October 2016 Case of the Month

A 40 year old woman with abdominal pain and bloating.

Contributed by:

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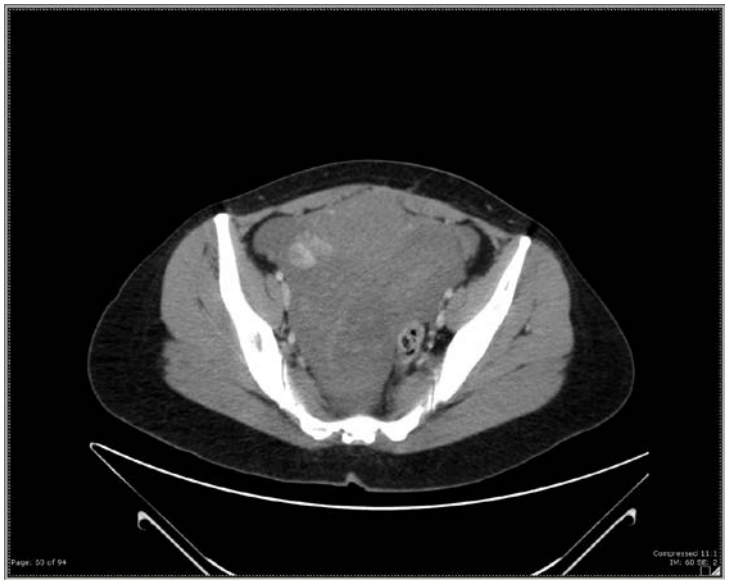
Clinical History:

The patient is a 40 year old woman with a medical history remarkable for gastroesophageal reflux disease and two previous caesarean sections. She presented to the emergency department where x-ray computed tomography imaging of her chest, abdomen, and pelvis demonstrated bilateral lung nodules and a very large and complex mass involving the central pelvis with associated ascites (figure 1). The patient subsequently underwent exploratory laparotomy with resection of the tumor.

Figure 1. CT scan of the pelvis demonstrating a large complex mass involving the central pelvis.

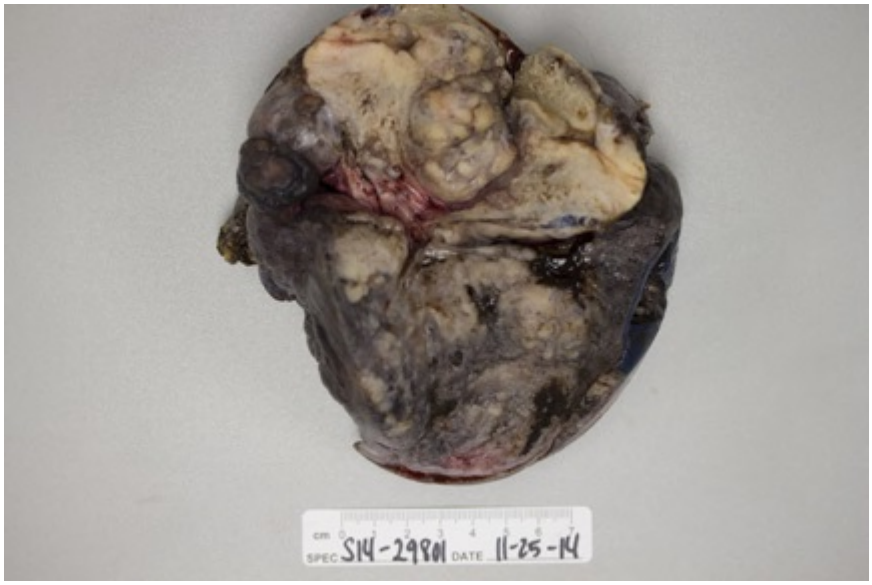


Gross Examination:

Gross examination of the specimen revealed a large gray-purple mass adherent to the posterior serosa of the uterus. Further sectioning demonstrated a white-tan nodular cut surface and

involvement of the mass with the myometrium and endometrial cavity. There was no gross-evidence of involvement of the cervix or bilateral fallopian tubes or ovaries.

Figure 2. Portion of the mass demonstrating a white-tan nodular cut surface and gray-purple external surface.



Microscopic Examination:

Histologic sections demonstrated an infiltrative mass characterized by cords and trabeculae of pleomorphic epithelioid cells with pale, granular cytoplasm and round nuclei with small nucleoli and granular chromatin in a densely sclerotic stroma with scattered blood vessels (figures 3 and 4). Only rare mitoses were seen and there was no evidence of necrosis. Metastases were present in several pelvic lymph nodes. Immunohistochemical stains demonstrated the tumor cells to be positive for SMA, HMB-45, MITF, cathepsin K, TFE3, desmin, ER, and PR. The tumor cells stained negatively for cytokeratin AE1/AE3, calretinin, inhibin, PAX8, CD10, CD34, CD31, and melan-A. FISH testing of tumor cells was positive for TFE3 translocation.

Figure 3. Low-power photomicrograph of a section of endomyometrium demonstrating cords and trabeculae of tumor cells in a densely sclerotic stroma with scattered blood vessels.

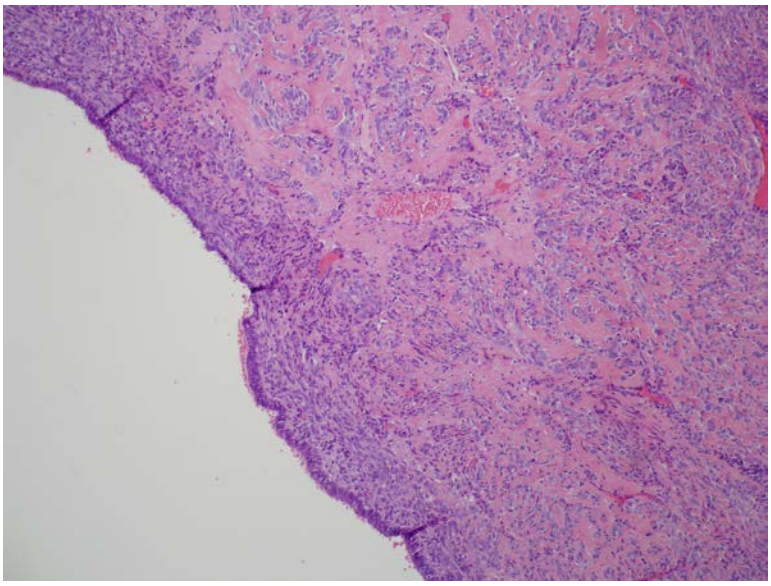
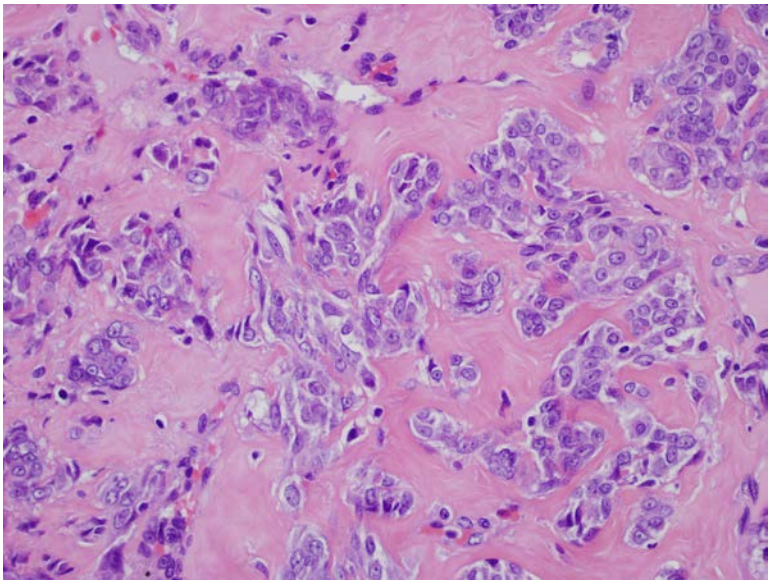


Figure 4. High-power photomicrograph demonstrating that the tumor cells are epithelioid and somewhat pleomorphic with pale, granular cytoplasm and round nuclei with small nucleoli and granular chromatin.



Final Diagnosis:

Malignant sclerosing perivascular epithelioid cell tumor (PEComa).

Discussion:

Perivascular epithelioid cell neoplasms (PEComas) are defined by the WHO as a rare mesenchymal tumor of the perivascular epithelioid cell lineage (1). The perivascular epithelioid cell lineage was first described in the seemingly disparate lesions of angiomyolipoma and clear cell “sugar” tumor of the lung which both feature unconventional cells that are epithelioid with clear to eosinophilic cytoplasm, perivascular in orientation, and express both melanocytic and muscle markers (2). No normal histologic counterpart has been identified for the perivascular epithelioid cell lineage (3).

PEComas are a family of tumors linked by its similar morphologic and immunohistochemical characteristics and include angiomyolipoma, clear cell “sugar” tumor of the lung, and lymphangioleiomyomatosis among others (3). Regardless of their name, each neoplastic tumor features a proliferation of perivascular epithelioid cells which are defined by the WHO as peritheliomatous cells of epithelioid or spindled morphology with myomelanocytic differentiation (1).

In regards to PEComas of the gynecologic tract, it is a rare tumor with less than 100 cases reported in the literature (4). The majority arise from the uterine corpus, but tumors may arise from the cervix, vagina, adnexa, broad ligament, or vulva.

In regards to tumors of the uterine corpus, the median age at time of diagnosis is 47.5 years (4). The most common presenting symptom is abnormal uterine bleeding or pelvic pain (5). The average tumor measures around 5 cm at the time of resection (4).

Histologically, PEComas of the gynecologic tract are cellular with a nested growth pattern with the cells within the nests demonstrating a loose and somewhat detached appearance (5). Some tumors exhibit intratumoral stromal hyalinization, the so called sclerosing variant. The majority of PEComas demonstrate an epithelioid morphology but occasionally there is mixed epithelioid and spindled morphology and rarely a spindle cell only morphology (4).

The cells are remarkable for clear, eosinophilic granular cytoplasm (5). Occasionally there can be necrosis or significant nuclear atypia present (4). Mitoses are usually rare. Immunohistochemically the cells are usually positive for at least two melanocytic markers (HMB45, MITF, melan-A, & S100 in order of relative frequency) and one muscle marker (desmin, SMA, h-caldesmon in order of relative frequency) (5).

Most recently, a subset of PEComas have been identified that are remarkable for TFE3 translocation (6). This portion of tumors have somewhat differing morphology and immunoreactivity when compared with their non-translocation counterparts. Typically, they are composed of purely epithelioid cells with an alveolar architecture with mostly clear cytoplasm and a round nucleus. They demonstrate diffuse immunostaining for TFE3, HMB45, cathepsin K, and either focal or no immunostaining for melan-A and variably weak immunoreactivity for smooth muscle markers.

Overall, the prognosis for gynecologic tract PEComas is variable. Clinicopathologic criteria suggestive of malignancy in PEComas include gross size > 5 cm, infiltrative growth, high-grade nuclear features, necrosis, vascular invasion, or a mitotic index ≥1/50 HPF (5). Tumors with two or more of these features are considered malignant. In the largest case series, with a median follow up of 20 months, 16% of patients had died of disease, 14% of patients were alive with disease, and 70% had no evidence of residual disease (4).

List of References:

1. Fletcher, Christopher D. M. *WHO Classification of Tumours of Soft Tissue and Bone*. Lyon: IARC, 2013.

2. Bonetti, F., M. Pea, G. Martignoni, C. Doglioni, G. Zamboni, P. Capelli, P. Rimondi, and A. Andrion. "Clear Cell ("Sugar") Tumor Of The Lung Is A Lesion Strictly Related To Angiomyolipoma—the concept of a family of lesions characterized by the presence of the perivascular epithelioid cells (PEC)." *Pathology* 26.3 (1994): 230-36.

3. Martignoni, Guido, Maurizio Pea, Daniela Reghellin, Giuseppe Zamboni, and Franco Bonetti. "PEComas: The Past, the Present and the Future." *Virchows Archiv Virchows Arch* 452.2 (2007): 119-32.

4. Conlon, Niamh, Robert A. Soslow, and Rajmohan Murali. "Perivascular Epithelioid Tumours (PEComas) of the Gynaecological Tract."*Journal of Clinical Pathology J Clin Pathol* 68.6 (2015): 418-26.

5. Schoolmeester, John Kenneth, Brooke E. Howitt, Michelle S. Hirsch, Paola Dal Cin, Bradley J. Quade, and Marisa R. Nucci. "Perivascular Epithelioid Cell Neoplasm (PEComa) of the Gynecologic Tract." *The American Journal of Surgical Pathology*38.2 (2014): 176-88.

6. Schoolmeester, J. Kenneth, Linda N. Dao, William R. Sukov, Lu Wang, Kay J. Park, Rajmohan Murali, Meera R. Hameed, and Robert A. Soslow. "TFE3 Translocation–associated Perivascular Epithelioid Cell Neoplasm (PEComa) of the Gynecologic Tract." *The American Journal of Surgical Pathology* 39.3 (2015): 394-404.