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Short Running Title: Pigmented PEComa of the lung

Guarantor of Submission: The corresponding author is the guarantor of submission.
TITLE: PEComa (Perivascular Epithelioid Cell) of the Lung with Focal Pigment Production

ABSTRACT

Introduction
Perivascular Epithelioid Cell (PEC) tumors are rare mesenchymal tumors defined by the presence of peri-vascular epithelioid cells that express muscle and melanocytic markers and have no known normal tissue counterparts. These include wide range of tumors like angiomyolipoma (AML), lymphangioleiomyomatosis (LAM) and clear cell “sugar” tumor of the lung (CCST). These are associated with tuberous sclerosis. PEComa with pigment production is rare and it can be a diagnostic challenge to distinguish it from malignant melanoma. The immunoprofile of the tumor with strong human melanocytic black -45 (HMB-45) expression and the absence of other melanocytic markers like S-100 and SOX-10 suggests the diagnosis of PEComa.

Case Report
We report a 34 year old female with past medical history of hypothyroidism who presented with right upper back pain for past 6 months. Chest X-ray performed at that time revealed a lung mass. CT chest showed a multi-lobular 3.4 x 2.2 cm soft tissue mass in the right lower lobe. Bronchoscopy was undiagnostic. CT guided biopsy revealed atypical spindle cells strongly positive for HMB-45 and vimentin, negative for melanoma markers like S100. She eventually underwent a VATS procedure with complete resection of the tumor. Pathology of the lung mass confirmed the same.

Conclusion
Pigmented PEComas are rare and difficult to distinguish from malignant melanoma. Findings of atypical spindle cell neoplasm with focal pigment production which is positive for HMB-45 and negative for S-100 stain makes PEcoma more likely. Pigmented PEComas of the lung have not been reported so far to our knowledge.
Keywords: PEComa of lung, pigmented PEComa, HMB-45.
**TITLE:** PEComa (Perivascular Epithelioid Cell) of the Lung with Focal Pigment Production

**INTRODUCTION**
Perivascular Epithelioid Cell (PEC) tumors are rare mesenchymal tumors defined by the presence of peri-vascular epithelioid cells that express muscle and melanocytic markers and have no known normal tissue counterparts [1]. Angiomyolipoma (AML), clear cell “sugar” tumor (CCST) of the lung, lymphangioleiomyomatosis (LAM), clear cell melanocytic tumor of the falciform ligament/ligamentum teres, and rare clear cell tumors of other anatomical sites, such as the liver, uterus, vulva, rectum, urinary bladder, abdominal wall and pancreas are tumors which have both muscle and melanocytic markers which fall in the category of PEComa [2,3,4]. These tumors are usually associated with tuberous sclerosis complex with female predominance, especially AML and LAM [5]. Pigmented PEComas are rare and difficult to differentiate from metastatic melanoma. The pigmented PEComa, unlike the typical PEComa, occurs in females without tuberous sclerosis [5]. So far only 10 reported cases of pigmented PEComas of the kidney and one in liver have been reported [6,7]. The immunoprofile of the tumor with strong human melanocytic black-45 (HMB-45) expression and the absence of other melanocytic markers like S-100 and SOX-10 suggest the diagnosis of PEComa [7]. To the best of author’s knowledge, this is the first reported PEComa of the lung with pigment production.

**CASE REPORT**
34 year old female with a medical history of hypothyroidism presented with a lung mass on chest X-ray performed to evaluate chronic right upper back pain present for past 6 months. Physical exam and laboratory results were unremarkable. A previous chest x-ray done 2 years ago on a routine visit to her primary care doctor has shown a smaller lesion but was not followed up until she became symptomatic. CT chest confirmed a multi-lobular 3.4 x 2.2 cm soft tissue mass in the right lower lobe (figure-1). Bronchoscopy with biopsy was negative for malignant cells and micro-organisms. CT guided biopsy revealed atypical spindle cells strongly positive for HMB-45 and vimentin expression, negative for S100, SOX-10, cytokeratin, CD20, LCA, CD15,
desmin and SMA. PET scan confirmed uptake of FDG in the right lung mass with no other pulmonary, mediastinal, cervical, intra or retro abdominal foci of increased uptake. Lymph nodes were unremarkable in all regions. She had wedge resection of the right upper lobe mass through video assisted thoracoscopic surgery (VATS). Grossly it was 3.5 x 2.5 x 2.0 cm bulging dome shaped mass. There were no post-operative complications and the patient was discharged seven days after the surgery. A thorough gynecological examination did not reveal any pathology.

Pathology:
Macroscopic findings after VATS showed right upper lobe of the lung measuring 9.0 x 8.5 x 6.0 cm and weighing 64 grams. Along the hilum was a bulging dome shaped mass measuring 3.5 x 2.5 x 2.0 cm. On section, the mass consisted of friable soft gray-white tissue. The pleural surface was smooth and showed moderate congestion.
Light microscopic examination revealed a relatively well defined sub-pleural densely cellular mass composed of sheets and short fascicles of tumor cells with scattered lymphoid aggregates. The predominant tumor cell population was ovoid to spindle, with a moderate amount of pale eosinophilic cytoplasm, vesicular chromatin and tumor giant cells, as well as cells containing fine brown intracytoplasmic pigment (figure-2). It had conspicuous intratumoral lymphoid infiltrate with numerous eosinophils. Mitotic figures were scattered throughout the specimen with an average of 2 mitoses per 2 square mm. Focal necrosis was seen.
Immunohistochemical stains were positive for HMB 45 (figure-3), focally for Melan-A (figure-4), vimentin (figure-5) and negative for S-100 (figure-6) and SOX-10. Ki-67 immunostain was positive in 5% of the tumor cells. Remaining immunohistochemical stains are shown below in the table-1. Table-2 shows immunostains which help in differentiating between Pigmented PEComas and malignant melanoma.

DISCUSSION
Typically PEComas of the lung are characterized by the presence of epithelioid or spindle cells with clear or granular eosinophilic cytoplasm. These tumors are also
known as Clear Cell ‘sugar’ tumor of the Lung (CCTL) as the PAS stain shows glycogen granules in the cytoplasm of these clear cells [8, 9]. Typically, CCTL is a rare benign pulmonary neoplasm which can occur in any age group (8-73 years) with slight female preponderance [9]. Most lesions are solitary, asymptomatic, located within the peripheral lung and pose a significant diagnostic problem. Only few develop symptoms like breathlessness, back pain, chest pain, fever and hemoptysis [9].

Macroscopically CCTL appear as well circumscribed, peripheral nodules usually less than 3 cm in diameter and cut surface is without evidence of hemorrhage, necrosis, cavitation or calcification. Histologically, they consist of mitotically inactive round or oval cells with clear or granular eosinophilic cytoplasm and distinct cell borders, with characteristic intervening thin-walled sinusoidal vessels [9]. Though most of these tumors are benign, malignant behavior is occasionally reported. The degree of malignancy is highly variable in PEComas. The size of the tumor and the mitotic rate seem to be the most reliable prognostic factors associated with recurrence after surgical resection [10]. Our patient had tumor <5 cm, mitotic rate of 2 mitoses per 50 hpf and absence of necrosis which makes the PEComa benign as per the modified Folpe criteria [10]. Repeat CT chest done 6 months later showed no evidence of recurrence of the tumor.

CONCLUSION

In summary, our patient had atypical spindle cell neoplasm with focal pigment production positive for HMB-45(figure-3) and negative for S-100 (figure-6) and SOX-10 immunostains. The differential diagnosis included metastatic melanoma and PEComa. While it is unusual for melanoma to be negative for both S-100 and SOX-10, it remained a diagnostic consideration as the tumor had melanin pigment and HMB-45 staining. However, the presence of atypical spindle shaped cells with an immunostain positive for Vimentin and HMB 45 made PEComa more likely. Our case is distinguished by the presence of the melanin pigment which is unusual in PEComa. The final morphologic and immunohistochemical findings are most consistent with a tumor with perivascular epithelioid cell differentiation (PEComa).
CONFLICT OF INTEREST

The authors declare no conflict of interest.

The corresponding author would be the guarantor of submission.

AUTHOR’S CONTRIBUTIONS

Sowmini Medavaram
Group 1 - Conception and design, Acquisition of data, Analysis and interpretation of data
Group 2 - Drafting the article, Critical revision of the article
Group 3 - Final approval of the version to be published

Trishala Agrawal
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Group 2 - Drafting the article, Critical revision of the article
Group 3 - Final approval of the version to be published

Gail Prado
Group 1 - Conception and design, Acquisition of data, Analysis and interpretation of data
Group 2 - Drafting the article, Critical revision of the article
Group 3 - Final approval of the version to be published

Maya Shah
Group 1 - Conception and design, Acquisition of data, Analysis and interpretation of data
Group 2 - Critical revision of the article
Group 3 - Final approval of the version to be published

REFERENCES

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### Table 1: Immunohistochemical stains performed on the tissue from the lung

<table>
<thead>
<tr>
<th>Stain</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vimentin</td>
<td>(+)</td>
</tr>
<tr>
<td>CK 7</td>
<td>(-)</td>
</tr>
<tr>
<td>Melan-A</td>
<td>(focally+)</td>
</tr>
<tr>
<td>CK 20</td>
<td>(-)</td>
</tr>
<tr>
<td>HMB-45</td>
<td>(focally+)</td>
</tr>
<tr>
<td>CD 43</td>
<td>(-)</td>
</tr>
<tr>
<td>S-100</td>
<td>(-)</td>
</tr>
<tr>
<td>CD 138</td>
<td>(-)</td>
</tr>
<tr>
<td>Calretinin</td>
<td>(focally+)</td>
</tr>
<tr>
<td>PAX-5</td>
<td>(-)</td>
</tr>
<tr>
<td>Desmin</td>
<td>(-)</td>
</tr>
<tr>
<td>PAX-8</td>
<td>(-)</td>
</tr>
<tr>
<td>CD34</td>
<td>(-)</td>
</tr>
<tr>
<td>CD 30</td>
<td>(-)</td>
</tr>
<tr>
<td>TTF-1</td>
<td>(-)</td>
</tr>
<tr>
<td>ALK</td>
<td>(-)</td>
</tr>
<tr>
<td>CD117</td>
<td>(-)</td>
</tr>
<tr>
<td>ER</td>
<td>(-)</td>
</tr>
<tr>
<td>CK</td>
<td>(-)</td>
</tr>
<tr>
<td>Low Ki-67 &lt; 5%</td>
<td></td>
</tr>
<tr>
<td>Sox-10</td>
<td>(-)</td>
</tr>
<tr>
<td>Iron</td>
<td>(-)</td>
</tr>
</tbody>
</table>
Table 2: Immunostains which help in differentiating between Pigmented PEComas and malignant melanoma.

<table>
<thead>
<tr>
<th>Pigmented PEComa</th>
<th>Malignant Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-100 negative</td>
<td>S-100 strongly positive</td>
</tr>
<tr>
<td>HMB-45 focally positive</td>
<td>HMB-45 strongly positive</td>
</tr>
<tr>
<td>Melan-A focally positive</td>
<td>Melan-A strongly positive</td>
</tr>
<tr>
<td>SOX-10 negative</td>
<td>SOX-10 positive</td>
</tr>
<tr>
<td>Vimentin positive</td>
<td>Vimentin positive</td>
</tr>
</tbody>
</table>
FIGURE LEGENDS

Figure 1: CT chest showing multi-lobular 3.4 x 2.2 cm soft tissue mass in the right lower lobe. It has well defined margins and does not contain macroscopic calcification.

Figure 2: Light microscopy reveals sheets and nests of spindle cells, and thin-walled blood vessels. The malignant cells have eosinophilic cytoplasm, and pleomorphic nuclei with vesicular chromatin and visible nucleoli. Also numerous cells contain brown intracytoplasmic pigmentation. Scattered abnormal mitotic figures are also seen averaging 2 mitoses per 2 mm$^2$.

Figure 3: HMB 45 positive stain

Figure 4: Melan-A focally positive

Figure 5: Vimentin positive

Figure 6: S-100 negative
Figure 1: CT chest showing multi-lobular 3.4 x 2.2 cm soft tissue mass in the right lower lobe. It has well defined margins and does not contain macroscopic calcification.
Figure 2: Light microscopy reveals sheets and nests of spindle cells, and thin-walled blood vessels. The malignant cells have eosinophilic cytoplasm, and pleomorphic nuclei with vesicular chromatin and visible nucleoli. Also numerous cells contain brown intracytoplasmic pigmentation. Scattered abnormal mitotic figures are also seen averaging 2 mitoses per $2\,\text{mm}^2$.

Figure 3: HMB 45 positive stain
Figure 4: Melan- A focally positive

Figure 5: Vimentin positive
Figure 6: S-100 negative