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Case Report

Hepatic epithelioid angiomyolipoma with an unusual pathologic appearance: expanding the morphologic spectrum

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Abstract: Hepatic epithelioid angiomyolipoma (AML) is a rare lesion that is characteristically composed of a predominant or exclusive population of epithelioid cells coexpressing melanocytic and myogenic markers. The cystic variant of epithelioid AML is exceedingly uncommon. In this study, we present the clinicopathological features of a case of hepatic epithelioid AML with remarkable cystic degeneration in a 34-year-old female as well as with a literature review. A magnetic resonance imaging scan revealed a well-defined 30 cm × 25 cm hepatic mass. Sectioning of the well-defined mass revealed a non-encapsulated tumor that was multiloculated with amorphous necrotic tissue and hemorrhagic fluid. The inner cystic wall was rough and brownish-black in color. Microscopically, the tumor largely consisted of epithelioid cells that comprised approximately 95% of the total neoplastic components but also contained some spindle myoid cells, mature fat, and a thick-walled vasculature. Both intracellular and extracellular hyaline globules were frequently identified. Necrosis and invasive growth patterns were also present. By immunohistochemistry, spindle-epithelioid neoplastic cells were variably positive for Melan-A, HMB45, and SMA but were uniformly negative for epithelial and hepatocytic markers. This is the third report of a cystic AML in liver. The patient was followed for 71 months without any evidence of metastasis or recurrence.

Keywords: Angiomyolipoma, cystic degeneration, liver, perivascular epithelioid cell tumor

Introduction

Angiomyolipoma (AML) is a well-recognized mesenchymal tumor that consists of a variable admixture of smooth muscle cells, mature adipocytes, and dysplastic, thick-walled blood vessels [1]. Though occasionally reported in diverse anatomic sites, AML is most often found in the kidneys, followed by the liver [2]. AML demonstrates a wide spectrum of morphological patterns according to the proportion and peculiar cellular features of three tissue components. Based on the dominant cell type, AML can be subdivided into various forms [3]. The epithelioid AML is predominantly or exclusively composed of a population of epithelioid cells [4]. AML is usually a solid neoplasm, both grossly and radiologically, and the cystic forms are exceedingly rare [1, 5]. To date, only 25 cases of cystic AML, 23 of which were located in kidney and the remaining 2 in liver have been reported in the English literature (**Table 1**) [6-15]. In this paper, we present the third case of cystic AML in the liver with an emphasis on discussing its clinicopathological features and provide a literature review.

Case presentation

A 34-year-old Chinese female was admitted for right upper abdominal discomfort for 2 months and recent (5 days) progressive deterioration. The patient's past medical history was unremarkable, and she did not consume alcohol or tobacco. The patient had no evidence of tuberous sclerosis complex. Her family history was significant for esophageal carcinoma and gastric carcinoma in her mother and father, respectively. Physical examination revealed a palpable tender liver without jaundice or

Table 1. Clinicopathologic data for reported cases of cystic angiomyolipoma

Reference	Sex/age (yr)	Location	Size of tumor (cm)	Outcome (mo)
Wendth, et al. [6]	M/2	Liver	NA	NA
Li, et al. [7]	M/58	Liver	37.0	NA
Present case	F/34	Liver	30.0	NED/71
Fine, et al. [8]	M/42	Kidney	2.8	NED/96
	M/76	Kidney	4.5	NED/60
	F/55	Kidney	2.5	NED/12
	F/37	Kidney	1.3	NED/6
Davis, et al. [9]	F/61	Kidney	6.0	NED/36
	F/45	Kidney	3.5	NED/108
	F/21	Kidney	7.0	NED/36
	F/37	Kidney	5.0	NED/36
	F/39	Kidney	NA	NA
	M/20	Kidney	5.0	NA
	M/70	Kidney	4.0	NED/6
	F/27	Kidney	3.0	NA
	F/61	Kidney	5.0 and 3.5	NA
	M/50	Kidney	NA	NA
	M/67	Kidney	3.0	NA
Armah, et al. [10]	F/39	Kidney	2.5	NED/12
Mikami, et al. [11]	M/55	Kidney	3.0	NED/24
Rosenkrantz, et al. [12]	F/39	Kidney	3.4	NA
Chung, et al. [13]	F/48	Kidney	NA	NA
Karafin, et al. [14]	F/75	Kidney	2.8	NA
	M/17	Kidney	4.5	NA
	F/51	Kidney	1.5	NA
Filho, et al. [15]	M/46	Kidney	5.0	NA

yr: Year; mo: Month; M: Male; NA: Not available; F: Female; NED: No evidence of disease.

varices. Blood tests were significant for anemia, elevated levels of γ-glutamyltransferase, alkaline phosphatase, total bile acid, alanine aminotransferase, aspartate amino transferase, total bilirubin, direct bilirubin, and indirect bilirubin and decreased levels of total protein, albumin, and globulin. Carbohydrate antigen 19-9, carcinoembryonic antigen, and alpha-fetoprotein levels were within the normal range. A serum hepatitis survey was negative. A magnetic resonance imaging (MRI) scan revealed a well-defined 30 cm × 25 cm mass occupying nearly the entire left three lobes of the liver. The neoplasm was a complex, mostly cystic lesion that was subdivided into multilocular lesions by septa. Following endovenous administration of contrast medium, heterogeneous enhancement was noted in the cystic wall and septa (**Figure 1**). During surgery, the entire left three lobes of the liver, with the exception of minor portions of the left lateral lobe, were observed to be replaced by a large, sharply demarcated tumor, which measured 30 cm × 25 cm × 15 cm. The patient underwent left-three-lobe hepatectomy and cholecystectomy without complication. Her postoperative course was uneventful. She is still alive and well, without evidence of recurrence or metastasis, 71 months after surgery.

On macroscopic examination, the specimen consisted of a giant nodular mass measuring 30 cm × 25 cm × 15 cm with an attached portion of grossly normal liver tissue. The external surface of the mass was smooth and brownish in color. Sectioning revealed that the well-circumscribed,non-encapsulatedtumor was multiloculated with amorphous necrotic tissue and hemorrhagic fluid. The inner cystic wall was rough and brownish-black in color. The cystic wall was variable in the level of thickness, ranging from 0.3 cm to 1.2 cm, with a yellowish cut surface.

The entire solid components of the specimen were submitted for microscopic inspection, which revealed an unencapsulated lesion that was sharply demarcated from the adjacent hepatic parenchyma. The tumor mainly consisted of epithelioid cells that comprised approximately 95% of the total neoplastic components but also contained some spindle myoid cells, mature fat, and thick-walled vasculature (**Figure 2A**). The epithelioid cells were polygonal or spheroidal and were arranged in broad solid sheets with a prominent network of sinusoidal-like vessels. A trabecular pattern could be focally observed. The epithelioid cells exhibited a wide morphological spectrum. The cells exhibited abundant cytoplasm that varied from clear and finely vacuolated to eosinophilic granular (**Figure 2A**). In some cells, the peripheral cytoplasm was clear and reticular, and perinuclear cytoplasm was condensed and eosinophilic granular, demonstrating a spider web appearance. The eccen-

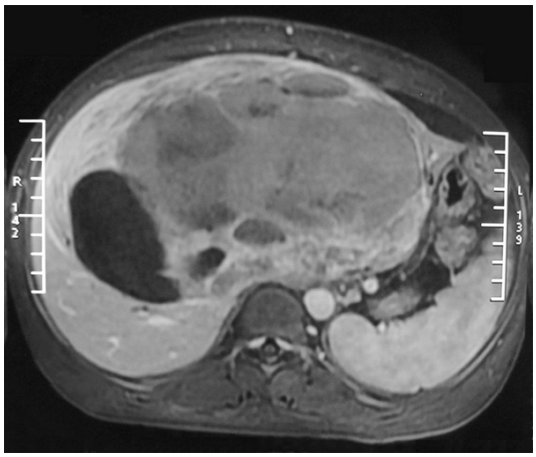

Figure 1. MRI scan revealed a well-defined, cystic mass located in the left three lobes of liver.

tric nuclei exhibited a variety of features, including rare intranuclear pseudoinclusions, clumped chromatin, pyknosis, and vesicular nuclei. Epithelioid neoplastic cell invasion into the surrounding hepatic parenchyma was identified. Frequent multinucleate cells, one to several macronucleoli cells, and bizarre pleomorphic giant cells were present. Occasional nucleoli were present, and mitoses were scanty, with an index < 1/50 high-power fields. Both intracellular and extracellular hyaline globules were frequently identified singly and in clusters (**Figure 2B**). Spindle myoid cells arranged in whorled and interlacing fascicles, scattered mature lipocytes, and tortuous vessels typically surrounded by mantles of epithelioid cells were rarely appreciated; however, these features occupied less than 5% of the whole tumor. Focal areas of necrosis and hemorrhage were present (**Figure 2C**). Extramedullary hematopoiesis was absent.

Immunohistochemical analysis revealed that the epithelioid neoplastic cells were strongly and diffusely positive for Melan-A (cytoplasmic) (**Figure 3A**) and patchily positive for HMB45 (cytoplasmic) (**Figure 3B**), and a minority exhibited weak positivity for smooth muscle actin (SMA) in the cytoplasm. Conversely, the spindle myoid cells exhibited strong and diffuse reactivity for SMA, but only a few were weakly immunostained for Melan-A and HMB45. S-100 protein labeling was detected in individual epithelioid cells but in whole fat cells (cytoplasmic and nuclear). Both the epithelioid and spindle cells were negative for CD10, CD34, CD117, DOG-1, ER, PR, desmin, CK AE1/AE3, epithelial membrane antigen (EMA), HepPar-1, Alpha fetal protein, CD1a, chromogranin A, and synaptophysin. The proliferation marker Ki-67 was expressed in less than 1% of epithelioid and spindle tumor cells.

Discussion

We describe a case of hepatic epithelioid AML with a striking cystic degeneration in a 34-year-old woman. The present neoplasm exhibited the 3 basic components of AML, including spindle-epithelioid cells, mature fat, and tortuous blood vessels with a predominance of epithelioid cells, which occupied approximately 95% of the entire tumor. The diagnosis of AML was confirmed by spindle-epithelioid cells that were positive for melanocytic (Melan-A, HMB45) and myogenic (SMA) markers, despite some variation in the degree of intensity in different types of tumor cells, but negative for epithelial (CK, EMA) and hepatocytic (HepPar-1) markers.

The current tumor exhibited three unusual characteristics. First, the present epithelioid AML was prominently and grossly cystic. This phenotype is exceedingly rare, as AML is typically solid [1, 5]. There are only 3 reported cases of hepatic cystic AML, including our case (**Table 1**) [6, 7]. Wendth et al. first described cystic AML of the liver in a 2-year-old boy in 1976, and the second such case was not documented until 2010 by Li [6, 7]. The intracystic contents of the latter two neoplasms described by Li and our group were necrotic tissue and hemorrhagic fluid, and the cystic change of the latter two was due to necrosis and hemorrhage. No lining epithelial cells were appreciated within the cystic wall [7]. With respect to renal cystic AML, 23 cases have been previously reported (**Table 1**). Contrary to the hepatic cystic AML, the cystic spaces of similar tumors in kidneys were lined by epithelium that varied from flat to cuboidal to columnar [8-15].

Second, the present tumor exhibited three ominous characteristics, including a large tumor size (30 cm), an invasive growth pattern into the adjacent liver tissue, and multiple foci of coagulative necrosis, which suggested malignancy. However, the present patient is free of disease, with no evidence of local recurrence or

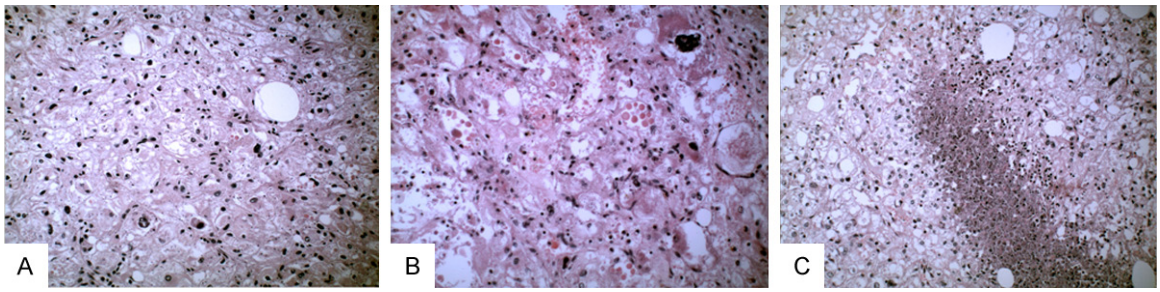

Figure 2. Histological features of cystic epithelioid AML (hematoxylin-eosin, original magnification × 200). A: The tumor was predominantly composed of sheets of epithelioid cells with clear to eosinophilic cytoplasm. B: Cluster of hyaline globules were present. C: Obvious necrosis was present.

distant metastases within 71 months of follow-up despite the above-mentioned worrisome features. Classic AMLs are usually regarded as benign tumors, and the epithelioid AMLs are thought to possess malignant potential [16]. Four cases of malignant hepatic AMLs have been described based on the presence of local recurrence, distant metastasis, or death due to the tumor [17-20]. Thus far, definitive criteria for malignant AMLs have not yet been fully established. Folpe et al. proposed the criteria based on Perivascular epithelioid cell tumors (PEComas), which were classified as benign, uncertain malignant potential, or malignant. According to their criteria, PEComas with two or more of the following unfavorable histological features are regarded as malignant: tumor size > 5 cm, infiltrative growth pattern, high nuclear grade, mitosis > 1/50 HPF, necrosis, and vascular invasion [21]. Our case exhibited three adverse factors (larger tumor size, infiltrative growth pattern, and necrosis), which should be classified as malignant based on the criteria of Folpe et al. However, our patient was free of disease at the 71-month follow-up. Meanwhile, Parfitt, et al. documented a case of liver PEComa with benign histologic characteristics that nonetheless presented with multiple metastatic foci nearly 9 years after surgery [18]. In addition, the following features of renal AMLs, including perirenal invasion and involvement of the renal vein and regional lymph nodes, are not regarded as reliable markers of malignancy [22, 23]. Nguyen et al. reported that cytologic atypia and infiltrative growth patterns could be observed both in benign and malignant hepatic AMLs [19]. Recently, Nese et al. proposed a risk stratification model, similar to the approach adopted for gastrointestinal stromal tumors, to classify the renal epithelioid AMLs into low-, intermediate-, and high-risk categories rather than using morphology to define a truly benign or malignant subset of tumors. In the model of Nese et al., clinicopathologic parameters that were associated with tumor progression (local recurrence, distant metastasis, or death due to tumor) included concurrent AML or associated tuberous sclerosis complex, necrosis, tumor size > 7 cm, extrarenal extension and/or renal vein involvement, and a carcinoma-like growth pattern. Based on the number of adverse prognostic parameters possessed by tumors, epithelioid AMLs were classified into low- (with < 2 unfavorable parameters), intermediate- (with 2 to 3 unfavorable parameters), and high-risk (with > 3 unfavorable parameters) categories, with 15%, 64%, and 100% risk for tumor progression in each of the categories, respectively [24].

Thirdly, our case revealed the presence of intracellular and extracellular hyaline globules. This morphologic feature is unique in AML and has been reported occasionally. Nguyen et al. reported a case of malignant hepatic AML demonstrating intracytoplasmic hyaline globules [19]. Subsequently, Xie et al. also described a case of liver AML with intracellular and extracellular hyaline globules distributed singly and in clusters [25]. Furthermore, the authors proposed that hyaline globules likely represented abnormal permeability for plasma proteins because the globules were immunohistochemically positive for Factor VIII and α1-antitrypsin [25].

Considering the histological features, including the epithelioid appearance, clear to eosinophilic cytoplasm, broad solid sheet and trabecular structures, and the invasive growth pattern demonstrated by epithelioid AML, the major differential diagnoses considered should include

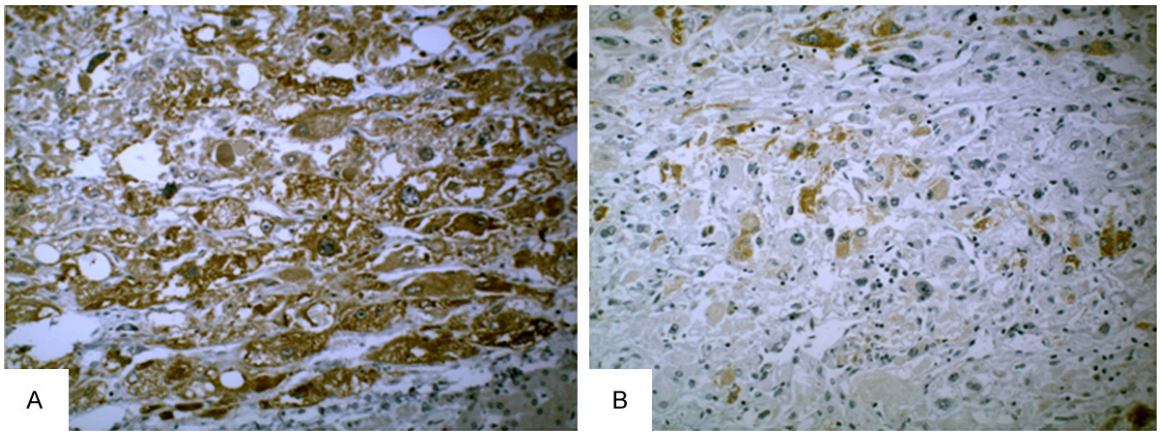

Figure 3. Immunohistochemical stains for Melan-A (A) and HMB-45 (B) (diaminobenzidine chromagen, hematoxylin counterstain, original magnification × 200). A: The tumor cells were strongly and diffusely positive for Melan-A. B: The tumor cells patchily expressed HMB-45.

hepatic adenoma, hepatocellular carcinoma, metastatic carcinoma (particularly from kidney or adrenal gland), melanoma, epithelioid smooth muscle tumor, and epithelioid gastrointestinal stromal tumor, which all share some morphologic features of epithelioid AML. Briefly, the above-mentioned lesions could be excluded based on the immunohistochemical results that the epithelioid AML is positive for both melanocytic and myogenic markers but negative for CK AE1/AE3, EMA, HepPar-1, Alpha fetal protein, CD10, CD34, CD117, and DOG-1 [1].

In conclusion, we report a case of giant cystic variant of epithelioid AML with unusual morphologic features in the liver. To our knowledge, this is the third case of hepatic cystic AML. This case adds to a small body of literature on hepatic AML and widens the spectrum of its morphological features. More cases of hepatic AML must be studied to draw definitive conclusions on its distinctive behavior and appropriate management.

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Disclosure of conflict of interest

None.

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