Case Report
Malignant perivascular epithelioid cell tumor (PEComa) of cervix with TFE3 gene rearrangement: a case report

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Abstract: In this study, we reported the first PEComa arising within the cervix with TFE3 gene rearrangement and aggressive biological behavior. Morphologically, the tumor showed infiltrative growth into the surrounding parenchyma. The majority of tumor cells were arrayed in sheets, alveolar structures, or nests separated by delicate fibrovascular septa. There was marked intratumoral hemorrhage, necrosis, and stromal calcifications. The tumor cells had abundant clear cytoplasm, focally containing finely granular dark brown pigment, morphologically considered to be melanin. Immunohistochemically, the tumor cells demonstrated moderately (2+) or strongly (3+) positive staining for TFE3, HMB45, and Melan A but negative for CKpan, SMA, S100, PAX8, and PAX2. The presence of Ki-67 protein demonstrated a moderate proliferation rate, with a few Ki-67-positive nuclei. Using a recently developed TFE3 split FISH assay, the presence of TFE3 rearrangement was demonstrated. All these clinicopathologic features are suggestive of TFE3-rearranged PEComas of the cervix. Our results both expand the known characteristics of primary cervix PEComas and add to the data regarding TFE3 rearrangement-associated PEComas.

Keywords: TFE3, translocation, rearrangement, perivascular epithelioid cell tumor, FISH, immunohistochemistry

Introduction

The perivascular epithelioid cell tumor (PEComa) family includes angiomyolipoma (AML) of the kidney and liver, clear cell sugar tumor of the lung (CCST), lymphangioleiomyomatosis (LAM), lymphangiomyoma, cutaneous clear cell myomelanocytic tumor, clear cell myomelanocytic tumor of the falciform ligament/ligamentum teres, sclerosing PEComas and a group of uncommon tumors (nonspecified PEComas) that arise in soft tissue, visceral organs, bone and skin [1-17].

Within the PEComa family, there is a strong association between AML and LAM and the tuberous sclerosis complex (TSC), an autosomal dominant genetic disease due to losses of TSC1 (9q34) or TSC2 (16p13.3) gene, which seems to have a role in the regulation of the rapamycin (mTOR) pathway [11, 14, 18]. The mTOR inhibitor sirolimus has demonstrated benefit in patients with metastatic PEComas [19].

Recently, a small subset of PEComas harboring gene fusions involving the TFE3 gene has been recognized, suggesting a role for TFE3 in the development of a subset of PEComa family tumors [20-25]. TFE3 is one of four members of the microphthalmia-associated transcription factor (MITF) family, which includes MITF, TFEB, TFEC and TFE3. Several distinct tumors associated with the overexpression of this gene family, including melanoma, clear cell sarcoma, alveolar soft part sarcoma and translocation-associated renal cell carcinomas have been considered as a member of the microphthalmia-associated transcription factor family of tumors [26-31].

The overall clinicopathologic features of this distinctive subgroup of PEComas remains poorly understood because of their extreme rarity. It
was difficult to predict their clinical behavior, and easy to be misdiagnosed or neglected as common PEComas. Herein we reported the first PEComa arising within the cervix with TFE3 gene rearrangement and aggressive biological behavior, and provided detailed clinical, histological, immunohistochemical, and molecular genetic features as well as follow-up data contributing to the number of cases reported in the literature.
Case report

Clinical history

A 34-year-old female with no significant past medical history was found abnormal vaginal bleeding 3 days. Vaginal ultrasound examination showed a 9 × 8 cm sized cervical mass. The mass resection was performed showing a 9.5 × 8.3 × 6 cm partly-encapsulated brownish-white tumor with multifocal hemorrhage areas. There was no familial history or clinical evidences of tuberous sclerosis. The tumor was found recurrence 2 months after operation and was partly resected. 5 months after the first operation, the patient was clinically suspicious for pelvic lymph nodes metastasis by imaging studies of abdomen, though she was alive.

Histopathological and immunohistochemical findings

Morphologically, the tumor showed infiltrative growth into the surrounding parenchyma. The majority of tumor cells were arrayed in sheets, alveolar structures, or nests separated by delicate fibrovascular septa. There was marked intratumoral hemorrhage, necrosis, and stromal calcifications. The tumor cells had abundant clear cytoplasm, focally containing finely granular dark brown pigment, morphologically considered to be melanin, and had uniform round nuclei with small visible nucleoli. Mitotic activity was occasionally observed (Figure 1A-C).

Immunoreaction was performed using the labelled streptavidin–biotin method and overnight incubation as previously described [32-33]. Immunohistochemically, the tumor cells demonstrated moderately (2+) or strongly (3+) positive staining for TFE3, HMB45, and Melan A but negative for CKpan, SMA, S100, PAX8, and PAX2. The presence of Ki-67 protein demonstrated a moderate proliferation rate, with a few Ki-67-positive nuclei (Figure 1D, 1E).

TFE3 FISH analysis

As previous study, a split FISH ('break-apart') assay with probes centromeric (Green 5-fluorescein dUTP) and telomeric (Red 5-ROX dUTP) for TFE3 was conducted to determine if a TFE3 gene rearrangement was present [34]. The normal result is a combination (green and red) signal, whereas TFE3 fusion results in a split signal. Signals were considered to be split when the green and red signals were separated by a distance >2 signal diameters. A positive result included 1 fused or closely approximated green-red signal pair (representing the uninvolved copy of the 6 chromosome) and an additional pair of split signals. A minimum of 100 tumor cell nuclei were examined under fluorescence microscopy at × 1000 magnification. Only nonoverlapping tumor nuclei were evaluated. Based on other commercially available break-apart FISH assays, a positive result was reported when >10% of the tumor nuclei showed the split-signal pattern [34]. The tumor showed an abnormal signal pattern consistent with both TFE3 translocation and X chromosome polysomy locus in 45% of the cells (Figure 1F).

Discussion

Recently, it has been recognized that a subset of PEComas harbor translocations involving TFE3. These tumors are often associated with some distinctive pathologic features such as relatively young patient age, lack of tuberous sclerosis, epithelioid cytology with predominant nested-alveolar architecture, overlapping significantly with that of other TFE3-associated tumors (alveolar soft part sarcoma and Xp11.2 translocation renal cell carcinoma), no expression of smooth muscle actin or desmin and strong TFE3 immunoreactivity that contrast to those of PEComas without TFE3 rearrangement. To our knowledge, only 9 molecularly confirmed cases have been described in the literature [20-25]. In this article, we report a case of malignant primary cervical PEComa with TFE3 gene translocation detected by FISH. The case seems to fit this subset characterization and is the first reported primary cervical PEComa with molecular confirmation of this genetic alteration.

With respect to the cervix, morphology of epithelioid cytology with clear cytoplasm and predominant nested-alveolar architecture may suggest several soft tissue tumors, such as epithelioid leiomyosarcoma, metastatic malignant melanoma, clear cell sarcoma, and alveolar soft part sarcoma. Epithelioid leiomyosarcoma typically show immunoreactivity to antibodies against muscle marker SMA and lack immunoreactivity for melanocytic markers HMB45 and
Melan A. Positive melanocytic markers in combination with epithelioid cytology could be suggestive of a metastatic malignant melanoma and clear cell sarcoma. However, PEComas less frequently express S-100, and this serves as an important differentiating marker. Alveolar soft part sarcoma possesses TFE3 rearrangement and characteristically shows positive immunostaining for TFE3 but does not show melanocytic differentiation.

TFE3 gene is one of four members of the microphthalmia-associated transcription factor (MITF) family, along with TFEB, TFEC, and MiTF, which is located at chromosome Xp11.2. This site is also initially notable for its involvement in Xp11.2 translocations renal cell carcinomas and alveolar soft part sarcoma [26-28]. The true pathogenic contribution of the TFE3 gene to PEComa tumors remains unclear, and it is difficult to predict the clinical behavior and obtain treatment experience of this subset, because of its rarity. In a previous study conducted by Agarni et al., as loss of heterozygosity for TSC2 appears to be absent, it has been suggested that treatment modalities that have begun to be investigated for PEComas not otherwise specified, such as mTORC1 inhibitors, may not be useful in TFE3-rearranged PEComas [24, 35].

The criteria currently used for the malignant classification of PEComas was first proposed by Folpe et al. and includes tumor size, infiltrative growth, nuclear grade, cellularity, necrosis, vascular invasion, and mitotic rate as important prognostic factors [8]. The tumor in this study including infiltrative growth, size >5 cm, and necrosis met the criteria for malignant behavior and unfortunately pursued an aggressive course resulting in the tumor recurrence and pelvic lymph nodes metastasis. Our findings with an increasing number of TFE3 rearrangement-associated PEComas demonstrating poor prognoses indicate that they also sometimes pursue an aggressive course [24]. Whether or not this malignant classification system should fit TFE3 rearrangement-associated PEComas remains an open question, requiring further investigation of a larger number of cases.

In summary, we report on the first case of PEComa arising from the cervix associated with a TFE3 gene break visible by FISH. The significance of TFE3 gene rearrangement remains unclear, although this may represent a unique subset of PEComas with a distinctly biological course. These findings add to the data regarding TFE3 rearrangement-associated PEComas.

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Disclosure of conflict of interest
None.

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TFE3 rearrangement-associated PEComas


