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Multifocal Epitheloid Hemangioendothelioma of Liver after Long-Term Oral Contraceptive Use—A Case Report and Discussion of Management Difficulties Encountered

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Abstract
Case Report A 43-year-old woman presented with right upper abdominal pain, on and off for 3–4 years. One year prior to her presentation, a space-occupying lesion was found in the right lobe of the liver, which was suspected to be hemangioma, as the patient had history of combined oral contraceptive pill use for the last 15 years. On examination, she was thinly built and had pallor; abdominal examination revealed tender hepatomegaly 3 cm below the costal margin, smooth surface, sharp regular edge with left lobe enlargement, and no bruit.
Results All routine biochemical and hematologic investigations were normal, except hemoglobin of 7.6 gm/dl. On triple-phase CT scan, there were hypodense ill-defined lobulated area in right lobe of liver; similar lesions were also seen in segments V and VII of liver along with a few sub-diaphragmatic and para-aortic nodes. Liver biopsy showed features suggestive of hemangioendothelioma, and immunohistochemistry showed CD 31 and CD 34 positivity but negative for estrogen receptors. Laparoscopy revealed presence of multiple deposits on left lobe of liver and ascites.
Discussion Tumor was unresectable, and the patient was found to be a candidate for liver transplant. Chemoembolization was tried as a palliation awaiting transplant, but the procedure was unsuccessful due to the hypovascular nature of the tumor. The patient died within 4 months of diagnosis due to liver failure, awaiting liver transplant, as a suitable donor was not available.
Conclusion A clinical suspicion based on demographics, risk factors and imaging, familiarity with the pathologic findings, and utilization of advanced imaging techniques may allow early diagnosis of these tumors and hence their appropriate management.

Keywords epitheloid · hemangioendothelioma · liver · oral contraceptive

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Introduction

Epithelioid hemangioendothelioma (EHE) is a rare neoplasm of vascular origin with unpredictable malignant potential. Hepatic EHE usually affects adult women and presents as multiple hepatic nodules with mainly peripheral distribution. It poses special difficulties for clinicians in its diagnosis and treatment because of its non-specific clinical manifestations and findings on imaging, and it is easy to be misdiagnosed pathologically.

Although a possible association of hepatic hemangiomas with estrogen use has been found by various authors, the possible association of EHE with estrogen is still debatable. We report a case of EHE from India and compare it with other cases from the west along with two previously

reported cases from India [1, 2] and also discuss the role of estrogens in these tumors and highlight the treatment difficulties encountered.

Case Report

We report a case of 43-year-old woman who presented with mild upper abdominal pain, on and off for 3–4 years, with no aggravating or relieving factors, flatulence, weakness, loss of appetite for 2 years, and fever that was mild grade on and off for 1 year. She was investigated several times, but there was no positive clue to the etiology of her complaints until, 1 year prior to her presentation, a space-occupying lesion (SOL) was found in the right lobe of liver on ultrasonography (USG), which was suspected to be hemangioma, as the patient had history of combined oral contraceptive pill (ethinyloestradiol 0.03 mg + levonorgestrel 0.15 mg) use for the last 15 years for menorrhagia. She had two term deliveries with no other significant past history.

On examination, she was thinly built and had pallor; abdominal examination revealed tender hepatomegaly 3 cm, left lobe enlarged, smooth surface, sharp regular edge, and no bruit. All routine biochemical and hematologic investigations, including α-fetoprotein, carcinoembryonic antigen, and viral markers for hepatitis B and C, were normal except hemoglobin of 7.6 gm/dl. USG revealed hepatomegaly with left lobe hypertrophy and ill-defined multifocal hypoechoic SOL in the right lobe of the liver. On triple-phase CT scan, there were hypodense ill-defined lobulated areas in the right lobe of the liver (Fig. 1) with few areas of patchy enhancement in portovenous phase. Similar lesions were also seen in segments V and VII of the liver along with a few sub-diaphragmatic and para-aortic nodes.

A CT-guided liver biopsy was done, which revealed distortion of the liver architecture by diffuse presence of tumor cells, which were large oval to polygonal with ill-defined cell boundaries, and moderate to abundant eosinophilic cytoplasm (epithelioid cells) and moderate degree of pleomorphism, with some cells showing presence of intracytoplasmic lumina, a characteristic finding of EHE (Figs. 2 and 3). These were poorly demarcated from the surrounding liver and composed of cords and nests of cells forming irregular anastomosing channels. There were also foci of stroma with myxoid/chondroid-like matrix. Immunohistochemistry revealed it to be CD 31 and CD 34 positive and cytokeratin negative, suggestive of EHE (Fig. 4). The tumor was found to be negative for the estrogen receptors. Diagnostic laparoscopy revealed the presence of multiple deposits on the left lobe of the liver, while the right lobe was not well visualized; there was no evidence of peritoneal metastasis. There was also presence of free fluid in abdomen, which was negative for malignant cells. Due to the presence of extrahepatic spread, instead of resection other modalities of treatment in the form of interferon (IFN) alpha-2B, chemoembolisation and liver transplant were considered. Due to lack of substantial evidence about the usefulness of IFN in hemangioendotheliomas with extrahepatic spread and concerns about tolerability of IFN due to coexistent anemia, the patient was advised a liver transplantation. Chemoembolisation was tried as a palliation until liver transplant was available, but the procedure was abandoned due to the hypovascular nature of the tumor. Patient died within 4 months of diagnosis due to liver failure, awaiting liver transplant, as a suitable donor was not available.

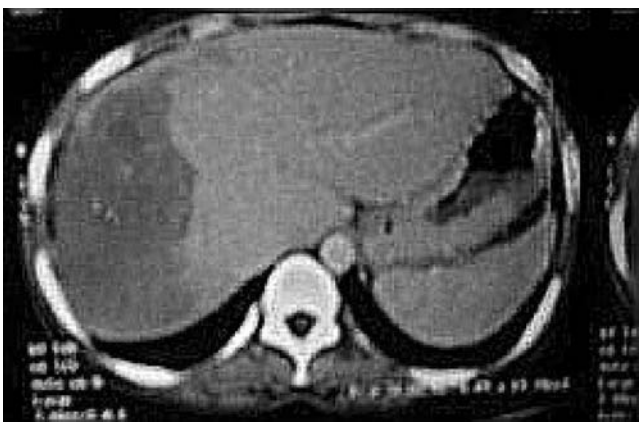

Fig. 1 CT scan showing hypodense ill-defined lobulated areas in right lobe of liver

Discussion

Epithelioid vascular tumors are neoplasms formed by endothelial cells, morphologically similar to epithelial cells.

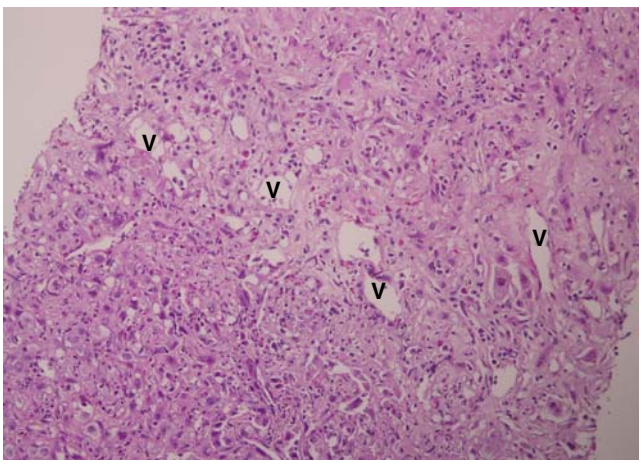

Fig. 2 Liver biopsy showing replacement of parenchyma by many irregularly dilated anastomosing channels (V), which are lined by epitheloid cells

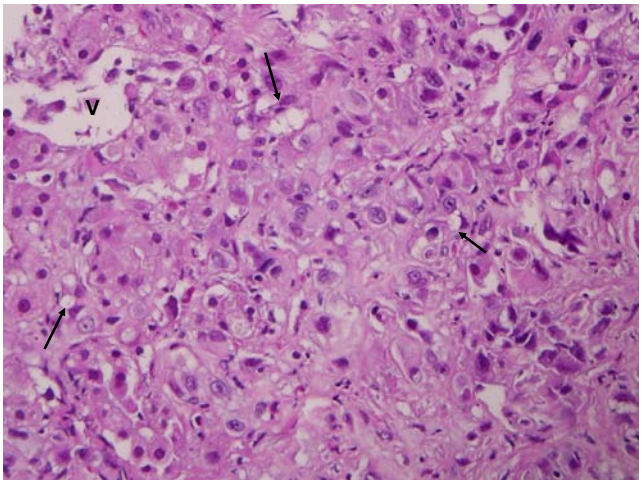

Fig. 3 The epitheloid cells are large polygonal with abundant eosinophilic cytoplasm, enlarged nuclei with prominent nuceoli with few of them showing intracytoplasmic lumina (*arrow*)

Morphological shape of the cells in these tumors varies from benign to malignant forms, causing the diverse biological potential of the tumors. In the WHO classification of mesenchymal tumors, hemangioendotheliomas have been defined as vascular tumors of "intermediate" or "borderline" malignancy, and spindle-cell hemangioendothelioma (SHE), EHE, and rare malignant endovascular papillary angioendothelioma (Dabska's tumor) have been included in this category. Some other forms described, such as kaposiform, retiform, polymorphous, and composite haemangioendothelioma may also be included. EHE has been reported to involve various sites, such as skin, soft tissue, lung, anterior mediastinum, oral/nasal cavity, bone, heart valves, brain, thyroid, veins, arteries, intestine, and lymph nodes; however, liver has been described as the commonest site.

The clinical course and prognosis of hepatic EHE is variable but supposed to be an intermediate between hemangioma and angiosarcoma [3]. There have been various case reports in the literature [4–10] describing the clinical presentation, radiologic, and histopathologic features, as well as management strategies in these rare liver tumors; only two cases are reported from India [1, 2]. Although it is usually characterized by a good long-term prognosis, its growth can be progressive and lead to hepatic failure, extrahepatic metastasis, and death.

Although EHE of liver has been found in adults of both sexes, there is a female predominance, and the largest series to date [4] has found F/M ratio to be 1.6:1. Both of the earlier cases reported from India are female. It is important to highlight that EHE form other sites like bone and soft tissue has no sex predilection [4]. The occurrence of hepatic EHE in women particularly during the reproductive years gives a clue to the possibility of reproductive hormones having some role in the etiology. Similar to this patient who had taken oral contraceptives for 15 years, history of oral contraceptive intake has been reported earlier also [4, 6], but no conclusion has been drawn due to small number of

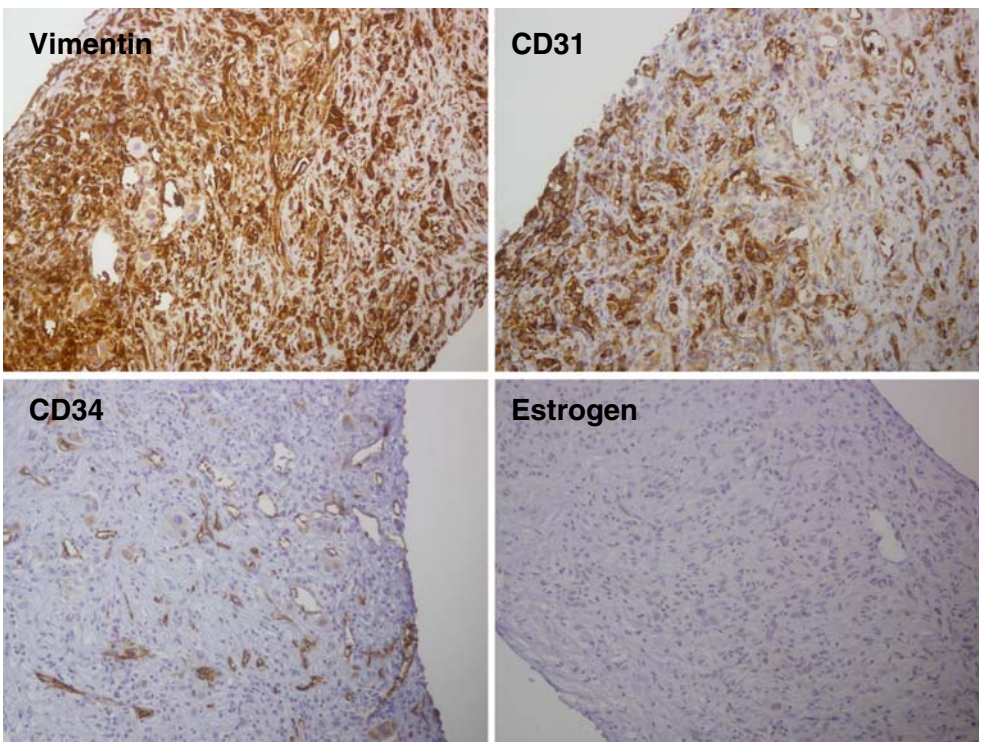

Fig. 4 Strong cytoplasmic imunoreactivity for vimentin and CD31 and focal staining with CD34 while no staining with estrogen in epitheloid cells

cases. The estrogen receptors were not found on the tumor tissue in our study. Although, in a study earlier carried by Ohori et al. [11], estrogen receptors have been demonstrated in EHE of lung, to best of our knowledge, these receptors have not been reported to be positive in EHE of liver. Evidence available to date suggests that there can be a role of estrogen in EHE of liver, which can have potential therapeutic implications. However, the occurrence of these tumors in children and men raises doubts about the presumed hypothesis.

The clinical presentation of tumor as classically described [4–9] began with nonspecific complaints such as abdominal discomfort, mild grade fever, and anorexia, and the tumor was detected on USG examination long after the complaints started. The clinical course of EHE as reported in the literature appears to be quite variable, but none of the cases reported from India had an atypical presentation. This patient survived only 4 months after a diagnosis of EHE was made, but this short survival may be explained by the delay in diagnosis due to misinterpretation of lesion on USG as hemangioma.

The combination of demographic and clinical features as well as imaging such as USG and CT scan can be highly suggestive of diagnosis, but it can only be confirmed by histology and immunohistochemistry of the tissue specimen, which can be obtained by an USG/CT-guided biopsy as in our case.

Imaging studies [13, 14] generally reveal presence of multifocal abnormalities involving both lobes of the liver. Parenchymal calcification may occur, being sufficiently dense in some cases for depiction on abdominal radiographs. On sonography, discrete nodules may be seen; individual lesions have variable echogenicity, but most frequently, the lesions are hypoechoic relative to adjacent hepatic parenchyma. The liver may have a diffusely heterogeneous echotexture in regions of extensive diffuse involvement, which points toward EHE. A CT scan can be helpful in appreciating peripheral lesions extending to the capsular margin. On contrast, some tumor nodules display marginal enhancement during the arterial phase, which, on late scans, may become isodense to liver parenchyma. Enhancing margins and capsular retraction, though seen only in selected cases, can be a distinguishing feature from hemangiomas and angiosarcomas. Although USG/CT scans might have a limited role in diagnosis, they are an important tool to follow up lesions and to look for recurrence after resection or transplant [13].

The typical histologic features described for diagnosis of EHE are (1) presence of the characteristic dendritic and/or epithelioid cells with evidence of vascular differentiation and identification of intracytoplasmic lumina containing red blood cells and (2) myxomatous to densely fibrotic stroma, both of which were present in our case. Both of these features are not seen in hemangiomas. Preservation of the hepatic acinar structure, dense sclerosis, hyalinization, and calcification of tumor nodules help to differentiate EHE from angiosarcoma, which is an important differential diagnosis. Evidence of endothelial differentiation as evidenced by reactivity to FVIII-RAg (von Willebrand's factor), CD31, and Q-Bend 10 (CD34) on immunohistochemistry along with features described above provides a definitive diagnosis [4, 8, 12] The histologic features in our case were diagnostic and were further confirmed by CD31 and CD34 positivity.

Prognosis in EHE as described earlier is unpredictable with rapid growth leading to liver failure [15] in occasional patients to spontaneous resolution without treatment [4]. Surgical excision has been shown to be the primary treatment of choice [16], but in the majority of cases, the multicentricity of the lesions makes complete local resection impossible [17]. Because of the unpredictable nature of the tumor, the indications of liver transplant in patients without evidence of liver function derangement need careful evaluation. Presence of extrahepatic disease increases the chances of recurrence [17]. Controlled clinical studies are lacking, and there are no factors that predict the clinical course or serve as a guide to the most effective treatment.

Since, in our case, the tumor was multicentric and there were multiple deposits over the left lobe of the liver along with presence of ascites, the tumor was not found resectable. Although IFN has been tried for the treatment of multifocal EHE to avoid liver transplantation [18], the role of such treatment in EHE with extrahepatic spread is dubious. The patient was considered as a candidate for liver transplantation. Due to the progressive increase in size of tumor over the next 1 month, palliative chemoembolisation was thought of as a possibility to suppress tumor growth, but on digital substraction angiography, the tumor was found to be hypovascular for arterial embolization. The hypovascularity could be explained by the growth of the tumor cells into the lumen of vessels occluding them [4]. The patient died awaiting a liver transplant.

We conclude by a note that, a clinical suspicion, familiarity with the pathologic findings, and better access to advanced imaging techniques may allow early diagnosis of these tumors and hence their appropriate management.

References

1. Pokharna RK, Garg PK, Gupta SD, Dutta U, Tandon RK. Primary epithelioid haemangioendothelioma of the liver: case report and review of the literature. J Clin Pathol. 1997;50:1029–31.
2. Ramakrishna B, Loganathan G. Epithelioid haemangioendothelioma of the liver. Indian J Pathol Microbiol. 2002;45(3):329–31.

3. Enzinger FM, Weiss SW. Soft tissue tumors. St. Louis: Mosby; 1995. p. 579–626.
4. Makhlouf HR, Ishak KG, Goodman ZD. Epithelioid hemangioendothelioma of the liver: a clinicopathologic study of 137 cases. Cancer. 1999;85(3):562–82.
5. Ishak KG, Sesterhenn IA, Goodman ZD, Rabin L, Stromeyer FW. Epithelioid hemangioendothelioma of the liver: a clinicopathologic and follow-up study of 32 cases. Hum Pathol. 1984;15(9):839–52.
6. Dean PJ, Haggitt RC, O'Hara CJ. Malignant epithelioid hemangioendothelioma of the liver in young women: relationship to oral contraceptive use. Am J Surg Pathol. 1985;9(10):695–704.
7. Kelleher MB, Iwatsuki S, Sheahan DG. Epithelioid hemangioendothelioma of liver. Clinicopathological correlation of 10 cases treated by orthotopic liver transplantation. Am J Surg Pathol. 1989;13(12):999–1008.
8. Dietze O, Davies SE, Williams R, Portmann B. Malignant epithelioid haemangioendothelioma of the liver: a clinicopathological and histochemical study of 12 cases. Histopathology. 1989;15(3):225–37.
9. Scoazec JY, Lamy P, Degott C, Reynes M, Feldmann G, Bismuth H, et al. Epithelioid hemangioendothelioma of the liver. Diagnostic features and role of liver transplantation. Gastroenterology. 1988;94(6):1447–53.
10. Ponferrada A, Salcedo M, Matilla A, Nunez O, Banares R, Alvarez E, et al. Clinical heterogeneity and distinct outcomes in hepatic epithelioid hemangioendothelioma. Gastroenterol Hepatol. 2005;28(6):321–5.
11. Ohori ON, Yousem SA, Sonmez-Alpan E, Colby TV. Estrogen and progestron receptors in lymphangiomyomatosis, epithelioid hemangioendothelioma and sclerosing hemangioma of the lung. Am J Clin Pathol. 1991;96(4):529–35.
12. Tsuneyoshi M, Dorfman HD, Bauer TW. Epithelioid hemangioendothelioma of bone: a clinicopathologic, ultrastructural, and immunohistochemical study. Am J Surg Pathol. 1986;10:754–64.
13. Dighe MK, Parnell S, Yeh MM, Lalani T. Hepatic epitheloid hemangioendothelioma: multiphase CT appearance and correlation with pathology. Crit Rev Comput Tomogr. 2004;45(5–6):343–54.
14. Lyburn ID, Torreggiani WC, Harris AC, et al. hepatic epithelioid hemangioendothelioma: sonographic, CT, and MR imaging appearances. Am J Roentgenol. 2003;180:1359–64.
15. Buccellato A, Cabibbo L, La Seta F, Milazzo G, Pisa R, Rinaldi F. Emangioendotelioma epithelioid maligo epatico: descrizione di un caso [malignant epithelioid hemangioendothelioma of the liver: a case report]. Radiol Med. 1990;79(6):634–6.
16. Läuffer JM, Zimmermann A, Krähenbuhl L, Triller J, Baer H. Epithelioid hemangioendothelioma of the liver: a rare hepatic tumor. Cancer. 1996;78:2318–27.
17. Ben-Haim M, Roayaie S, Ye MQ, Thung SN, Emre S, Fishbein TA, et al. Hepatic epithelioid hemangioendothelioma: resection or transplantation, which and when? Liver Transpl Surg. 1999;5(6):526–31.
18. Galvao FH, Bakonyi-Neto A, Machado MA, Farias AQ, Mello ES, Diz ME, et al. Interferon alpha-2B and liver resection to treat multifocal hepatic epithelioid hemangioendothelioma: a relevant approach to avoid liver transplantation. Transplant Proc. 2005;37(10):4354–8.