SMALL CELL CARCINOMA OF THE OVARY
OF HYPERCALCAEMIC TYPE (SCCOHT):
UNRAVELLING THE MYSTERIES OF A
TUMOUR UNIQUE TO THE OVARY

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CASE PRESENTATION

- F23
- Unilateral 15 cm ovarian mass
SMARCA4 (BRG1)
IMMUNOHISTOCHEMISTRY
DIAGNOSIS- SMALL CELL CARCINOMA OF OVARY OF HYPERCALCAEMIC TYPE- SCCOHT

- usually young females (peak in 2nd and 3rd decades); not usually in first decade
- may occur in older females (large series of 150 cases; AJSP 1994;18;1102-1116; age 9-43; average 24 years)
- hypercalcaemia in two-thirds
- usually unilateral ovarian tumour
- rare familial cases (very occasionally may be bilateral)
- extremely aggressive tumours with poor prognosis
MORPHOLOGY
MORPHOLOGIC VARIATIONS

- large cells in 40%- when predominate or are exclusive, referred to as large cell variant of SCCOHT; large cells may have rhabdoid appearance
- may get mucinous elements (glands or signet ring cells)
LARGE CELL VARIANT OF SCCOHT
LARGE CELL VARIANT OF SCCOHT
MUCINOUS EPITHELLEIUM
MUCINOUS EPITHELIUM

CK7

CK20
MORE STROMA
SPINDLE CELLS
Small Cell Carcinoma of Ovary of Hypercalcaemic Type- MISNOMER

- **Small**- cells not always small
- **Carcinoma**- no proof that epithelial neoplasm
- **Hypercalcaemic**- serum calcium only elevated in 2/3 cases
HISTOGENESIS- SCCOHT

- unknown (WHO 2014- categorised among miscellaneous ovarian neoplasms)
- epithelial, germ cell, sex cord and neuroendocrine origin suggested
- until relatively recently never described in association with another neoplasm (except 1 case of mucinous borderline tumour; PMID 21623206)
IMMUNOHISTOCHEMISTRY

• until recently no specific (or even very useful) marker (immunohistochemistry of limited value)
• most (not all) WT1 positive (usually diffuse nuclear positivity)
• many other markers may be positive- usually focal- CD10, calretinin, EMA, cytokeratins, CD99, CD56
• hormone receptors, inhibin negative (differential with JGCT and other sex cord-stromal tumours)
WT1 IN SCCOHT
“EPITHELIAL” MARKERS IN SCCOHT

AE1/3

EMA
DIFFERENTIAL DIAGNOSIS OF SCCOHT (small cell or large cell tumour)

- ovarian small cell neuroendocrine carcinoma
- metastatic small cell carcinoma
- sex cord-stromal tumour (AGCT, JGCT, SLCT)
- desmoplastic small round cell tumour (DSRCT)
- PNET/Ewing family of tumours
- endometrial stromal sarcoma
- malignant melanoma
- undifferentiated carcinoma
- rhabdomyosarcoma, neuroblastoma, haematopoietic neoplasms
- germ cells tumours

- MANY OF THESE NEOPLASMS OFTEN OCCUR IN YOUNG FEMALES, ARE HIGHLY AGGRESSIVE AND REQUIRE SPECIFIC TREATMENTS
OVARIAN SMALL CELL NEUROENDOCRINE CARCINOMA

- this is a high-grade neuroendocrine carcinoma
- WHO 2014 - “ovarian small cell carcinoma of pulmonary type”- POOR TERM; will be removed in WHO 2020
- TOTALLY DIFFERENT TUMOUR TYPE TO SCCOHT which is not a neuroendocrine tumour
- identical histologically to pulmonary small cell carcinoma (and small cell neuroendocrine carcinomas at other sites)
- usually older age group than SCCOHT
- sometimes associated with an ovarian carcinoma (especially endometrioid) or a teratoma
- need to exclude secondary if no other tumour type
- extremely aggressive behaviour
synaptophysin
Juvenile Granulosa Cell Tumour
MALIGNANT MELANOMA OVARY
DEVELOPMENTS REGARDING SCCOHT

- 3 papers in Nature Genetics 2014
- SMARCA4/BRG1 mutated in almost all SCCOHT (somatic or germline mutations)
- SMARCA4/BRG1 (2%) and SMARCB1/INI1 (98%) mutated in virtually all malignant rhabdoid tumours and atypical teratoid tumours
- SMARCA4 and SMARCB1 are members of SWI-SNF complex (also includes SMARCA2/BRM; ARID1A, ARID1B)
Germline and somatic SMARCA4 mutations characterize small cell carcinoma of the ovary, hypercalcemic type

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GERMLINE SMARCA4 MUTATIONS

• Up to 43% of SCCOHT in some studies
• Almost certainly marked overestimate-referral bias
• Reason why not more familial tumours-patients often diagnosed at young age so don’t reproduce; some inherit mutation from father; some have new mutation; need second somatic mutation in tumours; penetrance unknown
IS SCCOHT A FORM OF MALIGNANT RHABDOID TUMOUR?

- Clinical similarities (young, aggressive neoplasms)
- Morphological similarities (rhabdoid and non-rhabdoid cells)
- Molecular similarities (SMARCA4, SMARCB1)
- SCCOHT could be regarded as a form of malignant rhabdoid tumour (could be renamed malignant rhabdoid tumour of the ovary) (BUT SCCOHT TERMINOLOGY IS WELL ESTABLISHED AND NOT LIKELY TO CHANGE)
No small surprise – small cell carcinoma of the ovary, hypercalcaemic type, is a malignant rhabdoid tumour

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**SMARCA4 (BRG1) IMUNOHISTOCHEMISTRY**

- Loss of nuclear staining in most SCCOHT secondary to mutation
- **Very useful marker of SCCOHT**
- Retention of nuclear staining in almost all mimics (occasional exceptions)
- SMARCA4/BRG1 lost in 49 of 51 SCCOHT (retained cases could be due to *SMARCB1/INI1* mutation or type of *SMARCA4 mutation which does not result in protein loss*) (Histopathology 2016;69;727-738)
- Occasional SCCOHT exhibit weak retained nuclear staining
- Concurrent loss of SMARCA4 and **SMARCA2** seems to be specific for SCCOHT; occasional tumours only loss of SMARCA2
SMARCA4 (BRG1)
IMMUNOHISTOCHEMISTRY
RARELY RETENTION OF SMARCA4 BUT SMARCA2 MAY BE LOST
HIGH-GRADE NEUROENDOCRINE CARCINOMA OVARY

SMARCA4
DIAGNOSTIC/GENETIC TESTING ALGORITHM FOR SCCOHT

• Have the tumour reviewed by a gynaecological pathologist and the diagnosis confirmed (this may necessitate SMARCA4 (BRG1) immunohistochemical staining)

• Once the diagnosis is confirmed, counsel the patient for germline *SMARCA4* testing

• In the case of a germline mutation, consider removal of the unaffected ovary in unilateral SCCOHT if only one ovary has been removed

• In the case of a germline mutation, test family members for mutation
2 cases of SCCOHT in association with teratomas
Several similar cases reported in literature
SUGGESTS THAT SCCOHT MAY BE A PRIMITIVE GERM CELL TUMOUR ARISING FROM A TERATOMA
Often positive with SALL4
CASE ASSOCIATED WITH TERATOMA
PROGNOSTIC FACTORS IN SCCOHT

- review of all published cases and unpublished series of SCCOHT (Gynecologic Oncology 2016;141;454-460) (293 cases)
- stage- most important prognostic factor (stage 1- 5 year survival 54%; stage 2-3- 41%, stage 4- all with follow up died)
- next most important prognostic indicator was treatment type- HDC-aSCR had better overall survival than other adjuvant treatments (81% of stage 1 and 71% of stage 2-4 patients alive after 24 months (only significant in stage 2-4)
- worse prognosis over age 40
- if no relapse within 5 years, high chance of “cure”
- patients with germline mutations significantly younger (all less than 15 years had germline mutations)
- no significant prognostic difference between those who carried germline mutations and those who did not
- NEWLY CHARACTERISED MOLECULAR EVENTS MAY OPEN WAY FOR TARGETTED THERAPY; immune checkpoint inhibitors- some promising results
GROWING NUMBER OF TUMOURS WITH SMARCA4 LOSS

- SCCOHT
- Undifferentiated/ dedifferentiated carcinomas endometrium and ovary
- Undifferentiated uterine sarcomas
- Similar lung, mediastinal and GI tumours
- ? ARE THESE CARCINOMAS/ SARCOMAS/ RHABDOID TUMOURS (dyscohesive, sometimes rhabdoid, limited expression of epithelial markers)(? Are dedifferentiated endometrial carcinomas really funny carcinosarcomas)
WHY ARE THESE TUMOURS NOT FOUND IN THE TESTIS?

- ? Misdiagnosed as something else (unlikely)
- Teratoma theory (more common in ovary; not picked up as early in ovary)
- ? Derived from neural crest cells (found in ovary but not in testis apparently)
WHO Classification of Tumours
ONLINE

Now available at: [tumourclassification.iarc.who.int](http://tumourclassification.iarc.who.int)

Access to the following books:

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Breast Tumours

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More details from the IARC team – Booth A14, 2nd level, Agora 2 Hall  
9am to 5.15pm, from Sunday 8 to Tuesday 10 September