Malignant perivascular epithelioid cell tumor (PEComa) of uterus: A case report with literature review

Joseph J. Noh 1, Sir-Yeon Hong 1, Byeong-gie Kim 1

1 Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 06351 Seoul, South Korea

Summary

Perivascular epithelioid cell tumor (PEComa) is a rare mesenchymal neoplasm involving various organs. Approximately 70 cases of gynecologic PEComas have been reported in the literature. Due to the paucity of cases, there is no definite treatment regimen established. We describe disease progression in a case of uterine PEComa with pulmonary metastasis in a 37-year-old woman who had been treated with surgery and various regimens of adjuvant treatment including vincristine, ifosfamide, cisplatin, sirolimus, doxorubicin, olaratumab, pazopanib and dacarbazine. Adequate management and prognosis still seem inconclusive and further case reports with randomized trials are needed to delineate the nature of this neoplasm.

Key words: Perivascular epithelioid cell tumor (PEComa); Uterus; Adjuvant chemotherapy; Vincristine; Sirolimus; Dacarbazine.

Introduction

Perivascular epithelioid cell tumor (PEComa) is one of the rarest mesenchymal neoplasms originating from the perivascular epithelioid cell line. These tumors have been reported in a variety of anatomic locations including the liver, kidneys, lungs, orbits, and uterus. According to Agaimy and Wunsch, about one-fourth of the PEComa cases reported in the literature occurred in the gynecologic tract [1]. Approximately 70 cases of gynecologic PEComas have been reported in the literature. Due to the paucity of cases, there have been many controversies over the adequate management and prognosis of this neoplasm. In the present report, we describe a case of uterine PEComa with multiple pulmonary metastasis in a 37-year-old woman that progressed despite treatment with surgery and various regimens of adjuvant chemotherapy.

Case report

A 37-year-old G0P0A0 woman with no past medical history was referred to our institution for adjuvant treatment for malignant perivascular epithelioid cell tumor (PEComa) with multiple pulmonary metastases. Before she was referred to our institution, she had already undergone total abdominal hysterectomy, left salpingo-oophorectomy, bilateral pelvic lymph node dissection, bilateral para-aortic lymph node dissection, total omentectomy, appendectomy, and right ovarian transposition. Initially she was planned to receive myomectomy under the presumed diagnosis of uterine leiomyoma, but frozen pathology during the operation could not exclude malignancy. Therefore she received the surgical procedures listed above. The initial mass was discovered incidentally by transvaginal ultrasound when she visited her health care provider for a gynecologic checkup. The abdominopelvic computed tomography (CT) taken before the operation revealed a 13.2 cm heterogeneous enhancing lobulated mass originating from the uterus (Figure 1). It contained necrotic lesions encapsulated inside and the mass seemed to adhere to the left pelvic wall and adjacent adnexal structures. No other abnormal findings were seen in the abdominal cavity. The cancer antigen 125 (CA-125) was elevated to 107.2 U/mL before the operation, while all other tumor markers including CA 19-9, tumor antigen-4 (TA-4), carcinoembryonic antigen (CEA), and alpha-fetoprotein (AFP) were within normal limits. The microscopic appearance of the removed tumor revealed a 15.0 × 9.7 × 8.3 cm inhomogeneous mass with hyper-vascularity that contained necrotic lesions inside. Hematoxylin and eosin (H & E) staining of the lesion revealed an infiltrative growth pattern of epithelioid cells with moderate nuclear pleomorphism and 10/10 high-power fields (HPF) mitotic activity. Lymphovascular invasion was absent. Strong positive immunostaining for HMB-45 (human melanoma black-45), SMA (smooth muscle actin), desmin, ER (estrogen receptors), and PR (progesterone receptors) were seen while negative immunostaining for CK (cytokeratin), CD10 (cluster of differentiation 10), p53, and hepatocyte antigen resulted (Figure 2). The resection margins were free of tumor. The final diagnosis of PEComa of the uterus was made. A chest CT was taken after the operation to examine potential metastasis that revealed multiple variable size masses in bilateral hemithoraces that were suggestive of metastatic lesions. The largest lesion measured 7.5 × 5.3 cm and was pushing the parenchyma outward. The patient was started on adjuvant chemotherapy with vincristine, ifosfamide, and cisplatin for six cycles at three week intervals. The tumor markers, including CA-125, that
were elevated prior to the operation decreased and stayed within the normal range throughout the cycles. After six cycles of the adjuvant chemotherapy, the chest CT revealed a marked decrease in the extent of pulmonary metastatic lesions (largest lesion measured 1.5 cm in diameter with an almost 80% reduction in size from the original metastatic lesion). However, since lesions still remained, three additional cycles of chemotherapeutic treatments were performed with the same regimen. After the third additional cycles of chemotherapy, the CT scans showed stable disease according to the RECIST (Response Evaluation Criteria in Solid Tumors) criteria (Figure 3). Therefore, no further chemotherapy was performed, and the patient was followed up in the outpatient clinic every three months thereafter. The pulmonary metastatic lesions remained the same in terms of size and number for the next 15 months. At 22 months after the initial surgical treatment, however, the chest CT showed progression of the largest lesion to 2.3 cm with an additional three newly-detected lesions. A gun biopsy was done at one of the new lesions and immunohistochemical staining was performed. Results revealed strong positivity in HMB-45, consistent with PEComa that was diagnosed earlier. The patient was started on 4 mg sirolimus daily for the next 8 months. Despite the treatment, the size of the tumor increased from 2.3 cm to 3.1 cm. We changed the regimen to doxorubicin and olaratumab, and she was treated for three cycles. However, the size of the tumor increased to 5.9 cm. The regimen was changed to 800 mg pazopanib daily for 7 months. Despite the treatment, the lesion progressed to 8.6 cm (Figure 4). She is now undergoing her second cycle of 250 mg dacarbazine. Due to the persistent progression of the disease after various regimens of treatment, a next-generation sequencing (NGS) cancer panel was performed, that revealed BRCA2, NOTCH1, IDH1, and APC mutations.

**Discussion**

In the present report, we describe a case of malignant PEComa that originated from the uterus with pulmonary metastasis. A good initial response to vincristine, ifosfamide and cisplatin was observed, but the tumor progressed 15 months after the treatment. The tumor grew persistently despite various other therapeutic attempts (Table 1).

The notion of PEComa was first introduced by Zamboni et al. to describe a family of soft-tissue tumors characterized by melanocytic and smooth muscle differentiation [2]. The distinctive feature of PEComa is the perivascular epithelioid cell, a mesenchymal cell type frequently seen adjacent to blood vessels. A number of additional types of tumors that exhibit similar morphologic and immunohistochemical phenotypes are grouped together in the so-called PEComa family. They include angiomylipoma, clear-cell sugar tumors of the lung, lymphangioleiomyomatosis, and unusual clear-cell tumors occurring in the kidney, pancreas, or liver among others [3]. PEComas have been described in a variety of anatomic locations, including the ovary, vulva and vagina [4], several visceral sites [5], soft tissues [6], and bones [7]. These tumors occur frequently in the gynecologic tract, including the uterine cervix, corpus, and vagina [8, 9]. Clinical presentation of gynecologic PEComa is nonspecific and a correct diagnosis is difficult to make. The vast majority of tumors arise in the uterine corpus, while the cervix is less frequently involved [10-12].

PEComas are generally benign tumors and usually do not recur after surgical resection. However, a subgroup of PEComas exhibit a malignant behavior, with either local recurrence or metastatic spread, most commonly to the lungs. Criteria to classify PEComa were recently proposed by Folpe et al. [8]. Six high-risk criteria were recognized: tumor size equal to or greater than 5 cm, infiltrative growth pattern, high nuclear grade cellularity, mitotic rate greater than 1/50 HPF, necrosis, and vascular invasion. Based on these criteria, three categories of PEComas were established – benign, uncertain malignant potential, and malignant. Benign is defined as tumors without features typically associated with malignancy. Tumors of uncertain malignant potential are defined as having only a single histological feature including nuclear pleomorphism, or multinucleated giant cells, or a size equal to or greater than 5 cm. Tumors are classified as malignant if they clearly show 2 or more of the atypical criteria mentioned above. There is a significant association between these criteria and consequential aggressive disease behavior. Despite the difficul-

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**Table 1. ** Various regimens of adjuvant treatment and their responses.

| Order | Regimens (dosage) | Duration | Response |
|-------|-------------------|----------|----------|
| 1     | Vincristine (75 mg/m²) | 7 months (9 cycles) | SD* (initial) |
|       | Ifosfamide (1200 mg/m²) |          | PD* (after 15 months) |
|       | Cisplatin (20 mg/m²) |          |          |
| 2     | Sirolimus (4 mg, daily) | 8 months | PD* |
| 3     | Doxorubicin (75 mg/m²) | 2.5 months (3 cycles) | PD* |
|       | Olaratumab (15 mg/kg) |          |          |
| 4     | Pazopanib (800 mg, daily) | 7 months | PD* |
| 5     | Dacarbazine (250 mg/m²) | Current regimen | To be determined |

*SD: stable disease; PD: progressive disease.
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Figure 1. — Abdominopelvic computed tomography (CT) axial view taken prior to operation. Heterogeneous enhancing lobulated mass originating from the uterus was measured at 13 cm.

Figure 2. — (A) The microscopic findings of the pulmonary metastatic lesion with hematoxylin and eosin staining showing infiltrative growth pattern of epithelioid cells with moderate nuclear pleomorphism and 10/10 high-power fields mitotic activity (Hematoxylin and eosin (HE), magnification ×400), (B) Strong positive immunostaining of the lesion with HMB-45 (HMB-45, magnification ×400).

dities in diagnosing PEComas clinically, they tend to manifest distinctive microscopic and immunohistochemical features. In a recent review conducted by Fadare et al., the following immunophenotype was found: HMB45 100% positive, SMA 73% positive, vimentin 56% positive, CD10 25% positive, and Melan-a 24% positive [10].

Due to the paucity of cases, no optimal management strategy for PEComas has been established yet. Primary surgical excision with the aim of negative margins remains the mainstay treatment in gynecological PEComas. In the literature, the vast majority of patients affected by uterine PEComas received a total hysterectomy with or without bilateral salpingo-oophorectomy [9]. Heterogeneous results were achieved with chemotherapy treatment. Different drugs have been used (dacarbazine, ifosfamide, doxorubicin, and vincristine), as well as different combinations of these [13-16]. Targeted therapies using the mechanistic target of rapamycin (mTOR) inhibitors seem to provide encouraging results. Several cases of treatment with mTOR inhibitors in advanced PEComa have been described in recent years [17-22]. In 10% of PEComa cases, genetic alterations in the tuberous sclerosis complex (TSC) (losses of 9q34 (TSC1) or 16q13.3 (TSC2)) have been reported [5]. These genetic alterations activate mTOR in
AMP-activated protein kinase and Ras/mitogen-activated protein kinase pathways, resulting in high mTOR activity [23]. This leads to a lack of regulation of cell proliferation, migration, and differentiation [24]. Therefore, inhibition of mTOR resulted in significant clinical activity in patients with PEComas. Absence of immunohistochemical evidence of TSC expression may be a predictive marker for responsiveness to inhibitors of mTOR [22]. However, this relationship should be explored further.

In conclusion, we report a case of malignant PEComa with pulmonary metastasis that showed a good initial response to vincristine, ifosfamide, and cisplatin but later progressed and showed unfavorable response to various regimens including mTOR inhibitor. Further cases should be reported to delineate the nature of this neoplasm and establish adequate treatment modality.

**Author Contributions**

The present study was designed, directed and coordinated by BG Kim, as the principal investigator. BG Kim provided conceptual and technical guidance for all aspects of the project. The literature search for pertinent information was performed by JN. The manuscript was written by JN and commented on by all authors. All the authors meet the recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals provided by the International Committee of Medical Journal Editors.

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**Conflict of interest**

The authors of this publication disclose that there are no relevant financial, personal, political, intellectual or religious interests to declare. The terms of this arrangement...
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Corresponding Author:
BYEONG-GIE KIM, M.D., Ph.D.
Department of Obstetrics and Gynecology, Samsung Medical Center Sungkyunkwan University School of Medicine 81, Irwon-ro, Gangnam-gu Seoul, South Korea
Email: bksong.kim@samsung.com