

Case Report

Malignant perivascular epithelioid cell tumor of the retroperitoneum

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Abstract: Perivascular epithelioid cell tumors (PEComas) are a rare type of mesenchymal neoplasms characterized by a proliferation of perivascular cells with an epithelioid phenotype and expression of myo-melanocytic markers. The majority of PEComas seem to be benign and usually their prognosis is good. Malignant cases are extremely rare, exhibiting a malignant course with local recurrences and distant metastases. We herein report a case of a malignant PEComa arising in the retroperitoneum. The patient was a 55-year-old woman experiencing abdominal discomfort for approximately one month. Ultrasound and computer tomography (CT) scans of the abdomen revealed a solid mass arising from the retroperitoneum. Microscopically, the tumor was composed of epithelioid cells mixed with spindle cells. The nucleus had significant atypia, and the mitoses were obvious. The focal intravascular tumor embolus was visible. Immunohistochemically, the epithelioid tumor cells were positive for HMB45 and Melan-A, and the spindle tumor cells were positive for SMA and desmin. Seven months after a surgical resection, an ultrasound revealed liver metastases. In conclusion, the malignant PEComas of the retroperitoneum is a very rare neoplasm with unique morphological and immunohistochemical characteristics. It should be differentiated from other epithelioid cell tumors of the retroperitoneum.

Keywords: Retroperitoneum, perivascular epithelioid cell tumors, clinicopathology

Introduction

Perivascular epithelioid cell tumors (PEComas) are a rare mesenchymal neoplasm composed of perivascular epithelioid cells in which their histomorphology and immunophenotype perform in a unique way. Most PEComas are benign and do not recur after surgical resection. Malignant cases exist but are extremely rare [1-5]. We present our first case of a malignant PEComas of the retroperitoneal region, and discuss the clinicopathological features, the immunophenotype and the differential diagnosis to improve awareness about this type of tumor and how to diagnose it.

Case description

A 55-year-old female was complaining of right lower abdominal discomfort. A swelling pain occurred at night when she was resting, and it lasted about 10 minutes each time. The pain was accompanied by sweating, and the loss of

appetite. A physical examination confirmed that the abdomen was flat, and a hard mass (6.0 cm in diameter) could be touched on the inner side of the iliac spine in the right lower abdomen. When pressed, it produced pain, but with no abnormal pulsation. An abdominal ultrasound inspection revealed that the middle of the right ureter was depressed with the inner diameter of upper-mid segment measuring approximately 0.7-1.8 cm, and the length was approximately 7.2 cm, however the display of the lower segment was unclear. A lower echo (ranging approximately 5.8 × 4.3 cm) could be seen above the right iliac artery and vein. The border was clear, but irregular in shape. A color Doppler inspection revealed a visible blood flow signal in the surrounding area and inside, which was recorded in the spectrum of the arterial blood flow. A pelvic CT inspection displayed a shadowy soft tissue mass with uniform density and rough edges, measuring approximately 5.1 × 4.4 × 5.5 cm in the bifurcation of the retroperitoneal iliac vessel on the right side (CT value was

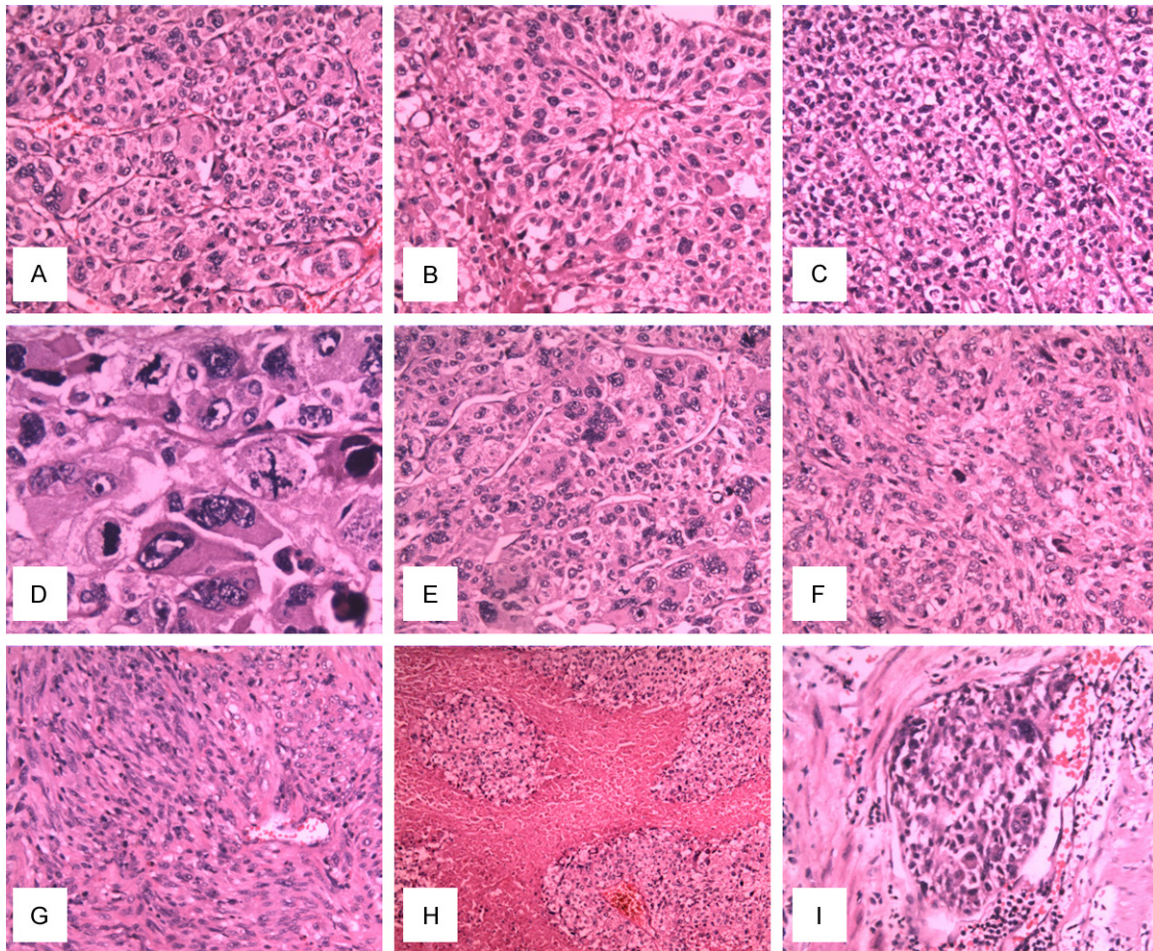


Figure 1. Histologic features of malignant perivascular epithelioid cell tumor of the retroperitoneum. A: The tumor is primarily composed of epithelioid cells. HE, $\times 100$. B: The epithelioid cells are arranged radially around the blood vessels. HE, $\times 100$. C: The neoplasm cytoplasm is transparent. HE, $\times 100$. D: The irregular mitoses. HE, $\times 200$. E: The multinucleated giant cell. HE, $\times 100$. F: The spindle cells show sarcoma-like structure. HE, $\times 100$. G: Smooth muscle-like cells. HE, $\times 100$. H: Geographic necrosis. HE, $\times 100$. I: Intravascular tumor thrombus. HE, $\times 100$.

approximately 27.0 HU). This strip liquid low density shadow was also seen in the surrounding adipose tissue. In addition the right ureter and nearby muscle were depressed, and the upper ureter and right renal pelvis were dilated. Clinical diagnosis was a tumor of the retroperitoneum. During retroperitoneal tumor resection, a round solid mass approximately 6.0×5.0 cm in size was located in the front of the right psoas muscle. The mass was connected to the right ureter, depressing it. The mass was also near the inferior vena cava and the bifurcation of the right common iliac artery.

Material and methods

The surgical specimen was fixed in 10% neutral formalin solution, embedded in paraffin and stained with hematoxylin-eosin (HE). Using the

EnVision method, immunohistochemical staining was performed on the tissue sections for the following markers: HMB45, Melan-A, chromogranin (CgA), inhibin- α , SMA, membrane antigen (EMA), cytokeratin (CK), synaptophysin (Syn), desmin, S-100, vimentin, CD117, CD34, and calretinin (CR).

Results

Grossly, the resection specimen was a grayish red spherical mass, approximately $7.5 \times 5.0 \times 4.5$ cm in size. It seemed to be enveloped and there was little adipose tissue attached to the surface. On sectioning, most of the tumor was necrotic, yellowish and soft and the residual tissue near the envelope was grayish-white and grayish-red, with a delicate fish-like texture.

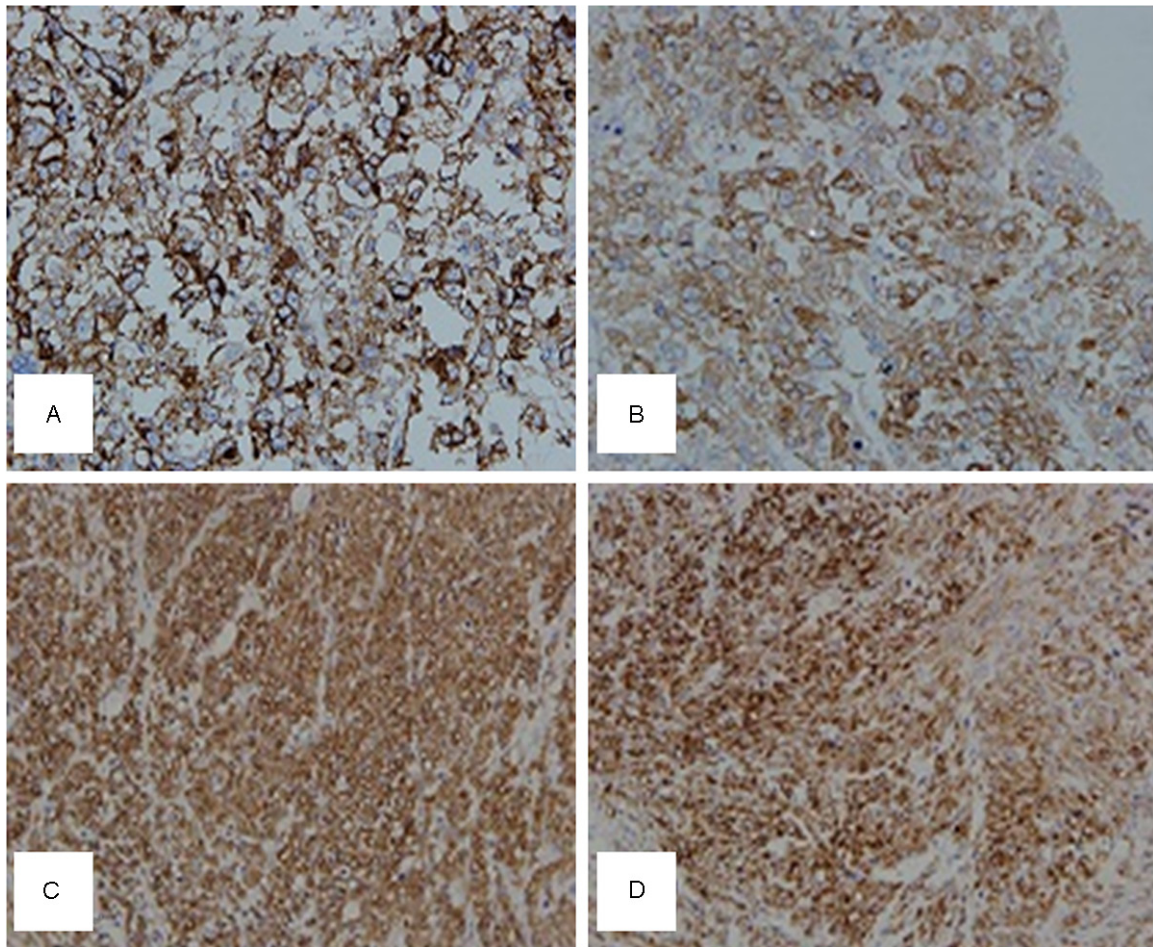


Figure 2. Immunohistochemical features of malignant perivascular epithelioid cell tumor of the retroperitoneum. The epithelioid cells are positive for HMB45 (A), MelanA (B). The spindle cells are positive for SMA (C) and desmin (D). Immunostaining, $\times 400$.

Microscopically, the tumor cells were primarily composed of round and polygonal epithelioid cells (**Figure 1A**) forming a nest or mass with obvious pleomorphic features. There was less interstitial tissue that consisted of the thin sinus vessel. In some areas, the epithelioid cells arranged radically around the blood vessels (**Figure 1B**). The cytoplasm was abundant, most of which were eosinophilic granular, some were transparent (**Figure 1C**) and others were granular and lightly stained. The cytoplasm of a few epithelioid cells was spider-shaped, lightly stained, and translucent in surrounding areas. The nucleus had significant atypia, and mitotic activity was common and irregular mitotic figures were quite visible (**Figure 1D**). In the tumor tissue, there were a lot of single nucleus, dual-nucleus and multi-nucleus giant tumor cells (**Figure 1E**) in a vari-

ety of shapes. The chromatin was deeply stained, appearing in a mass; some nucleoli were visible. In some sections of the tumor there were sarcomatoid changes, and the tumor cells were lined in spindle-shaped bundles (**Figure 1F**). A few cytoplasm were stained red, like smooth muscle cells (**Figure 1G**). The necrosis sections of the tumor showed geographic necrosis change (**Figure 1H**), and the tumor thrombus (**Figure 1I**) could be seen in the vessels near the capsule.

Immunohistochemically, in the tumor tissue, the epithelioid cells were diffusely positive for HMB45 (**Figure 2A**) and Melan-A (**Figure 2B**), as well as focal positive for vimentin and EMA. In the sarcomatoid area, the spindle-shaped cells were diffusely positive for SMA (**Figure 2C**) and desmin (**Figure 2D**). The neoplastic cells

were negative for the remaining antibodies, including CgA, Syn, S-100, CD117, CD34, CK, calretinin and inhibin- α .

On the basis of the above histopathological and immunohistochemical features, a diagnosis of malignant PEComa of the retroperitoneum was made. The patient chose not to have any adjuvant chemotherapy or radiotherapy. An ultrasound inspection performed 7 months after surgery revealed liver metastases.

Discussion

As a rare kind of soft tissue neoplasms composed of a pure proliferation of the perivascular epithelioid cell, PEComas was first reported by Zamboni *et al* [6] in 1996. In 2002 the World Health Organization officially defined it as a mesenchymal tumor composed of histologically and immunohistochemically distinctive perivascular epithelioid cells [1]. The PEComas tumor family includes: angiomyolipoma (AML), Clear cell "sugar" tumor (CCST), lymphangio-myomatosis (LAM), Clear cell myomelanocytic tumor of the ligamentum teres/falciform ligament (CCMMT), and some clear cell tumors in the pelvic cavity, the abdominal cavity, the digestive tract, the genitourinary tract, the surrounding soft tissue and skin which can not be classified into the above special types. Except for AML, CCST, LAM and CCMMT, the remainder of PEComas are referred to as nonspecific perivascular epithelioid cell tumors (PEComa-NOS) [7]. The names of these nonspecific perivascular epithelioid cell tumors vary in the literature, including extrapulmonary sugar tumor, perivascular epithelioid cell tumor, monomorphic epithelioid vascular smooth muscle lipoma etc. The PEComas-NOS is very rare [8, 9], it is commonly found in the uterus and gastrointestinal tract, most are benign, however, a few are malignant.

More than 20 cases of retroperitoneal PEComas are documented in the literatures [5, 8, 10-13], the age of the patients range from 34 to 73 years old, most of them being female. The clinical symptoms often lack specificity. Most patients did not have any discomfort, and the tumor was discovered accidentally by the patient or during a physical examination. For the few patients with a larger tumor, the adjacent organs and tissues may have been depressed, so there may be a series of symptoms such as abdominal discomfort, abdomi-

nal bloating, abdominal pain, reduction in food intake, frequent urination, leg pain and numbness. Individual patients may have symptoms such as lower back pain or a rise in blood pressure. Usually, the tumor is large and invasive. It may recur and distant metastasis can also occur. The latter can spread to the liver, lung, brain and bones, and can lead to the death. A patient in such a case manifested abdominal discomfort, and the abdominal pain was obvious, especially at night when resting.

Morphologically, the visible tumor is often larger in size; the diameter of the largest one can be up to 30 cm. Most of this type has envelopes. The section is gray red, gray or taupe; and the texture is solid, tough or brittle; a few of them are fish-like which may be associated with hemorrhage, cystic degeneration and necrosis. Observed under the microscope, the tumor cells are located around the blood vessels and usually are radically arranged around the vessel lumen. The tumor cells are mainly composed of the epithelioid cells and spindle-shaped cells, and the proportion of the two kinds of cells vary in different tumors. The epithelioid cells are located around the vessels, and are arranged in a solid nest, sheet, cord or organ-like arrangement; the cytoplasm is transparent to slight eosinophilic, granular; the nucleus is round or oval, and it may have nuclear atypia. The cytoplasm and nucleus of the spindle-shaped cells look like the smooth muscle cells, and often are away from the vessels and arranged in bundles. In some cases, there are multinucleated giant cells, and the deposition of brown particles can be found in a few cases. The interstitial tissue is rich in blood vessels, and it often is a delicate vascular network. The thick-walled blood vessel is rare, and the wall may have hyaline degeneration. In some cases, the tumor interstitial tissue may show varying degree of hyaline degeneration. In obvious cases of hyaline degeneration appear as a single or small nest embedded in the hyaline degeneration or fibrous interstitial tissue, which is also called sclerosing PEComas [10]. The sclerosing PEComas is common in the retroperitoneum, and was described by Hornick and Fletcher first and they found 11 cases of sclerosing PEComas in 17 cases of retroperitoneal PEComas in their study. In the cases of PEComa, the tumor cells were primarily composed of round and polygonal epithelioid cells with obvious pleomorphic features, arranged in

the shape of a card, beam, nest or mass. The interstitial tissue was less, which were composed of the thin sinus vessel. In some areas, the tumor cells grew around the blood vessels. The cytoplasm of the tumor cells were abundant, most of which were eosinophilic granular, some were transparent to lightly stained granular. The nucleus had significant atypia, and mitotic activity was common. In the tumor tissue, there were a lot of single nucleus, dual-nucleus and multi-nucleus giant tumor cells. In some areas, the tumor showed sarcomatoid changes. However, the sclerosing fibrous stroma was not obvious.

In the immunologic phenotype, the characteristics of PEComas are the expression of melanin cell marker and the muscle cell marker at same time, but the expression of the two markers vary in different cases [1, 10, 13-15]. In the melanoma cell markers, the most sensitive one is HMB45, and followed by Melan A, in which mainly the epithelioid cells are positive. In muscle cell markers, SMA and desmin are commonly positive, mainly for the spindle-shaped cells. In addition, vimentin is positive. CK, EMA, S-100, and CD117 are negative. In such cases, the epithelioid cells of the tumor tissue show HMB45, Melan A diffusely positive, and vimentin and EMA focally positive; in the sarcomatoid areas.

Because the PEComas case is rare, its biological behavior is uncertain, and there is no unified diagnostic criteria for benign and malignancy. The currently accepted classification criteria of benign and malignancy were proposed by Folpe *et al* [16] in 2005, that is, the malignant PEComas shall comply with the following two or more items: tumor: > 5 cm, infiltrative growth, higher nuclear grade and higher cell density, mitotic figures: $\geq 1/50$ HPF, coagulation necrosis, and vascular invasion. For the PEComas (its malignant potential is undecided), the tumor cells are only shown as pleomorphic/multinucleated giant cells, or only if the tumor is bigger than 5 cm (> 5 cm) without any histological abnormalities. For the benign PEComa, the tumor diameter is less than 5 cm (< 5 cm) without any histological abnormalities. In this case, the maximum tumor diameter was 7.5 cm, the nucleus had significant pleomorphic feature, and the mitosis was common, most of which were coagulation necrosis, and there was vascular invasion in some areas, so it was met the diagnostic criteria of malignant

PEComas. Seven months after the tumor was removed, the liver in a B-ultrasound inspection revealed liver metastases, further supporting the diagnosis of malignant PEComa.

The malignant PEComas of retroperitoneum shall be differentiated from the epithelioid cells tumors such as the metastatic renal cell carcinoma, the malignant melanoma or clear cell sarcoma, the paraganglioma, the gastrointestinal stromal tumors focused on epithelioid cells, the epithelioid malignant neuroma and so on. (1) Metastatic renal cell carcinoma is similar to PEComas in the morphology, the cytoplasm is translucent or eosinophilic, and the interstitial tissue is rich in the vascular network, but the metastatic renal cell carcinoma often occurs in primary kidney disease, the cytoplasm of typical renal clear cell carcinoma is more translucent, the nucleus is small and the nucleolus is not obvious, the tumor cell expresses CK and EMA but HMB45 and Melan-A. (2) Malignant melanoma or clear cell sarcoma, the nucleolus of the tumor cell is more obvious, and there is an obvious lack of rich vascular network structure and sinus blood vessels, the tumor cells are positive for HMB45, Melan-A and S-100 but no myogenic markers. (3) Paraganglioma, the main difference is that the cytoplasm is not very transparent, the tumor cells are positive for neuroendocrine markers, rather than expressing the melanoma cell and muscle cell markers. (4) Epithelioid Gastrointestinal stromal tumors, the eosinophilic feature of the cytoplasm of the tumor cell is more obvious, but the interstitial tissue lacks vascular network structure, and it is important that the tumor cells are positive for CD117 and CD34, and negative for HMB45 and Melan-A. (5) Epithelioid malignant schwannoma, the tumor cells are separated by fibrous tissues in nest or mass, there may be adenoid differentiation, the vascular network structure is not obvious, and S-100 is positive, while HMB45, Melan-A, SMA and desmin are negative.

For the treatment of PEComas, surgical resection is mainly used currently. For the malignant PEComas, the effect of radiotherapy and chemotherapy is not obvious except for surgery. Recently, some studies [5, 11, 17] reported that oral administration of mTOR inhibitor Sirolimus has a certain effect on the malignant PEComas, suggesting that Sirolimus can be used as the target drug in the treatment of PEComas, which needs further study.

In short, as a kind of rare mesenchymal tumor with uncertain differentiation, PEComas has unique histological and immunohistochemical features. Because PEComas is relatively rare, its biological behavior is uncertain, there is no clear diagnostic criteria of malignancy, as such there needs to be an accumulation of cases with long-term clinical follow-up.

Disclosure of conflict of interest

None.

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