Malignant Perivascular Epithelioid Cell Tumor (PEComa) of the Uterus as Part of the Hereditary Cancer Syndrome: A Case Diagnosed with Multiple Malignancies

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ABSTRACT

A perivascular epithelioid cell tumor (PEComa) is an uncommon mesenchymal tumor composed of perivascular epithelioid cells. These tumor cells show variable immunoreactivity for both melanocytic and myogenic markers. Occurrence of PEComa has been reported at various anatomical sites, including the gynecological tract, uterus being the most common. Although most patients have sporadic PEComas, a subset may be associated with the inactivation of TSC1 or TSC2 genes and the occurrence of TFE3 gene fusions. However, a relationship between PEComas and other tumors is rare. We report a 41-year-old female patient with malignant PEComa who was admitted to the hospital with a complaint of vaginal bleeding. Because she had previously been diagnosed with colorectal and breast carcinomas at an early age, we performed a comprehensive genetic analysis to identify molecular alterations present in her background that unveiled multiple malignancy predispositions. Next-generation sequencing (NGS) analysis revealed two heterozygous germline pathogenic variants in the ATM and TP53 genes and a heterozygous variant of unknown significance (VUS) in the BRCA2 gene. The patient was diagnosed with the Li-Fraumeni Syndrome owing to the medical and family history and also the presentation of a pathogenic mutation of the TP53 gene. There are very few case reports in the literature describing PEComa in the Li-Fraumeni syndrome, and this is the first report of a uterine PEComa in a patient with Li-Fraumeni syndrome.

Keywords: PEComa, Uterine, Malignant, Breast carcinoma, Colorectal carcinoma

INTRODUCTION

Perivascular epithelioid cell tumor (PEComa) is a family of tumors originating from a distinct cell type that is called perivascular epithelioid cells. It has been reported at a wide variety of anatomical locations, including lungs, colon, skin, kidney, bladder, and pancreas, and is also rarely seen in the gynecological tract (1-3). The recent World Health Organization (WHO) tumor classification (2020) defines the perivascular epithelioid cell tumor as “a member of a family of mesenchymal neoplasms composed of perivascular epithelioid cells (PECs) that express melanocytic and smooth muscle markers” (2).

Most of the uterine PEComas show benign/uncertain malignant potential; however aggressive behavior has also been increasingly reported. Some authors have developed classifications based on some features of the tumor to predict outcome in these tumors (2,4-7,8). In 2005, Folpe et al. analyzed 26 PEComas of the soft tissue and gynecologic tract and suggested some criteria for the classification of these tumors as “benign,” “of uncertain malignant potential,” and “malignant” according to tumor size and histological findings (4). Schoolmeester et al. have analyzed 16 gynecologic PEComas and suggested a modified gynecologic-specific algorithm (5). They proposed making a diagnosis of malignant PEComa based on the presence of at least four of the following features: a size of ≥5 cm, high-grade atypia (excluding degenerative atypia), mitotic rate of > 1/50 HPFs, necrosis, and lymphovascular invasion. Additionally, they suggested reducing the number of categories from three to two categories, namely “benign/uncertain malignant potential” and “malignant.” Bennett et al. analyzed 32 uterine PEComas which constitute the largest series in the literature so far (7). They proposed that a threshold of three (as opposed to four) atypical features more properly classifies a PEComa as malignant. The two proposed algorithms for stratifying the behavior of uterine PEComas were included in the latest version of the WHO tumor classification of female genital tumors (2020) (2).

The tumor group of the PEComa family may be related to genetic alterations of the tuberous sclerosis complex (TSC), an autosomal dominant genetic disease due to loss of function mutations in the TSC1 (9q34) or TSC2 (16p13.3) genes, which play a role in the regulation of the Rheb/mTOR/p70S6K pathway (1,6,9). TFE3 and RAD51B gene rearrangements have been also described in a subset of PEComas (2,6,9,10). Because of the sharing of similar genetic features, including AKT, mTOR, and p70S6K signaling pathways, PEComas are a part of the TSC tumor group.

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genetic features, it is not surprising that tumors associated with TSC can be observed in patients with PEComa as well. However, occurrence of other carcinomas in patients with PEComa is rare. In this report, we describe histopathological and immunohistochemical features of malignant uterine PEComa in a patient who had an early-onset of multiple malignancies, and a family history of recurring cancers. We also performed comprehensive genetic analyses to identify genetic alterations leading to a predisposition to multiple types of cancer.

**CASE REPORT**

**Clinical Information**
A 41-year-old woman presented with a history of irregular vaginal bleeding for a period of twenty days. She was diagnosed with multiple cancers including metachronous bilateral breast cancer and colorectal cancer, at an early age. At 32 years of age, she was admitted to the hospital when she found a palpable painless mass in her left breast; she was diagnosed with an invasive carcinoma of no special type (ER positive/PR positive/HER2 negative). Afterwards, she underwent a left segmental mastectomy and was treated with chemotherapy and radiotherapy for 2 years. Three years later, at 35 years of age, she was admitted to the hospital with a complaint of rectal bleeding that had continued for a duration of 4 months. She was diagnosed with colorectal well-differentiated adenocarcinoma and underwent low anterior resection (pT2 N0). Furthermore, at 38 years of age, another mass was found on her right breast on the follow-up mammography; she was diagnosed with an invasive carcinoma of no special type (ER negative/PR negative/HER2 positive). She underwent a right segmental mastectomy and axillary dissection (pT1c N0).

During another follow-up examination, a uterine mass was determined at the corpus posterior and was thought to be leiomyoma on the transabdominal ultrasonography. Magnetic resonance imaging confirmed a 6.3 x 6 cm mass originating from the left side of the uterus and a nearly two-fold increase in the size of the mass compared to ten months prior. Due to the the rapid growth of the mass, she underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy.

**Histopathologic, Immunophenotypic, and Molecular Findings**
Macrosopically, the uterus was measured as 10 x 7.5 x 7.4 cm and there was a nodular, smooth-bordered, intramural mass arising from the left side of the uterine corpus. The dimensions of the mass were 5 x 4.8 x 4.5 cm. The cut surface of the mass was solid and gray-white in color, and several foci of hemorrhage and necrosis were present (Figure 1A). Microscopically, the mass had an expansile border and consisted of single, discohesive atypical epithelioid cells. Cellularity was moderate, and there was a trace amount

![Figure 1: Macroscopic appearance of tumor (A). Tumor was composed of discohesive atypical epithelioid cells with inclusion-like eosinophilic nucleoli (B, C), binucleated and multinucleated atypical cells (D). Tumor cells expressed HMB-45 (E) and Melan A (F).](image-url)
of intervening and focal hyalinized stroma which was rich in lymphocytes, plasma cells, and thin- and thick-walled blood vessels. Areas of necrosis constituted less than 50% of the tumor. The tumor cells had distinct atypical features characterized by a large size, pleomorphic shape, and an eosinophilic/pale granular cytoplasm with macronuclei. There were many binucleated and multinucleated tumor cells. Most tumor cells had large, inclusion-like eosinophilic nucleoli similar to melanoma cells. Some of the cells had large intranuclear pseudoinclusions (Figure 1B-D). The mitotic count was 15 mitoses/50 HPFs. Lymphovascular invasion was detected. There was a brown-black melanin pigment within the histiocytes.

Immunohistochemically, the tumor cells were focally positive for HMB-45 (HMB45, Ventana) (Figure 1E), Melan-A (A103, Ventana) (Figure 1F), TFE-3 (MRQ-37, Cell Marque), vimentin (V9, Ventana), SMA (1A4, Cell Marque), desmin (DE-R-11, Ventana), caldesmon (E89, CellMarque), CD-68 (Kp-1, Cell Marque), and progesterone receptor (1E2, Ventana). The tumor cells were negative for cytokeratin (AE1/AE3/PCK26, Ventana), S100 (Ventana), SOX-10 (SP267, Cell Marque), estrogen receptor (Sp1, Ventana), CD10 (EP195, BioSB), GATA-3 (L50-823, Cell Marque), CD61 (2F2, Cell Marque), CD117 (9.7, Ventana), CD45 (RP2/18, Ventana), and cyclin D1 (SP4, Ventana). The Ki67 (GM010, Genemed) index was 30%. The endometrium, cervix, both ovaries and fallopian tubes were tumor-free. However, multiple “p53 signature” foci were identified in both fimbrial epithelia (Figure 2A-C). The tumor was diagnosed as PEComa based on histopathological and immunohistochemical findings. The tumor was categorized as malignant due to its possessing all the atypical criteria according to WHO classification (2).

Because the patient had a diagnosis of early-onset bilateral breast cancer, colorectal cancer, and the presence of the “p53 signature” in the tubal fimbrial epithelium, genetic testing for germline BRCA1-BRCA2 mutations (BRCA MASTR Plus Dx; Multiplicom, Niel, Belgium) with a comprehensive hereditary cancer panel (Qiagen, Hilden, Germany) was performed. Next-Generation Sequencing (NGS) (Illumina, San Diego, CA, USA) analyses with Comprehensive Hereditary Genes Panel (including ABRAXAS1, AIP, APC, ATM, ATR, AXIN2, BAP1, BARD1, BLM, BMAP1, BRIP1, BUB1B, CDH1, CDK4, CDKN2A, CHEK2, CTNNAL1, EPCAM, FANCC, FLCN, GALNT12, GEN1, GPC3, GREM1, HOXB13, MEN1, MET, MLHI, MRE11, MSH2, MSH6, MUTYH, NBN, NTHL1, PALB2, PALLD, PIK3CA, PMS1, PMS2, POLD1, POLE, PRSS1, PTP1, PTEN, RAD50, RAD51B, RAD51C, RAD51D, RINT1, SDHB, SDHC, SDHD, SMAD4, SMARCA4, STK11, TP53, VHL, XRCC2, RET, TSC1, TSC2 genes) and germline Multiplex Ligation Probe Amplification (MLPA) analyses for both BRCA1 and BRCA2 genes were performed with patient’s blood. NGS analysis revealed 2 heterozygous germ-line pathogenic variants in the ATM (Figure 3A) and TP53 (Figure 3B) genes, and a heterozygous variant of unknown significance (VUS) in the BRCA2 gene (Figure 3C). The first variant was localized in the ATM, namely NM_000051.3(ATM):c.5979_5983delTAAAG (p.Ser1993ArgfsTer23) in exon 40, and the second one was localized in TP53, namely NM_001126112.2(TP53):c.700T>C (p.Tyr234His) in exon 7. BRCA2 gene analysis revealed NM_000059(BRCA2):c.9409A>T (p.Thr3137Ser) in the exon 25. Both ATM:c.5979_5983delTAAAG (p.Ser1993ArgfsTer23) (rs876606134, ClinVar Accession: RCV000219008.5) and NM_001126112.2(TP53):c.700T>C (p.Tyr234His) (rs864622237, RCV000492782.1) are known pathogenic variants for hereditary cancer syndromes (11,12). Germline pathogenic mutations of TSCI or TSC2 genes were not detected.

**Figure 2:** p53 signature of fimbrial epithelium of tuba uterina. Strong nuclear p53 staining in more than 12 cells of fimbrial epithelia at low power (A), and high power (B), and appearance of the same fimbrial epithelia at hematoxylin-eosin stained section (C).
Perivascular epithelioid cell tumors are rarely seen in gynecological organs, and the uterus is the most common site of involvement (2,6,13). Although most patients had sporadic PEComas, a subset of PEComas (~10%) may be seen within TSC. The most common genetic alterations in sporadic and hereditary PEComas demonstrate inactivation of the \( TSC2 \) (16p13.3) and \( TSC1 \) (9q34) genes. These genes are inactivated, and then subsequently activated by the mammalian target of the rapamycin (mTOR) pathway, providing a potential focus for targetable therapy (3,14). The gene rearrangement of the MIT/TFE family of transcription factors member \( TFE3 \) (chromosome Xp11.23) has been reported in a small minority of
PEComas, including SFPQ/PSF-TFE3 fusion and DVL2-TFE3 fusion (14,15). TFE3-related PEComas share similar histopathological features, such as epithelioid appearances, alveolar or nested growing patterns, and low nuclear atypia (5,6,15,16). RAD51B (14q24) translocation, related to RAD51B-RRAGB or RAD51B-OPHN1 gene fusions, was demonstrated in three uterine PEComa patients (10). Zhang et al. found the most frequent somatic mutations were demonstrated in three uterine PEComa patients (10).

Histopathological features, such as epithelioid appearances, fusion (14,15). TFE3-related PEComas share similar histopathological features, such as epithelioid appearances, alveolar or nested growing patterns, and low nuclear atypia (5,6,15,16). RAD51B (14q24) translocation, related to RAD51B-RRAGB or RAD51B-OPHN1 gene fusions, was demonstrated in three uterine PEComa patients (10). Our patient had all of the histopathological criteria of the modified gynecologic-specific algorithm and was reported as malignant PEComa. The patient had no TSC1/TSC2 and RAD51B mutations and no clinical TSC findings either. We detected focally TFE3 positivity as per the immunohistochemical protocol (an automatic protocol) that may reveal TFE3 translocation-associated PEComas. However, we did not confirm this by either FISH or RT-PCR. We found germline pathogenic mutations in ATM and TP53 genes and a variant of unknown significance in the BRCA2 gene, which is clarified by the multiple carcinogenesis background of the patient and indicated in hereditary cancer syndromes, particularly the Li-Fraumeni Syndrome.

The Li-Fraumeni Syndrome (LFS) is a hereditary cancer syndrome associated with germline pathogenic mutations of the TP53 tumor suppressor gene. A wide spectrum of tumors including soft tissue sarcomas, osteosarcomas, early-onset breast cancers, brain tumors, colon cancer, gastric cancer, leukemia, and adrenocortical carcinomas has been associated with this syndrome (20). Classical LFS is diagnosed when a patient has all of the following three criteria; a sarcoma diagnosed before 45 years of age, a first-degree relative with any cancer diagnosed before 45 years of age, a first- or second-degree relative with any cancer diagnosed before 45 years of age or a sarcoma diagnosed at any age (20,21). Tumors seen in the patient’s family members including premenopausal breast cancer, embryonal rhabdomyosarcoma, and tumors of the central nervous system are well-defined cancer types in LFS. Because our patient had all of these criteria in addition to a mutant TP53 gene, she was diagnosed with LFS. PEComas located in various sites have also been described in LFS/TP53 mutation carriers. Neofytou et al. described two synchronous primary PEComa of the liver and the right kidney in a 24-year-old patient with LFS (22). Galera López et al. reported a simultaneous diagnosis of PEComa of the liver in two siblings with an LFS (23). Butz et al. reported a malignant, metastatic PEComa of the thigh muscle harboring a novel TP53 germline splice mutation in an attenuated LFS patient (24). Our case is the first uterine PEComa with related LFS.

Biallelic germline mutations of the ATM gene are associated with the autosomal recessive ataxia-telangiectasia syndrome, characterized by cerebellar degeneration, telangiectasia, immunodeficiency, cancer susceptibility, and radiation sensitivity (25). Carriers of monoallelic pathogenic germline mutations of the ATM gene have also been related with varied tumor predisposition, particularly lymphomas and leukemia (26,27). Some tumors that are seen in the patient’s family may be associated with carrying an additional mutant ATM gene over the mutant TP53 gene. However, the patient does not have any neurological symptoms such as ataxia, dysarthria, and postural instability; or other symptoms of the ataxia-telangiectasia syndrome.

CONCLUSION

Uterine PEComas are very rare tumors and can be associated with syndromes, particularly TSC. Rarely, PEComas may be related to hereditary cancer syndromes other than TSC, and these patients may have other malignancies that have specific gene mutations such as TP53. It is important to make a true diagnosis of PEComa for the patient and to screen the family for possible cancers. With respect to family history, genetic analyses and counseling can be helpful for the family’s future assessments.

Conflict of Interest
The authors declare no conflict of interest.

Authorship Contributions
REFERENCES


