IMMUNOHISTOCHEMISTRY

• lot of immunophenotypic overlap between cervical MGH and changes on surface of endometrioid adenocarcinoma
• ? vimentin and p16 may be of value
• IN PRACTICE- IMMUNOHISTOCHEMISTRY OF LIMITED VALUE
CONFUSION WITH SEROUS/ CLEAR
CELL CARCINOMA COMPONENT
WHY IS IT SO DIFFICULT TO TYPE ENDOMETRIAL CARCINOMAS?

- mixed tumours
- no good marker (WT1 in ovary)
- lot of endometrial carcinomas exhibit microsatellite instability- prone to mutations with different clones emerging
- can we define a “bad actor” as a Tp53 mutated tumour and use immunohistochemistry as a surrogate (similarities to ovarian carcinomas)
OVARY

• Type 1 carcinomas (good prognosis)- endometrioid, clear cell, mucinous, low grade serous (no Tp53 mutation)

• Type 2 carcinomas (poor prognosis)- high grade serous (undifferentiated, carcinosarcoma) (Tp53 mutation)

• SAME IN UTERUS BUT BECAUSE OF MORPHOLOGICAL OVERLAP AND LACK OF GOOD MARKER- use p53 immunohistochemistry
UNDIFFERENTIATED ENDOMETRIAL CARCINOMA

• category included in WHO classification
• concept popularised in recent years by MD Anderson group
• expanded definition- “a tumour composed of medium or large cells with complete absence of glandular or squamous differentiation and with absence or minimal (<10%) neuroendocrine differentiation”
UNDIFFERENTIATED ENDOMETRIAL CARCINOMA

• 9% of all endometrial cancers
• specific histological diagnosis
• pathologists often miss-reluctant to make diagnosis
• may be associated with low grade endometrioid adenocarcinoma (dedifferentiated endometrioid adenocarcinoma or mixed endometrioid and undifferentiated carcinoma)
• undifferentiated/dedifferentiated element may be seen in recurrence or metastasis
• DYSCOHESSIVE TUMOUR CELLS
UNDIFFERENTIATED CARCINOMA
IMMUNOHISTOCHEMISTRY

• usually positive for keratins and EMA but staining may be very focal, although strong
• EMA staining more consistent than cytokeratins
• minor neuroendocrine marker positivity not uncommon (definition allows 10%)
• often diffuse p16 and aberrant p53
• ER often negative
IMMUNOHISTOCHEMISTRY

- p53
- TTF1
- p16
- CD56
OTHER MORPHOLOGICAL FEATURES

• rhabdoid cells
• myxoid stroma
• tumour giant cells
• lymphoepithelioma-like
UNDIFFERENTIATED ENDOMETRIAL CARCINOMA
DEDIFFERENTIATED ENDOMETRIOID ADENOCARCINOMA- mixed low grade endometrioid adenocarcinoma and undifferentiated carcinoma
PROGNOSIS

• extremely poor prognosis (worse than grade 3 endometrioid carcinoma)

• largest study- 54% presented with advanced stage, 75% died of tumour; corresponding figures for grade 3 endometrioid carcinoma- 30% and 30%
DIFFERENTIAL DIAGNOSIS

• grade 2 or 3 endometrioid adenocarcinoma
• undifferentiated sarcoma (some may have epithelioid appearance) (value of EMA)
• solid variant of serous carcinoma
• carcinosarcoma
• small cell or large cell neuroendocrine carcinoma (minor degree of neuroendocrine marker positivity allowable)
• malignant lymphoma, plasmacytoma
• PNET
• epithelioid sarcoma, rhabdomyosarcoma
DIFFERENTIAL DIAGNOSIS - grade 3 endometrioid adenocarcinoma

Glands - not in undiff Ca

Squamous elements - not in undiff Ca
DIFFERENTIAL DIAGNOSIS - grade 2 endometrioid adenocarcinoma
DIFFERENTIAL DIAGNOSIS-
carcinosarcoma

2 elements and sharp
demarcation may suggest
carcinosarcoma

Epithelial component is
low grade in
dedifferentiated carcinoma
and high grade in
carcinosarcoma

Immunohistochemistry
(cytokeratins and EMA)
DIFFERENTIAL- SOLID VARIANT OF SEROUS

p53

p16
MMR ABNORMALITIES

• ? dedifferentiated/ undifferentiated carcinomas more common with MMR abnormalities, including HNPCC/Lynch syndrome

• also LUS location, tumour infiltrating lymphocytes, Crohn’s like lymphoid aggregates, tumour heterogeneity, synchronous ovarian clear cell carcinoma (PATHOLOGISTS NEED TO BE AWARE)

• often get loss of MLH1/PMS2- can be Lynch or secondary to MLH1 methylation
MMR IMMUNOHISTOCHEMISTRY

MLH1  PMS2
Distinction Between Endometrial and Cervical Adenocarcinoma (Pitfalls in Immuno Panel)

- primary management and adjuvant therapy often differs
- radiology often not definitive
Panel

- ER
- vimentin
- monoclonal CEA
- p16
- HPV studies (PCR or ISH)
Endometrial Adenocarcinoma of Endometrioid Type- Classic Immunophenotype

• ER diffusely positive
• vimentin diffusely positive
• CEA negative (squamoid areas may be positive) or rarely focally positive
• p16 negative, focal or diffuse (but patchy/mosaic pattern) positivity (squamous areas may be positive) (VERY FEW CASES TOTALLY NEGATIVE)
vimentin
p16 in endometrioid ca
Cervical Adenocarcinoma- Classic Immunophenotype

- ER negative or weakly positive
- vimentin negative
- CEA usually positive
- p16 diffusely positive
Bcl2

endometrioid ca uterus
cervical adenocarcinoma
Pitfalls in Immunohistochemical Panel

- only useful for well differentiated tumours (low grade endometrioid versus usual endocervical)
- not useful for non-HPV related cervical adenocarcinomas
- small biopsies
- HIGH GRADE ENDOMETRIAL CAS (serous, undifferentiated etc) often diffusely p16 positive (sometimes ER negative)-
**SIGNIFICANT PITFALL** (value of HPV studies and p53)
- mucinous carcinoma of endometrium (or mucinous areas in endometrioid) has inconsistent immunophenotype
- **UNEXPECTED ABERRANT STAINING PATTERNS**
Bcl2
CERVICAL ADENOCARCINOMA- ER
ENDOMETRIOID ADENOCARCINOMA- ER NEGATIVE
MELF (MICROCYSTIC ELONGATED AND FRAGMENTED) PATTERN MYOMETRIAL INVASION

- common pattern of myometrial involvement in low grade endometrioid carcinomas
- glands associated with fibromyxoid stromal reaction
- flattened epithelium, microcysts
- elongation and fragmentation of glands
- may simulate vascular invasion (may also be associated)
- may get single invasive cells deep in myometrium (CKs may be useful)
- may be poor prognostic feature/ risk of nodal involvement
- PATHOLOGISTS SHOULD REPORT
MELF- cytokeratin
MELF IS MANIFESTATION OF EPITHELIAL-MESENCHYMAL TRANSITION (EMT)

- reduced expression of E-cadherin and beta catenin
- cadherin switching
- increased expression of cyclin D1/fascin/CK7/CK19/p16 compared to non-MELF glands
- decreased hormone receptors/galectin 3/MIB1
- MELF changes represent specific tumour-stroma interaction
MELF

CK19  

p16
LYMPHOVASCULAR INVASION IN ENDOMETRIAL ADENOCARCINOMAS

• independent prognostic factor in stage 1 endometrioid adenocarcinomas
• more likely with deep myometrial invasion and at advancing edge of tumour
• NOW decisions regarding management taken on presence or absence (IMPORTANT TO DIAGNOSE ACCURATELY)
• lymphoid aggregates may be a clue
• DO NOT UPSTAGE IN ABSENCE OF TUMOUR OUTSIDE VESSELS- BUT MENTION IN REPORT
• MELF may simulate vascular invasion (may also be associated)
LVI IN ADNEXAE - DOESN’T UPSTAGE
CHANGES ASSOCIATED WITH LAPAROSCOPIC HYSTERECTOMY AND INTRAUTERINE MANIPULATORS

• common with laparoscopic hysterectomies and intrauterine manipulator
• more common with polypoid tumours
• VASCULAR PSEUDOMETASTASES - predominantly thick-walled vessels in outer half of myometrium
• degree of vascular invasion inconsistent with low tumour grade and stage
• FEW STUDIES WITH LONG TERM FOLLOW UP
OTHER FEATURES

• disruption of endometrial lining
• endometrial and myometrial clefts
• floaters in tubal lumina and cervix
• serosal carry over
• increased incidence of positive peritoneal washings
VASCULAR PSEUDOMYXOMA
FEATURES
CONCLUSIONS

• many problems in subtyping endometrial cancers
• WE NEED TO DO BETTER (COMPARISONS WITH OVARIAN CARCINOMA)