Perivascular epithelioid cell tumor (PEComa) of gynecologic origin: a clinicopathological study of three cases

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Summary

Perivascular epithelioid cell tumors (PEComas), occasionally associated with the tuberous sclerosis complex, are characterized by varying amounts of spindle and epithelioid cells with clear to eosinophilic cytoplasm that display immunoreactivity for melanocytic markers, most frequently HMB-45. Perivascular epithelioid cell tumor of gynecologic origin is very rare, and there have been only a few reported cases. This study describes the clinical, histological, and immunohistochemical features and prognoses of three cases of gynecologic origin. Two of the three tumors were confined to the uterus and one to the vagina. None of the patients had tuberous sclerosis complex. Immunohistochemistry indicated that all three cases expressed at least one melanocytic marker, and HMB45 was a positive marker for all of them. These markers can be found in both epithelial cells and spindle cells. Except for MiTF, which was located in the nucleus, all the other antibodies were located in the cytoplasm. The three cases have been followed up for 26, 22, and three months, respectively, with disease-free survival in all cases. We conclude that PEComas of gynecologic origin have morphological and immunohistochemical features of the PEComa family, which are rare and should be included in the differential diagnosis with other tumors. Until more cases of this rare tumor are evaluated with longer follow-up, firm criteria for malignancy remain uncertain.

Key words: PEComa; Perivascular epithelioid cell tumors; Gynecologic origin.

Introduction

PEComas were defined by the World Health Organization (WHO) in 2002 as "mesenchymal tumors composed of histologically and immunohistochemically distinctive perivascular epithelioid cells." The concept of a family of neoplasms derived from these distinctive cells was first advanced by Bonetti *et al*. They noted the presence in both angiomyolipoma (AML) and clear cell "sugar" tumor of the lung (CCST) of "an unusual cell type … immunoreactive with melanocytic markers, and exhibit[ing] an epithelioid appearance, a clear-acidophilic cytoplasm, and a perivascular distribution" [1].

The PEComa family of tumors has subsequently grown to include AML, CCST, lymphangioleiomyomatosis (LAM), and a number of unusual visceral, intraabdominal, soft tissue, and bone tumors, which have been described under a variety of names, including clear cell

myomelanocytic tumor of the falciform ligament/ligamentum teres, abdominopelvic sarcoma of perivascular epithelioid cells, and primary extrapulmonary sugar tumor, among others [2].

In the 2003 WHO classification of gynecologic neoplasms, only PEComas of the uterine corpus were recognized. However, PEComas have also been described in the cervix [3], vagina [4], pelvis [5], broad ligament [6] and ovary [7]. They are also known to show an overwhelming female preponderance [8, 9]. The uterus seems to be one of the two most frequently reported anatomic sites of origin for PEComas [10]. To better understand the pathological features, immunophenotype, clinical behavior, and prognosis of these rare tumors, we studied three PEComas of gynecologic origin that had been defined as PEComas by immunohistochemistry in the Department of Gynecology and Obstetrics of our hospital since 1998.

Methods

Cases and inclusion criteria

Cases that had been previously coded as "perivascular epithelioid cell neoplasm" since 1998 in the Department of Gynecology and Obstetrics of our hospital were retrieved from our consultation archives. Three cases of gynecologic origin were retrieved for this study. Two of the three tumors were confined to the uterus and one to the vagina. The patients were 50, 44, and 33 years old, and none had tuberous sclerosis complex.

Clinical data collection and follow-up

All cases were studied with respect to general state of health with special attention to features predictive of clinical behavior and whether they had tuberous sclerosis complex. All were followed to better understand the prognosis of these rare tumors.

Pathological features

All cases were studied with respect to tumor site and size, growth pattern (circumscribed or infiltrative), cellularity and nuclear grade, mitotic figures/50 high power fields (HPF), atypical mitotic figures, coagulative tumor cell necrosis, vascular invasion, and epithelioid or spindled morphology.

Immunohistochemical studies

Immunohistochemical studies for pan-cytokeratin (AE1/AE3, 1:100, Dako), S-100 protein (polyclonal, 1:2000, Dako), [alpha]-smooth muscle actin (1A4, 1:100, Dako), desmin (DER-11, 1:50, Dako), vimentin (Vim3B4, 1:200, Dako), melanoma

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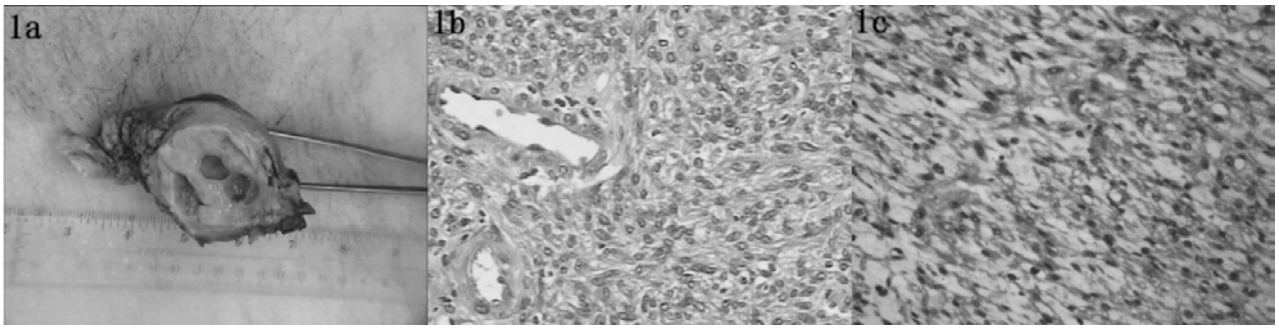

Figure 1. — Total removal of the uterus showed several cystic nodules (1a).The cells of PEComa of the uterus were epithelioid or spindle cells with light eosinophilic or translucent cytoplasm. Mitotic figures were rare and necrosis was not observed (1b, 1c). Vaginal tumor (2a). The cells of PEComa that occurred in the vagina were clear cells with transparent cytoplasm and small round nuclei. Mitotic figures were rare, and tumor cells had an adenoid or acinar-like structure (2b, 2c).

(HMB45, 1:100, Maixin), Melan A (A103, 1;40, Dako), microphthalmia transcription factor (D5, 1;50, Dako), c-kit (CD117,1:100, Dako), and CD34 (QBEND10, 1:200, Dako) were performed. Cases were scored as negative, 1+ (5-25% positive cells), 2+ (26-50% positive cells), and 3+ (> 51% positive cells). Appropriate negative controls were used.

Results

Pathomorphology features

In the present study, it was shown that the cells of perivascular epithelioid cell tumor of the uterus were epithelioid or spindle cells with light eosinophilic or translucent cytoplasm. Mitotic figures were rare and necrosis was not observed. Thin- or thick-walled blood vessels were readily visible around the smooth muscle with unclear boundaries. The remaining small nodules were formed by smooth muscle cells and were proliferating without atypia or invasive growth. The cells of the perivascular epithelioid cell tumor in the vagina were clear cells with transparent cytoplasm and small round nuclei. Mitotic figures were rare, and tumor cells had an adenoid or acinar-like structure. These pathological features were similar to those of vascular epithelial cells described in the past.

Immunohistochemical findings

In this study, the tumors were positive for HMB45(3/3), SMA(2/3), HHF35(2/3), Vim(+) (1/3), and MITF (2/3). They were uniformly negative for Melan-A, CD10 (-), and S100 (-). All of the three cases expressed at least one kind of melanocytic marker, and HMB45 was a positive marker for all. These markers can be found in both epithelial cells and spindle cells. Except for MITF, which was positively positioned in the nucleus, all other antibodies were located in the cytoplasm.

Prognosis

In the present study, the three cases were followed for 26, 22, and three months, respectively, and disease-free survival was observed in all cases. None had tuberous sclerosis complex.

Discussion

Bonetti *et al*. first proposed a cellular link among these unusual mesenchymal lesions and lymphangiomyomatosis (LAM) [11], following reports of HMB-45 immunoreactivity and the presence of premelanosomes in both clear cell "sugar" tumor (CCST) of the lung and the epithelioid clear cell component of angiomyolipoma (AML) of the kidney and liver [12-15]. They subsequently suggested the descriptive term "perivascular epithelioid cell" (PEC) for the distinctive cell type found in these three lesions, and hypothesized that the so-called PEC may originate from the walls of blood vessels, based on the observation that these cells are frequently intimately related to such structures [1]. Folpe *et al*. presented their experience with 26 PEComas of soft tissue and the gynecologic tract, the largest reported series to date [2]. Their study indicated that there was a marked female predominance. They concluded that PEComas of soft tissue and gynecologic origin may be classified as benign, of uncertain malignant potential, or malignant. Small PEComas without any worrisome histologic features are most likely benign. PEComas with nuclear pleomorphism alone ("symplastic") and large PEComas without other worrisome features have uncertain malignant potential. PEComas with two or more worrisome histological features should be considered malignant. Almost all uterine PEComas were located in the body of the uterus; however, an unusual instance of this rare tumor presenting as a polypoidal cervical mass in a young female was also reported [3].

From a molecular genetic perspective, the recurrent chromosomal alterations in both renal and extrarenal tumors further support the concept of PEComa as a distinctive tumor entity regardless of anatomical location [16]. PEComas are related to genetic alterations of the tuberous sclerosis complex (TSC), an autosomal dominant genetic disease due to loss of TSC1 (9q34) or TSC2 (16p13.3) genes, which seem to have a role in the regulation of the Rheb/mTOR/p70S6K pathwa [17].

PEComas show a marked female predominance and are usually composed of epithelioid, but occasionally spindled cells with clear to granular eosinophilic cytoplasm and focal perivascular accentuation [18]. Our study

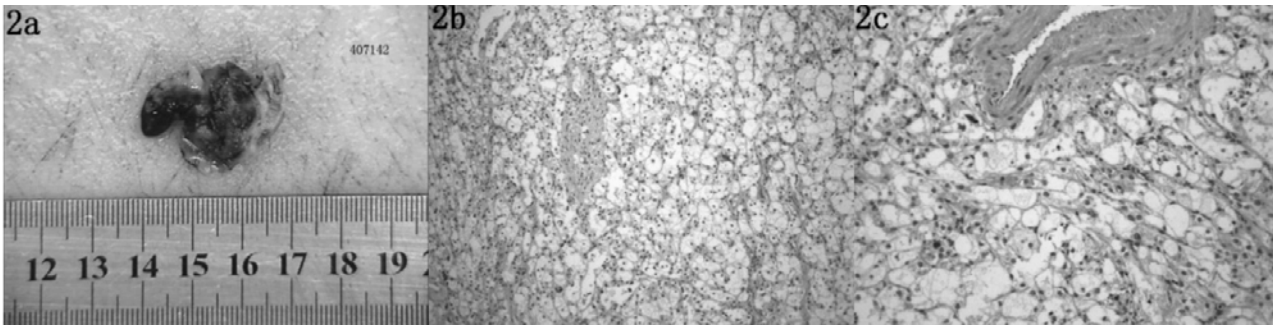

Figure 2. — Tumors were positive for HMB45 (2A), MITF (2B), and SMA (2C).

showed that the cells of perivascular epithelioid cell tumors of the uterus were epithelioid or spindle cells with light eosinophilic or translucent cytoplasm. Mitotic figures were rare and necrosis could not be observed. Thin- or thick-walled blood vessels were readily visible around the smooth muscle with unclear boundaries. The remaining small nodules were formed by smooth muscle cells that were proliferating without atypia or invasive growth. The cells of perivascular epithelioid cell tumor occurring in the vagina were clear cells with transparent cytoplasm and small round nuclei. Mitotic figures were rare, and the tumor cells had an adenoid or acinar-like structure. These pathological features were similar to those of vascular epithelial cells described in the past.

Nearly all PEComas show immunoreactivity for both melanocytic (HMB-45 and/or Melan A) and smooth muscle (actin and/or desmin) markers [8]. Fukunaga [7] described four cases of uterine PEComa in 2005. Immunohistochemically, the tumors were positive for vimentin (4/4), HMB45 (4/4), h-caldesmon (4/4), alpha-smooth muscle actin (3/4), muscle actin (2/4), and desmin (3/4). They were uniformly negative for Melan A, CD10, and S-100 protein. In this study, the tumors were positive for HMB45 (3/3), SMA (2/3), HHF35 (2/3), vim(+) (1/3), and MITF (2/3). As in Fukunaga's study, they were uniformly negative for melan A, CD10(-), and S100(-).

The prognosis of PEComas has received close attention. A 79-year-old woman with a large uterine mass that recurred two years following resection was reported. The patient died within months after resection of the recurrent tumor. It was suggested that uterine PEComas should be regarded as tumors with uncertain malignant potential [19]. Among the four cases of uterine PEComa reported by Fukunaga, one patient died of intestinal metastases 17 months after surgery. The other patients were well with no evidence of disease 8, 12, and 36 months after surgery [7]. Jeon reported a 9-year-old girl who was diagnosed with PEComa of the uterus with metastasis. After multimodal treatment with chemotherapy as well as radiotherapy after surgery, there was no evidence of recurrence or further metastasis. She remained disease-free 1.5 years after her initial diagnosis [20, 21]. In our study, the three cases were followed for 26, 22, and three months, respectively, and disease-free survival was observed in all cases. Because of the limited data about the prognosis of PEComas, it is still difficult to establish firm criteria for malignancy.

In conclusion, PEComas of gynecologic origin have the morphological and immunohistochemical features of the PEComa family. These tumors are rare, and differential diagnosis is needed. Until more cases of this rare tumor are evaluated, with longer follow-up, firm criteria for malignancy remain uncertain.

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