Neoplasms with Perivascular Epithelioid Cell Differentiation: An Overview and Update

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Background

- 1900: Angiomyolipoma recognized
- 1911: Association of AML and TSC
- 1937: Lymphangioleiomyomatosis described
- 1963: Clear cell sugar tumor described
- 1973: LAM associated with TSC
- 1974: AML and LAM associated
- 1991: HMB-45 positivity and pre-melanosomes identified in AML and CCST
The PEComa Concept

• Bonetti et al (1992)
  • Noted the presence in both AML and CCST of “an unusual cell type... immunoreactive with melanocytic markers, and exhibit(ing) an epithelioid appearance, a clear-acidophilic cytoplasm, and a perivascular distribution”.
The PEComa Family

- Angiomyolipoma
- Clear cell “sugar” tumor
- Lymphangio-leiomyomatosis
- Visceral, intra-abdominal, and soft tissue/bone
  - “Clear cell myomelanocytic tumor”
  - “Abdominopelvic sarcoma of PEC”
  - “Primary extrapulmonary sugar tumors”
  - “Extra-renal epithelioid AML”
PEComas and Tuberous Sclerosis Complex

- Almost 50% of TSC patients develop AML
  - 80% of AML arise in non-TSC patients

- LAM arises in only 0.1-2.3% of TSC patients

- Nearly 50% of LAM patients also have AML

- CCST has been reported in association with LAM and TSC
Clinical Features

- **Age**
  - TSC-associated AML (20%): mean age 45-55 years
  - Non-TSC-associated AML (80%): mean age 25-35 years
  - LAM: 4th decade
  - CCST: 6th decade

- **Sex**
  - Renal AML: 80% in women
  - Hepatic AML: Far more common in women
  - LAM: Almost exclusively in women
  - CCST: Slight female predominance
Genetics

- **TSC1/hamartin (9q34) and TSC2/tuberin (16p13.3)**
  - Hamartin and tuberin interact and function as tumor suppressor genes
  - LOH for TSC1 and TSC2 and loss of hamartin/tuberin expression seen in AML and LAM
  - Small number of falciform ligament PEComas reported tuberin negative

- Neoplastic origin of AML supported by cytogenetics, CGH, and X-chromosome inactivation studies
Angiomyolipoma

- Expansile, non-infiltrative, hemorrhagic masses
- Triphasic histology
  - Abnormal thick walled vessels
  - Spindled to epithelioid PEC
  - Lipid distended PEC (“adipocytes”)
- Variants and pitfalls
  - “Adipocyte”-rich variant
  - Spindle cell-rich variant
  - Epithelioid variant
  - Lymph node involvement
  - Cytologic atypia
LAM

• Almost always in women
• Progressive pulmonary insufficiency
• Proliferation of myoid-appearing PEC around lymphatics, septa, pleura
• May resemble “micro-CCST”
• May involve lymph nodes and thoracic duct

CCST

• More common in women
• Solitary, peripheral nodules
• Entrap alveoli
Immunohistochemistry

- "Myomelanocytic" phenotype with co-expression of muscle markers and melanocytic markers
- Typically S100 and desmin negative
- Epithelioid PEC tend to express more melanocytic markers; spindled PEC more muscle markers
Other Reported PEComas

- Falciform ligament/ ligamentum teres
- Uterus
- Abdominal cavity and mesentery
- Soft tissue
- Bone
- Skin
Malignancy in PEComas

- Well-recognized that AML may simulate a malignancy
  - Histologic mimicry of LMS, WDL, carcinoma
  - Pseudomalignant nuclear changes
  - Pseudometastases in lymph nodes

- General dogma that all AML are benign

- 1988: Malignant CCST reported
- 1991: Sarcomatous renal AML with lung metastases described
- 1994: 2nd reported clinically malignant renal AML
- 2000-2001: Multiple reports of malignant PEComas of various sites
Perivascular Epithelioid Cell Neoplasms of Soft Tissue and Gynecologic Origin: A Clinicopathologic Study of 26 Cases

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Study Aims

- Clinical and pathologic study of soft tissue and gynecologic PEComas
- Determine prognostic factors
- More fully characterize the immunophenotype
Methods

• 32 cases previously diagnosed as PEComa retrieved from archives
  • Any immunophenotype if typical
  • “Myomelanocytic” immunophenotype if unusual
  • Excluded AML, uncertain diagnoses

• Immunohistochemistry for SMA, desmin, S100 protein, pan-cytokeratin, HMB45, Melan A, MiTF, vimentin, TFE3, CD117, CD34

• Statistical analysis
Demographics

• 26 cases

• Age: Median 46 years (range 15-97 years)

• Sex: 22 female and 4 male

• Locations
  • Gynecologic tract: 8 cases
  • Abdomen/pelvis/retroperitoneum: 7 cases
  • Mesentery/omentum: 6 cases
  • Somatic soft tissue: 5 cases

• Size: Median 7.8 cm (range 1.6-24 cm)
Histopathologic Features

- **Growth pattern**
  - Circumscribed (14 cases)
  - Infiltrative (12 cases)

- **Cell type**
  - >95% epithelioid (9 cases)
  - >95% spindled (7 cases)
  - Mixed (10 cases)

- **Giant cells**
  - Multinucleated (18 cases)
  - “Spider cell-like” (9 cases)

- **Nuclear grade**
  - Low to intermediate (16 cases)
  - High (10 cases)

- **Cellularity**
  - Low to moderate (19 cases)
  - High (7 cases)

- **Mitotic activity**
  - Median 0/50 HPF (range 0-50/50 HPF)

- **Atypical mitotic figures**
  - 6/26 (23%) cases

- **Necrosis**
  - 8/26 (31%) cases

- **Vascular invasion**
  - 3/26 (12%) cases
## Immunohistochemistry

<table>
<thead>
<tr>
<th>Antigen</th>
<th>3+</th>
<th>2+</th>
<th>1+</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMA</td>
<td>7</td>
<td>5</td>
<td>9</td>
<td>21/26 (81)</td>
</tr>
<tr>
<td>HMB45</td>
<td>9</td>
<td>5</td>
<td>8</td>
<td>22/25 (88)</td>
</tr>
<tr>
<td>Melan A</td>
<td>1</td>
<td>5</td>
<td>7</td>
<td>13/19 (68)</td>
</tr>
<tr>
<td>MiTF</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>9/19 (47)</td>
</tr>
<tr>
<td>Desmin</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>8/23 (35)</td>
</tr>
<tr>
<td>S100</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>8/25 (32)</td>
</tr>
<tr>
<td>Pan-CK</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3/24 (13)</td>
</tr>
<tr>
<td>Vimentin</td>
<td>10</td>
<td>2</td>
<td>0</td>
<td>12/14 (86)</td>
</tr>
<tr>
<td>TFE3</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>5/17 (29)</td>
</tr>
<tr>
<td>CD117</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1/20 (5)</td>
</tr>
<tr>
<td>CD34</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0/7 (0)</td>
</tr>
</tbody>
</table>
Follow-up Data

(24/26 (92%) cases, mean 30 months, median 30 months, range 10-84 months)

<table>
<thead>
<tr>
<th></th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local recurrences</strong></td>
<td>3/24 (13%)</td>
</tr>
<tr>
<td><strong>Metastases</strong></td>
<td>5/24 (21%)</td>
</tr>
<tr>
<td>Liver</td>
<td>3 events</td>
</tr>
<tr>
<td>Lung</td>
<td>2 events</td>
</tr>
<tr>
<td>Bone</td>
<td>1 event</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
</tr>
<tr>
<td>DOD</td>
<td>2/24 (8%)</td>
</tr>
<tr>
<td>AWD</td>
<td>4/24 (17%)</td>
</tr>
<tr>
<td>ANED</td>
<td>18/24 (75%)</td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>3/24 (13%)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>5/24 (21%)</td>
</tr>
</tbody>
</table>
### Statistical Analysis: Study Group

<table>
<thead>
<tr>
<th></th>
<th>With recurrences or metastases</th>
<th>Without recurrences or metastases</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size &gt; median (8 cm)</strong></td>
<td>6/6</td>
<td>7/16</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Mitoses &gt; 1/50 HPF</strong></td>
<td>6/6</td>
<td>3/16</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Necrosis</strong></td>
<td>4/6</td>
<td>3/16</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Patient age &gt; 46 years</strong></td>
<td>3/6</td>
<td>8/16</td>
<td>1.0 (NS)</td>
</tr>
<tr>
<td><strong>Infiltrative growth</strong></td>
<td>5/6</td>
<td>6/16</td>
<td>0.15 (NS)</td>
</tr>
<tr>
<td><strong>High cellularity</strong></td>
<td>3/6</td>
<td>4/16</td>
<td>0.33 (NS)</td>
</tr>
<tr>
<td><strong>High nuclear grade</strong></td>
<td>3/6</td>
<td>5/16</td>
<td>0.62 (NS)</td>
</tr>
<tr>
<td><strong>Atypical mitoses</strong></td>
<td>2/6</td>
<td>3/16</td>
<td>0.59 (NS)</td>
</tr>
<tr>
<td><strong>Vascular invasion</strong></td>
<td>2/6</td>
<td>1/16</td>
<td>0.17 (NS)</td>
</tr>
<tr>
<td><strong>&gt;95% spindled</strong></td>
<td>1/6</td>
<td>5/16</td>
<td>0.63 (NS)</td>
</tr>
<tr>
<td><strong>&gt;95% epithelioid</strong></td>
<td>3/6</td>
<td>5/16</td>
<td>0.62 (NS)</td>
</tr>
</tbody>
</table>
Previously Reported Soft Tissue and Gynecologic PEComas

- 61 cases
- 55F; 6M
- TSC in only 5 of 38 informative patients
- Median 38 years (range 3-87 years)
- Median size 5.3 cm (range 0.5-29 cm)
- Locations: GYN (21), soft tissue (28), viscera (10), bone (2)
- Follow-up (45 cases): 35 ANED, 5 alive with recurrence/metastasis, 4 DOD
# Statistical Analysis: All Cases

<table>
<thead>
<tr>
<th>Feature</th>
<th>With recurrences or metastases</th>
<th>Without recurrences or metastases</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size &gt; median (5 cm)</td>
<td>15/18</td>
<td>19/49</td>
<td>0.01</td>
</tr>
<tr>
<td>Mitoses &gt; 1/50 HPF</td>
<td>16/17</td>
<td>8/49</td>
<td>3.2 x 10^-8</td>
</tr>
<tr>
<td>Necrosis</td>
<td>11/18</td>
<td>8/50</td>
<td>0.002</td>
</tr>
<tr>
<td>Infiltrative growth</td>
<td>12/15</td>
<td>26/49</td>
<td>0.03</td>
</tr>
<tr>
<td>High cellularity</td>
<td>9/18</td>
<td>9/50</td>
<td>0.03</td>
</tr>
<tr>
<td>High nuclear grade</td>
<td>9/18</td>
<td>9/50</td>
<td>0.03</td>
</tr>
<tr>
<td>Patient age &gt; 46 years</td>
<td>9/17</td>
<td>22/51</td>
<td>0.57 (NS)</td>
</tr>
<tr>
<td>&gt;95% spindled</td>
<td>2/18</td>
<td>11/43</td>
<td>0.31 (NS)</td>
</tr>
<tr>
<td>&gt;95% epithelioid</td>
<td>11/18</td>
<td>25/50</td>
<td>0.26 (NS)</td>
</tr>
<tr>
<td>Atypical mitoses</td>
<td>Not evaluable</td>
<td>Not evaluable</td>
<td>NA</td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>Not evaluable</td>
<td>Not evaluable</td>
<td>NA</td>
</tr>
</tbody>
</table>
## Proposed Classification

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Percentage with aggressive behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benign</strong></td>
<td>0 of 22 (0%)</td>
</tr>
<tr>
<td>No worrisome features (&lt;5 cm, non-infiltrative, non-high nuclear grade and cellularity, mitotic rate &lt; 1/50HPF, no necrosis, no vascular invasion)</td>
<td></td>
</tr>
<tr>
<td><strong>Uncertain malignant potential</strong></td>
<td>1) 0 of 6 (0%)</td>
</tr>
<tr>
<td>1) Nuclear pleomorphism/ multinucleated giant cells only</td>
<td></td>
</tr>
<tr>
<td>or</td>
<td></td>
</tr>
<tr>
<td>2) Size &gt; 5cm only</td>
<td>2) 2 of 17 (12%)</td>
</tr>
<tr>
<td><strong>Malignant</strong></td>
<td>12 of 17 (71%)</td>
</tr>
<tr>
<td>Two or more worrisome features (&gt;5 cm, infiltrative, high nuclear grade and cellularity, mitotic rate &gt; 1/50HPF, necrosis, vascular invasion)</td>
<td></td>
</tr>
</tbody>
</table>
Differential Diagnosis

- Melanoma
- Conventional clear cell sarcoma
- Gastrointestinal clear cell sarcoma-like tumor
- Gastrointestinal stromal tumor
- Clear cell carcinoma
- Leiomyosarcoma
Melanoma/ Conventional Clear Cell Sarcoma

- Admixture of spindled and epithelioid cells with prominent nucleoli
- Touton-type tumor giant cells in conventional CCS
- Strong S100 (+), HMB45/Melan A (+), SMA (-)
- t (12; 22) (EWS-ATF1) in CCS
Gastrointestinal Clear Cell Sarcoma-like Tumor

- Recently described, extremely rare sarcoma with aggressive behavior
- Round cell tumor with osteoclastic giant cells
- S100 (+), HMB45/Melan A (-), SMA (-)
- \textit{EWS-CREB1}
Gastrointestinal Stromal Tumor

- Spindled to epithelioid with fibrillar cytoplasm
- Usually SMA (-), HMB45/Melan A (-), CD117 and CD34 (+)
- Mutations in c-kit gene
Clear Cell Renal Cell Carcinoma

- Optically clear cells without “stringy” eosinophilia
- Cytokeratin (+), SMA/HMB45/ Melan A (-)
Cytokeratin
Leiomyosarcoma

- Diffuse cytoplasmic eosinophilia, perinuclear vacuoles, cigar-shaped nuclei
- Thick-walled vessels without arborizing capillary network
- SMA (+), usually desmin (+)
- *May rarely be* HMB45 (+); Melan A (-)
Summary: Clinical Features

- Middle aged patients (median age 37 years)
- Striking female predominance (7:1)
- TSC association in < 10% of cases
- Most commonly involve the gynecologic tract, abdomen/retroperitoneum, and mesentery/omentum, but also soft tissue and skin
Summary: Immunohistochemistry

• S100 protein and desmin may be expressed by ~30% of otherwise typical cases

• Occasional typical PEComas may be SMA-negative

• HMB45 is the best melanocytic marker in PEComas

• TFE3 may drive the “myomelanocytic” phenotype in MiTF-negative cases
Summary: Behavior

- Many gynecologic and soft tissue PEComas are clinically malignant
- Large size, infiltrative growth, high nuclear grade and cellularity, vascular invasion, necrosis and elevated mitotic activity are significantly associated with aggressive behavior
- “Symplastic” PEComas and large but otherwise typical tumors have “uncertain malignant potential”
- PEComas without atypical histologic features may be confidently labeled as “benign”
PEComas: Conclusions

- Family of tumors
- No normal cellular counterpart
- “Myomelanocytic” phenotype
- Strong association with TSC and TSC-associated genes for AML, LAM, CCST; weak association for ST and GYN tumors
- Spectrum from benign, to “pseudomalignant”, to fully malignant
- Distinguish from melanoma, GIST, clear cell carcinoma, true smooth muscle neoplasms