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***TFE3* Translocation Associated Perivascular Epithelioid Cell Neoplasm (PEComa) of the Gynecologic Tract: Morphology, Immunophenotype, Differential Diagnosis**

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Abstract

TFE3 translocation associated PEComa is a distinct form of perivascular epithelioid cell neoplasm, the features of which are poorly defined owing to their general infrequency and limited prior reports with confirmed rearrangement or fusion totaling nine cases. Recent investigation has found a lack of *TSC* gene mutation in these tumors compared to their nonrearranged counterparts which underscores the importance of recognizing the translocated variant due to hypothetical ineffectiveness of targeted mTOR inhibitor therapy. Six cases were identified and *TFE3* rearrangement was confirmed by FISH. Patient age ranged 46 to 66 years (median 50) and none had a history of tuberous sclerosis complex. Three cases arose in the uterine corpus, one in the vagina, and one pelvic tumor and one pulmonary tumor were likely a recurrence/metastasis from a probable uterine primary. Five cases had purely clear cell epithelioid morphology that showed a spectrum of atypia while one case had a mixture of clear cell epithelioid and spindle cells. A mostly consistent immunophenotype was observed in the purely clear cell epithelioid cases: each demonstrated diffuse *TFE3*, HMB45, CathepsinK labeling, either focal or no melanA staining and variably weak reactivity to smooth muscle markers. The mixed clear cell epithelioid and spindle cell case had a similar pattern in its epithelioid component, but strong muscle marker positivity in its spindle cell component. Follow up ranged 1 to 57 months. Three cases demonstrated aggressive behavior and three cases had no evidence of recurrence. Both GYN-specific and traditional sets of criteria for malignancy were evaluated. The GYN model showed improved inclusion and specificity in comparison to the traditional model.

Introduction

Advances in both light microscopic and molecular genetic studies have shown that a distinct subset of PEComa carry gene rearrangements involving *TFE3* or transcription factor E3, a member of the MiTF-TFE family of transcription factors that assist in development of cells such as melanocytes(1, 2). These tumors appear to have a unique morphology and specific

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immunophenotype when compared to their conventional (non-rearranged) counterparts(1, 3-7). They typically are composed of purely clear cell epithelioid cells with an alveolar architecture, mostly clear cytoplasm, round nuclei and label strongly for TFE3 and HMB45 while minimally expressing muscle markers. Yet, a single reported *TFE3* rearranged case has deviated from this pattern: it involved the urinary bladder of a 55 year old woman and showed not just a biphasic pattern of clear cell epithelioid and spindle cells, but also diffuse positivity for smooth muscle actin and MiTF(6). An explanation for this unusual case was a site-specific phenomenon or variations in the mechanism of gene fusion.

Conventional PEComa of either the sporadic or syndromic type frequently harbor mutation and loss of heterozygosity (LOH) of *TSC2* and much more rarely, *TSC1*. One investigation(8) found LOH involving the *TSC2* locus in nearly two-thirds of their cases and LOH of *TSC1* in only one case. The significance of LOH at *TSC1/2* is the subsequent upregulation of mTOR signaling which is the basis of mTORC1 targeted therapy that is often utilized in PEComa treatment. Recently, *TFE3* rearranged tumors were shown to lack *TSC2* inactivating mutations(9). These findings have theoretically critical treatment implications, particularly for the efficacy of targeted mTOR inhibitors since hypothetical benefit from this therapy is likely minimized. Therefore, recognition of the rearranged variant of PEComa may assist in important decisions for clinical management.

To date, reports of confirmed (either by FISH or RT-PCR) *TFE3* rearranged PEComa are few with only nine cases(1, 3-7). The clinicopathologic findings in these cases suggest a mostly consistent morphology and immunoprofile, a disposition toward younger age and no association with tuberous sclerosis complex. To better define the characteristics of *TFE3* rearranged PEComa, we identified six cases originating in the gynecologic tract from our combined institutional archives, the largest series to date. We evaluated their morphologic and immunohistochemical features, discuss differentiating these tumors from relevant morphologic mimics, compared recently proposed gynecologic tract-specific prognostic criteria(10) to previous criteria(11), suggest a classification scheme for more consistent diagnosis and reporting and review the literature's cases of translocation associated PEComa occurring in any organ.

Materials and Methods

Case Identification

The archives of Mayo Clinic's Department of Laboratory Medicine and Pathology and Memorial Sloan Kettering Cancer Center's Department of Pathology were searched for cases matching keywords "PEComa" or "perivascular epithelioid cell neoplasm" arising in any site of the gynecologic tract. From this cohort, a case was retrieved for review if mention was made of uniform TFE3 immunoexpression, extensive clear cell epithelioid morphology, HMB45 diffuse positivity or negative reactivity to smooth muscle markers such as smooth muscle actin, desmin or h-caldesmon in the diagnostic report. Six cases with at least one of the aforementioned features were identified in total from both institutions. All available H&E slides were examined. Formalin-fixed paraffin-embedded tissue blocks were used for IHC and FISH studies. Clinical history, gross pathologic features and patient follow up were obtained from institutional records or referring physicians.

Morphology

Each case was assessed for several morphologic features: pattern of invasion (infiltrative or carcinoma-like; permeative or endometrial stromal sarcoma-like; pushing or invasion along a broad front), growth pattern, degree of cytologic atypia (determined as low or high grade), lymphovascular invasion, necrosis, multinucleated tumor cells, melanin-containing cells, mitotic figures per 10 high power fields (hpf) and per 50 hpf.

Immunohistochemistry

IHC was performed using an antibody panel consisting of TFE3 (clone MRQ-37; no dilution; Ventana Medical Systems, Tucson, AZ), HMB45 (clone HMB45; no dilution; Ventana), A103/MelanA (clone A103; no dilution; Ventana), SOX10 (polyclonal; 1:50 dilution; Cell Marque, Rocklin, CA), microphthalmia transcription factor (MITF) (clone D5; 1:50 dilution; Dako, Carpinteria, CA), cathepsinK (clone 3F9; dilution 1:500; Abcam, Cambridge, MA), smooth muscle actin (SMA) (clone alpha-sm-1; 1:50 dilution; Vector Laboratories, Burlingame, CA), desmin (clone DE-R-11; no dilution; Ventana), h-caldesmon (clone E89; no dilution; Ventana). The Optiview or iView detection system (Ventana) was utilized for all antibodies with positive and negative controls as necessary.

Tumor cell immunoreactivity was semiquantitatively graded: 0 (negative); 1+ (1-25%); 2+ (26-50%); 3+ (51-75%); 4+ (>75%). Tumor cell immunoreactivity was also semiquantitatively graded as weak (W) or strong (S). For calculation of IHC totals, a minimum score of 1+ with weak or strong staining was considered positive with the exception of TFE3 which a 4+ and strong pattern was expected for a correlative *TFE3* rearrangement.

Fluorescence in situ hybridization

Fluorescence in situ hybridization was performed on paraffin embedded tissue sectioned at 4 microns. Custom laboratory developed probes designed to flank *TFE3* were applied to interphase nuclei utilizing custom bacterial artificial chromosomes (BAC) from the BACPAC Resources Center at Children's Hospital Oakland Research Institute (Oakland, CA). *TFE3* hybridization set consisted of red 5' centromeric and green 3' telomeric probes as well as an aqua X centromere probe. A pattern of 2 yellow and 2 aqua signals indicative of normal or intact *TFE3* present on both X chromosomes. Balanced break apart of *TFE3* showed spatially split red and green signals resulting in a 1 red, 1 green, 1 fusion and 2 aqua ratio per nucleus. A case was scored as positive if at least 10% of 100 scored nuclei showed a split signal pattern.

Results

Clinical Findings and Patient Outcomes

Clinical features are summarized in Table 1. The six patients ranged in age from 46 to 66 years (median 50). Three patients presented for clinical evaluation secondary to symptoms related to a uterine or pelvic mass. Two patients had their lesion discovered incidentally either by radiologic screening for an unrelated neoplasm or by microscopic assessment of a hysterectomy performed for symptomatic leiomyomata. The remaining patient developed

hemoptysis as a consequence of an endobronchial mass. None had a history of tuberous sclerosis complex (TSC) and one patient had previously been treated by systemic chemotherapy for Hodgkin lymphoma six years preceding her PEComa diagnosis. Notably, two patients had undergone hysterectomy for symptomatic leiomyomata, both of which resulted in recurrence or metastasis. Three cases occurred in the uterine corpus, one in the vagina, one recurred in the pelvis from what was likely a consequence of pelvic seeding from uterine morcellation for leiomyomata and the one removed from the lung was a probable metastasis from a lesion in her hysterectomy performed for leiomyomata given that this patient had no other oncologic history. The size of each tumor was highly variable ranging from 1 to 17 cm (mean 6.5, median 3.3). Treatment depended on the site and size of the lesion. Total or eventual completion hysterectomy was required to achieve a negative margin for all corporeal tumors. Local excision resulted in positive margins for the vaginal primary. Likewise, in case 4, local resection of the pelvic mass was performed in addition to surgical staging. No patient had distant disease at time of surgical intervention. However, recurrence or metastasis developed in three patients: one had regional recurrence involving the urinary bladder that was excised, another had a single metastasis to the lung removed by wedge resection and the last patient had regional recurrence involving the cervix and metastases involving the omentum two months after her supracervical hysterectomy followed 11 months later by adjuvant chemotherapy for extensive abdominopelvic disease which was debulked. Importantly, this patient had a prior diagnosis of high grade leiomyosarcoma until her intraabdominal tumor showed features of PEComa. All available prior material was reviewed and the morphology of each lesion was similar. Her adjuvant chemotherapy regimen was then switched from platinum based to mTOR targeted therapy. Follow up was available for all of the remaining five patients (case 6 was a recent case) and ranged 1 to 57 months (mean 23, median 17). Every patient was alive without evidence of disease at their latest clinical examination.

Morphologic Features

Purely Clear Cell Epithelioid Morphology, Cases 1-5—Morphology findings are summarized in Table 2. These five tumors showed entirely clear cell epithelioid morphology and a spectrum of cytologic features (Figs. 1, 2). All cases demonstrated some form of invasion, whether permeative, infiltrative or pushing, into surrounding myometrium or vaginal soft tissue and a combination of invasion patterns was seen in some tumors. A nested growth pattern defined as a clustered or alveolus-like collection of cells partially encircled by either a thin-walled vessel and/or delicate collagenous stroma was maintained in every case (Figs. 1A-F). Diffuse, sheet-like growth was present in one tumor aside from other areas having the more usual nested appearance (Fig. 1F). There was variability in the degree of nuclear atypia. Low grade atypia was observed in three cases and consisted of a uniform population of cells with well defined and thin cell membranes, predominantly clear cytoplasm with some eosinophilic granularity, consistently round to somewhat ovoid nuclear shape and a prominent small or medium single nucleolus (Figs. 1B,C,D). High grade atypia was noted in two cases and manifested as a range of cells with pleomorphism to frank anaplasia that maintained round nuclear membrane contours, clustered coarse chromatin and large or multiple nucleoli (Figs. 1E,F). Dense to granular eosinophilic cytoplasm was present in these two cases along with the typical clear cytoplasm. Both lymphovascular

invasion and necrosis were observed in four cases. Multinucleated tumor cells were seen in every case and their atypia correlated with nuclear atypia of the main neoplastic cells. Melanin-containing cells were found in two cases and comprised approximately 1% of the total cell volume (Fig. 1B). These cells showed accumulation of abundant intracytoplasmic melanin pigment and were intermixed and scattered throughout the tumor. Mitotic activity was present in five cases, mostly as low indices of 1-3/10hpf or 2-5/50 hpf, but one case showed numerous figures up to 14/10 hpf or 66/50 hpf.

Mixed Clear Cell Epithelioid and Spindle Cell Morphology, Case 6—This case showed a mixed appearance consisting of spindle cells and epithelioid cells (Figs. 1G,H). The spindle cell form predominated as an estimated 70% of the tumor while the epithelioid form was about 30%. The clear cell epithelioid cells were nearly identical to those in the purely epithelioid group with clear or somewhat eosinophilic cytoplasm, mostly uniform nuclear atypia and a small to medium nucleolus. The spindle cell component had a fascicular growth consisting of cells with moderate amounts of eosinophilic to clear granular cytoplasm, hyperchromatic, enlarged nuclei with occasionally prominent nucleoli. While thin-walled vessels were seen in the spindled portion, the cells were not encircled by them to impart a nested or alveolar architecture found in their epithelioid counterpart. Mitotic activity was 1/10 hpf and 2/50 hpf. Multinucleated tumor cells, necrosis or melanin-containing cells were not identified.

Immunophenotypic Profile

Purely Clear Cell Epithelioid Morphology, Cases 1-5—Immunohistochemical features are summarized in Table 3. A strikingly mostly consistent immunophenotype was seen in all five cases. HMB45 and cathepsinK were strongly and diffusely expressed in every case (Figs. 1J,K). Nuclear TFE3 was equally strong and diffuse in four cases (Fig. 1I), but the one case with pleomorphic features (case 2) showed a weaker, but diffuse, pattern. MelanA was positive in a subset of cells in two tumors while the other three tumors were negative. MiTF and SOX10 were negative. Muscle marker expression was essentially absent with the exception of one case showing desmin labeling very focally.

Mixed Clear Cell Epithelioid and Spindle Cell Morphology, Case 6—The immunophenotype in this case differed from its purely epithelioid counterparts except for its robust, uniform expression of TFE3. While strong positivity for HMB45 was seen, it was confined to the epithelioid cell component. Similarly, melanA and MiTF were positive, strongly, but focally, in the epithelioid cell component. Both the epithelioid and spindle cell portions showed diffuse labeling by h-caldesmon with strong and focal expression of SMA in the spindle cells. Desmin and SOX10 were entirely negative.

TFE3 Fluorescence In Situ Hybridization Findings

FISH identified balanced *TFE3* rearrangement in all six cases (Fig. 1L).

Discussion

In 2002, Vang and Kempson published a foundational study of gynecologic PEComa(12). In it, they examined a series of eight cases of uterine PEComa to more fully define the clinical, morphologic and immunohistochemical findings of these tumors and to refine features that improve recognition from smooth muscle tumors (SMT). One observation was that a subset of PEComa was purely epithelioid with a fairly uniform cytologic appearance, had strong expression of HMB45 while negative or focal positivity for melanA and muscle markers — all in keeping with the *TFE3* rearranged variant — while the remaining cases showed a combination of epithelioid and spindle cells with focal or scattered expression of HMB45 and strong positivity for muscle markers — all mostly in keeping with the conventional variant. The inconsistency in this histologic-genetic correlation is the recently described mixed epithelioid and spindle cell *TFE3* rearranged tumors. To date, only a single prior case has been reported(6). Its IHC reactivity showed strong and diffuse expression of HMB45 in the epithelioid component, as expected for a rearranged tumor, but then had unexpectedly diffuse and strong SMA in the spindle cell portion in addition to diffuse and strong MiTF in the epithelioid portion. Aside from this example, such an IHC profile has not been described in any other case with a confirmed rearrangement (Table 4). However, there is still a clear constant pattern of morphology and IHC in the several forms of gynecologic PEComa that correlate very well with the presence of rearrangement and, importantly, probable lack of underlying *TSC1* or *TSC2* mutation. Our series of six *TFE3* rearranged cases, five which are purely clear cell epithelioid with a range of cytologic atypia and one which is mixed clear cell epithelioid and spindle cell, exhibits a possible complete spectrum of these tumors.

Review of literature's cases of confirmed *TFE3* rearranged PEComa of any organ(1, 3-7) (Table 4) indicate that these neoplasms have an extreme predisposition to women (all nine examples have occurred in women), no association with tuberous sclerosis complex and a wide age spectrum (9 to 57 years, median 32). Our findings for gynecologic tumors are essentially identical. All six women had no history of tuberous sclerosis complex, but their age tended to be older (46 to 56 years, median 50). So far, including the present series, the number of cases in the gynecologic tract are six in the uterine corpus, one in the ovary and one in the vagina. However, this tally includes two patients in our series without an established diagnosis of gynecologic PEComa who underwent hysterectomy for symptomatic leiomyomata and had no other oncologic history. We believe this is explained by either a sampling issue, misrecognition or in the one case of uterine morcellation, seeding of the pelvic cavity. Additional support for these explanations is exemplified by the sometimes small size of these tumors. The smallest in our series was 1 cm and the next two smallest were 3 cm and 3.3 cm. Gross size is just one of several important criteria recommended for evaluating a tumor for malignant potential.

Recently, gynecologic organ-specific criteria for malignancy were proposed(10) and were shown more inclusive and specific than conventional criteria(11). Each system is outlined in Tables 5 and 6. The difference in the GYN model, which was developed after extensively assessing the pathologic features in 16 tumors of the female genital tract, is exclusion of invasion as a criterion (since it did not prove statistically significant in the prior analysis), increased threshold for a diagnosis of malignant PEComa (from 2 features to 4) and revision

of “uncertain malignant potential” that was based on identifying either nuclear pleomorphism or multinucleated giant cells or a gross size greater than 5 cm and instead using this label for tumors that do not meet criteria for malignant (or have 1-3 features). Both sets of criteria were applied to the present series and an identical outcome of improved inclusion and specificity were seen when using the GYN model. Particularly, GYN-specific criteria correctly identified all cases that had shown aggressive behavior as malignant and labeling those without such an outcome as of uncertain malignant potential or benign. While the conventional method also appropriately flagged the three malignant tumors in this series, it incorrectly classified two cases as malignant that have not shown any clinical evidence of recurrence. Further, one case could not be categorized as any prognostic type because it showed only one feature which was not listed in the uncertain malignant potential grouping, hence the problem with inclusion. We believe our comparison of criteria systems demonstrates clear improvement in classification by using GYN-specific criteria when evaluating any type of PEComa arising in the female genital tract. To date, after merging the literature's cases of *TFE3* PEComa of any site and this series of gynecologic *TFE3* PEComa, four of fifteen cases have shown aggressive behavior (Table 4). Properly diagnosing patients and offering the most accurate prognostic assessment of their tumor is obviously of tremendous clinic value.

Accurate diagnosis of PEComa is more challenging in the female genital organs owing to its morphologic and immunohistochemical overlap with SMTs and other clear cell tumors. A definition of PEComa was recently proposed to aid in making this diagnosis(10): in the appropriate cytologic context, demonstrating expression of two markers such as HMB45, melanA or CathepsinK in addition to smooth muscle positivity. The utility of this definition comes in its recommendation of finding convincing positive staining for two melanocytic stains in the context of a sometimes morphologically ambiguous spindle cell tumor (HMB45 and melanA are among the most tested stains followed by CathepsinK with some reports observing tyrosinase labeling although experience with this latter marker is limited(6)). Demonstrating at least strong focal staining by two markers provides convincing evidence that the lesion in question is best regarded as PEComa since SMTs have been shown to label with HMB45(13), but not melanA(10). Further, in the differential diagnosis of either PEComa or SMT, in most cases smooth muscle positivity is expected, and, therefore, IHC for this component is often omitted in our routine workup. We recommend a three stain panel for this differential consisting of HMB45, melanA and TFE3. The pattern of these stains will discern all forms of PEComa and SMT accordingly: 1. *TFE3* rearranged clear cell epithelioid PEComa shows a profile of marked and diffuse HMB45 and TFE3 expression and focal or negative melanA expression; 2. *TFE3* Rearranged mixed clear cell epithelioid and spindle cell PEComa shows a profile of marked expression of HMB45, melanA and TFE3 in its epithelioid cells; 3. Conventional, non-rearranged PEComa shows a profile of patchy or focal expression of HMB45 and melanA and weak/negative expression of TFE3; 4. SMTs show a profile of patchy or negative HMB45 expression, negative melanA expression and weak/negative TFE3. Gynecologic PEComa may be organized according to morphologic findings, but we believe IHC is a useful and reliable adjunct to support its diagnosis. The distinct immunophenotype of each form of PEComa permits a simplified approach to diagnosis and we believe inherently structures a classification that provides

more reproducibility in diagnosis as well as in reporting (Fig. 2). It is important to recognize that the TFE3 protein is ubiquitously present at low levels and weak labeling of this immunohistochemical stain is normal and not indicative of underlying rearrangement(14). To this end, accurately assessing TFE3 immunoexpression can be difficult owing to significant differences in technique and staining platforms(14). We recommend the use of *TFE3* FISH in cases with equivocal qualitative (weak to moderate rather than strong and robust) or less than expected quantitative (<90% of tumor cells) labeling in tumors otherwise morphologically and immunohistochemically appropriate for *TFE3* PEComa. This same panel distinguishes translocation associated PEComa from gynecologic clear cell morphologic mimics such as clear cell carcinoma and alveolar soft part sarcoma. Clear cell carcinoma shows no expression of TFE3, melanA or HMB45. Alveolar soft part sarcoma, while diffusely and strong positive for TFE3, is negative for HMB45 and melanA and harbors a unique *ASPL-TFE3* translocation which has not been observed in any tested case of rearranged PEComa to date.

Conventional PEComa displays a range of classic features of the perivascular epithelioid cell: clear to granular eosinophilic cytoplasm, round to ovoid nucleus, a prominent nucleolus, that clusters into nests or spindle into fascicles in differing proportions. The histologic features of this subtype are well described in prior reports(10, 12, 15). Translocation associated PEComa in gynecologic organs is currently recognized as involving the *TFE3* gene. What is expected for a *TFE3* gynecologic tumor is the more frequent pattern of nests or sheets of uniform epithelioid cells with mostly clear to slightly granular eosinophilic cytoplasm, small or large round or ovoid nucleus surrounding by a smooth nuclear membrane containing a single prominent nucleolus. Variations of this morphology include the pleomorphic and mixed clear cell epithelioid and spindle cell forms, both of which are unusual manifestations of a tumor with an underlying rearrangement because rearranged neoplasms tend to show consistency in their appearance(1, 16). As such, PEComa is not the only tumor with *TFE3* rearrangement. Alveolar soft part sarcoma (unbalanced *ASPL-TFE3*)(17, 18), Xp11.2 renal cell carcinoma (balanced *TFE3-ASPL* among other fusion partner genes *PRCC*, *PSF*, *CLTC*, *NONO*)(19) and melanotic Xp11 neoplasm (*TFE3* rearrangement with one case reported partnering with *PSF*)(20, 21) resemble *TFE3* PEComa in both their alveolar or nested architecture and clear or eosinophilic cytology while the most recent member of the *TFE3* tumor family, a subset of epithelioid hemangioendothelioma (*YAPI-TFE3*)(22), has entirely divergent features related to its vascular phenotype. Accordingly, it is likely that the mixed clear cell epithelioid and spindle cell and pleomorphic forms of these tumors are explained either by *TFE3* fusing with different partners or undergoing breakage at different points along the gene.

Currently, a single case of translocated PEComa has demonstrated *TFE3* partnering with *PSF*(7). Subsequent evaluation by Argani et al(1) did not find *PSF-TFE3* in two tested rearranged PEComa cases. Interestingly, *PSF-TFE3* is the same fusion found in one case of melanotic Xp11 neoplasm(21), a tumor with very similar morphology and often identical immunophenotype (the sole exception being patchy HMB45 in some cases rather than diffuse labeling) to *TFE3* rearranged PEComa(20, 21, 23). We identified scattered melanin-containing cells in two of our cases, but they comprised no greater than 1% the total cell volume which contrasts their widespread distribution in melanotic Xp11 neoplasm. The

significance, if any, of this histologic overlap is not yet known and may simply be a manifestation of their melanosomic nature.

Lastly, although some investigators may call into question the validity of assigning the name “PEComa” to these translocation associated tumors, particularly due to their infrequent muscle marker expression, we believe it appropriate within the constraints of a morphologic and immunohistochemical study. It is increasingly recognized that the concept of PEComa as a “myomelanocytic tumor” has evolved to include a family of mesenchymal tumors, each with its range of clinical associations, morphology, immunophenotype and genetic aberrations. The melanocytic properties of *TFE3* translocated tumors are evident by their robust expression of melanosomic antibodies, HMB45 and tyrosinase (although experience with tyrosinase is limited) and sometimes focal expression of melanA. Even though muscle marker labeling by SMA, desmin or hcaldesmon is uncommon, it is not negative and may possibly be underreported because of its focality. Some investigators have even proposed that demonstration of smooth muscle differentiation by immunohistochemistry isn't necessary which is reflected in the definition found in the recent WHO classification of soft tissue(24) as well as our omission of muscle markers in personal diagnostic workup.

In sum, we present the clinicopathologic findings of six cases of translocated associated PEComa, *TFE3* variant, arising in gynecologic organs. These tumors often have a distinct appearance and immunohistochemical features which allow for their separation from conventional PEComa. Identification of translocation associated PEComa may offer important clinical insight into behavioral potential and use of targeted therapeutic modalities. More, recently proposed GYN-specific prognostic criteria are more specific and inclusive than traditional criteria when evaluating either rearranged or conventional PEComa in the female genital tract.

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Figure 1.

TFE3 translocation associated PEComa typically shows a nested or alveolar architecture supported by thin-walled vascular spaces, but has a spectrum of cytologic appearance. *TFE3* rearranged tumors may show the typical PEC morphology of a cell with clear to granular eosinophilic cytoplasm, round to ovoid nucleus, prominent nucleolus (A, 200×). These neoplasms tend to have a uniform appearance and scattered melanin-containing cells are sometimes seen (B, 400×). Infiltration is routinely identified, in this case into myometrium (C, 200×) although the cells have low grade features and are associated with equally low grade appearing multinucleated tumor cells. Some tumors demonstrate extensively clear cytology (D, 200×). High grade features are seen in this case: nuclear enlargement, coarse chromatin and conspicuous nucleoli, but the cells maintain their nested pattern and have correspondingly high grade multinucleated tumor cells (E, 400×). Sheet-like growth and

considerable pleomorphism may be found in some cases. A helpful feature for assessing grade is the degree of atypia present in the multinucleated tumor cells (F, 200×). The mixed clear cell epithelioid and spindle cell rearranged case showed features of purely epithelioid tumors (G, 400×), but also had distinct areas of spindling and fascicular architecture (H, 400×). The expected immunophenotype of *TFE3* translocation associated PEComa is strong and diffuse TFE3 (I, 200×), HMB45 (J, 200×) and CathepsinK (K, 200×). *TFE3* FISH consisted of red 5' centromeric and green 3' telomeric probes as well as an aqua X centromere probe. A pattern of 2 yellow and 2 aqua signals indicative of normal or intact *TFE3* present on both X chromosomes. Balanced break apart of *TFE3* showed spatially split red and green signals resulting in a 1 red, 1 green, 1 fusion and 2 aqua ratio per nucleus (L).

Figure 2.

Recommended classification of gynecologic PEComa.

* Rearranged mixed clear cell epithelioid and spindle cell type shows marked expression of HMB45, melanA and TFE3 in its epithelioid cells.

Table 1

Clinical features of gynecologic *TFE3* translocation associated PEComa.

Case	Age	Clinical Presentation	Relevant PMH	Location and Extent of Disease	Size (cm)	Treatment	Metastasis at Surgery	Recurrence	Time to Recurrence	Duration of Follow Up	Outcome
1	50	Incidental finding from surveillance	Ovarian left-sided serous borderline tumor and right-sided serous cystadenoma	Vagina	3	Local excision, positive margins	None	None	NA	17 months	Alive, NED
2	53	Symptomatic uterine leiomyomata	None	Uterine corpus	17	Supracervical hysterectomy, RSO	None	2 months: cervix and metastases to omentum treated by radical trachelectomy, upper vaginectomy, omentectomy and adjuvant chemotherapy 11 months: small and large intraabdominal cavity treated by debulking and adjuvant chemotherapy	2 months; 11 months	13 months	Alive, NED; intraabdominal recurrence led to diagnosis revision from high grade LMS to PEComa; recently started sirolimus regimen
3	49	Uterine mass	Hodgkin lymphoma treated with ABVD chemotherapy (6 years prior)	Uterine corpus	3.3	H-BSO	None	None	NA	25 months	Alive, NED
4	47	Pelvic pain	Morecellated supracervical hysterectomy with cellular leiomyomata (1 year prior)	Pelvis	8	Local excision of pelvic mass, radical trachelectomy, BSO, pelvic and paraaortic LND, omentectomy, staging biopsies	None; leiomyomata seeding in one LN, peritoneum and pelvic side wall likely secondary to prior morcellation	Urinary bladder treated by excision	15 months	57 months	Alive, NED
5	46	UNK	None	Uterine corpus	1	Hysterectomy	None	None	NA	1 month	Alive, NED
6	66	Hemoptysis	Hysterectomy for leiomyomata (unspecified date)	Lung	UNK	Wedge resection	NA	NA	UNK	Recent case	Alive, NED

PMH (past medical history); NA (not applicable); NED (no evidence of disease); RSO (right salpingo-oophorectomy); H-BSO (hysterectomy and bilateral salpingo-oophorectomy); LND (lymph node dissection);LMS (leiomyosarcoma); ABVD (adriamycin, bleomycin, vinblastine, dacarbazine); UNK (unknown)

Table 2

Morphologic features of gynecologic *TTF3* translocation associated PEComa.

Case	Pattern(s) of Invasion	Growth Pattern	Cytologic Atypia	LVI	Necrosis	Multinucleated Tumor Cells	Melanin-containing Cells	Mitotic Index (/10 hpf, /50 hpf)
1	Infiltrative, permeative	Nested	Low	+	+	+	+	3/10, 5/50
2	NA *	Sheet-like, nested	High	+	+	+	-	14/10, 66/50
3	Pushing, permeative	Nested	Low	+	+	+	-	1/10, 2/50
4	Pushing	Nested	High	+	+	+	+	1/10, 3/50
5	Infiltrative	Nested	Low	-	-	+	-	0
6	NA *	Nested (epithelioid component); short fascicles (spindle cell component)	Low	NA	-	-	-	1/10, 2/50

+(present); - (absent); NA (not applicable)

* Pattern of invasion was not assessed for these patients' recurrent or metastatic tumors.

Table 3

Immunohistochemical profile of gynecologic *TFE3* translocation associated PEComa.

Case	HMB45	A103/MelanA	Cathepsin K	MITF	SOX10	TFE3	SMA	Desmin	h-Caldesmon
1	4+, S	0	4+, S	0	0	4+, S	0	0	0
2	4+, S	2+, S	4+, S	0	0	4+, W	0	0	0
3	4+, S	0	4+, S	0	0	4+, S	0	0	0
4	4+, S	1+, S	4+, S	0	0	4+, S	0	1+, S	0
5	4+, S	0	4+, S	0	0	4+, S	0	0	0
6	2+, S (epithelioid component)	2+, S (epithelioid component)	NP	1+, S (epithelioid component)	0	4+, S	1+, S (spindle cell component)	0	4+, S
Total (%)	6/6 (100%)	3/6 (50%)	5/5 (100%)	1/6 (17%)	0/6 (0%)	5/6 (83%)	1/6 (17%)	1/6 (17%)	1/6 (17%)

W (weak); S (strong); NP (not performed).

Table 4
Reported Cases of *TFE3* Translocation Associated PEComa of Any Site*

Reference	Relevant Medical History	Age	Sex	Site	Size (cm)	Management	Metastasis	Morphology	Immunophenotype	<i>TFE3</i> Status and Detection Method	Outcome
Argani et al	No TSC	9	F	Uterus	5	Hysterectomy, Pelvic LND	Pelvic LN	Purely Epithelioid	TFE3+, HMB45+, CathepsinK+; MelanA-, MiTF-, SMA-, Desmin-	Rearranged, FISH	Died of ALL, no evidence of PEComa; 33 mos.
Argani et al	No TSC	16	F	Colon	1.8	UNK	None	Purely Epithelioid	TFE3+, HMB45+, CathepsinK+; MelanA-, MiTF-, SMA-, Desmin-	Rearranged, FISH	NED; 41 mos.
Argani et al	UNK	33	F	Buttock	UNK	UNK	None	Purely Epithelioid	TFE3+, HMB45+, CathepsinK+; MelanA-, MiTF-, SMA-, Desmin-	Rearranged, FISH	UNK
Argani et al	UNK	46	F	Thigh	6.5	UNK	None	Purely Epithelioid	TFE3+, HMB45+, MelanA focal+, CathepsinK+; MiTF-, SMA-, Desmin-	Rearranged, FISH	UNK
Tanaka et al	Advanced stage neuroblastoma of the adrenal status post chemoradiation	14	F	Colon	6.4	Subtotal excision	None	Purely Epithelioid	TFE3+, HMB45+; MelanA-, SMA-, Desmin-	Rearranged, FISH; <i>SFPQ/PSF::TFE3</i> fusion, RT-PCR	Alive with recurrent neuroblastoma, no evidence of PEComa
Ohe et al	No TSC	57	F	Kidney	2.5	Total nephrectomy	None	Epithelioid and focally spindle cell	TFE3+, HMB45+; MelanA-, SMA-	Rearranged, FISH	NED; 18 mos.
Williamson et al	No TSC	55	F	Urinary bladder	5.0	TUR	None	Mixed epithelioid and spindle cell	TFE3+, HMB45+, MiTF+, SMA+; Desmin-	Rearranged, FISH	DOD with bladder recurrence and widespread abdominal metastases; 12 mos.
Lee et al	No TSC	33	F	Ovary	2.5	H-BSO	None	Purely epithelioid with focal melanin pigment	TFE3+, HMB45+; Desmin-, Actin-	Rearranged, FISH	UNK
Russell et al	No TSC	27	F	Urinary bladder	4.2	TUR followed by cystectomy and pelvic LND	None	Purely epithelioid	TFE3+, HMB45+, SMA-	Rearranged, FISH	Metastases of hypogastric LN, lower abdominal wall; 6 mos.

TSC (tuberous sclerosis complex); LND (lymph node dissection); ALL (acute lymphoblastic leukemia); NED (no evidence of disease); UNK (unknown); TUR (transurethral resection); H-BSO (hysterectomy and bilateral salpingo-oophorectomy)

Table 5

Classification of gynecologic *TFE3* translocation associated PEComa by clinical outcome using criteria for any site.*

Classification	Criteria	Cases with Known Metastasis Meeting Criteria	Cases without Known Metastasis Meeting Criteria
Benign	Tumors showing: <5cm, noninfiltrative, non-high grade nuclear features, no necrosis or vascular invasion and a mitotic rate <1/50 hpf	0 of 2	0 of 3
Uncertain Malignant Potential	Tumors with only one of the following: 1) nuclear pleomorphism or multinucleated giant cells or 2) gross size >5cm	0 of 2	0 of 3
Malignant	Tumors with two or more features: gross size >5cm, infiltrative growth, high grade nuclear features, necrosis, vascular invasion or a mitotic index 1/50 hpf	2 of 2	2 of 3
Total		2 of 2 cases (100%)	2 of 3 cases (67%)**

*Case 6 was excluded since it was metastatic and the primary tumor could not be evaluated.

**1 case without known metastasis could not be classified using criteria for any site of PEComa due to having only a single feature concerning for malignancy that did not qualify it as uncertain for malignant potential (for example: infiltrative growth only or mitotically active only)

Classification of gynecologic PEComa by clinical outcome using recently proposed criteria specific to tumors arising in the gynecologic tract. *

Table 6

	Criteria	Cases with Known Metastasis Meeting Criteria	Cases without Known Metastasis Meeting Criteria
Benign or Uncertain Malignant Potential	Tumors with fewer than 4 features: (gross size >5cm, high grade nuclear features, necrosis, vascular invasion or a mitotic rate 1/50 hpf)	0 of 2	3 of 3
Malignant	Tumors with 4 or more features	2 of 2	0 of 3
Total		2 of 2 cases (100%)	3 of 3 cases (100%)

* Case 6 was excluded since it was metastatic and the primary tumor could not be evaluated.