PERIVASCULAR EPITHELIOID CELL TUMOR WITH OVERT MALIGNANCY: A CASE REPORT

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Perivascular epithelioid cell (PEComa) is a group of rare tumors composed of epithelioid cells with characteristic perivascular distribution and co-expression of the melanogenic marker HMB-45 and muscular markers. There are no documented parameters referring to the biologic behavior of PEComa. We report an abdominopelvic PEComa with overt malignancy in a 16-year-old girl. Histologically, the tumor showed the typical morphophenotypic characteristics of PEComa. Though the cytologic appearance of the tumor cells was relatively bland, the extensive necrosis, presence of lymph node metastases, and surrounding tissue invasion were all indicative of malignancy. Relapse of the tumor with multiple lymphadenopathy shortly after debulking surgery for the primary lesion, and postoperative adjuvant chemotherapy, further denoted its aggressive behavior.

Key Words: perivascular epithelioid cell, PEComa, angiomyolipoma, clear cell sarcoma, clear cell renal cell carcinoma

Perivascular epithelioid cells, first discussed by Bonetti et al [1], are found in a group of disorders including angiomyolipoma (AML), lymphangioleiomyoma (LAM), and clear-cell “sugar” tumor (CCST) of the lung. The term “PEComa” (perivascular epithelioid cell tumor) refers to tumors composed primarily of perivascular epithelioid cells [2]. More tumors are being reported and categorized as members of the PEComa family, including monotypic epithelioid AML [3–9], pulmonary or extrapulmonary CCST [10–13], and clear-cell myomelanocytic tumor (CCMMT) of the falciform ligament/ligamentum teres [14,15]. They all share common morphophenotypic features: round to polygonal (epithelioid) tumor cells, clear to variable eosinophilic granular cytoplasm, round vesicular usually centrally located nuclei, as well as immunoreactivity to both the melanogenic-related marker HMB-45 and muscular markers.

The biologic behavior of PEComa has not been well documented, perhaps due to the rarity of these disease entities and because the duration of follow-up is too short. In general, most AMLs [4,6,16], CCSTs of the lung and pancreas [10,12,13], and CCMMTs of the falciform ligament/ligamentum teres [14,15] are thought to follow a benign course. However, malignant AML [16], malignant pulmonary CCST [10], and malignant PEComas of the prostate and uterus [17,18] have also been reported, as well as four cases of abdominopelvic sarcoma with perivascular epithelioid cells reported by Bonetti et al in 2001 [18]. We report a case of abdominopelvic PEComa in a 16-year-old girl with overt malignancy shown by extensive necrosis, surrounding tissue invasion, and lymph node metastases at diagnosis.

CASE PRESENTATION

A 16-year-old girl was referred to the gyneco-obstetric outpatient department of our hospital on January 7, 2003, due to left lower quadrant abdominal pain and a huge intra-abdominal mass with bilateral hydronephrosis found by
abdominal ultrasonography at a regional hospital. Physical examination revealed a distended abdomen with a palpable mass. Hematologic examination revealed normocytic anemia (red blood cells, 3.35 × 10^9/L; hemoglobin, 93 g/L; hematocrit, 0.31; mean corpuscular volume, 92.2 fl), while biochemistry parameters were all within normal limits. Magnetic resonance imaging (MRI) of the abdomen revealed a lobulated, relatively solitary tumor mass occupying the lower abdomen mainly in the pelvic area, with bilateral compressive obstructive uropathy over the distal lower ureter and a small amount of ascites. No remarkable fat component was discernable. Serum levels of human chorionic gonadotropin β subunit, α-fetoprotein, carcinoembryonic antigen, CA19-9, tissue polypeptide-specific antigen, and squamous cell carcinoma antigen were all within normal ranges, but the serum lactate dehydrogenase level was 1,645 U/L (normal range, 91–180 U/L) and the CA125 level was 141,300 U/L (normal range, < 35,000 U/L). Laparotomy showed a huge, encapsulated, hypervasculated tumor in the pelvis with invasion to the rectosigmoid colon and mesocolon and adhesion to the uterus. The tumor was partially covered by the mesocolon. Bilateral ovaries were grossly normal. Several enlarged lymph nodes over the mesocolon, iliac region, and pelvic floor were also found. Intraoperative frozen-section analysis of the tumor revealed a nested arrangement of bland-looking cells with clear-to-fine eosinophilic granular cytoplasm segregated by a delicate vascular network, mimicking the architecture of clear-cell renal cell carcinoma. In addition to excision of the tumor, resection of the sigmoid colon with Hartmann's procedure, wedge resection of bilateral ovaries, and pelvic floor lymph node dissection were performed.

On pathologic examination, the tumor mass measured 27 × 22 × 9 cm and weighed 1,500 g. Grossly, it was partially encapsulated by thin membranous tissue. The cut surfaces were grayish-white with areas of fresh and old hemorrhage and necrosis. The tumor had adhered to the serosa of the large bowel, but the mucosa and muscle wall of the colon were not involved.

Histologically, the tumor was composed of cells with abundant clear-to-fine eosinophilic granular cytoplasm and round, rather uniform, nuclei arranged in nests or wide fascicles with delicate vascular septae (Figures 1 and 2A). Mitoses were inconspicuous. Proliferation of thin-walled capillary-like vessels with occasional glomerulus-like vascular tuft formation was also noted in foci. There was extensive coagulative necrosis and hemorrhage. No mature adipose tissue, spindle-shaped smooth-muscle bundles, or abnormal thick-walled blood vessels characteristic of classic AML were found. The tumor extended to the colonic serosa without penetrating to the muscular bowel wall. Surprisingly, despite the bland cytologic appearance of the tumor cells, lymph node metastases were found. The bilateral ovaries were unremarkable. Immunohistochemically, the tumor cells were negative for cytokeratin (CK), epithelial membrane antigen (EMA), vimentin, and chromogranin-A, but strongly expressed the melanogenic marker HMB-45 (Figure 2B) and focally positively stained with smooth muscle actin (SMA) (Figure 2C). Intracytoplasmic or
intercellular brown-to-black pigmented granules were not infrequently seen and these stained with Fontana-Masson stain but not Prussian blue stain, indicative of their melanin nature.

Under electron microscopic examination, abundant intracytoplasmic free glycogen particles or membrane-bound collections of glycogen were seen, corresponding to the clear cytoplasm of the tumor under light microscopy. Thin filaments with focal densities indicative of smooth muscle differentiation were also found in the cytoplasm of the epithelioid tumor cells. In addition, an intercellular junction was observed.

After surgery, the patient underwent adjuvant chemotherapy and the serum CA-125 level decreased to normal. However, tumor recurrence developed 2 months after debulking surgery.

**Discussion**

PEComas other than AML, CCST, LAM, or CCMMT have a predilection for females with a wide age distribution. They have been reported in the uterus, large and small intestines [19], pelvic sidewall, vulva, thigh [20], heart, and prostate [17]. Extra-uterine PEComas usually present as a painless mass, while PEComas growing in the uterus typically manifest by vaginal bleeding.

The microscopic morphology of the present case was reminiscent of clear-cell renal cell carcinoma at first glance, mostly due to the nested arrangement of the epithelioid round tumor cells with moderate to abundant clear or eosinophilic cytoplasm, as well as the numerous delicate vascular stroma. However, the absence of a discernible space-occupying lesion in bilateral kidneys on MRI, the immunohistochemical negativity of the tumor cells for CK and EMA stains, and the lack of ultrastructural evidence of epithelial differentiation all opposed the diagnosis of clear-cell renal cell carcinoma. Another important differential diagnostic consideration is clear-cell sarcoma (also known as “melanoma of soft parts”). Although they may share some phenotypic features, including positive reactivity to the melanocytic marker HMB-45, morphologically, clear-cell sarcoma differs from PEComa by the presence of dense fibrous septae rather than the delicate vascular-rich stroma of the latter. The present case showed focally positive reactivity to S-100 protein, an unusual finding in PEComa, which may cause diagnostic confusion with clear-cell sarcoma (which always shows S-100 positivity); we presumed that the S-100 reactivity in the present case was the result of adipocytic differentiation of the tumor cells.

Based on the characteristic epithelioid appearance of the tumor cells with clear-to-fine granular eosinophilic cytoplasm and the unique phenotypic feature of co-expression of the melanogenic marker HMB-45 and muscular marker SMA, our case was diagnosed as PEComa. Though, morphologically, it lacked the obvious fat and smooth muscle components, the presence of numerous capillary-like small-caliber vascular proliferations and the tendency for neoplastic cells to be arranged surrounding the vessels, the focal positive reactivity to S-100 protein, and the ultrastructural evidence of lipid droplets and thin filaments with focal densities indicative of adipocyte and smooth-muscle differentiation all implied differentiation toward monotypic epithelioid AML. This supported the concept proposed by Zamboni et al that the PEComa family represents a spectrum of lesions from typical AML as the full-blown prototype to lesions composed completely of epithelioid cells (PEComa) [12]; the present case falls within this range.

The prognosis and biologic behavior of PEComa have not been well documented. Classical AML was thought to pursue a benign clinical course, despite the presence of lymph node or multiorgan involvement, cytologic pleomorphism, and intravascular growth [16]. However, there are reports of malignant behavior of pleomorphic or monotypic epithelioid AML. Lowe et al reported a case that developed multiple sarcomatous lesions 18 months after resection of a primary pleomorphic renal AML [4]. Several cases first diagnosed as renal cell carcinoma and reclassified by Pea et al as monotypic epithelioid malignant AML also showed aggressive clinical behavior [5]. L’Hostis et al demonstrated a case of “monophasic epithelioid pleomorphic AML” with perivertebral and liver metastases [6]. Cibas et al described a case of renal AML showing both classic and epithelioid AML subtypes [7]. Three years after nephrectomy, metastases in the liver with phenomorphologic characteristics of epithelioid AML were noticed, confirming the existence of a malignant epithelioid AML. Yokoo et al reported a patient with retroperitoneal epithelioid AML who died of the disease 4 years after the initial symptoms; histologic features of tumor samples from autopsy confirmed the fatal behavior of the tumor [8].

CCST of the lung and pancreas seem to follow a benign clinical course, as described by Zamboni et al [12]. Five of seven CCMMTs of the falciform ligament/ligamentum teres reported by Folpe et al showed no evidence of malignant behavior, although the follow-up period was short, and radiographically presumed pulmonary metastasis was
documented in one case [14].

According to these reports, PEComas with the following features must be regarded as malignant: infiltrating growth pattern, marked hypercellularity, high nuclear to cytoplasmic ratio and nuclear hyperchromasia, high or atypical mitotic figures, and coagulative necrosis. Malignant PEComas are highly aggressive and fatal.

In conclusion, our case belonged to the PEComa family with morphophenotypic and ultrastructural evidence of monotypic epithelioid AML differentiation. Due to the limited case numbers and the short follow-up period, no definite prognostic factors for PEComa have been established. In our case, extensive necrosis, microscopically documented lymph node metastases, obvious invasion to adjacent tissue at diagnosis, and recurrence soon after debulking surgery combined with postoperative adjuvant chemotherapy all indicated the overt malignancy of this tumor.

REFERENCES

腹腔骨盆腔恶性血管旁類上皮細胞瘤 — 病例報告

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血管旁類上皮細胞瘤 (perivascular epithelioid cell tumor，PEComa) 包含一群由類上皮細胞所構成的罕見疾病。這些類上皮細胞的特徵是會圍繞著血管分布，並且可以同時表現出物黑色素分泌功能的標記，以及肌肉組織的標記。到目前為止，並沒有指標可以來預測血管旁類上皮細胞瘤的生物行為。

我們提出了一個發生在 16 歲年輕女孩身上，具有明顯惡性行為的血管旁類上皮細胞瘤案例報告。在組織學上，這個腫瘤具有典型的血管旁類上皮細胞瘤之特徵。雖然構成這個腫瘤的腫瘤細胞型態看起來相當的良性，但大範圍的壞死、合併淋巴結的轉移，以及侵犯到鄰近的組織等現象都再再地顯示出這個是一種惡性腫瘤。在做完減積手術及術後輔助性化療治療後沒多久，腫瘤便又復發了，且伴隨多處的淋巴腺轉移，更進一步證實了此一腫瘤的具侵襲性行為。

關鍵詞：血管旁類上皮細胞，血管旁類上皮細胞瘤，血管肌脂瘤，透明細胞肉瘤，透明細胞腎細胞癌
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