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IMPROVE RECOGNIZE OF PERIVASCULAR EPITHELIOID CELL TUMORS IN THE HEPATIC: CASE REPORT AND BRIEF LITERATURE REVIEW

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Abstract: Hepatic perivascular epithelioid cell tumor (PEComa) is currently a rare and unexplained tumor with biological behavior, and lacks a systematic description of clinical diagnosis and treatment. It is mostly benign in literature reports. Most of them do not have specific clinical manifestations or imaging findings and are difficult to distinguish from other liver tumors, so PEComas are easily to misdiagnosed and can only be diagnosed by immunohistochemistry. Most of the opinions on treatment are claims of complete surgical resection of the tumor, and long-term follow-up observation after surgery. This article summarizes the diagnosis and treatment decisions of PEcomas and improves the understanding of PEComa diseases by reviewing previous cases and related literature experiences. It is suggested that when the possibility of excluding potential malignant tumors is excluded, tumor biopsy can be considered for diagnosis. Surgery may not be necessary for treatment, and follow-up observation may be selected.

Keywords: PEComa, Surgery, Differential diagnosis, liver tumor, immunohistochemistry

Introduction

Perivascular epithelioid cells were first proposedin 1992[1],the term of perivascular epithelioid cell tumor (PEComa) was introduced in 1996[2]. In 2002, the World Health Organization (WHO) defined PEComas as a “mesenchymal tumor with perivascular epithelial-like cells”[3]. PEComa is a family of tumors, including angiomyolipoma, clear-cell Sarcoma, lymphangiomyomatosis, and clear cell myosthema. And it rare occur in the pancreas, rectum, peritoneum, uterus, vulva, lower extremities, and heart. [4]. PEComas could come from many parts of the body. Clinically, PEComa is most common in the genitourinary system, about 40%, and secondly in the pancreas, intestine, biliary tract, breast, heart, skin, soft tissue, etc. Comparatively, PEComa, which occurs in the liver, is especially rare[5-14]. Liver PEComa related descriptions are relatively inadequate, which is difficult to

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diagnose before surgery or without biopsy, and there are no guidelines for diagnosis and follow-up treatment. This article is based on a case of hepatic PEComa diagnosed and treated in our hospital, and summarizes its clinical features diagnosis and treatment. We present the following article in accordance with the CARE reporting checklist.

Case report

A 30-years-old female, due to "abdominal swelling for half a year ", was admitted to hospital on Oct. 8th 2018. In the past 1 month, the weight has dropped about 4 kg, her general conditions were normal. She had no history of hepatitis.

Blood routine examination: WBC: 4.15x10^9　N: 64.5%.

Blood biochemical indicators: ALT: 7U / L. Tumor marker: AFP: 3.15ng/ml

CT：Dynamic enhancement of obvious uneven enhancement of arterial lesions，Decreased intensity of lesions in the portal and delayed phases，The strengthening method is “fast forward and fast out”, and the low density area is not strengthened. Considering hepatocellular carcinoma（**Fig.1**）

Fig.1 CT A: The arterial phase, B: The portal phase

MRI：In the S8 segment of the liver, a circular mass was seen, the edge was unclear, T1W1 showed a low signal, T2W2 showed a slightly higher signal, DWI showed a slightly higher signal, and the lesion showed a long T1 short T2 signal. The dynamic enhancement of the arterial phase showed significant uneven enhancement, and the degree of enhancement of the portal phase and delayed phase of the lesion rapidly decreased, and the enhancement mode was “fast-forward and fast-out”. Consider hepatocellular carcinoma (**Fig.2**).

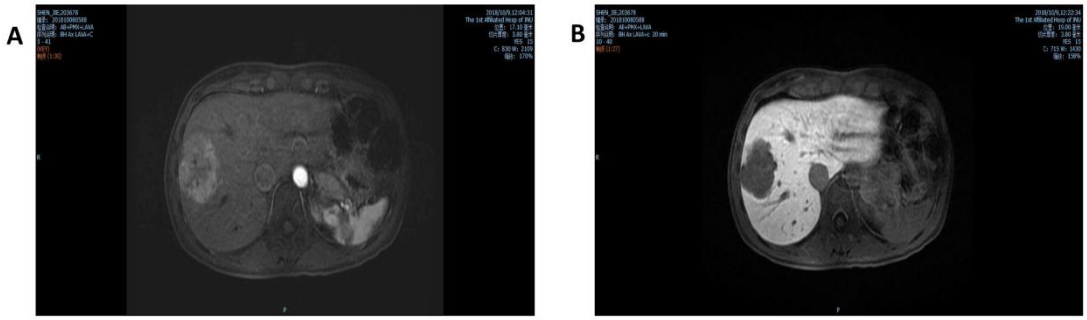

Fig.2 MRI A: The arterial phase, B: The portal phase

After admission examinations, It was suspected that the possibility of liver cancer was large, and the right liver cancer resection was to performed. The size of the surgically resected tumor was about 4 cm X 4 cm X 3 cm. Intraoperative pathology report: Consider highly differentiated hepatocellular carcinoma.

Pathology：Microscopically, the tumor cells were rich in cytoplasm, translucent or faintly red, round or polygonal, with round or elliptical nuclei, vesicular nucleus, obvious nucleoli, nuclear deviation, and mitotic less than 1/50 HPF. Tumor cells were arranged in an acinar shape, and there was a rich and slender vascular network between the nests of tumor cells. the tumor was accompanied by hemorrhage and local foam cells gather. (**Fig.3)**

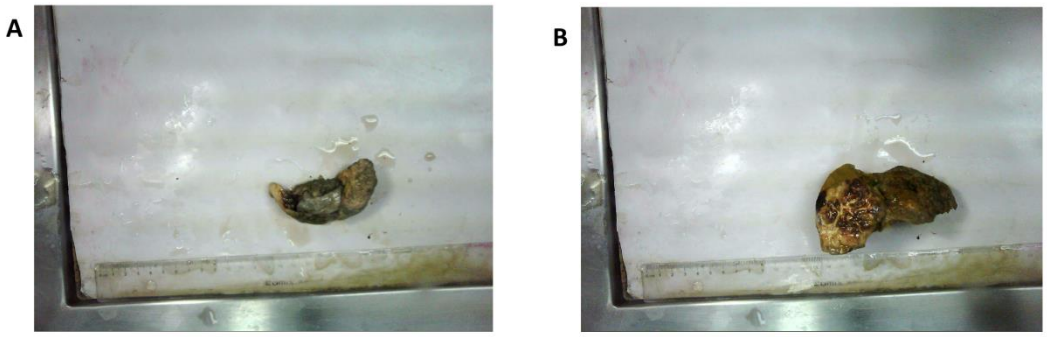

Fig.3 A and B Tumor specimen

Immunohistochemistry: A:HMB-45(few, +)(×20), **B:**CD68(+)(×10), **C**:SMA(+) (×20), **D**:Vim(+)(×10), **F:**MelanA(+)(×10) , Comform to: liver PEComa-NOS)（**Fig.4**）

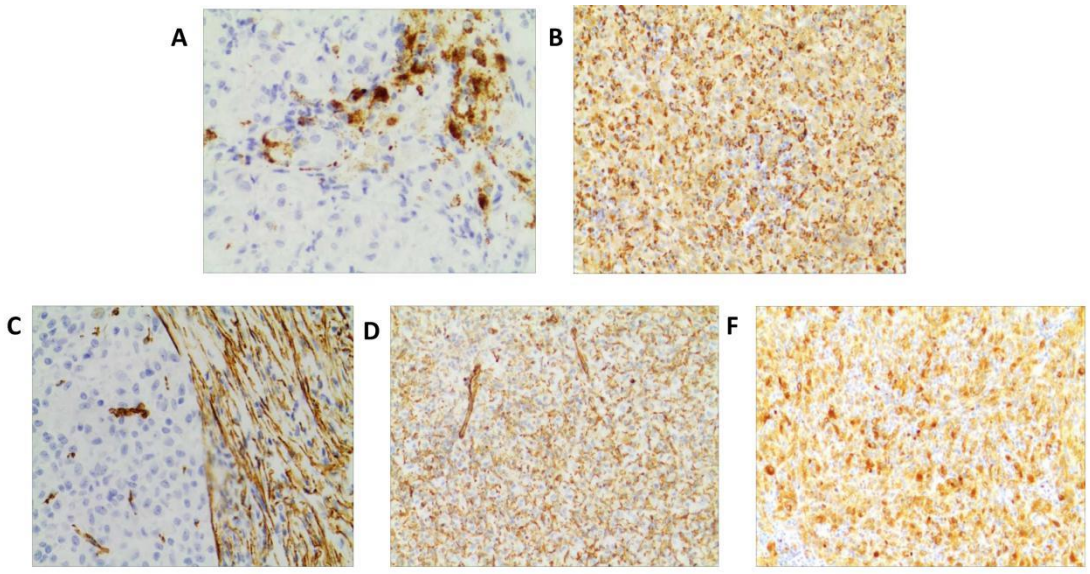

Fig.4 Pathology of PEComa

Discussion

Hepatic PEComas mainly occur in adults, especially in young women [10]. They are generally non-specific manifestations such as abdominal distension, abdominal pain, vomiting, nausea, and weight loss. And most patients were often found by chance during other disease examinations[15]. PEComa imaging and laboratory tests also have no specific characteristics. Therefore, liver PEComas were also easily misdiagnosed. They were mainly diagnosed through imaging, the absence of elevated alpha-fetoprotein (AFP) and no history of hepatitis or cirrhosis in the preoperative [16]. In the five PEComa cases of Liu Z, only one case was diagnosed with liver PEComa before surgery, three cases were misdiagnosed as hepatocellular carcinoma, and one case was misdiagnosed as hepatic adenoma[17].

PEComas are mainly identified by immunohistochemistry currently. PEComa can simultaneously express the major markers of muscle cells (desmin, SMA, muscle-specific actin, HHF 35 and Cal ponin, etc.) and melanocytes (HMB 45, Melan A, tyrosinase and small-eye transcription factors) [18]. Because the difference of the proportion of various markers in tumor tissues, when a single marker appears in the tumor, it is often misdiagnosed. For example, when the markers hinted it was mainly smooth muscle, it was easily misdiagnosed as leiomyosarcoma, malignant fibrous histiocytoma, and even hepatocellular carcinoma. Therefore, it was necessary to pay attention to the full markers of specimen. The

application of immunohistochemical markers were of great value for differential diagnosis[17, 19].

Therefore, liver PEComas should be identified with the following diseases. ①Hepatocellular carcinoma, especially AFP-negative hepatocellular carcinoma（AFP as a reliable HCC biomarker, but it is positive rate is only 60%-80% of cases）[20]. If trabecular structures appeared in the tumor, malignant PEComas were easily misdiagnosed as hepatocellular carcinoma. Malignant PEComa can be distinguished from hepatocellular carcinoma by most hepatocellular carcinomas have background of hepatitis and cirrhosis, the density of cancer cells is higher than that of malignant PEComa, and hepatocellular carcinoma immunohistochemical staining is positive for hepatocyte, and HMB45 and SMA are negative. ②Focal nodular hyperpiasia (FNH) consists of abnormally arranged hepatocytes, kupffer cells, blood vessels, bile ducts central stellate scars, and radially arranged fibrous septa. There is no specificity in the radiography. The characteristics of FNH containing kupffer cells, radionuclide scanning is a more effective method for the diagnosis of FNH [21]. ③Melanoma, In a few cases, liver PEComas were very similar to the histological features of melanoma and clear cell sarcoma, and also expressed melanin markers (HMB 45, Melan A, tyrosinase and small-eye transcription factors), and they were difficult to identify. The expression of S-100 was negative and that of SMA was positive in hepatic PEComa, while S-100 was positive and SMA was negative in melanama. Studies have shown that a small number of S-100-positive PEComa cases were also expressed SMA, while the simultaneous expression of these two antibodies in melanoma was rare. ④Clear cell acinar soft tissue sarcoma, sometimes expressed myogenic markers (desmin, SMA, muscle-specific actin, HHF 35 and Cal ponin, etc.), but not express HMB45[22, 23].

It is not clear what the pathogenesis of PEComa will be [24] because the disease was extremely rare. Most of the literature reports showed that women were more likely to get sick, and estrogen may play a key role in pathophysiology [25]. It was either not clearly understood what the biological behavior of PEComa will be, but most hepatic PEComas showed good biological behavior and prognosis. Only a few cases of malignancy have been reported [26-31]. Malignant PEComa was also rare in other body parts[5, 32]. At present, there was no

recognized standard for malignant diagnosis and prognosis. It was generally determined by clinically used methods for distinguishing benign and malignant tumors, such as tumor size, tumor cell density, polymorphism, atypicality, nuclear atypia, nuclear separation, coagulative necrosis, whether the tumor invades blood vessels, lymph nodes, local recurrence, etc. Criteria to classify PEComa were proposed by Folpe et al(**Table.1**)[6]. But there was still much controversy about this standard.

Benign *（No worrisome features）*	**<5 cm** **noninfiltrative,** **non–high nuclear grade and cellularity** **mitotic rate ≤1/ 50 HPF** **no necrosis, no vascular invasion**
Uncertain malignant potential	Nuclear pleomorphism/multinucleated giant cells only Or Size >5 cm only
Malignant *（Two or more worrisome features）*	>5 cm Infiltrative high nuclear grade and cellularity mitotic rate ≥1/ 50 HPF necrosis, vascular invasion

Table.1 Classification of PEComas.

For this patient, PEComa was still a benign tumor, but PEComa patients often need to follow up to observe the development of disease.

Complete resection of the lesion was the main treatment of hepatic PEComa [33]. Some references showed that chemotherapy and radiation therapy could not improve patients' survival time [34]. In potential metastatic disease，Studies reported that the mTOR inhibitor sirolimus for neoadjuvant therapy contributes to surgery and early control [35]. New adjuvant therapy can be performed before surgery to improve the therapeutic effect of the tumor in high-risk patients and patients with large inoperable tumor and tumor spread or multiple metastases. The diagnosis and treatment of tumors often involve various professional fields, and multidisciplinary treatment should be the most promising method in PEComas treatment decision-making.

Conclusion

Hepatic PEComa is primarily a benign tumor, so surgery may not be necessary. But the current research does not clarify the pathogenesis and biological characteristics of the tumor,

and it is impossible to accurately judge the benign and malignant tumors. It has no specific clinical and laboratory performance with lack of specific examination methods, and is easily misdiagnosed in clinical diagnosis and treatment. Excluded the possibility of not potential malignancy and patients without a history of hepatitis and cirrhosis, negative tumor makers, *patients* especially female patiens can be performed puncture pathological biopsy. The material of biopsy can be fully taken to avoid misdiagnosis when the tumor appears as a single component. Complete resection of the operation is the best treatment at present. In some patients with high-risk or tumors that are too large to be resection, the mTOR inhibitor sirolimus can be used firstly to observe the curative effect. The prognosis of PEComa remains unpredictable and requires strict and long-term follow-up to determine the nature of the tumor.

In the future, by further exploring the pathogenesis of PEComa and establishing effective preoperative diagnostic methods and evaluation criteria, patients excluding malignant tumors can be performed regular follow-up observations instead of surgical resection.

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Footnote

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