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Differential diagnosis of epithelioid and clear cell tumors in the liver

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ABSTRACT

A tumor composed of large eosinophilic cells in the liver raises concern for hepatocellular carcinoma, which is typically composed of such cells. However, there are other tumors, both primary and metastatic, that may be composed predominantly of large epithelioid cells. Distinction of these tumors from hepatocellular carcinoma and from each other is of obvious importance for patient management. Similarly, a clear cell tumor anywhere in the body triggers suspicion for renal cell carcinoma. However, other tumors, including hepatocellular carcinoma can rarely be composed entirely of cell cells and the distinction of these from one another, and of primary from metastatic disease is vital. As with the latter, accurate diagnosis is essential for patient management. Using illustrative examples, this article discusses differential diagnosis of liver tumors comprised predominantly of epithelioid cells or clear cells.

A needle biopsy of a liver mass is likely to show hepatocellular carcinoma (HCC), cholangiocarcinoma, a metastatic lesion or another primary liver tumor. The likelihood of each depends on the epidemiological context of the patient and state of the underlying liver. In Western countries, metastatic lesions are more common than primary liver tumors in a non-cirrhotic liver. The presence of underlying cirrhosis or advanced fibrosis tips the scales towards hepatocellular carcinoma; however, the latter may arise in non-cirrhotic and non-fibrotic liver in areas where vertical transmission of hepatitis B is endemic. Similarly, the likelihood of a cholangiocarcinoma is high in countries where infection with liver flukes is endemic, although the incidence of cholangiocarcinoma is reported to be increasing in Western countries as well.[1,2]

A tumor composed of large eosinophilic cells in the liver raises concern for hepatocellular carcinoma, which is typically composed of such cells. However, there are other tumors, both primary and metastatic, that may be composed predominantly of large epithelioid cells. Distinction of these tumors from hepatocellular carcinoma and from each other is of obvious importance for patient management. Similarly, a clear cell tumor anywhere in the body triggers suspicion for renal cell carcinoma. However, other tumors, including hepatocellular carcinoma can rarely be composed entirely of cell cells and the distinction of these from one another, and of primary from metastatic disease is vital[3,4] As with the latter, accurate diagnosis is essential for patient management. Using illustrative examples, this article discusses differential diagnosis of liver tumors comprised predominantly of epithelioid cells or clear cells.

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Case 1

A 41-year-old female with no significant past medical history presented with left flank pain, myalgia, and fatigue for one month. Computed tomography (CT) revealed left lower lung nodules (largest 1.5 cm) and a right hepatic mass up to measuring 8 cm. Fine needle aspiration (FNA) of the lung nodules was non-diagnostic. A biopsy of the right liver mass was reported as hepatocellular carcinoma. The patient was referred to our institution for a second opinion and another liver biopsy was performed.

Pathologic findings

The biopsy of the right liver mass showed nests and cords of large cells with abundant eosinophilic cytoplasm, large nuclei, prominent nucleoli, and open chromatin. Interspersed among the tumor was a hypocellular matrix including adipocytes and thick-walled vessels (Fig. 1A and B). The adjacent liver parenchyma was normal in appearance. Immumohistochemical stain for HMB45 was positive in the tumor cells (Fig. 1C). Hepatocyte specific antigen (Fig. 1D) and glypican-3 were positive only in adjacent benign hepatocytes.

Diagnosis: Angiomyolipoma

Discussion

Angiomyolipoma is currently considered to be a member of the PEComa (tumor of perivascular epithelioid cells) family.[5,6] More commonly found in the kidney, angiomyolipoma may rarely occur in the liver, where the epithelioid variant is more common. Composed predominantly of large eosinophilic cells, these tumors may be mistaken for a hepatocellular neoplasm.

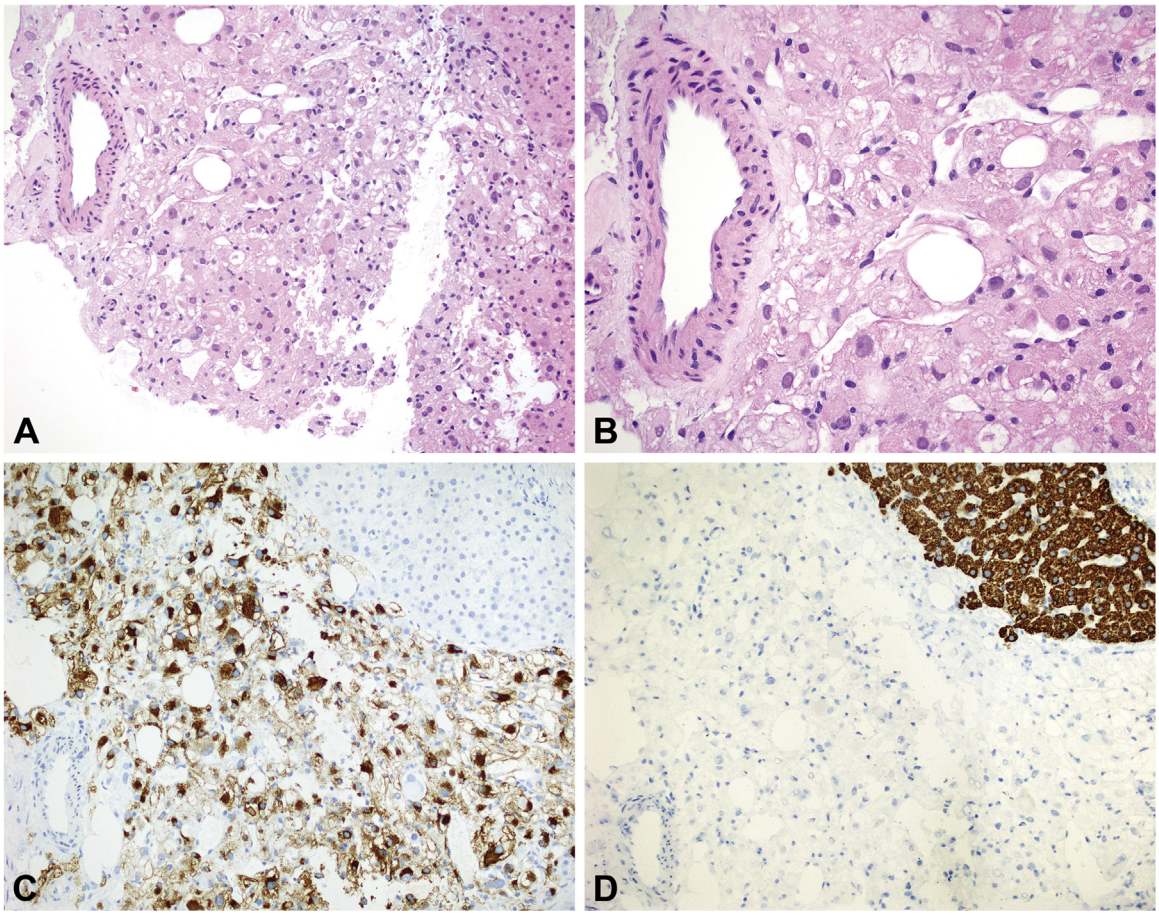

Fig. 1. Angiomyolipoma consisting predominantly of epithelioid cells with interspersed thick walled blood vessels and adipocytes (A, B). The individual cells have abundant eosinophilic cytoplasm and a central to eccentric nucleus with a variably prominent eosinophilic nucleolus (B). The tumor is positive for HMB-45 (C) and negative for hepatocyte specific antigen, which stains adjacent benign liver in the upper right (D).

Hepatic angiomyolipoma occurs in middle-aged individuals and may present with abdominal pain or generalized symptoms such as fever, malaise, and anorexia. Rarely, the tumor may rupture and present with hemorrhage.[2,6] Some cases are discovered incidentally during imaging for an unrelated condition. Despite the association with tuberous sclerosis, most cases are sporadic.

Grossly, angiomyolipoma appears well circumscribed but not encapsulated. The cut surface is heterogeneous and often variegated, usually with prominent hemorrhage and necrosis. The coloration is usually tan to yellow, depending on the composition of the cellular components, especially the amount of fat. Histologically, as its name implies, angiomyolipoma is composed of variable combination of three cell types: a smooth muscle-like component, vascular component, and fat cell component. The myoid cells may be either epithelioid or spindle in shape. The epithelioid variant, composed predominantly of epithelioid myoid cells may display a trabecular growth pattern, thus closely mimicking a hepatocellular neoplasm. Their cytoplasm sometimes demonstrates perinuclear condensation (classically described as a “spider-web” appearance), mimicking glycogenated hepatocytes or clear cells. Myoid cells are seen intimately associated with and surrounding blood vessels. The vascular component consists of thick-walled arterial or venous channels that lack elastic tissue lamina and thin-walled venous spaces. The fat component may be scant or absent in liver tumors, but when present, it may simulate simple steatosis.[7] Despite its well-circumscribed appearance, angiomyolipoma demonstrates infiltrative borders on microscopy. Using immunohistochemical stains, HMB-45 stains stronger in epithelioid myoid cells, while smooth muscle actin is stronger in spindle shaped myoid cells. Angiomyolipoma may mimic metastatic melanoma, a problem compounded by immunohistochemical positivity of epithelioid myoid cells and fat cells for S100.[2]

Hepatic angiomyolipoma is a benign tumor; rare examples of malignant cases have been reported.[8] Microscopic features that are associated with worse outcomes are predominant epithelioid morphology, nuclear atypia, high proliferation rate, and necrosis.[6]

Case 2

A 33-year-old female with a history of treated tuberculosis presented with worsening left pelvic pain for six months. CT showed multiple non-enhancing, hypodense lesions throughout the liver (largest 6 cm), right adrenal gland enlargement up to 5 cm, and a 2.5 cm sclerotic lucency in the left ilium. Two of the lesions in the right hepatic lobe were biopsied under ultrasound guidance.

Pathologic findings

The liver biopsy revealed a tumor composed of cords and single cells within a fibromyxoid background (Fig. 2A). These cells infiltrated hepatic sinusoids and appeared to occlude large vascular structures (Fig. 2B). Signet ring-like cells were identified, some of which contained red blood cells within intracytoplasmic lumina (Fig. 2B and C). Immunohistochemical stain for CD34 was positive with a membranous pattern in the tumor cells (Fig. 2D).