding in HEHE. In the arterial phase, some of the lesions demonstrate a mild homogeneous enhancement which does not increase in the portal venous or delayed phases. Some lesions show a ring-like arterial phase enhancement followed by a central filling on the portal venous and delayed phases, the characteristic “halo sign.” Few lesions have heterogeneous enhancement pattern that progresses during the portal and delayed phases. The enhancement pattern appears to be directly proportional to the tumour size; with lesions more than 3 cm showing a delayed heterogeneous enhancement, lesions less than 2 cm showing homogeneous enhancement and 2–3-cm-sized tumours exhibiting the halo sign that is, ring-like enhancement (8).

Alomari described the characteristic “Lollipop” sign on either contrast-enhanced CT or MRI which is more specific to HEHE than the halo sign. The HEHE infiltrates sinusoids, venules and veins causing narrowing of these structures which resembles the stick of a lollipop ending in a well-defined tumour resembling the candy (9). One-fourth of the lesions might have intra-tumoral calcification, which when present, is a very helpful diagnostic feature. Mehrabi et al

found out that 36.6% of patients had evidence of extra-hepatic involvement at the time of initial diagnosis. The most common site of extra-hepatic disease being the lungs, followed by the regional lymph nodes, peritoneum, bone, spleen and the diaphragm in that order (3).

Fortunately, even the HEHE with extra-hepatic spread at the time of diagnosis have favourable outcomes and good long-term disease-free survival rates after liver transplantation (10). On gross examination, depending on the stage of the tumour, it presents either a nodular or diffuse pattern, with ill-defined nodules that are firm in consistency and a white gritty cut surface resembling a cholangiosarcoma (11). The tumour cells are composed of basically three different types of cells, that includes the main round epithelioid cells, spindled or stellate dendritic cells with their cytoplasmic processes dispersed among the main cells, and the intermediate cells that has features of both the epithelial and dendritic cells. These cells tend to infiltrate the liver parenchyma either in a single cell or a linear cord-like growth pattern, invading the sinusoids and making use of them as a platform, the cells destroy the hepatocytic plates, sinusoids and the blood vessels. HEHEs are vascular tumours that mimic epithelial tumours, which can be delineated well with the help of endothelial immunohistochemical markers such as CD34, CD31, factor VIII, FLI-1 protein, podoplanin (D2-40) etc.

Conventional HEHEs have a distinctive morphologic appearance and are usually characterised by the presence of a WWTR1–CAMTA1 fusion gene due to recurrent t(1;3) translocation. Recently, a novel YAPI–TFE3 fusion was detected, further validated by fluorescence in situ hybridization and reverse transcription polymerase chain reaction which has been reported as having a distinct morphology with more obvious vasoformation, voluminous eosinophilic cytoplasm and TFE3 positivity on immunohistochemistry (12). TFE3 gene rearrangement is more common in young individuals with equal male:female distribution and a mean age of 30 years (13).

The unpredictable nature of this tumour and availability of different therapeutic strategies with various outcomes makes the management of HEHE challenging. The armamentarium should include a wide range of treatment approaches right from performing a partial hepatectomy, chemoradiotherapy, ablative therapies and liver transplantation depending on the presentation. Incidentally found small lesions have been successfully managed without any therapeutic intervention (14). Since HEHE is usually multifocal and bilobar, partial hepatectomy is less feasible. Only in cases of focal resectable HEHE does partial hepatectomy provide a reasonable survival and is also a justified treatment in the background of coexistent extra-hepatic tumour metastasis (15). Overall, liver transplantation has been the most common and most successful treatment modality with a 5-year survival rate of 82% and a low recurrence rate of 36.4% (3).

Although HEHE is supposed to be a malignant and probably aggressive hepatic vascular tumour with the risk of recurrence post-immunosuppression, with just adequate immunosuppression, careful close monitoring and strict post-operative vigilance, liver transplantation can serve to be an ultimate cure for HEHEs.

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