Diagnostic Mistakes in Gynecological Pathology

Case 1

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Case History

• 27 year old G2P2 woman
• presented with abdominal pain 1 month postpartum
• a “fibroid” was previously noted on prenatal ultrasounds. On imaging, she now has a 17cm pelvic mass.
• Her LDH is 376 (100-250U/L). AFP, HCG and Ca125 were normal
Paraaortic lymph nodes
• What is your differential diagnosis?
• What immunohistochemical and/or molecular studies would you order?
Ki-67
Other stains not shown: CD10 +, chromogranin -, SALL4 -, glypican -, Sox 10 -, S100 -, CD45 -
WT1
Diagnosis:
Small Cell Carcinoma of Hypercalcemic Type
Clinical Features

- Most common undifferentiated ovarian carcinoma <40 years
- Range 9-43 years, mean 24 years
- 60% have hypercalcemia, serum calcium can be used to monitor disease and therapy response
  - Some tumors have been found to express parathyroid related protein
  - Possible explanation for hypercalcemia
- Histogenesis
  - Uncertain origin
  - May be of germ cell origin or variant of rhabdoid tumor

Foulkes et al. J Pathol. 2014.
Gross Features

- Typically large, >15cm
- Unilateral or bilateral
- Fleshy
- Areas of cystic change and necrosis
Microscopy

- Sheets, nests, cords and follicular-like spaces with eosinophilic fluid
- Brisk mitotic activity
- Predominantly small cells with scant cytoplasm and monomorphic nuclei
- 50% of cases contain a large cell component
- 10% of tumors contain a minor associated mucinous gland component, ranging from benign to atypical glands to even signet ring cells
- Rarely found in association with mature teratoma

Morphologic Differential Diagnosis

- Juvenile granulosa cell tumor (JGCT)
- Sex cord stromal tumors (SCST)
- Germ cell tumor
- Primitive neuroectodermal tumor (PNET)
- Rhabdomyosarcoma (RMS)
- Desmoplastic small round cell tumor (DSRCT)
- Lymphoma
- Melanoma
- Undifferentiated carcinoma
- Metastatic pulmonary small cell carcinoma

### Immunohistochemistry

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**SALL 4** - 50% +  
**OCT 4** -  
**AFP** -  
**Glypican 3** - negative to weakly +

**UNIQUE COMBINATION FOR SCCOHT**

Unlike Pulm. type SmCC---

Unlike PNET ---

Unlike DSRCT, RMS ---

Unlike Melanoma --

Unlike JGCT, SCST ---

Unlike Met pulm SmCC---

Unlike dysgerminoma -

Unlike from YST-

Immunohistochemistry and Molecular Analysis

- >90% of SCCOHT have an inactivating mutation in a chromatin remodelling gene SMARCA4 (encoding for BRG1, one of two ATPases in the SWI/SNF chromatin remodelling complex)
- The other ATPase, BRM, is absent in SCCOHT due to epigenetic silencing of gene SMARCA2 or due to mRNA degradation
- Re-expression of SMARCA4 or SMARCA2 inhibits cell growth
- BRG1 expression is a good surrogate of SMARCA4 mutation
- Combined BRG1 and BRM IHC loss is specific for SCCOHT

Prognosis

• Stage is the most important prognostic factor
  – 1A patients – 1/3 disease free for 1 to 13 years
• Other favorable characteristics:
  – >30 years
  – Normal preoperative calcium serum level
  – Tumor size <10cm
  – Absence of larger tumor cells

Therapy

• Multiagent adjuvant chemotherapy (vinblastine, cisplatin, cyclophosphamide, bleomycin, doxorubicin and etoposide) in combination with radiotherapy – more effective than standard carbotaxol therapy
  – Median survival of 14.9 months

• Patients receiving surgery, chemotherapy, radiotherapy and/or radiotherapy with autologous stem cell rescue had 71% median survival rate at 5 years

Callegaro-Filho et al. Gynecol Oncol. 2015.
Wallbillich et al. Gynecol Oncol. 2012.
Possible future targeted therapies

- Histone methyltransferase E2H2 is overexpressed in 80% of SCCOHT. E2H2 inhibition induced cell cycle arrest and apoptosis in SCCOHT cells.

- Receptor tyrosine kinase inhibitor Ponatinib was effective against SMARCA4 mutated SCCOHT in vitro and in vivo preclinical models.

- Despite a low mutational burden, SCCOHT has an immunogenic environment resembling that of tumors which respond well to PD-1/PD-L1 blockade.

Rhabdoid Tumor Family

• Germline mutations in ATPase SMARCA4 (BRG1) of the SWI/SNF chromatin remodeling complex and one of the main core subunits SMARCB1 (INI1)

• Autosomal dominant pattern of inheritance, poorly differentiated tumors = Rhabdoid Tumor Predisposition Syndrome
  – Ovary: SCCOHT (SMARCA4)
  – CNS: atypical teratoid/rhabdoid tumor (SMARCB1 and occasionally SMARCA4)
  – Bone: poorly differentiated chrodoma (SMARCB1)
  – Kidney: malignant rhabdoid tumor (SMARCB1)

Foulkes et al. J Pathol. 2014.
Figure 1. Morphological and immunohistochemical comparisons of AT/RTs and SCCOHT: (left column) Histopathology of SMARCB1-deficient ATRT; (middle column) SMARCA4-deficient ATRT; (right column) MRTO/SCCOHT: (A–C) H&E staining; (D–F) immunohistochemistry for SMARCB1/INI1; (G–I) SMARCA4/BRG1 expression. Note the similarity in appearance and immunohistochemical staining profile of SMARCA4-deficient ATRT and MRTO/SCCOHT. Scale bars = 50 μm (A–C) or 100 μm (D–I).
Genetic Counselling

• Patients with SCCOHT can have germline and/or somatic SMARCA4 mutations
• SCCOHT patients should be referred for genetic counselling
• Female SMARCA4 mutation carriers should be offered prophylactic oophorectomy

Pejovic et al. Gynecol Oncol Reports. 2019.
Summary

• SCCOHT is a tumor found in girls and young women

• Morphologic differential is wide
  – presence of mucinous epithelium helps
  – immunohistochemistry confirms the diagnosis

• Important to recognize for prognostic and therapeutic purposes

• Implications for patient genetic counselling
Thank You