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LETTER TO THE EDITOR

Hepatic perivascular epithelioid cell tumors: The importance of preoperative diagnosis

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Abstract

Accurate preoperative diagnosis is highly important for the treatment of perivascular epithelioid cell tumors (PEComas) because PEComas are mainly benign tumors and may not require surgical intervention. By analyzing the causes, properties and clinical manifestations of PEComas, we summarize the challenges and solutions in the diagnosis of PEComas.

Key Words: Hepatic perivascular epithelioid cell tumors; Liver; Preoperative diagnosis; Angiomyolipomas; Mesenchymal tissue-derived tumors

Core Tip: Hepatic perivascular epithelioid cell tumors (PEComas) are mesenchymal tumors composed of histologically and immunohistochemically unique perivascular epithelioid cells. They have nonspecific clinical manifestations, inconspicuous and variable imaging features and complex pathological phenotypes, which make preoperative diagnosis very difficult. By enumerating the practical problems faced by clinicians in the diagnosis and treatment of PEComa patients, we analyzed the methods and ideas used to improve the accuracy of preoperative diagnosis of PEComas and provided new insights into the choice of conservative treatment and surgical treatment.

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TO THE EDITOR

We read the recently published papers of Kou *et al*[1] and express our satisfaction and congratulations on their excellent work. This is a well-written case report. By introducing three rare cases of hepatic perivascular epithelioid cell tumors (PEComas), they further noted the practical challenges faced by clinicians in the face of hepatic PEComas (HPEComas). We fully understand Kou *et al*'s concerns about the preoperative misdiagnosis of HPEComas[1]. Although the accuracy of a single examination may be insufficient to meet diagnostic requirements, combined examination of multiple imaging and immunohistochemical markers may be an effective method for improving accuracy. Accurate preoperative diagnosis is highly important for the treatment of HPEComas because PEComas are mainly benign tumors and may not require surgical intervention. Blind surgery without adequate diagnosis may introduce unnecessary treatment risks to patients.

In 2002, the World Health Organization (WHO) formally defined "PEComas" as mesenchymal tumors composed of histologically and immunohistochemically unique perivascular epithelioid cells (PECs), and PEComas include many different clinicopathological entities. Among them are angiomyolipoma, lymphangioma, lymphangioleiomyomatosis, clear cell tumor sugar and tumor types not otherwise specified[2]. Although PEComas and angiomyolipomas (AMLs) are theoretically subordinate, many clinical experts believe that the two are actually different manifestations of the same disease[3]. Therefore, in the following, we will discuss AMLs and PEComas as unified concepts and no longer make a special distinction.

DEFINITION AND TUMOR PROPERTIES

It is currently clear that PEComas are mesenchymal tissue-derived tumors that are usually composed of blood vessels, smooth muscle and adipocytes[4]. However, the proportions of these tissue components tissue components differ among patients[5]. These patients often complain of abdominal discomfort but do not present accompanying abnormal serological test results[6-8]. At present, the pathogenesis of this tumor has not been elucidated[5,6]. Although more than 50% of renal AMLs are associated with tuberous sclerosis (TSC), it is estimated that only 5%-15% of patients with solitary liver tumors have such a link[4]. The vast majority of PEComas are benign, and malignant forms are extremely rare[9]. In view of the relatively few reports on malignant PEComas, a clear malignant standard has not yet been established[9]. However, even if PEComas are identified as benign, their boundary with malignant tumors is not very clear. First, cytological atypia, a characteristic of malignant tumors, is present in benign liver PEComas[10], while the consistent characteristic of malignant liver PEComas is considered to be coagulative necrosis[9]. Therefore, only when the tumor has necrosis, a large mass (> 10 cm), CD117 negativity, invasive behavior or other clinical evidence may it be considered a malignant liver PEComa[10]. Second, it has been reported that benign PEComas may even undergo malignant transformation during development, eventually displaying sarcomatoid or cancer-like characteristics[11]. Moreover, some patients have also been found to have advanced metastasis many years after the diagnosis of primary benign tumors[11]. Furthermore, in a recently proposed classification system, Folpe *et al*[12] divided PEComas into benign, uncertain malignant potential (UMP) and malignant tumor categories. We think that this classification may be appropriate because it identifies a variety of tumor behaviors shown during the development of PEComas, clearly specifying UMP and recognizing that malignant tumors may occur given malignant behaviors or features. When there are multiple malignant changes, the tumor can be defined as malignant. Finally, regarding the factors that lead to the malignant transformation of PEComas, several hypotheses have been proposed. It has been reported that malignant behavior occurs mainly in epithelioid PEComas and can be observed in the early stage of tumorigenesis[13]. The diagnosis of epithelioid PEComa in a patient by clinical examination indicates that there is a greater possibility of malignant transformation, and a treatment strategy for malignant tumors should be provided.

PREOPERATIVE DIAGNOSIS

As discussed by Kou *et al*[1], PEComas have a very high preoperative misdiagnosis rate. According to Yang *et al*[14], Zeng *et al*[15] and Jung *et al*[16], only 18%-26% of patients with histopathologically confirmed PEComas were correctly diagnosed before surgery. This phenomenon may be due to many factors.

Imaging examination

In terms of preoperative imaging data, according to two case reports covering 92 patients[17] and 94 patients[18], the accuracy of ultrasound was 0%-33%, that of computed tomography (CT) was 15.7%-18.2%, and that of magnetic resonance imaging (MRI) was 4.3%-22.7%. This may be due to the variability of the proportion and distribution of different tissue components on the image, hindering the diagnosis[8]. For example, the most prominent imaging features

of PEComas are mature adipose tissue and central thick-walled blood vessels[4]. This makes PEComas that are characterized by adipose tissue easy to diagnose. However, PEComas are variable and can also manifest as tumors containing low-fat tissue or nonfat tissue[4]. Moreover, the presence of fats has been found to be unreliable because some hydrocarbons contain fat, and these fats may also mimic PEComas during presentation[7]. This will negatively affect imaging experts and easily lead to incorrect diagnoses. To solve this problem, many clinical experts have adopted various approaches. For example, Ding *et al*[19], through the combined examination of ultrasound, CT, MRI and angiography in 79 patients, achieved a diagnostic accuracy of 52%. Wang *et al*[20] used complementary B-ultrasound and contrast-enhanced ultrasound (CEUS) to distinguish PEComas from other benign liver tumors. This may suggest that the combined examination of multiple images can improve the diagnostic rate. In a recent report, positron emission tomography (PET)/CT appeared to be an effective tool for diagnosing PEComas. The authors reported that PEComas exhibited strong 68Ga-FAPI uptake and slight 18F-FDG activity. This means that 68Ga-FAPI PET/CT has the potential to become a diagnostic tool for PEComas[21].

Laboratory examination

Preoperative laboratory tests may only meet the requirements for excluding certain diseases. For example, in the three patients reported by Kou *et al*[1], except for the increase in CA-125 in Patient 3 with an ovarian tumor, the patients did not have abnormal serum tumor marker levels, which was consistent with previous findings that PEComas were not accompanied by abnormal serological results[7,8]. This approach may help clinicians rule out the diagnosis of some common tumors or simply make them doubt the proposed diagnosis.

Liver biopsy

However, in a recent multicenter study, even histological analysis of preoperative liver biopsy data yielded a misdiagnosis rate of approximately 15%[22]. However, liver biopsy is still the best way to determine the diagnosis of such liver lesions before surgery. The presence of adipose tissue is helpful for distinguishing this disease from other malignant entities. However, due to the variability of the lesion and the small amount of tissue obtained by puncture, the fat area may be sampled or not, making diagnosis from puncture biopsies challenging[3]. However, compared with that of conventional imaging, the diagnostic accuracy of biopsy has increased considerably. Notably, almost all the PEComas were strongly positive for Human melanoma Black-45 (HMB-45), S-adenosyl methionine (SAM) and melan-A[23-25]. Ameurtesse *et al*[26] also reported that HMB-45 cells were generally positive; melan-A and SMA were frequently expressed. The negative expression of S100, desmin and vimentin may be specific signs of HPEComas. If preoperative puncture or intraoperative frozen pathological examination can comprehensively account for the difference between the imaging and microscopic examination results of such patients and common tumors and if HMB-45, Melan-A and other rare liver cancer histopathological immunohistochemical indicators are used, the accuracy of preoperative diagnosis may also increase considerably.

PREOPERATIVE DIFFERENTIAL DIAGNOSIS

According to the misdiagnosis results, the main preoperative misdiagnosis of liver PEComas is hepatocellular carcinoma (HCC)[27]. The reasons are diverse. The multiple components of PEComas vary among individuals, and the proportion of fat and hemangioma components in the tumor volume varies from less than 10% to more than 90%[28,29]. Variable imaging results can confound the diagnosis and thus increase the probability of misdiagnosis as common HCC[10]. As mentioned above, benign PEComas are characterized by cytological atypia and are easily confused with other malignant tumors. The most common confounding factor is HCC[30]. As a representative malignant PEComa, epithelioid angiomyolipoma (EAML) does not contain or contains only a small amount of eye fat; this feature manifests as arterial enhancement and delayed washout and is also consistent with the general characteristics of HCC. Even if there are many complex disturbance factors, the identification of HCC and PEComas is not straightforward. First, unlike in general, the patient's conventional serum tumor marker, hepatitis marker, and alpha-fetoprotein results are negative. Second, in imaging, compared with HCC, PEComas lack a capsule, have reduced peripheral enhancement of the tumor, and may not exhibit use of the portal vein as a feature of their drainage, which might otherwise facilitate identification[31-33]. In a recent study, gadoxetic acid-enhanced MRI was also used to distinguish PEComas from HCC[34]. Kim *et al*[34] reported that 100% of PEComas and 85% of HCCs showed arterial enhancement and delayed washout on gadoxetic acid-enhanced MRI. Compared with HCC, PEComas showed a greater frequency of homogeneous low signals in delayed hepatobiliary phase (HBP) imaging (83% *vs* 41%). These authors believe that this is due to the lack of hepatocytes in PEComas, which results in a more uniform low SI on HBP images, while HCC may contain some poorly developed hepatocytes, resulting in more uneven high signal intensity on HBP images. Therefore, HBP examination *via* GA-enhanced MRI will be a powerful way to differentiate PEComas from HCC. Finally, due to the rarity of PEComas, many pathologists or imaging experts are not familiar with these tumors, leading to the most common HCC often being considered the final result. However, although the clinical and radiological features of these lesions often overlap, careful observation of histological clues can help to eliminate various diseases of the same species to obtain the most accurate diagnosis.

TREATMENT AND COMPLICATIONS

Treatment

As stated above, if a patient has been clearly diagnosed with PEComa before surgery, the treatment is not only as simple as surgical resection. First, the study data showed that the risk of metastasis and death from surgical treatment was estimated to be 0.8% (2/247 for metastasis and death, mortality = 0.8%). Progression occurred in 6/35 (21.4%) patients who received conservative treatment[4].

Conservative treatment: The basis for choosing conservative treatment is as follows. First, PEComas can be not only single tumors but also manifestations of TSC. TSC is a hereditary disease characterized by seizures, tumor development in the the brain, heart, kidney and skin, and a unique set of neurodevelopmental syndromes known as TSC-associated neurological disease (TAND)[35]. PEComas occur in TSC patients due to biallelic inactivation of TSC2 (more common) or TSC1[36]. The first mutation event (HIT) in TSC2 is a germline mutation, which is the cause of an individual TSC. The second 'HIT' event leads to excessive activation of mTORC1 (a mammalian target of rapamycin complex 1) and promotes tumor development[37,38]. The changes caused by these genes have been proven to be related to the etiology of PEComas. In view of the above findings, inhibitors of the mTOR signaling pathway, such as sirolimus or everolimus, are considered likely to play a role in the treatment of PEComas[24,39]. A study by Martignoni *et al*[24] showed that activated mTORC1 has important functions regardless of whether it is associated with PEComas. In an animal TSC model study before the clinical stage study, the mTOR inhibitor sirolimus showed substantial efficacy[27]. In further experimental studies, Wagner *et al*[40] reported the positive efficacy of the oral mTOR inhibitor sirolimus in the treatment of three patients with malignant PEComas based on changes in tumor imaging data, indicating that this drug may be useful as an immunotherapy for PEComas. Italiano *et al*[41] also reported this. Moreover, in PEComas, which are unresectable in clinical surgery, the use of the mTOR inhibitor sirolimus for neoadjuvant therapy can help the tumor shrink tumors and enable surgical resection[42]. In a recent study, immunohistochemistry and multiple immunofluorescence analyses revealed that HPEComas contain a large number of nontumor cells, mainly lymphocytes and CD68+ macrophages. This phenomenon indicates that HPEComas have a high level of immune cells, which may suggest that the tumor has inert behavior[43]. This provides additional indications for conservative treatment. In summary, conservative treatment and follow-up examination may be effective ways to treat PEComas, especially for patients who are asymptomatic, have small tumors or are considered unsuitable for surgery[6]. Overall, the vast majority of PEComas are benign and tend to grow slowly, while malignant PEComas are extremely rare. Moreover, long-term conservative treatment and follow-up may also have a positive effect or timely effect on the malignant transformation of PEComas at a certain node in the development process. Thus, the survival time of patients should be prolonged. However, additional clinical trials are still needed to confirm these findings.

Surgical treatment: The choice of direct surgical treatment is mainly due to the following considerations. First, in patients undergoing surgical treatment, the risk is estimated to be 0.8% (2/247 metastasis and death, mortality rate = 0.8%)[4]. This approach can completely reach the standard of clinical remission. Second, if the preoperative diagnosis of liver PEComas is confirmed by imaging technology or fine needle aspiration biopsy and if the patient has symptoms or may rupture due to a substantial increase in the size of the lesion under continuous observation, surgical resection should be recommended[9]. Furthermore, because the risk of malignant transformation during the development process is unknown, surgical resection should be selected when there is no definite treatment for advanced PEComas[44]. Moreover, Panahova *et al*[45] reported that performing only perforation biopsy may not be sufficient to assess whether a PEComa is a malignant tumor because only surgical resection specimens can reveal the ratio of invasive growth to mitosis. Finally, liver transplantation is the final treatment for unresectable PEComas with large or numerous liver tumors[17,46]. If the patient's tumor cannot be surgically removed, neoadjuvant conversion therapy seems to be a good strategy for treating PEComas that are positive for PET tracers according to imaging, as this approach can transform the tumor and make the patient eligible for surgical treatment[47].

Based on the above analysis, the treatment strategy proposed by Yang *et al*[14] may be appropriate. The authors advocated imaging observation and conservative treatment for patients who: (1) Had a first diagnosis of PEComa; (2) had a lesion size < 5 cm, (3) were expected to have good compliance with follow-up; and (4) did not have viral hepatitis. Because the cumulative estimated increase in the size of these tumors is only 0.77 cm/year, the first surveillance imaging can be performed 1 year after diagnosis, followed by two years of surveillance. When the imaging diagnosis is uncertain, biopsy can be performed. Resection is recommended if the biopsy provides an uncertain diagnosis or if the patient has malignant risk factors such as epithelioid features or high proliferative activity. Other indications for resection include symptoms or invasive growth[4]. In addition, TSC patients may require longer or more frequent monitoring because TSC appears to be a risk factor for progression[4].

Complications

In terms of complications during tumor development, the most common complication of PEComas is malignant behavior, although there is no consensus on what factors constitute invasive or malignant PEComas[3]. At present, imaging evidence of liver PEComa invasion is rare. To date, only 16 patients with liver, omentum, lung or bone metastases have been reported in the literature[14,15,19,30,48-60]. In addition, spontaneous bleeding may also occur in liver AML patients, but the risk of occurrence seems to be lower in liver AML patients than in renal AML patients, possibly because a single vessel is usually involved in the latter and is associated with aneurysms[61]. Arterial embolization is sometimes necessary when spontaneous bleeding occurs[62]. At present, only 8 cases of hepatic angiomyolipoma (HAML) have been reported to cause spontaneous rupture and hemorrhage. The median size of these tumors was 8.5 cm (range: 2.5 cm to 12.5 cm),

and 3 of them were treated with hepatectomy after arterial embolization; these patients were formally diagnosed with HAML[39]. This may indicate that spontaneous bleeding usually occurs from larger lesions[28].

In conclusion, Kou *et al*'s concern about the preoperative misdiagnosis of liver PEComas is entirely reasonable and necessary[1]. The preoperative diagnosis of HPEComas is very important. Accurate diagnosis can change the treatment and prognosis of patients. Imaging and serological tests are the first step, followed by biopsy. However, we also need to point out that the clinical reality is often more complex than theoretical accounts, as in the three cases reported by Kou *et al*[1]. Although all the patients were subjected to ultrasound, three-phase enhanced tomography, enhanced MRI, and intraoperative frozen pathology, the results still suggested HCC. This suggests that clinicians, imaging experts, and surgical pathologists must be aware of other rare disease entities that may be involved in the diagnosis of liver tumors and should not directly ignore suspicious signs that may point to other diagnoses, such as normal serum tumor markers. Maintaining a skeptical attitude toward the diagnostic results and carefully verifying them are the keys to revealing additional unknown clinical problems. In 2002, WHO formally defined "PEComas" as mesenchymal tumors composed of histologically and immunohistochemically unique PECs, and PEComas include many different clinicopathological entities. Among them are angiomyolipoma, lymphangioma, lymphangioleiomyomatosis, clear cell tumor sugar and tumor types not otherwise specified[2]. Although PEComas and AMLs are theoretically subordinate, many clinical experts believe that the two are actually different manifestations of the same disease[3]. Therefore, in the following, we will discuss AMLs and PEComas as unified concepts and no longer make a special distinction.

Definition and tumor properties: It is currently clear that PEComas are mesenchymal tissue-derived tumors that are usually composed of blood vessels, smooth muscle and adipocytes[4]. However, the proportions of these tissue components tissue components differ among patients[5]. These patients often complain of abdominal discomfort but do not present accompanying abnormal serological test results[6-8]. At present, the pathogenesis of this tumor has not been elucidated[5,6]. Although more than 50% of renal AMLs are associated with TSC, it is estimated that only 5%-15% of patients with solitary liver tumors have such a link[4]. The vast majority of PEComas are benign, and malignant forms are extremely rare[9]. In view of the relatively few reports on malignant PEComas, a clear malignant standard has not yet been established[9]. However, even if PEComas are identified as benign, their boundary with malignant tumors is not very clear. First, cytological atypia, a characteristic of malignant tumors, is present in benign liver PEComas[10], while the consistent characteristic of malignant liver PEComas is considered to be coagulative necrosis[9]. Therefore, only when the tumor has necrosis, a large mass (> 10 cm), CD117 negativity, invasive behavior or other clinical evidence may it be considered a malignant liver PEComa[10]. Second, it has been reported that benign PEComas may even undergo malignant transformation during development, eventually displaying sarcomatoid or cancer-like characteristics[11]. Moreover, some patients have also been found to have advanced metastasis many years after the diagnosis of primary benign tumors[11]. Furthermore, in a recently proposed classification system, Folpe *et al*[12] divided PEComas into benign, UMP and malignant tumor categories. We think that this classification may be appropriate because it identifies a variety of tumor behaviors shown during the development of PEComas, clearly specifying UMP and recognizing that malignant tumors may occur given malignant behaviors or features. When there are multiple malignant changes, the tumor can be defined as malignant. Finally, regarding the factors that lead to the malignant transformation of PEComas, several hypotheses have been proposed. It has been reported that malignant behavior occurs mainly in epithelioid PEComas and can be observed in the early stage of tumorigenesis[13]. The diagnosis of epithelioid PEComa in a patient by clinical examination indicates that there is a greater possibility of malignant transformation, and a treatment strategy for malignant tumors should be provided.

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FOOTNOTES

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Cai WH reviewed the literature and contributed to drafting the manuscript; Chen L critically reviewed the manuscript for important intellectual content. All the authors provided final approval for the version to be submitted for publication.

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