Case Report

Hepatic monotypic epithelioid angiomyolipoma with concomitant hepatocellular carcinoma

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Abstract: Hepatic monotypic epithelioid angiomyolipoma (AML) is a rare lesion in which the predominant population of an epithelioid component can mimic hepatocellular carcinoma (HCC). The hepatic epithelioid AML with concomitant HCC is extremely uncommon. In this study, we present the clinical and pathologic features of a case of hepatic monotypic epithelioid AML with concomitant HCC in a 63-year-old man. Imaging examinations revealed two masses located in the liver, measuring 83×63 mm and 37×27 mm separately, which exhibited an early contrast enhancement and a rapid washout on enhanced computed tomography (CT), so that HCC with intrahepatic metastases was suspected. The small tumor was removed for intraoperative frozen section examination. Grossly, the tumor was solitary, well-circumscribed, and non-encapsulated. Microscopically, it was composed purely of a trabecular arrangement of epithelioid cells with a sinusoidal pattern. Immunohistochemically, it was positive for HMB45, Melan-A, and alpha smooth muscle actin (α-SMA). Interestingly, the large tumor has the histologic features similar to those of the small one. However, it was positive for epithelioid markers and negative for the melanocytic markers. It reminds us that there is a possibility of coexistence of HAML and HCC in the liver. We believe that this might be the first case report of a hepatic monotypic epithelioid AML with concomitant HCC. The patient gave up treatment and died in 6 months after the operation in the follow-up.

Keywords: Hepatic epithelioid angiomyolipoma, hepatocellular carcinoma, concomitant

Introduction

Angiomyolipoma (AML) is a rare benign tumor that consists of a variable admixture of smooth muscle cells, mature adipocytes, and dysplastic, thick-walled blood vessels. AML is most often found in the kidney, followed by the liver. According to the proportion and peculiar cellular features of three components, AML can be subdivided into classic mixed and several variants. The epithelioid variant of hepatic angiomyolipoma (HAML) with predominant epithelioid cells and inconspicuous fat can mimic hepatocellular carcinoma (HCC) in radiology and histopathology presentation and become a diagnosis challenge for both radiologists and pathologists. Coincidentally, we recently encountered a patient with hepatitis B surface antigen (HBsAg) expression who presented with HCC and concurrent epithelioid AML in liver. To our knowledge, coexistence of HAML and HCC is extremely rare. Up to date, only three cases of typical HAML with concomitant HCC were described [1-3] in the English literature. Here, we present a case of rare monotypic epithelioid HAML and concurrent HCC in a hepatitis B virus (HBV) infected patient: the clinical presentation, radiological and pathological findings, differential diagnosis, and biological behavior are discussed.

Case presentation

A 63-year-old man was admitted for abdominal discomfort for 1 month. He had a history of viral hepatitis without evidence of the tuberous sclerosis complex. Laboratory test showed positive of hepatitis B surface antigen (HBsAg), liver dysfunction, elevated alpha fetoprotein (AFP) level (8035 ng/mL) and decreased total serum protein level. Real-time quantitative polymerase chain reaction (PCR) test revealed a high viral
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load: hepatitis B virus (HBV)-deoxyribonucleic acid (DNA) was 2940000 IU/ml (normal, < 20 IU/ml). Concentration of serum AFP was 8035 ng/mL (normal, < 20 ng/mL). Liver function tests showed transaminase was elevated and total protein was reduced. Abdominal ultrasonography (US) indicated two hypoechoic masses in the liver: one with irregular shape, located in the left liver lobe and the size was 83×63 mm (Figure 1A); the other one was well-circumscribed and located in the right liver lobe with a size of 37×27 mm (Figure 1B). After administration of intravenous contrast material, both masses exhibited hyperenhancement in the arterial phase and the portal phase, and hypoenhancement in the late phase (Figure 2A-F). A plain computed tomography (CT) scan showed the larger tumor was of mixed hypodensity in the left liver lobe, and the small one was of uniform hypodensity in the right liver lobe (arrow, Figure 3). On dynamic contrast-enhanced CT, two masses were contrast enhanced in the arterial phase (Figure 4A) and rapid contrast material washout in the venous phase (Figure 4B). These clinical findings indicated that it might be HCC with intrahepatic metastases.

An operation was performed and both masses were identified. The large tumor had penetrated the capsule of the left liver with satellite tumorlets around; whereas the small one was...
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well-circumscribed, encompassed in the right liver lobe. The large tumor was removed entirely, and the small tumor was sampled for intraoperative frozen section examination.

Grossly, the small tumor was solid, grayish brown, well-circumscribed, and non-encapsulated. Microscopically, the tumor cells were purely epithelioid and arranged in sheet or trabecular pattern with a rich network of sinusoidal blood vessels (Figure 5A). At first glance, a sinusoidal type HCC entered the diagnosis. However, the unique histologic features of tumor in this lesion, which showed some tumor cells with clear cytoplasm and eosinophilic condensation around the nucleus, attracted our attention (Figure 5B). A few lipid droplets were detectable in the cytoplasm of the trabecular cells (Figure 5C) although mature adipocytes were rare. No thick-walled vessels were found in the tumor. Based on the histologic features, HAML was considered. Following immunohistochemical analysis was performed and the epithelioid cells exhibited a strong cytoplasm granular positivity with HMB45 (Figure 6A) and Melan-A (Figure 6B). Alpha smooth muscle actin (α-SMA) was positive in the perimembrane and cytoplasm in majority of tumor cells (Figure 6C). S-100 protein was positive in a minority of tumor cells (Figure 6D). However, tumor cells were negative for vimentin (Figure 6E), CK8 (Figure 6F), epithelial membrane antigen (EMA), and p53 (not shown).

The large tumor had similar histopathological features (Figure 7A-C) to those of the small one, but we detected positive staining for CK8 (Figure 7D), AFP (Figure 7E) and negative staining for HMB45 (Figure 7F). Therefore, a monotypic epithelioid HAML with concomitant HCC was finally diagnosed. The patient gave up treatment and died in 6 months after the operation by our follow-up.

Discussion

AML was firstly described in the liver by Ishak in 1976 [4]. The tumor usually follows a benign clinical course. Although 5-15% of HAML are estimated to be associated with tuberous sclerosis characterized by the loss of heterozygosity at TSC1 and TSC2, which are considered to be present in more than half of the renal AMLs [5-8], the etiology of most HAML remains elusive.

Clinically, the natural history of HAML has not been entirely clarified. Abdominal pain was the...
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most common symptom, which can be observed in almost 75% patients [9], followed by abdominal fullness and body weight loss. On US, HAML presents as mixed echogenic nodules, and shows remarkable hyperechogenicity with a hypoechoic portion. On contrast-enhanced ultrasound (CEUS), the majority of HAMLs exhibit arterial hyperenhancement and subsequent sustained enhancement [10]. Plain CT scan shows it is a hypodensity mass with variable amounts of fatty density depending on the relative portion of fat cells in the tumor. Sporadic HAML shows as a hypervascular fat-containing mass in the early phase by dynamic contrast-enhanced CT [11]. Because of its rarity and nonspecific clinical symptoms, imaging studies play a key role in the diagnosis of HAML preoperatively, and pathologic examination is required for a definitive diagnosis. However, variation of the three histological components of the HAML poses a diagnostic challenge radiologically and pathologically [12, 13]. Thus, the overall preoperative diagnostic rate of HAML was 18%, and the most common misdiagnosis was HCC [14]. In literature, nearly half of the HAML cases presented as a solid mass with a small portion of fat component [15]. It usually shows as a low echoic image on US, and

Figure 5. Morphologic features of the epithelioid angiomyolipoma in the small mass of liver (A-C). The purely epithelioid tumor cells arranged in sheet or trabecular pattern with a rich network of sinusoidal blood vessels (A, H&E staining; ×200). Some tumor cells showing clear cytoplasm with eosinophilic condensation around the nucleus (B, H&E staining; ×200). Lipid droplets were found in cytoplasm of the tumor cells (C, H&E staining; ×200).

Figure 6. Immunohistochemical findings in the epithelioid hepatic angiomyolipoma (A-F). Epithelioid cells showing strong cytoplasmic granular immunoreactivity with HMB45 (A, ×200) and Melan-A (B, ×200), perimembranous and cytoplasmic immunopositivity for α-SMA (C, ×200). A small fraction of epithelioid cells were positive for S-100 protein (D, ×200). However, tumor cells were negative for Vimentin (E, ×400), CK8 (F, ×400).
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posed almost exclusively of epithelioid cells and contained less pronounced blood vessels. It is ‘the first’ monotypic epithelioid HAML [18]. Recently, AML has been considered as a member of perivascular epithelioid cell tumor (PEComa) family [19]. These tumors are composed of perivascular epithelioid cells and possess a similar immunohistochemical profile, including positive staining for SMA and melanocytic markers [20]. Positive HMB45 staining is specific and regarded as definitive criterion of AML or related tumors [15-21]. Equally important is the negative staining for vimentin. In addition, α-SMA, desmin, and S-100 can be positive but not specific [14]. CK18, CK19, CAM 5.2, HepPar-1 were negative in the tumor. The expression of α-SMA and absence of vimentin help the distinction of HAML from malignant melanoma. Ultrastructurally, premelanosomes in AML show evidence of melanogenesis [22, 23]. Considering the histologic features of the epithelioid appearance, clear to eosinophilic cytoplasm, broad solid sheet and trabecular structures presented by epithelioid AML, the major differential diagnoses considered should include a variety of tumors such as epithelioid melanoma, epithelioid peripheral nerve sheath tumor, epithelioid smooth muscle tumor, renal oncocytoma and renal cell carcinoma [22]. In the liver, the epithelioid features of the tumor

an earlier contrast enhancement and a rapid contrast material washout on dynamic contrast-enhanced CT. The enhancement pattern is similar to that of HCC [16]. In our case, adipocytes were scarce, and the tumor presented a fat-poor lesion, mimicking the HCC in another lobe of the liver. Therefore, imaging studies could not get enough evidence in the differential diagnosis. In addition, our laboratory data showed the concentration of serum AFP markedly increased. Therefore, HCC with hepatic metastases was considered preoperatively.

Morphologically, a typical AML presents as a well-defined, non-encapsulated mass and has mature adipocytes, thick-walled blood vessels, and spindle-epithelioid cells. Among the three histologic components of AML, mature fat and tortuous or thick-walled vessels are most characteristic. However, several histologic variants have been verified in AML, including classic mixed, lipomatous, myomatous, and angiomatous type [15]. In 1998, Martignoni et al. reported three cases of renal AML composed purely of epithelioid cells with complete lack of adipocytes and abnormal vessels. He considered these tumors close relatives of the AML variants, and designated them as ‘monotypic epithelioid AML’ [17]. In 2000, Yamasaki et al reported an AML in liver, which was composed almost exclusively of epithelioid cells and contained less pronounced blood vessels. It is ‘the first’ monotypic epithelioid HAML [18].

![Figure 7. Microscopical and immunohistochemical features of HCC in the large mass of liver (A-D). The tumor cells had some similar histopathologic features to those of the hepatic angiomyolipoma (A-C, H&E staining; [A, B] ×100, [C] ×200). Immunohistochemistry was positive for CK8 (D, ×200), AFP (E, ×200) and negative for HMB45 (F, ×200) in tumor cells.](image)

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cells and the trabecular growth pattern notably mimic a sinusoidal type HCC [14]. The finding of epithelioid cells with eosinophilic condensation around the nucleus should alert the pathologist to consider the tumor might be an AML [14]. The tumor in our case is composed mainly of epithelioid cells, but with few lipocytes or abnormal vessels. Although its histological features are somewhat similar to those of HCC, the typical immunohistochemical pattern is diagnostically different. The differential diagnosis between HCC and HAML with rare adipocytes and rich epithelioid components should be noticed.

The treatment of HAML remains controversial. Usually following a benign clinical course, most HAML could be conservatively treated [24]. However, HAML might not be in consistently stable condition. The risk of rupture is a guiding principle of surgery [25]. Recently, several malignant HAMLs have been reported. The features of malignant transformation include the large tumor size, pleomorphic nuclei with high proliferative activity, prominent vascular invasion, coagulative necrosis, and clinical evidence of aggressive behavior such as recurrence, metastasis, or even death [18, 26]. Therefore, it is very important to correctly diagnose HAML before surgery. The imaging studies combine a fine needle aspiration (FNA) biopsy are necessary for an accurate diagnosis. So, for patients with malignant HAML or potential risk of rupture, or significantly growing tumor during the observation [9-25], surgical resection should be suggested.

In summary, we reported here a rare case of monotypic epithelioid HAML with concomitant HCC. This case suggests considering the possibility of coexistence of HAML and HCC when multiple masses are found in the liver. Diagnosis of the AML variants with scanty fat component may be difficult. Immunohistochemistry provides an effective method to distinguish HAML from HCC and other mimics.

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Disclosure of conflict of interest

None.

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References

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