

Epithelioid Hemangioendothelioma of the Liver

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ABSTRACT

This is a case report of 52-year-old healthy male who was found two liver nodules in the right lobe during routine checkup. The physical examinations and laboratory investigations were unremanable. Core biopsy of the liver was done and the diagnosis of metastatic adenocarcinoma was suggested without a definite primary lesion. Since cholangiocarcinoma was suspected, subsegmently, partial hepatectomy and segmentectomy, segment 4, 6, and 7, was performed. Additional intraoperative findings were two peritoneal nodules in one kidney and duodenum. The hepatoduodenal and common hepatic lymph nodes were also enlarged.

Gross examination revealed light brown nodular lesions ranging from 2 to 2.3 cm in the right lobe and a gray white nodule, 0.6 cm in the greatest dimension, in the segment 4 of the liver. Histologic examination displayed expanding tumors comprised of epithelioid neoplastic cells in fibromyxoid stroma which may be difficult to distinguish from other carcinoma such as, cholangiocarcinoma, metastatic adenocarcinoma, and undifferentiated sarcoma.

Key words : epithelioid hemangioendothelioma, liver

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A 52-year-old healthy male came to the hospital for routine checkup. He was found to have 2 liver nodules in the right lobe by ultrasonogram. Physical examination revealed normal span of the liver and no other stigmata of liver disease. No bruit was audible. The spleen was not palpated. Tumor marker was also negative. A core biopsy of the liver was done and the diagnosis of metastatic poorly-differentiated adenocarcinoma with signet-ring features was suggested.

Primary lesion was obscure by multiple investigations. In addition, there was a cervical lymph node enlargement (1 × 0.8 × 0.5 cm.) Lymph node excision was performed and the diagnosis of reactive lymph node was entertained. Since cholangiocarcinoma was one of the possibility then, partial hepatectomy and segmentectomy, segment 4, 6, and 7, was executed. Additional intraoperative findings were two peritoneal nodules in one kidney and duodenum.

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Gross examination revealed a previously-resected liver tissue, weighing 103 gm and measuring $11 \times 4.5 \times 4.5$ cm. The outer surface displayed two firm and light brown nodular lesions, ranging from 2 to 2.3 cm in the greatest dimension (one liver parenchyma and another in the nearest resected margin). In addition, there was a gray white nodule, 0.6 cm in the greatest dimension, close to the liver capsule and 0.2 cm far from the resected margin, in the segment 4 of the liver. Two peritoneal nodules were also received together with hepatoduodenal and common hepatic lymph nodes.

Histologic examination of liver tissue displayed expanding tumor comprised of small groups of tumor cells surrounded by a distinctive fibromyxoid stroma. The tumor nodules were ill-defined. The neoplastic cells were "epithelioid" with a rounded shape and had

abundant eosinophilic cytoplasm and large vesicular and hyperchromatic nuclei with variable nucleoli. Focal area of small capillary-like lumina was noted. Mitoses were scanty seen. An area of the neoplastic cells infiltrating the sinusoids and resulting in ductular formation and obliteration of the hepatic plates was detected. The underlying lobular architecture was preserved and remnants of portal tracts were identified. The rest of liver parenchyma demonstrated preserved architecture and small numbers of lymphocytic infiltrated around the portal tracts. Resected margins illustrated no tumor involvement. Mucin stain was negative. Reticulin stain highlighted reticulin fibers surround nests of tumor cells. A basement membrane surrounded by many cords and nests of tumor cells was found by PAS stain after diastase digestion. Sections of peritoneal nodules from kidney and duodenum showed fibrofatty tissue containing diffuse vascular congestion and dilatation, focal fibrosis, granulation tissue formation, and scattered lymphoplasmacytic infiltrate. Mesothelial proliferation was also observed. Sections of left cervical node exhibited diffuse lymphoid hyperplasia. There was no malignancy seen. The initial diagnosis of vascular tumor, suggestive of hemangioendothelioma, was given and then, immunohistochemical staining was performed to confirm diagnosis. The special stain for immunoreactivity was positive with factor VIII-related antigen, vimentin, CD34, and CD31. In addition, weakly reactivity to bovine keratin was also detected. The diagnosis of epithelioid hemangioendothelioma was entertained.



Figure 1 There is slightly stained tumor which infiltrating and destroying the adjacent liver parenchyma

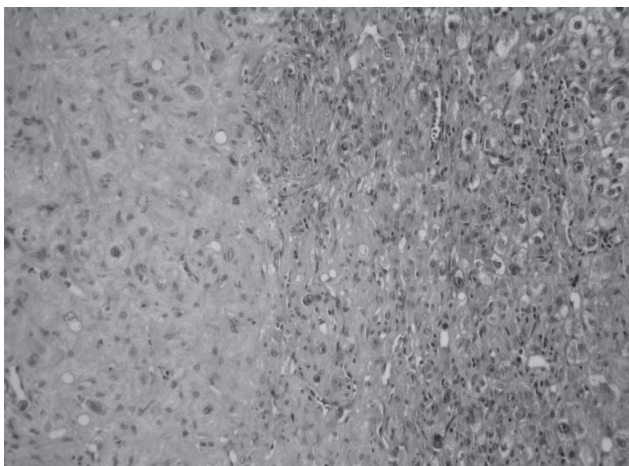


Figure 2 Epithelioid tumor cells diffusely infiltrated the hepatic sinusoids and destroyed the liver plates

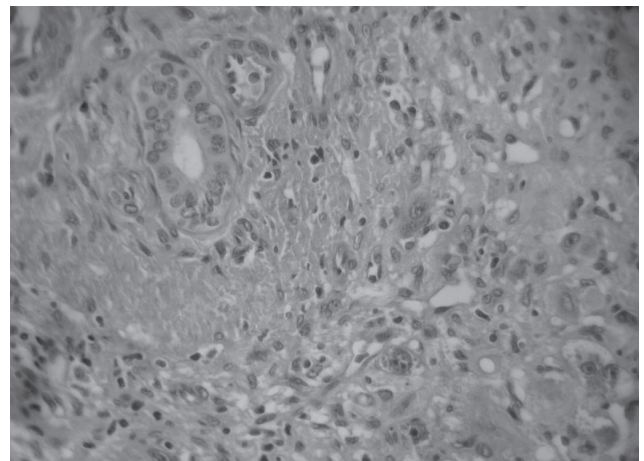


Figure 3 Epithelioid tumor cells diffusely infiltrated the sinusoids, particularly those surrounding the portal areas

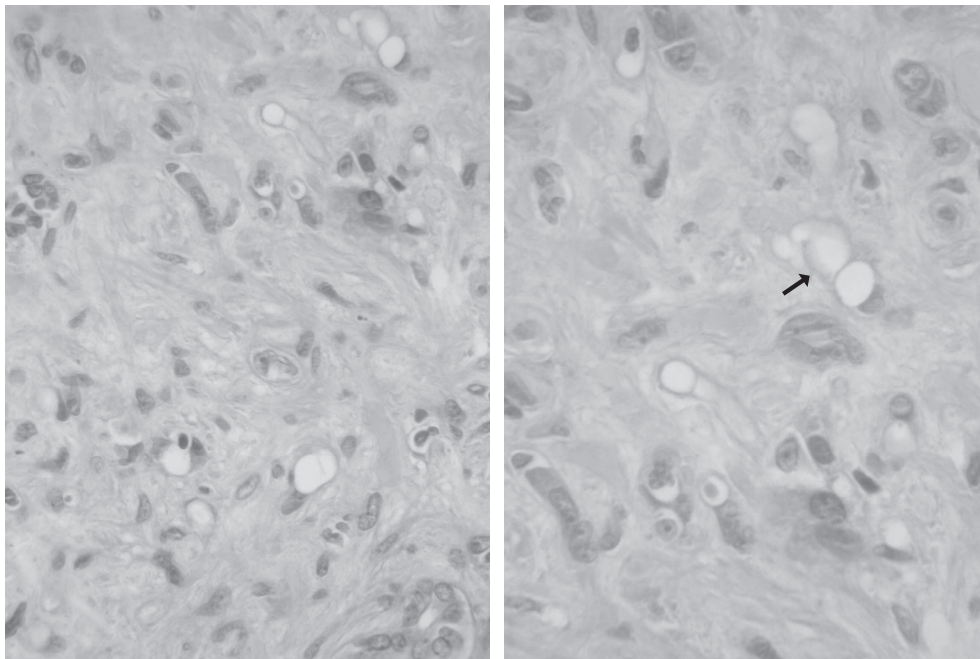


Figure 4 Tumor cells with intracytoplasmic vascular lumina (arrow)

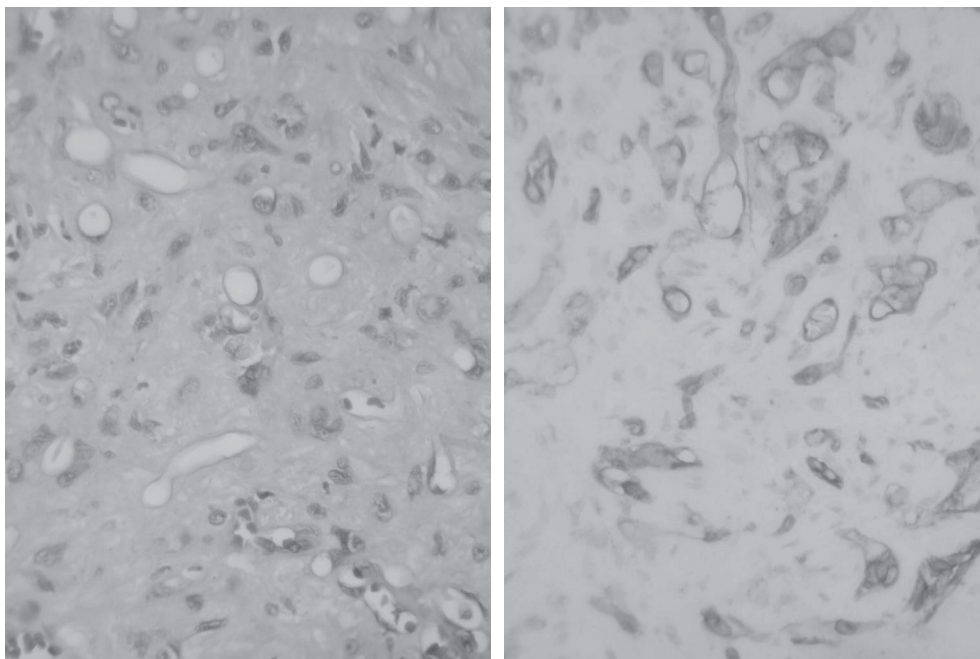


Figure 5 Tumor cells display positive factor VIII and negative mucin stain.

DISCUSSION

Epithelioid hemangioendothelioma (EH) is one uncommon vascular tumor of borderline malignancy⁽¹⁾ that preferentially arise from soft tissue of the extremities^(2,3) and lungs, where most of the cases were reported under the name of intravascular bronchioloal-

veolar tumor (IVBAT)⁽⁴⁻⁷⁾. Liver involvement is infrequent and most often occurs as a primary tumor^(1,8,9). Recently, Ishak *et al.* 1 reported a series of this tumor developed primarily in the liver. There were 20 women (62.5%) and 12 men (37.5%), ranging in age from 19 to 86 years (average, 50 years). The tumor was incidentally discovered in four patients (12.5%), whereas

others presented with jaundice, liver failure, hemoperitoneum, or non-specific complaints⁽¹⁾. Macroscopically, the white and hard tumoral nodules are often multiple and involve both lobes of the liver. Microscopically, neoplastic cells infiltrate the hepatic parenchyma along sinusoids, terminal hepatic venules, and portal vein branches. They form vascular lumina and capillary type vessels that lie within a stroma that varies from loose and myxoid to dense and fibrous with possible calcification. The largest series consist of 137 cases studied by Makhlof *et al.*⁽¹⁰⁾ at the Arm Force Institute of Pathology (AFIP). The age at presentation of the AFIP patients ranged from 12 to 86 years; 62% were women. Symptoms and signs included weakness, anorexia, nausea, episodic vomiting, upper abdominal aching and pain, jaundice, and hepatosplenomegaly^(1,10). However, significant numbers (42%) of the AFIP cases were an incidental finding. The diagnosis of epithelioid hemangioendothelioma of the liver may be difficult. Most often, original diagnoses are cholangiocarcinoma, metastatic carcinoma, and unclassified sarcoma as in our case. Most of the diagnostic difficulties arise from the fact that the vascular nature of epithelioid hemangioendothelioma is not overt on x-ray examination and may be easily overlooked by histologic examination. Indeed, the results of ultrasonography, computed tomography, and arteriography are not suggestive of vascular tumor and more consistent with metastatic carcinoma⁽¹¹⁾. Final diagnosis can only be reached by histopathologic examination of the appropriate material. The most important clues to histological diagnosis are a) multifocal pattern of liver involvement, b) the contrast between the fibrotic center and the cellular periphery of tumor foci, c) evidence of vascular differentiation, best detected at the edge of lesions because of the presence of well-defined neoplastic vessels, and d) characteristic pattern of involvement of adjacent sinusoids and of preexisting vessels^(1,12).

Diagnosis may be difficult from biopsy material especially samples circumstances from advanced lesions. In these instances, the vascular nature of the neoplasm is not obvious. The general appearance of the proliferation, consists of pleomorphic cells embedding in a dense extracellular matrix and sometimes simulating adenocarcinomatous cells because of the presence of large intracytoplasmic vacuoles. This may be easily confused with cholangiocarcinoma or metastatic carcinoma. In these cases, immunohistochemi-

cal and ultrastructural examination may be helpful for definite diagnosis. With immunohistochemical staining, neoplastic cells of epithelioid hemangioendotheliomas express several markers of normal endothelial cells including factor VIII-related antigen^(1,8,13), vimentin, and reactivity with *Ulex europaeus* I lectin^(14,15).

Epithelioid hemangioendothelioma of the liver is usually considered a tumor of borderline malignancy⁽¹⁾. However, although most of the patients experienced long-term survivals⁽¹⁾, in a significant proportion of cases, the disease flows a rapid progressive course with a fatal outcome^(8,12,16). The effective treatment of EH of the liver is currently far from curative without transplantation. Surgical resection is often impossible due to multiple areas of involvement in the liver by tumor. Chemotherapy is usually ineffective^(1,13). Therefore, epithelioid hemangioendothelioma is a possible indication for orthotopic liver transplantation, especially in young adults.

In summary, the diagnosis of epithelioid hemangioendothelioma of the liver is based on a suggestive association of clinical, radiologic, and histopathologic features that make it different from other vascular tumors of the liver. Unlike hemangiomas and juvenile hemangioendotheliomas, epithelioid hemangioendotheliomas those occur in adult, EH appears as multiple echo-poor or heterogeneous echogenic lesions, and does not present as a large vascular channel⁽¹⁷⁾. Unlike angiosarcomas, it usually behaves as a slowly evolving tumor and lacks an overt vascular nature on both radiologic and histologic examinations^(18,19). In addition, epithelioid hemangioendothelioma is not associated with particular etiological factors.

Attention must be paid to the following clinical features: 1) Majority of patients are young adults, 2) the contrast between presence of multiple intrahepatic tumors with good patient condition, 3) slow course of the disease suggested by a long-standing clinical history, and 4) presence of intratumoral calcification.

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