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Insights into clinical diagnosis and treatment of malignant hepatic perivascular epithelioid cell tumor

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SUMMARY Perivascular epithelioid cell tumors (PEComas) are infrequent mesenchymal tumors. They are usually benign, and only a few are malignant. These tumors are more commonly found in middle-aged women. PEComas are mainly composed of differentiated perivascular epithelioid cells arranged radially around the vascular cavity, and they are usually positive for melanocyte markers and smooth muscle cell differentiation markers. Among the PEComas, hepatic PEComas generally have no obvious symptoms and no typical imaging manifestations. Malignant hepatic PEComas are even rarer. So, we explained our insights into clinical diagnosis and treatment of malignant hepatic PEComas, in order to help clinicians and pathologists to further understand PEComas.

Keywords PEComa, liver tumor, hepatectomy, mTOR inhibitors, TFE3

Perivascular epithelioid cell tumors (PEComas) are extremely infrequent (roughly equivalent to 1 case per 4 million population) mesenchymal tumors and typically diagnosed in females of an age range of 39-56 years old. PEComas are difficult to diagnose, as their morphology can be analogous to that of smooth muscle tumors (*1,2*). The 2016 World Health Organization (WHO) Classification of Soft Tissue Tumors defined PEComa as a mesenchymal tumor composed of unique cells that focal associate with blood vessel walls and typically express melanocytic and smooth-muscle markers (*3*).

According to existing statistics, most PEComas are benign, and commonly occur in the uterus and gastrointestinal tract. Moreover, PEComas can also develop in organs such as the kidney, lung and liver. These tumors should be considered malignant only if any two or more of the following situations are found: a. tumor diameter > 5 cm; b. infiltrative growth; c. pronounced heteromorphic nuclei; d. number of mitotic figures ≥ 1/50 HPF; e. necrosis; and f. vascular invasion.

1. Clinical manifestation of a rare case

A 49-year-old female patient started to experience upper right abdominal pain and distention four months ago. Her symptoms worsened in the two weeks prior to admission. However, she did not present with fever, nausea, weight loss, general numbness or weakness. In terms of her past medical history, she had a laparoscopic fenestration and drainage of a liver cyst ten months prior and denied a history of hepatitis. Secondary infection of the liver cyst was reported in her last postoperative pathology. The laboratory data on admission were all within the normal range except that albumin was 28.7 g/L (normal range, 30-50 g/L), and CA-125 was 374.3 U/mL (normal range, 0-35 U/mL). The clinical abdominal examination showed normoactive bowel sound, no tenderness, no rebound pain, no muscle guarding and tympanic sound to percussion. Because her former cyst was 12 cm × 9 cm and the surgical wound was large, we first hypothesized that the abdominal pain and distention were caused by exudation accumulation. Therefore, we immediately completed the ultrasonography for the patient. The results indicated that there was indeed peritoneal effusion, so we gave the patient ultrasound-guided abdominal puncture catheter drainage. Then, approximately 1,000 mL of ascites was drawn out in a short time period. Her symptoms were relieved as well. However, in the next several days, 400 mL ascites was drawn out continuously every day. To determine the reason, we completed abdominal computed tomography (CT) and reperformed ultrasonography for the patient. CT revealed a mixed cyst and solid mass in the right lobe of the liver, and the lesion was obviously bulging out of the liver (Figure 1). Ultrasonography revealed a 16.1 cm × 13.2 cm mixed echo in the right lobe of the liver. After

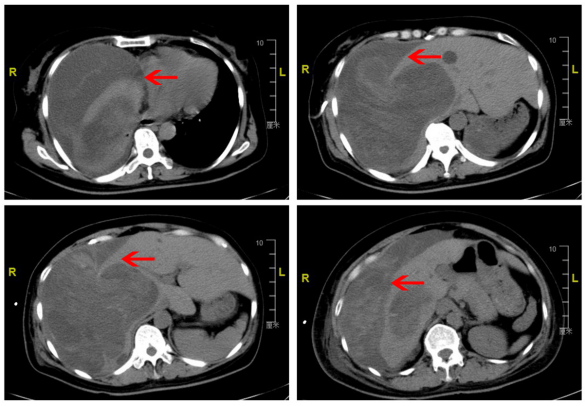

Figure 1. CT revealing a mixed mass of cysts and solids in the right liver, the largest diameter was approximately 15 cm.

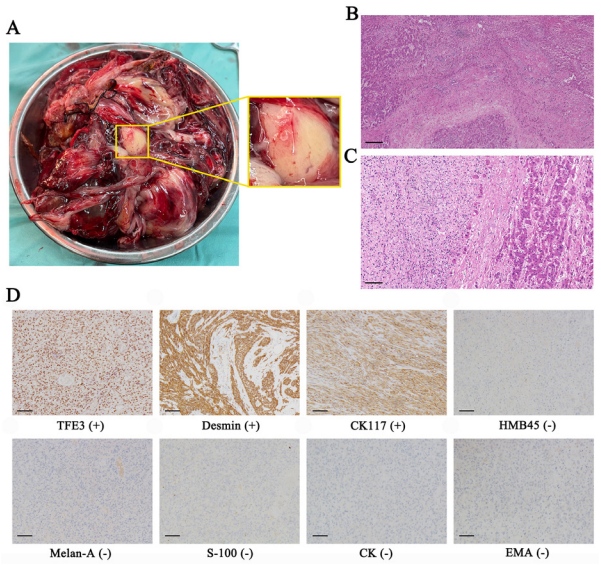

Figure 2. Specimens and Pathological Results. (A) The tissue specimens showed numerous cord-shaped lesions, accompanied by abundant blood filling. **(B)** Hematoxylin-eosin staining specimen under the 4× microscope. Scale Bar = 250 μm. **(C)** Hematoxylin-eosin staining specimen under the 10× microscope. Scale Bar = 100 μm. **(D)** Immunohistochemical results. Scale bar = 25 μm.

communicating with the patient and her daughter, we decided to perform an exploratory laparotomy.

At the moment of entering the abdominal cavity, a large amount of drainage gushed out. Then, we could see that not only the right hemiliver but also the patient's abdominal wall and omentum were covered with messy disordered cord-shaped lesions. We completely resected her right hemiliver, and all visible lesions. Furthermore, the excised specimens were subjected to pathological analysis. The pathological results revealed that the lesions were mesenchymal malignant tumors and considered malignant tumors with perivascular epithelioid differentiation (malignant PEComa). We found a large amount of tumor tissue and abundant blood vessels in some areas through observing the hematoxylin-eosin staining specimen under a 4× microscope. In addition, the tumor grew around the blood vessels and invaded the liver tissue. We also found some large solid areas in which blood vessels were not abundant, which is not typical of PEComas. Under a 10× microscope, we found residual normal liver tissue and abnormal blood vessels, and there was tumor tissue surrounding the abnormal blood vessels. In addition, large areas of necrosis were seen in the tumor tissue, indicating a high degree of tumor malignancy. In addition, the immunohistochemical expression profile was atypical. The tissue was positive for TFE3, Desmin and CD117, but it was negative for other typical markers, such as HMB45, Melan-A, S-100, CK and EMA (Figure 2). After the patient was discharged from the hospital, the medical oncologist advised her to take sirolimus and follow up closely. Currently, the patient's quality of life is good, and there is no recurrence. The informed consent was obtained from the patients for all descriptions.

2. Insights into hepatic PEComas

Hepatic PEComas are very rare, and usually these patients have no history of hepatis or factors that can damage the parenchyma (*4-6*). Most cases of hepatic PEComas are benign and have no specific clinical manifestations. Additionally, the onset is insidious and difficult to detect. However, when the lesion is large, abdominal distension, abdominal pain, ileus and other symptoms of abdominal compression may occur. In addition, many abdominal organs, such as the omentum, can be simultaneously affected by malignant PEComas originating from the liver. This can ultimately lead to massive bleeding into the abdominal cavity (*7*). However, there are generally no specific abnormalities observed in the laboratory tests (*8*).

Primary PEComas are usually well demarcated. Ultrasonography of the abdomen usually shows hyperechogenic cystic solid lesions with abundant blood supply. These tumors are hypodense to isodense on CT. MRI shows hypointense to isointense in comparison to skeletal muscle on T1-weighted imaging, and these tumors are heterogeneously hyperintense on T2-weighted imaging (*1,4*). Due to abundant vascularization from hepatic artery branches, we can observe that the lesion is strongly and heterogeneously enhanced in ultrasonography involving intravenous contrast media. Similarly, in CT and MRI, these tumors are characterized by intense enhancement in the arterial phase and an absence of contrast media in the veno-portal and delayed phases. (*5,9*). These imaging manifestations add to the difficulty of differentiating hepatic PEComas from hepatocellular carcinomas and hepatic adenomas. Furthermore, there are multiple enhancement characteristics of hepatic PEComas, and they may show persistent enhancement in the veno-portal and delayed phases in some cases. Thus, PEComas could be misdiagnosed as benign masses, such as focal nodular hyperplasia and hemangioma (*1,10*). Therefore,

the heterogeneous enhancement characteristic of hepatic PEComas is the main feature that distinguishes PEComas from other liver tumors.

In terms of its lack of clinical, laboratory and imaging manifestations, only histological and immunohistochemical analysis can provide a precise final diagnosis. PEComas are characterized by differentiated perivascular epithelioid cells arranged radially around the vascular cavity. These cells are typically epithelioid and spindle-shaped, which is analogous to smooth muscle cells. They also present with abundant transparent to eosinophilic granular cytoplasm and the specific expression of melanin cell markers and smooth muscle cell markers (*11*). On histopathology, adipose tissue and thick-walled vessels can be identified in most PEComas. Additionally, we found epithelioid cells with abundant transparent to eosinophilic cytoplasm forming nests and trabeculae. In smaller neoplastic lesions, there are fewer atypical epithelioid cells and more adipose tissue (*4,7,12,13*). Immunohistochemically, PEComas are usually positive for melanocyte markers (HMB45, Melan-A, Mitf) and smooth muscle cell differentiation markers (SMA, Desmin), while epithelial cell markers (CK, EMA) and endocrine markers (S-100, Syn and CgA) are negative. A novel marker, TFE3, which indicates the presence of TFE gene rearrangement, is highly expressed in 15% of PEComas. PEComas with TFE3 gene rearrangement can demonstrate robust staining for HMB45 and TFE3, but the staining of Melan-A and smooth muscle markers are focal or negative (*14*). Similar to other TFE3 translocation-associated tumors, acinar structure and epithelioid cell morphology can be found in TFE3 (+) hepatic PEComas. Moreover, TFE3 (+) hepatic PEComas usually exhibit aggressive biological behaviors and has a poor prognosis. However, existing research reveals that compared with TFE3 (+) PEComas in other organs, TFE3 (+) hepatic PEComas may be less malignant (*13*).

Surgical resection of the lesion is currently the most recommended treatment for PEComas. Simple resection of the tumor can be operated for small hepatic PEComas that are considered to be benign. However, extensive segmental hepatectomy or hepatic lobectomy is used for large and malignant hepatic PEComas. For benign hepatic PEComas, complete resection of the lesion can achieve a good therapeutic effect, and there are relatively few postoperative complications. However, even if the final diagnosis is benign, these patients need to be followed up as closely as patients with malignant liver tumors (*5,13,15*). It is recommended that patients with malignant hepatic PEComas should be treated with mTOR inhibitors, such as sirolimus and everolimus, regardless of whether the primary lesion can be surgically removed. The complex formed by tuberin and hamartin can regulate the mTOR signaling pathway. However, in most cases of PEComas, the function of tuberin and/or hamartin is lost. This induces the dysregulation of the mTOR signaling pathway and increases its activity. Activation of the mTOR pathway leads to increased ribosomal biogenesis, translation, proliferation and angiogenesis (*15,16*). Based on current research, mTOR inhibitors are expected to be the first-line therapy for advanced and metastatic PEComas (*13,15,16*). Beyond the above treatments, in some situations, hormonotherapy, transarterial chemoembolization and radiofrequency ablation are used (*17,18*).

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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