Perivascular epithelioid cell tumor (PEComa) of the uterus with aggressive behavior at presentation

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Perivascular epithelioid cell tumor (PEComa) is a rare mesenchymal tumor composed of histologically and immunohistochemically distinctive perivascular epithelioid cells (PECs). Both benign and malignant tumors have been identified, but the criteria for diagnosis of malignancy have not been fully established due to the rarity of the tumor. We report on a case of uterine PEComa in a 33-year old woman with lymph node metastasis at presentation. The tumor had the characteristic histologic features of PEComa with cytologic atypia, mitotic activity of 2/10 high power field (HPF), and necrosis; it exhibited immunopositivity for HMB-45, calponin and desmin and was negative for melan-A. The patient received neoadjuvant chemotherapy, debulking surgery and adjuvant chemotherapy. No evidence of recurrence or metastasis was apparent 8 months after surgery.

In 1994, Bonetti et al introduced the concept of a family of tumors that includes a clear cell sugar tumor (CCST) of the lung and angiomyolipoma (AML) of the kidney, and is characterized by the presence of a peculiar muscle cell that expresses different melanoma-associated antigens such as HMB45 and HMSA-1. In 1996, Zamboni et al described a case of a pancreatic tumor that consisted of "a population of large epithelioid cells with clear or eosinophilic, granular cytoplasm, rich in glycogen, with nuclear pleomorphism and no mitotic activity," and regarded it as a member of a new family of tumors named 'PEComas.' Cases of PEComa arising at various sites have been increasingly reported over the past decade, and it has now become a well-accepted entity. The World Health Organization defines PEComas as "mesenchymal tumors composed of histologically and immunohistochemically distinctive perivascular epithelioid cells," which include AML, CCST of the lung, lymphangioleiomyomatosis (LAM), clear cell myomelanocytic tumors of the fallopian ligament/ligament teres, and other unusual clear cell tumors at various locations. PEComas other than AML, CCST or LAM are rare mesenchymal tumors, and the uterus is the most commonly affected site. To the best of our knowledge, 44 cases of PEComa of the uterus have been reported in the English literature, of which 13 cases were malignant. We describe a case of malignant PEComa of the uterus.

CASE

Our patient was a 33-year-old previously healthy gravida 1 para 1 oriental woman who presented with menorrhagia and dysmenorrhea that had been ongoing for months. An ultrasound scan revealed a large tumor measuring 8.1×7.2×6.4 cm at the posterior wall of the uterine corpus. With a clinical diagnosis of leiomyoma, the patient first underwent laparoscopic tumor excision, and intraoperative histologic examination showed a uterine sarcoma and left retroperitoneal lymph node metastasis. An MRI after the first surgery showed an irregular infiltrative tumor measuring 10×8×6 cm on the posterior uterine wall and extending to the left paravertebral. The patient was given 3 courses of a combination neoadjuvant chemotherapy (C/T), including epirubicin, cisplatin and ifosfamide, after which the tumor exhibited relative shrinkage; she then underwent total hysterectomy, bilateral salpingo-oophorectomy (BSO), omentectomy, bilateral pelvic and para-aortic lymphadenectomy, and received another two courses of adjuvant chemotherapy including epirubicin, cisplatin and ifosfamide. No recurrence or distant metastasis was apparent 8 months after the operation.
The specimens obtained after surgery were fixed in 10% buffered formalin and processed for histologic examination by conventional methods. The sections were stained with hematoxylin and eosin stain. Immunohistochemical staining was carried out on paraffin sections with a panel of antibodies including calponin (Dako, clone: CALP), desmin (Dako, clone: D33), HMB-45 (Dako), melan-A (Dako, clone: A103), and CD10 (Thermo) using an autostaining system (Ventana Medical System, Tucson, Arizona). Clinical information was obtained from the medical records.

The first resected specimen consisted of several tumorous fragments measuring up to 6×4.5×4.5 cm in size. On cutting, sections were multilobular, gray, and elastic with central necrosis. The second resected specimen consisted of the uterus with bilateral adnexae, omentum, bilateral pelvic and para-aortic lymph nodes. The uterus measured 10×7×4.5 cm in size, and several infiltrative tumors in the myometrium measuring up to 1.7×1.5×1.5 cm in size were located in the lower segment of the posterior uterine wall. On cutting, sections were gray and elastic with necrosis. The bilateral adnexae were not remarkable.

The tumors from the two specimens revealed similar morphologic features; they showed multinodular growth of spindle to epithelioid cells with clear to eosinophilic cytoplasm and oval, hyperchromatic nuclei (Figure 1 and 2). The cytologic atypia was moderate to severe, and the tumor cells showed marked pleomorphism. Frequent large bizarre cells were present, and the foci of hemorrhage and necrosis were seen. The mitotic activity was 2/10 HPF, and lymphovascular permeation was seen. Immunohistochemical study demonstrated that the tumor cells were diffuse positive for calponin, desmin (Figure 3) and HMB-45 (Figure 4), and negative for melan-A and CD10.

**DISCUSSION**

PEC was first described in 1943 by Apitz in terms of the epithelioid feature in renal angiomyolipoma. It is characterized by an epithelioid appearance with a clear to granular cytoplasm, round to oval, centrally-located nuclei and a perivascular distribution. PEC can show any degree of atypia. Until recently, there has been no known normal counterpart of PEC. PEComa is now a widely-accepted type of neoplasm. Some authors still doubt the existence of this entity due to the overlapping morphologic and immunologic features with smooth muscle tumors and the absence of a normal counterpart for PEC; however, increasing genetic evidence has shown PEComa to be a distinct type of neoplasm.

About 10% of reported uterine PEComas have been...
related to the tuberous sclerosis complex (TSC), an autosomal dominant disease characterized by mental retardation, seizures and the development of tumors in multiple organs. However, our patient had no personal or family history of TSC.

Differential diagnoses of uterine PEComa include epithelioid leiomyosarcoma and endometrial stromal sarcoma (ESS). Epithelioid leiomyosarcoma and PEComa have many overlapping histologic features: both tumors are composed of spindle and/or epithelioid cells with variable stromal hyalinization; however, PEComa more often exhibits pale eosinophilic to clear cytoplasm, round to oval nuclei, and a prominent capillary network. Immunohistochemically, both tumors show variable reactivity for smooth muscle markers and melanocytic markers. Nearly all epithelioid smooth muscle tumors show immunoreactivity for smooth muscle actin, while 73% of PEComas show reactivity. All PEComas show immunoreactivity for at least one melanocytic marker, while only 56% of epithelioid smooth muscle tumors do.17 Epithelioid leiomyosarcoma typically shows focal and patchy reactivity for melanocytic markers, but this may also be seen in PEComa. The co-expression of smooth muscle markers and melanocytic markers in PEComas and smooth muscle tumors may imply that they have similar lines of differentiation. If a conventional smooth muscle tumor is encountered, one should not diagnose it as a PEComa owing to its melanocytic immunoreactivity. In our case, the tumor showed characteristic morphologic features of a PEComa, such as epithelioid cells with clear cytoplasm and oval nuclei, as well as immunohistochemical features. ESS may show irregular tongue-like nodular extensions into the myometrium, and the endometrium is usually involved; the tumor is typically composed of spindle to polygonal cells and shows reactivity for CD10. In our case the tumor did not resemble ESS, either histologically or immunohistochemically.

Due to the rarity of cases of PEComa, the criteria for the diagnosis of malignancy have not yet been fully established. The uterus is the most frequently affected organ, but only 13 cases showing malignant clinical features have been reported (Table 1). Folpe et al reported 26 cases of PEComa of soft tissue and gynecologic origin in 2005,6 and proposed provisional criteria that could be used to classify PEComa into “benign,” “of uncertain malignant potential,” and “malignant” categories. Benign tumors were classified as those that had no worrisome features (i.e., <5 cm, non-infiltrative, no-high nuclear grade and cellularity, mitotic rate ≤1/50 HPF, no necrosis or vascular invasion). Tumors of uncertain malignant potential were classified as having either nuclear pleomorphism/multinucleated giant cells only or being of a size >5 cm only, and those with two or more worrisome histologic features should be considered malignant. The application of these criteria to the uterus is still questionable, but it seems to be the most optimal classification for the moment. Our case had all the worrisome histologic features presented by Folpe. In 2008, Fadare reviewed 31 cases of previously reported uterine PEComas, and routine pathologic parameters were evaluated for the determination of malignant potential.18 The study concluded that the only features that indicate a definite potential for aggressive behavior are a mitotic count >1/10 HPF and/or coagulative necrosis, while cytologic atypia should be considered to be at least an indication of uncertain malignant potential. Although the size of the malignant and nonmalignant groups showed significant differences, using a size threshold to distinguish between them was not advised.

The management of PEComas is quite variable. Surgical excision is the most common approach for malignant uterine PEComa; some patients have also undergone R/T and/or C/T or even hormone therapy, but their effectiveness is still questionable. In our case, the patient received neoadjuvant C/T, but the effectiveness was not very significant. Three courses of adjuvant C/T were administered after surgery, and a longer follow-up time is needed in order to evaluate the effectiveness of the C/T. A therapeutic clinical trial for uterine PEComa is difficult to establish due to its rarity, but it appears that more and more cases have been reported since the turn of the century, and therefore a therapeutic trial may be able to be performed in the future.

We have reported herein the case of a uterine PEComa with both a malignant histologic picture and
# Table 1. Reported cases of uterine PEComa with malignant behavior.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>Symptoms</th>
<th>Management</th>
<th>Outcome</th>
<th>TSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonetti (2001)</td>
<td>19</td>
<td>Abdominal pain</td>
<td>Hysterectomy/ BSO/ pelvic and inguinal lymphadenopathy, vaginal cuff excision, adjuvant C/T and R/T</td>
<td>Lymph node metastases and vaginal extension at presentation; bone and lung metastases at 18 months; loss of follow-up</td>
<td>No</td>
</tr>
<tr>
<td>Bonetti (2001)</td>
<td>41</td>
<td>Abdominal mass</td>
<td>Hysterectomy/ BSO</td>
<td>Ovarian metastases at presentation; NED at 6 months</td>
<td>Yes</td>
</tr>
<tr>
<td>Dimmler (2003)</td>
<td>61</td>
<td>Abnormal uterine bleeding</td>
<td>Hysterectomy</td>
<td>Lung metastases at 7 years</td>
<td>No</td>
</tr>
<tr>
<td>Greene (2003)</td>
<td>79</td>
<td>Vague abdominal symptoms</td>
<td>Hysterectomy/ BSO, surgical debulking for recurrent tumor</td>
<td>Pelvic and colonic mesenteric recurrence at 2 years; DOD at several months later</td>
<td>No</td>
</tr>
<tr>
<td>Bosincu (2005)</td>
<td>59</td>
<td>Hemoperitoneum</td>
<td>Hysterectomy/ BSO, omentectomy</td>
<td>Pelvic recurrence at 6 months; DOD at 1 year</td>
<td>No</td>
</tr>
<tr>
<td>Bosincu (2005)</td>
<td>48</td>
<td>Abnormal uterine bleeding</td>
<td>GnRH analogues, hysterectomy, Tamoxifen therapy</td>
<td>NED at 36 months</td>
<td>No</td>
</tr>
<tr>
<td>Fukunaga (2005)</td>
<td>40</td>
<td>Abnormal uterine bleeding</td>
<td>Hysterectomy/BSO, omentectomy, adjuvant C/T and R/T</td>
<td>Ovarian and omental metastases at presentation, DOD at 16 months</td>
<td>No</td>
</tr>
<tr>
<td>Jeon (2005)</td>
<td>9</td>
<td>Abdominal pain and vaginal spotting</td>
<td>Neoadjuvant C/T, hysterectomy, lymphadenectomy, adjuvant C/T and R/T</td>
<td>Lymph node metastases at presentation, NED at 18 months</td>
<td>No</td>
</tr>
<tr>
<td>Folpe (2005)</td>
<td>59</td>
<td>NA</td>
<td>Adjuvant C/T</td>
<td>Liver and lung metastases at 30 months; alive with metastases at 30 months</td>
<td>No</td>
</tr>
<tr>
<td>Folpe (2005)</td>
<td>56</td>
<td>NA</td>
<td>Adjuvant C/T and R/T</td>
<td>Lung and bone metastases at 11 months; Alive with metastases at 11 months</td>
<td>No</td>
</tr>
<tr>
<td>Folpe (2005)</td>
<td>36</td>
<td>NA</td>
<td>Hysterectomy, adjuvant C/T</td>
<td>Lung metastases at 12 months; liver metastases at 36 months; DOD at 39 months</td>
<td>No</td>
</tr>
<tr>
<td>Liang (2007)</td>
<td>59</td>
<td>Abnormal uterine bleeding</td>
<td>Hysterectomy/BSO/Pelvic and para-aortic lymphadenectomy, omentectomy, appendectomy, hormonal therapy</td>
<td>Extension into endocervix at presentation; NED at 10 months</td>
<td>Yes</td>
</tr>
<tr>
<td>Armah (2007)</td>
<td>52</td>
<td>NA</td>
<td>Hysterectomy/BSO, resection of renal and pulmonary metastases</td>
<td>Renal and pulmonary metastases at 7 years; NED at 15 months after metastases</td>
<td>No</td>
</tr>
<tr>
<td>Present (2009)</td>
<td>33</td>
<td>Abnormal uterine bleeding</td>
<td>Partial tumor excision, neoadjuvant C/T; hysterectomy/ BSO/ omentectomy/ pelvic and para-aortic lymphadenectomy, adjuvant C/T</td>
<td>Lymph node metastases at presentation; NED at 8 months</td>
<td>No</td>
</tr>
</tbody>
</table>

R/T radiotherapy; C/T chemotherapy; BSO bilateral salpingo-oopherectomy; NED no evidence of disease; DOD dead of disease; NA not available
case report

clinically aggressive behavior. Immunohistochemical staining of HMB-45 should be performed on uterine epithelioid cell tumors with clear or pale eosinophilic cytoplasm in order to avoid misdiagnosis. The criteria for diagnosis of malignancy in the uterus have not fully been established due to the rarity of reported cases. We consider that all uterine PEComas should at least be regarded as tumors of uncertain malignant potential, and all patients diagnosed with uterine PEComa regardless of histologic features should receive long-term follow-up in order to determine the biological behavior of the tumor.

REFERENCES