

Original Article

Hepatic perivascular epithelioid cell tumor (PEComa): analyses of 13 cases and review of the literature

Yihui Ma^{1,3}, Pei Huang^{1,3}, Hanqing Gao^{1,3}, Wenlong Zhai²

Departments of ¹Pathology, ²Hepatobiliary Surgery, ^{1st} Affiliated Hospital, Zhengzhou University, Zhengzhou, China; ³Henan Key Laboratory for Tumor Pathology, Zhengzhou University, Zhengzhou, China

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Abstract: *Aim:* To study the clinicopathologic characteristics of perivascular epithelioid cell tumor (PEComa) in the liver and to improve the understanding and diagnosis of this tumor. *Methods and results:* 13 cases of primary liver PEComa were retrieved from our hospital from January 2007 to September 2017. The clinicopathologic features and the computer tomographic (CT) or/and magnetic resonance imaging (MRI) tests of each case were retrospectively reviewed. All 13 patients were female, with ages ranging from 22 to 72 years (median, 35 years). The sizes of the tumor ranged from 1.0 to 19.8 cm. Histologically, the tumors were comprised of polygonal cells with clear to granular eosinophilic cytoplasm and were accompanied by positive immunohistochemical expression of HMB-45 and/or Melan-A. 6 cases showed moderate cytological atypia. Hemorrhage was present in 7 of 13 cases, and necrosis in 2 cases. Mitoses were scant, averaged from 0 to 1/50 high-power fields in every case. No vascular invasion was present in any case. Follow-up data were obtained from 9 of 13 cases, and none showed any evidence of tumor recurrence or metastasis. *Conclusions:* There are no specific symptoms of hepatic PEComa, and the preoperative imaging tests are also insensitive. In view of diverse histological growth patterns with atypical cell features in part of cases, the possibility of PEComa should be considered whenever unfamiliar hepatic tumors are encountered. Immunoreactivity for HMB-45, MelanA, and SMA, especially HMB-45, is very useful for the diagnosis of this tumor.

Keywords: PEComa, liver, HMB-45, TFE-3, differential diagnosis

Introduction

Perivascular epithelioid cell neoplasms (PEComas) are formed as a rare group of related mesenchymal tumors composed of histologically and immunohistochemically distinctive perivascular cells, and were first proposed by Bonetti et al. in 1992 [1]. As a new classification category established in the World Health Organization Classification of Tumors in 2002, the members of this family include angiomyolipoma (AML), lymphangiomyomatosis, pulmonary clear cell "sugar" tumors and PEComa-NOS [2]. Many anatomic sites can be affected and the uterus is the more common [3]. Cases that arise from the liver are extremely rare. Because of its rarity, little is known about these tumors, followed by further difficulties in the establishment of the diagnosis. Herein, we present 13 hepatic PEComas proven by pathology and review of the literature.

Materials and methods

Collection of cases

On retrieval of the pathology archives system in the Department of Pathology at the 1st Affiliated Hospital of Zhengzhou University, dated January 2007 to September 2017, 13 cases of hepatic PEComa were identified. Hepatectomy was performed on all patients. The histological sections were retrospectively reviewed by three pathologists. Written informed consent was obtained from the patients before the publication of this report and accompanying images.

Clinical data

Clinical data were retrospectively retrieved from patients' records and included age, sex, location of tumor, clinical presentation, routine blood test, liver function tests, hepatitis B virus surface antigen (HbsAg), hepatitis C virus anti-

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gen, serum tumor markers such as alpha-feto-protein (AFP), cancer antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA), imaging findings, and preoperative diagnosis. Follow-up data were obtained from the clinical record or by telephone.

Immunohistochemistry

Immunohistochemical stains including HMB-45, Melan-A, S-100, SMA, Desmin, CD34, Hep-Par-1, TEF-3, Syn, CgA, CD56 and pan-cytokeratin (CK) were applied for diagnosis and differential diagnosis. All immunohistochemical staining were performed by the PV-6000 system. The primary antibodies were all ready-to-use as follows: anti-HMB-45 (mouse monoclonal antibody), anti-Desmin (mouse monoclonal antibody), anti-CD34 (mouse monoclonal antibody), anti-TEF-3 (rabbit monoclonal antibody), anti-Syn (mouse monoclonal antibody), anti-panCK (mouse monoclonal antibody) were all purchased from Fuzhou Maixin Biotech. Co. Ltd., anti-MelanA (mouse monoclonal antibody), anti-S-100 (rabbit polyclonal antibody), anti-SMA (mouse monoclonal antibody) were purchased from Beijing Zhong Shan Biotechnology Co. Ltd., anti-CgA (mouse monoclonal antibody) and anti-CD56 (mouse monoclonal antibody) were purchased from Shanghai Jie Hao Biotechnology Co. Ltd. The peroxidase reaction was developed with 3,3'-diaminobenzidine (DAB). Secondary antibodies and DAB were obtained from Beijing Zhong Shan Biotechnology Co. Ltd. Sections that were stained without the primary antibodies served as negative controls.

Results

Clinical findings

The age of the patients ranged from 28 to 72 years (middle age = 35 years), with 12 of the 13 patients being female. Four patients presented with right upper abdomen intermittent pain or discomfort, 9 patients were incidentally found to have a mass of the liver on physical examination. One patient was positive for HbsAg, and the remaining 12 patients were negative for HbsAg and hepatitis C virus antigen. Only 1 patient showed the increased level of the carbohydrate antigen 125 (CA125). None of these patients was associated with tuberous sclerosis complex, while 5 patients had cysts in the liver or kidney.

All the patients were examined by computer tomographic (CT) or magnetic resonance imaging (MRI), and the common radiologic feature on CT and/or scan was arterial phase enhancement and portovenous phase wash-out. The patients were preliminarily diagnosed as hemangioma (4 cases), hepatocellular adenoma (HCA, 1 case), angiomyolipoma (1 case), hepatocellular carcinoma (HCC, 4 case), focal nodular hyperplasia (FNH, 1 case), and hepatic tumors of uncertain nature (3 cases). All patients had primary liver tumors and none presented with extrahepatic metastasis at diagnosis. All the data are summarized in **Table 1**.

Pathology findings

By gross examination, the maximal size of the tumors ranged from 1.0 to 19.8 cm, and the mean and median sizes were 3.6 and 3.8 cm, respectively. All the cases showed unencapsulated lesion, 10 were sharply demarcated from the adjacent hepatic parenchyma while the other 3 were ill-defined. The cut surfaces were tan-colored or grey brown with tough texture, and local hemorrhage were observed in 7 cases.

Microscopically, 2 cases were diagnosed as the classical epithelioid angiomyolipoma, which showed a mixture of thick-walled blood vessels, epithelioid smooth muscle, and mature adipose tissue. In the 2 cases, smooth muscle cells were arranged in whorled and interlacing fascicles, and surrounded by the tortuous vessels with the mature lipocytes being scattered (**Figure 1A**). Another 3 cases were PEComas with a small account of lipocytes less than 5% in total. The remaining 8 cases were PEComas comprised solely of perivascular cells. The epithelioid tumor cells of PEComas were polygonal or spheroidal, characterized by abundant cytoplasm that varied from eosinophilic granular to clear, with distinct cell border (**Figure 1B**).

In most cases, they were arranged in solid nests or sheets, separated by a rich sinusoidal vascular network. The tumor cell had vesicular nuclei with a small or notable nucleoli. Six cases showed mild cytological atypia with small nucleus and invisible nucleolus. The remaining 7 cases showed moderate cytological atypia with enlarged vesicular nucleus and notable nucleolus. Bizarre pleomorphic multinucleated giant cells were present in 3 cases (**Figure 1C**). Extracellular hyaline globules were identified

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Table 1. Clinicopathologic data of the 13 cases

No.	Sex	Age	Symptom	Clinical diagnosis	Viral hepatitis history	Liver function (cirrhosis)	Associated diseases	Tumoral markers	Enhanced CT/MR		Treatment	Follow-up
									Arterial phase enhancement	Portovenous phase washout		
1	F	28	Poor appetite for 1 year, pain in the right upper abdomen for 1 month	Hemangioma	Negative	ALT↑	None	Negative	+	+	Partial hepatectomy	Loss
2	F	54	No symptom	AML	Positive for hepatitis B surface antigen	ALT↑	Multiple cysts in liver and kidney	Negative	Inhomogeneous	+	Partial hepatectomy	Disease-free survival (1 year)
3	F	48	No symptom	HCA	Negative	Normal	Multiple cysts in the liver	Negative	+	+	Partial hepatectomy	Loss
4	F	35	No symptom	FNH	Negative	Normal	None	CA125↑	+	+	Partial hepatectomy	Disease-free survival (1 year)
5	F	33	Pain in the right upper abdomen for 2 year	Hemangioma	Negative	ALT↑, GGT↑, ALP↑	None	Negative	+	+	Partial hepatectomy	Disease-free survival (half 1 year)
6	F	72	No symptom	Uncertain	Negative	Normal	None	Negative	Inhomogeneous	+	Partial hepatectomy	Disease-free survival (5 year)
7	F	32	No symptom	Uncertain	Negative	Normal	None	Negative	+	+	Partial hepatectomy	Loss
8	F	33	No symptom	Uncertain	Negative	Normal	None	Negative	+	+	Partial hepatectomy	Loss
9	F	33	Right upper abdomen for 4 days,	HCC	Negative	GGT↑	Multiple cysts in the kidney	Negative	+	+	Partial hepatectomy	Disease-free survival (half 1 year)
10	F	47	No symptom	HCC	Negative	Normal	One cyst in the kidney	Negative	+	+	Partial hepatectomy	Disease-free survival (3 month)
11	F	65	No symptom	HCC	Negative	Normal	None	Negative	+	+	Partial hepatectomy	Disease-free survival (15 month)
12	F	26	Pain in the right upper abdomen for 8 days	Hemangioma	Negative	GGT↑	Multiple cysts in the kidney and liver	Negative	+	+	Partial hepatectomy	Disease-free survival (2 month)
13	M	49	No symptom	Hemangioma or HCC	Negative	Normal	None	Negative	+	+	Partial hepatectomy	Disease-free survival (2 month)

CT = computer tomographic, MRI = magnetic resonance imaging, F = female, M = male, HCC = hepatocellular carcinoma, AML = angiomyolipoma, HCA = hepatocellular adenoma, HCC = hepatocellular carcinoma, FNH = focal nodular hyperplasia, ALT = alanine aminotransferase, GGT = glutamyl transpeptidase, ALP = alkaline phosphatase.

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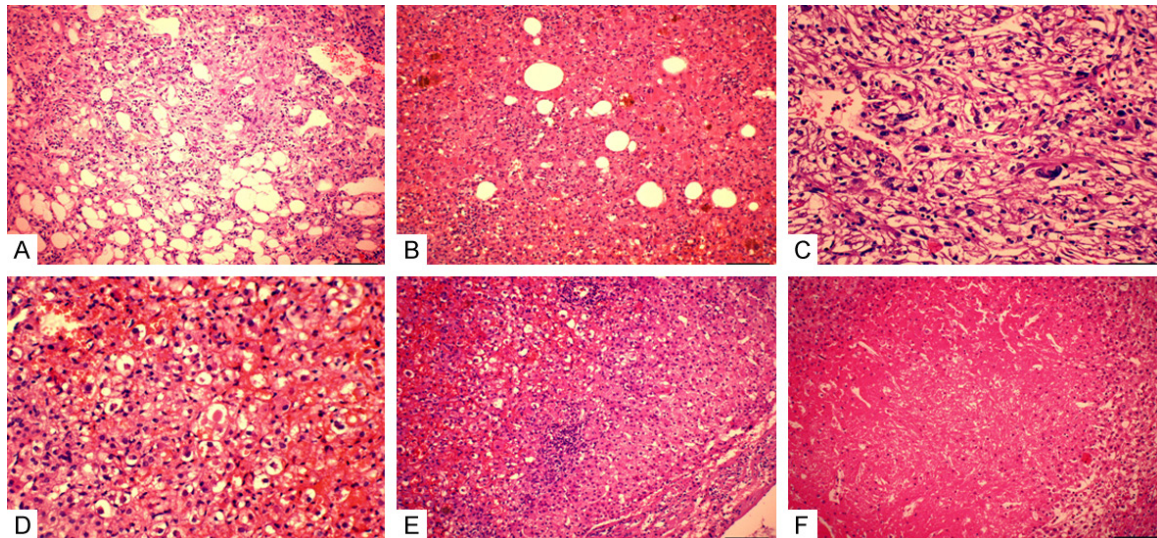


Figure 1. Histology of PEComas. A. Epithelial smooth muscle cells were arranged in whorled and interlacing fascicles, surrounded by the tortuous vessels with the mature lipocytes being scattered. B. The epithelioid tumor cells of PEComas are polygonal or spheroidal, characterized by abundant cytoplasm that varied from eosinophilic granular to clear, with distinct cell border. C. Moderate cytologic atypia with enlarged vesicular nucleus and notable nucleolus, bizarre pleomorphic multinucleated giant cells were present. D. Extracellular hyaline globules were seen singly or in clusters. E. Epithelioid neoplastic cell invaded into the surrounding hepatic parenchyma without clear boundary. F. Local necrosis was present.

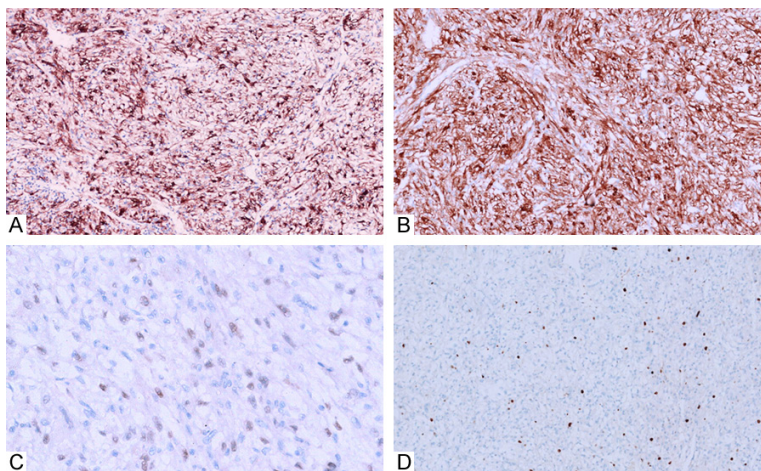


Figure 2. Immunohistochemical study showed a strong and diffuse expression of HMB45 (A) in all the cases and Melan-A (B) in part of cases. Only 1 case showed the weak positive expression of TFE-3 (C) in the nucleus. The proliferation indexes were also low with less than 5% in all the cases (D).

singly or in clusters in 2 cases (**Figure 1D**). In 3 cases, epithelioid neoplastic cell invaded into the surrounding hepatic parenchyma (**Figure 1E**), and the remaining 10 cases had distinct boundary with 6 cases showing partial fibrous capsule. No vascular invasion was present in any case. In all of the cases, obvious small lymphocytes invasion can be easily seen with lymphoid follicle even formed in 3 cases. In 4 cases, mast cells invasion can be discovered

simultaneously. Hemorrhage was present in 9 of 13 cases, and necrosis in 2 cases (**Figure 1F**). Mitoses were scant, averaged from 0 to 1/50 high-power fields in every case.

Immunohistochemical study showed a strong and diffuse expression of HMB45 in all the cases, and SMA in 9 cases, while Melan-A was just local positive in parts of cases (**Figure 2A, 2B**). In case No. 2, only the smooth muscle of the thick vascular wall was positive for SMA. The neoplastic cells were negative for S-100 protein, CD34 and panCK.

Only 2 of 13 cases showed the weak positive expression of TFE-3 in the cell nuclei (**Figure 2C**). The proliferation indexes were also low with less than 5% in all the cases (**Figure 2D**). All the data were summarized in **Table 2**.

Treatment and follow-up

In our study, all the patients were treated by partial hepatectomy and were discharged from

the hospital without postoperative complications. The follow-up study was completed for 9 of them. The longest follow-up time was 5 years for No. 5, and the shortest was 2 months for No. 11 and No. 12. No tumor recurrence or metastasis was found during the follow-up period. All the data are summarized in **Table 2**.

Discussion

PEComa is a rare tumor which arises from mesenchymal tissues. In 2002, the World Health Organization defined PEComa as a mesenchymal tumor composed of histologically and immunohistochemically distinctive perivascular epithelioid cells. The "PEComa family" includes many distinct clinicopathologic entities, such as AML, lymphangiomyomatosis and clear cell "sugar" tumors of the lung. Some of which have been linked to tuberous sclerosis complex, especially AML of the kidney. The group comprising solely perivascular epithelioid cells is rare, and it has been discriminated from classic angiomyolipoma by various appellations including monotypic epithelioid AML, clear cell myomelanocytic tumor, primary extrapulmonary sugar tumor, and PEComas-NOS or simple PEComa [4]. Until now, the etiology and histogenesis of PEComas has been incompletely unclear. However, perivascular epithelioid cells show evidence of both melanocytic and smooth muscle differentiation and do not recapitulate the differentiation of any known cell type in normal tissues [5]. In our study, 2 cases were diagnosed as the epithelioid AML, which showed a mixture of blood vessels, epithelioid smooth muscle and mature adipose tissue, while the other 11 cases were PEComas mainly comprised PECs.

Hepatic PEComa occurs most commonly in females, and usually show no specific symptoms. It was reported that the majority of patients had solitary lesions in the hepatic right lobe and were always found incidentally in health examinations. With increasing size of tumor, some patients may show symptoms caused by tumor compression. Compared with the PEComas in the renal, no association with the tuberous sclerosis complex was found [6-8]. In our study, 12 of 13 patients were female, and the tumors of 7 patients were located in the right lobes. Five patients had intermittent non-specific discomfort in the upper abdomen, and the remaining 8 ones

were asymptomatic and discovered by accident. Tuberous sclerosis complex was not found in any case, but 5 patients were presented with multiple cysts in liver or kidney, which had not been reported in previous reports.

The imaging characteristics of PEComas are correlated with its histological components. The fat content of classical PEComas produces a characteristic imaging appearance, which enables PEComas differentiation from other hepatic tumors clinically [9]. As shown in our study, only 1 patient was accurately diagnosed as AML before surgical resection just because of the abundant fat component. In fact, imaging studies could not add any valuable preoperative diagnostic clues, especially for tumors with a minimal fat component [10]. On the other hand, PEComas are euangiotic lesions, which show abundant blood vessels or blood sinus in the tumor mesenchyme. Contrast enhancement in arterial phase and hypoattenuation in portal phase on dynamic CT or MRI examination were a common finding on imaging for PEComas, and hence it is understood that PEComas are prone to be misdiagnosed as hemangioma [11]. Consistent with these studies, all the tumors in our study were markedly enhanced in the arterial phase and decreased obviously in the portal venous phase. Some studies on PEComas imaging features reported that central abundant vessels, especially thickly distorted vessels could be observed in PEComas compared with other hypervascular hepatic tumors including hemangioma or HCC. Alternatively, a part of PEComas with small or no vessels maybe showed prolonged enhancement in the portal venous, and this manifestation was supposed to differentiate PEComas from HCCs and cavernous hemangiomas to some extent [12]. However, all of these details were not observed in our study, and it remains to be discussed further. In fact, in our series only 1 patient was accurately diagnosed as AML before surgical resection, whereas the remaining were given preoperative diagnosis of HCC, HCA, hemangioma or undetermined lesions. This was probably attributed to the nonspecific clinical and radiologic features of PEComas.

Clinically, this entity tends to occur in middle age females, with the tumor nodules more frequently involving the right hepatic lobe. These data coincide with those of HCA [13]. Con-

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Table 2. Histopathological characters of the 13 cases

No.	Location, lobe	Numbers of nodules	Size (cm)	Boundary	Histology	Hemorrhage	Necrosis	Nuclear morphology	Mitotic count (/50HPF)	Immunohistochemistry					
										HMB45	S-100	MelanA	SMA	TFE-3	Ki-67 (%)
1	Right lobe	1	10	Ambiguous	Mainly PECs	+	-	Mild to moderate heteromorphosis, tumor giant cell could be seen	1	+	-	+	+	-	5
2	Right lobe	1	15	Distinct, part fibrous capsule	E-AML	-	-	Mild heteromorphosis	0~1	+	-	+	-	-	5
3	Right lobe	1	3	Distinct, part fibrous capsule	Mainly PECs	-	Local +	Mild to moderate heteromorphosis	0~1	+	-	+	+	-	5
4	Hepatic portal	1	3	Distinct, no fibrous capsule	Mainly PECs	+	-	Mild heteromorphosis	0~1	+	-	+	+	-	5
5	Right lobe	1	19.8	Distinct, part fibrous capsule	Mainly PECs	Local +	Local +	Mild heteromorphosis, tumor giant cell could be seen	0~1	+	-	+	+	-	3
6	Right lobe	1	4	Distinct, part fibrous capsule	E-AML	Local +	-	Mild to moderate heteromorphosis, tumor giant cell could be seen	0~1	+	-	+	+	-	5
7	Right lobe	1	5	Ambiguous	Mainly PECs	+	-	Mild to moderate heteromorphosis	0~1	+	-	+	+	-	5
8	Left lobe	1	1.2	Distinct, no part fibrous capsule	Mainly PECs	-	-	Mild heteromorphosis	0~1	+	-	+	+	-	2
9	Left lobe	1	6	Ambiguous	Mainly PECs	Local +	-	Mild to moderate heteromorphosis	0~1	+	-	+	+	Weak+	5
10	Right lobe	1	5	Distinct, part fibrous capsule	Mainly PECs	Local +	-	Mild heteromorphosis	0~1	+	+	+	+	-	1
11	Left lobe	1	3.8	Distinct, part fibrous capsule	Mainly PECs	-	-	Mild to moderate heteromorphosis	0~1	+	-	+	+	-	5
12	Left lobe and right lobe	3	1.0 2.8 3.4	Distinct, no part fibrous capsule	Mainly PECs	-	-	Mild to moderate heteromorphosis	0~1	+	-	+	+	-	1-5
13	Left lobe	1	2.0	Distinct, no part fibrous capsule	Mainly PECs	-	-	Mild heteromorphosis	0~1	+	-	+	+	-	3

Cm = centimeter, HPF = high power field, PECs = perivascular cells, E-AML = epithelioid angiomylipoma.

sidering the histological features, including the epithelioid appearance, clear to eosinophilic cytoplasm, a trabecular, sinusoidal or alveolar pattern structures, and the invasive growth pattern in some circumstances, the most important differential diagnoses should involve HCC (especially HCC with local fatty degeneration) [14] or metastatic renal cell carcinoma [15]. Other differential diagnosis should include epithelioid smooth muscle tumors, epithelioid gastrointestinal stromal tumor, melanoma, clear cell sarcoma of soft parts, and alveolar soft part sarcoma. These tumors can show epithelioid cell morphology, sometimes show striking nuclear pleomorphism such as prominent nucleoli and multinucleated tumor cells, and sometimes prominent mitoses and necrosis could be seen. However, these lesions do not generally show any characteristic perivascular orientation to some degree. In addition, just as discovered in this study, obvious small lymphocytes and mast cells invasion can be easily seen and lymphoid follicles were even formed in these lesions, together with local hemorrhage, inflammatory pseudo-tumor should be considered as another differential [16].

Despite the difficulties in making a correct diagnosis of PEComa by clinical findings and morphologic features, immunohistochemical staining is a favorable means to distinguish the entity from most of the differentials. Markers such as HMB-45, MelanA, and SMA are routinely expressed in PEComa, while panCK, EMA, HepPar-1, AFP, CD10, CD34, CD117 and DOG-1 are clearly negative [17, 18].

Recently, it has been reported that a small subset of PEComas harbor gene fusions involving the TFE3 gene, a member of the microphthalmia transcription factor-transcription factor E gene family (MiTF-TFE), located at chromosome Xp11.2 [19]. This site is also notable for its involvement in translocations in a subgroup of renal cell carcinomas [20]. In these renal cell carcinomas, translocations result in gene fusions between TFE3 and one of several fusion partners. The TFE3 gene is also involved in a balanced translocation with alveolar soft part sarcoma chromosome region 1 (ASPSR1) in alveolar soft part sarcomas (ASPS) [21]. PEComas harboring TFE3 gene fusion have been thus far found to preferentially exhibit “clear cells” morphology [22]. In our study, we

performed immunohistochemical staining of TFE-3 in all of the 13 cases, and only 2 cases showed weakly positive, and the expression of TFE-3 did not seem to be associated with “clear cells” morphology. Maybe this is because of the small sample size, and we will explore more cases in the future work [23].

Although classical AMLs are universally regarded as benign tumors and often grow slowly, it is becoming increasingly clear that some types of PEComas should be regarded as tumors of uncertain malignant potential. Indeed, PEComa encompasses a wide range of biological behavior including benign, uncertain malignant potential, and malignant [24]. Folpe et al. performed statistical analysis, and found that behavior of PEComa in gynecologic tract and soft tissue correlated with ① tumor size greater than 5 cm, ② infiltrative, ③ high nuclear grade and cellularity, ④ mitotic rate greater than 1/50 high-power fields (HPF), ⑤ necrosis, and ⑥ vascular invasion. PEComa showing 2 or more worrisome histological features should be classified as “malignant” [25]. The course of the disease in liver is unpredictable mainly due to the rarity of the tumor, especially for malignant ones. Several reported cases of malignant PEComa in the liver indicate that the malignant histological features includes coagulative necrosis, nuclear polymorphisms or multinucleated giant cells and > 5 cm size [26-28]. Although not considered to be ideal criteria, it appears to be the best approach at present. In our study, comprehensive analysis showed that 6 cases had tumor greater than 5 cm. Two cases showed tumor tissues infiltrated into adjacent nonneoplastic hepatic parenchyma, and no vascular invasion was seen in all the cases. Six cases showed moderate cytological atypia with increasing vesicular nucleus and notable nucleolus. In 3 cases, multinucleated tumor giant cells were observed. Mitoses were scant, and averaged from 0 to 1/50 high-power fields in every case. Proliferation indexes were also low with less than 5% in all the cases. As a result, only one case (No. 5) possessed 2 worrisome histological features, which indicated the malignant potency. Altogether, most PEComa inclined to be benign, and malignant cases are relatively rare. In the follow-up, survival data of 9 cases were obtained, and none had shown any evidence of tumor recurrence or metastasis including No. 5 followed by 1 year. The subsequent follow-up will continue.

Conclusion

In conclusion, there are no specific symptoms of hepatic PEComa, and the preoperative imaging tests are also insensitive. In view of diverse histological growth patterns with occasional atypical cell features, the possibility of PEComa should be considered whenever unfamiliar hepatic tumors are encountered. Immunoreactivity for HMB-45, MelanA, and SMA, especially HMB-45, is very useful for the diagnosis of AML.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yihui Ma, Department of Pathology, 1st Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, China. Tel: +86 13613820392; E-mail: allsunshine123@126.com

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