Uterine mesenchymal tumors: Hereditary perspectives

Two hereditary syndromes are known to be related to uterine mesenchymal tumors: Hereditary Leiomyomatosis and Renal Cell Carcinoma syndrome (HLRCC) and tuberous sclerosis complex (TSC). Both are discussed in detail below.

Hereditary Leiomyomatosis and Renal Cell Carcinoma Syndrome (HLRCC)

The Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC) syndrome is an autosomal dominant syndrome caused by germline mutations in the fumarate hydratase gene on chromosome 1q42.3. HLRCC predisposes patients to multiple cutaneous and uterine leiomyomas as well as renal cell carcinoma.\(^1\) HLRCC has incomplete and variable penetrance, making it difficult to identify patients by personal and family history.\(^2\) Virtually all women with HLRCC develop uterine leiomyomas (8-9 fold increased risk compared to the general population) while only a minority of patients (~15%) develop renal cell carcinoma. Women with HLRCC typically present early with uterine leiomyomas (median age at diagnosis is 28 years in contrast to 38 years for sporadic cases). HLRCC-associated uterine leiomyomas are frequently multiple, large and symptomatic resulting in early surgery (myomectomy and hysterectomy). HLRCC-associated renal tumors tend to present later, in the 4\(^{th}\) decade (median age at diagnosis is 44 years); these tumors often present at high stages resulting in substantial morbidity and mortality.\(^2-5\) Therefore early diagnosis of HLRCC presents an opportunity for clinical surveillance and timely detection of aggressive renal tumors in patients and their family members.

The challenge in effectively screening for HLRCC is that while uterine leiomyomas are extremely common, HLRCC is not. Potential screening criteria include personal history, family history, tumor morphology and immunohistochemical profile, all of which are discussed below. If a fumarate hydratase (FH) mutation is detected in a leiomyoma, often through loss of the FH immunohistochemical expression, it must be further investigated to differentiate a germline mutation, diagnostic of HLRCC, from a somatic mutation, the clinical significance of which is not currently clear.\(^6,7\)

1. Clinical features: As patients with HLRCC usually present with uterine leiomyomas roughly a decade earlier than their sporadic counterparts, very young age at presentation could be a clue. However, most leiomyomas even in young patients are sporadic. A recent study by us showed a 2.6% incidence of FH gene mutations amongst 194 women who underwent surgery for uterine leiomyomas at age less than 40 years.

   Personal history is useful if the patient has multiple cutaneous leiomyomas which often appear as papules on the chest or upper extremities. There is typically no history of renal cell carcinoma, as these present later in the 4\(^{th}\) decade and occur only in a minority of HLRCC patients.

   Family history, if documented well, can be helpful in raising the possibility of HLRCC. In many cases, there is a long history of multiple women in the family undergoing early hysterectomy for large symptomatic leiomyomas. Family history of cutaneous leiomyomas and/or RCC can also be useful. In our experience, clinical awareness of HLRCC is quite low, and such detailed clinical history is either not available or the possibility of HLRCC has not been considered despite a strong family history.
2. **Morphologic features of the leiomyomas:** Distinctive morphologic features associated with HLRCC tumors were originally observed in renal cell carcinomas, specifically large eosinophilic nucleoli surrounded by clear perinucleolar halos.\(^2,5\) Similar cytologic features were first noticed in HLRCC-associated uterine leiomyomas by Merino et al, and then further described by other groups.\(^8\) In addition to the large eosinophilic macronucleoli surrounded by clear halos, distinctive morphologic features of HLRCC-associated leiomyomas include hemangiopericytomatous blood vessels; fibrillary cytoplasm with eosinophilic cytoplasmic inclusions; hypercellularity; the presence of ovoid (rather than spindle) nuclei; symplastic atypia; multinucleation; and the presence of “alveolar edema”. The sensitivity and specificity of these findings is currently not entirely clear. In a study by our group, we found characteristic morphologic features to be present in 4 of 5 uterine leiomyomas with FH gene mutations.\(^10\) However, other studies have not found similar results. A recent study sought to test the ability of morphologic features to help screen for HLRCC in uterine leiomyomas.\(^12\) The study consisted of sporadic uterine leiomyomas and leiomyomas from patients with known germline FH mutations. Slides were reviewed by 6 pathologists blinded to the mutation status and 4 morphologic features were evaluated including increased cellularity, multinucleation, prominent eosinophilic nucleoli and perinucleolar halos. The morphologic features showed poor interobserver reproducibility as well as poor sensitivity and specificity for detection of HLRCC.\(^12\) Another study found FH deficient uterine leiomyomas to frequently display hemangiopericytomatous vessels, but the other features were not consistently demonstrated.\(^6\) In summary, the sensitivity, specificity and interobserver reproducibility of the above listed morphologic features to detect HLRCC in uterine leiomyomas is currently not clear and further studies are needed.

3. **Immunohistochemistry:** 2SC (2-succinocysteine) and FH (fumarate hydratase) stains have been evaluated for detection of HLRCC in renal cell carcinoma, uterine leiomyomas and cutaneous leiomyomas, and appear to be effective as outlined below. However, it must be emphasized that the immunohistochemical stains cannot distinguish between a germline mutation in the fumarate hydratase gene (i.e. HLRCC) and a sporadic somatic FH mutation.\(^6\)

**2-Succinocysteine (2SC):** FH deficiency (caused by FH mutation) leads to increased fumarate accumulation, which reacts spontaneously with cysteine to result in accumulation of 2-Succinocysteine (2SC). This 2SC accumulation can be detected immunohistochemically by increased 2SC protein expression\(^13\). Therefore in the presence of an FH mutation, the 2SC shows strong and diffuse staining while there is no staining in the absence of an FH gene abnormality. 2SC appears to be a sensitive and specific stain that correlates well with FH gene mutation status in RCC, uterine leiomyomas and cutaneous leiomyomas.\(^2,9,10\) Importantly, the 2SC stain is not currently commercially available and therefore cannot be used in clinical practice.

**Fumarate hydratase (FH):** More recently, the fumarate hydratase (FH) antibody has been shown to be helpful in the identification of RCC and uterine leiomyomas associated with HLRCC.\(^6,14\) The FH stain shows complete absence of staining in the setting of an FH mutation while staining is retained in the absence of a gene aberration. Loss of FH staining appears to be specific and correlates with the presence of an underlying FH gene mutation. However, many missense mutations in the FH gene can still produce non-functional protein rendering the IHC stain positive.\(^10\) Therefore, although specific, the
sensitivity of this stain is not known and the presence of retained FH staining cannot exclude a mutation in the FH gene.

2. Fumarate hydratase (FH) gene mutation analysis: This is the gold standard test to make a diagnosis of HLRCC, but makes for a poor screening tool given the low frequency of mutations, high cost, and limited availability.

Conclusions: A small minority of women who present with uterine leiomyomas have HLRCC which predisposes them to renal cell carcinoma. Young age at presentation and strong family history are useful clues. The presence of certain morphologic features, including eosinophilic cytoplasmic inclusions, prominent eosinophilic nucleoli and perinucleolar halos, could help suggest HLRCC, although this is currently controversial. The immunohistochemical profile of increased 2SC expression and FH loss may be useful. Mutational analysis of FH gene remains the gold standard of diagnosis.

Tuberous Sclerosis Associated Gynecologic Mesenchymal Lesions

Tuberous sclerosis is an autosomal dominant disorder caused by mutations in the TSC1 or TSC2 genes which encode for the proteins hamartin and tuberin respectively. TSC results in hamartomas and tumors of multiple organ systems, including tumors of PEC (perivascular epithelioid cell) origin, referred to as the PEComa family of tumors. The WHO defines PEComas as “mesenchymal tumors composed of histologically and immunohistochemically distinctive perivascular epithelioid cells.” This family of tumors includes clear cell sugar tumor of the lung (CCST), angiomyolipoma (AML), lymphangioleiomyomatosis (LAM), PEComas and some other unusual entities that can involve multiple organs. There is a strong association between TSC, AML and LAM; the association with PEComas is less prevalent. Overall it is thought that less than 10% of all PEComas involving the gynecologic tract are associated with TSC. TSC-associated lesions of the gynecologic tract include PEComa, PEComatosis, LAM and rarely AML. However, in most cases these lesions involve the gynecologic tract in a sporadic setting.

Many of these tumors have TSC loss of function due to mutation or loss of heterozygosity, leading to mTOR pathway activation. mTOR inhibitors have been reported to lead to remission in at least some patients with malignant PEComa.  

PEComa:

Gynecologic PEComa was first described in small case reports followed by a larger series of 8 cases by Vang and Kempson.  Subsequently, larger series of uterine PEComas have been published resulting in significant development in understanding of their morphologic, immunophenotypic, prognostic and genotypic characteristics.

Morphologic features: PEComas can be exclusively spindled and/or epithelioid, but most are composed of both components in varying proportions. They often display a striking nested growth pattern with
prominent vasculature. The cells are large with abundant clear to eosinophilic granular cytoplasm. Most cases show notable nuclear atypia. Mitotic activity can be variable and necrosis may be present. Some tumors can have cytoplasmic melanotic pigment. Large multinucleated cells or “spider cells” are occasionally seen. Tumors with prominent hyalinization are referred to as sclerosing PEComa.

**Immunophenotype:** The classic immunophenotype of PEComas is dual expression of myoid (SMA and desmin) and melanocytic (HMB-45, Melan-A, MITF) markers. Varying levels of expression for these markers can correlate with morphology and underlying genetic abnormalities (discussed in more detail below). In general, epithelioid tumors often show increased expression of melanocytic markers and less staining for muscle markers and the reverse is true for tumors with spindle cells. PEComas are often positive for ER and PR. Some PEComas with TFE3 rearrangements can show strong and diffuse labeling for TFE3. CathepsinK has more recently emerged as a highly sensitive marker for PEComa.²¹

**Genetic abnormalities:** Recent work has demonstrated that uterine PEComas come in two broad flavors. The first is the conventional type associated with TSC1/TSC2 alterations while the second group consists of tumors with TFE3 translocations.¹⁹ The two molecular alterations appear to be mutually exclusive and lead to tumors with distinct morphology and immunophenotype (table 1). Furthermore this distinction carries important therapeutic implications since the tumors with TSC1/TSC2 abnormalities have the potential to respond to mTOR inhibitors while the TFE3 translocation associated tumors likely will not. More recently, Agaram et al identified a novel recurrent RAD51B gene associated fusion in 3 cases of uterine PEComa, 1 of which also had a TSC2 mutation (the remaining 2 cases were not tested).²⁰

**Conventional PEComas (TSC1/TSC2 mutation or LOH):** This group of tumors results from loss of function of the TSC1/TSC2 gene, either from germline mutation (tuberous sclerosis) or more frequently due to sporadic loss of function mutation or LOH. These tumors are often spindled and epithelioid. They usually show focal staining for HMB-45 and are positive for smooth muscle markers and Melan-A and are negative for TFE3.

**TFE3 translocation associated PEComas:** These tumors show TFE3 gene translocations and lack TSC1/TSC2 abnormalities. Their morphology is typically purely epithelioid, often with clear cytoplasm, and shows striking nested growth. These tumors often show strong staining for HMB-45 and TFE3 and are negative for Melan-A and smooth muscle markers.

Table 1. Sub-grouping of PEComas based on genetic abnormalities.

<table>
<thead>
<tr>
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<th>TSC1/TSC2 loss of function associated PEComa</th>
<th>TFE3 translocation associated PEComa</th>
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<tbody>
<tr>
<td><strong>Morphology</strong></td>
<td>Spindled and/or epithelioid</td>
<td>Epithelioid with clear cells</td>
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<td><strong>Immunophenotype</strong></td>
<td></td>
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<tr>
<td>HMB-45</td>
<td>Focal</td>
<td>Strong</td>
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<tr>
<td>Melan-A</td>
<td>Positive</td>
<td>Often negative</td>
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<tr>
<td>Smooth muscle markers</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>TFE3</td>
<td>Negative</td>
<td>Positive</td>
</tr>
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Syndromic association | May be associated with TSC | No association with TSC

Therapeutic implications | Potential for response to mTOR inhibitors | Unlikely to respond to mTOR inhibitors

**Prognosis:** Specific criteria for malignancy in PEComas were first outlined by Folpe et al (table 2).\(^\text{17}\) He proposed 6 criteria that include size $\geq 5$ cm, infiltrative borders, high grade nuclear features, necrosis, vascular invasion and mitotic count $\geq 1$ mitosis per 50 high power fields (hpfs). Tumors were divided into benign, uncertain malignant potential and malignant based on the overall score. Recently, Schoolmeester et al found that these criteria applied to PEComas of the gynecologic tract were very sensitive at detecting tumors with aggressive clinical outcomes. However, the specificity was not as high and they proposed a modified system (table 3) with a higher threshold for malignancy resulting in intact sensitivity but improved specificity.\(^\text{18}\)

Table 2. PEComa prognostic classification proposed by Folpe et al.\(^\text{17}\)

<table>
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<th>Criteria</th>
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<tr>
<td><strong>Benign</strong></td>
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<tr>
<td>No worrisome features (size $&lt; 5$ cm, non-infiltrative borders, no high grade nuclear features, no necrosis, no vascular invasion and mitotic count $&lt; 1$ mitosis per 50 hpfs)</td>
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<tr>
<td><strong>Uncertain malignant potential</strong></td>
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<tr>
<td>Nuclear pleomorphism/multinucleated giant cells</td>
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<tr>
<td>Or</td>
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<tr>
<td>Size $&gt; 5$ cm</td>
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<tr>
<td><strong>Malignant</strong></td>
</tr>
<tr>
<td>$\geq 2$ worrisome features (size $\geq 5$ cm, infiltrative borders, high grade nuclear features, necrosis, vascular invasion and mitotic count $\geq 1$ mitosis per 50 hpfs)</td>
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Table 3. Modified PEComa prognostic classification proposed by Schoolmeester et al.\(^\text{18}\)

<table>
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<th>Criteria</th>
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<tr>
<td><strong>Benign or uncertain malignant potential</strong></td>
</tr>
<tr>
<td>Tumors with $&lt; 4$ worrisome features (gross size $\geq 5$ cm, high grade nuclear features, necrosis, vascular invasion, mitotic rate $\geq 1$ per 50 hpfs)</td>
</tr>
<tr>
<td><strong>Malignant</strong></td>
</tr>
<tr>
<td>Tumors with 4 or more features</td>
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**PEComatosis:** PEComatosis refers to the presence of multiple microscopic aggregates of PEComa cells, often in the background of one dominant mass. PEComatosis can involve multiple organs and has been described in the cervix, uterus, ovary, broad ligament, peritoneum and omentum. A high proportion of cases involving the gynecologic tract have been associated with tuberous sclerosis.\(^\text{22,23}\)
Lymphangioleiomyomatosis (LAM): LAM is a rare, systemic disorder that almost exclusively affects young women and is characterized by a proliferation of abnormal smooth muscle-like cells (LAM cells) in the lungs and along the lymphatic system. LAM can be sporadic or can occur in association with tuberous sclerosis, and can involve the gynecologic tract (uterus and cervix) in both settings.\(^{24,25}\) LAM can also be seen in lymph nodes as an incidental finding, including pelvic and para-aortic lymph nodes removed for gynecologic malignancies. The presence of nodal LAM does not appear to correlate with synchronous pulmonary LAM or the development of pulmonary LAM.\(^{26,27}\) Incidentally found nodal LAM is unlikely to be related to tuberous sclerosis.

Conclusions: PEComa family of tumors (including PEComa, PEComatosis, LAM and AML) can involve the female genital tract and a small proportion of these cases may be associated with the tuberous sclerosis complex (although most are sporadic). Most patients with tuberous sclerosis have an established diagnosis at the time of presentation and it would be unusual to make a primary diagnosis of TSC based on the gynecologic lesions. However, it may be reasonable to discuss the association with TSC when diagnosing female genital tract PEComas with recommendations for clinical correlation.

References:


