Diagnostic Immunochemistry in Gynaecological Neoplasia Guide to Diagnosis


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Abstract- AIM AND OBJECTIVE - This short review provides an updated overview of the essential immunochemical markers currently used in the diagnostics of gynaecological malignancies along with their molecular rationale. The new molecular markers has revolutionized the field of IHC

MATERIAL METHODS - We have reviewed the recent ihc markers according to literature revision and our experience, we have discussed the the use of ihc ,

CONCLUSION- The above facts will help reach at a diagnosis in morphologically equivocal cases of gynaecology oncology pathology, and guide us to use a specific the panel of ihc ,which will help us reach accurate diagnosis.

I. INTRODUCTION

IHC combines microscopic morphology with accurate molecular identification and allows in situ visualisation of specific protein antigen. IHC has definite role in guiding cancer therapy. The role of pathologist is increasing beside tissue diagnoses, to performing IHC biomarker analyse, assisting the development of novel markers. IHC markers are being in used in new perspective, in guiding anticancer therapy. IHC represents a solid adjunct for the classification of gynaecological malignancies that improves intraobserver reproducibility and has potential of revealing unexpected features(1)

OVARIAN IHC:

- PAX -8 is the most specific marker, emerging to diagnose primary ovarian cancer, but it lacks sensibility as it is also expressed in metastasis from endocervix, kidney and thyroid. Fig 1 table2(1)
FIG-1 (A) Is the immunohistochemical algorithm for a PRIMARY AND METASTATIC CARCINOMA. The (A) algorithm addresses the markers which help to distinguish morphologically equivocal primary ovarian cancers using five to nine markers. The (B) algorithm the step wise immunohistochemical approach of metastatic ovarian carcinoma, six main immunospecific stains and tissue specific markers. CK-7 and CK-20 are co expressed, they are schematically represented as continuous vertical from the prevalent (CK-7) positivity at the upper end to CK-20 positivity at the lower end, the frequency (upper end) to prevalence CK-20 positive at lower end. The frequency of metastatic disease is correlated with font size. CC is clear cell carcinoma, ccRCC clear cell renal carcinoma, CK cytokeratin, EAC endocervical adenocarcinoma, EMC endometroid carcinoma, ER estrogen receptor, GCDP-15 gross cystic disease protein-15, HGSC high grade serous carcinoma, LGSC low grade serous carcinoma, MC mucinous carcinoma, Mmgb mammoglobin, NAPSA NAPSIN A, PR progestrone receptor, UEMC uterine endometroid adenocarcinoma.
<table>
<thead>
<tr>
<th>Primary ovarian tumours</th>
<th>PAX8*</th>
<th>WT1†</th>
<th>ER</th>
<th>p53</th>
<th>ARID1A</th>
<th>β-catenin</th>
<th>calr</th>
<th>CK7</th>
<th>CK20</th>
<th>CEA</th>
<th>Specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGSC</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>M</td>
<td>wt</td>
<td>wt</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>p16</td>
</tr>
<tr>
<td>LGSC</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>wt</td>
<td>wt</td>
<td>wt</td>
<td>-/+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Kras mut, BRAF mut</td>
</tr>
<tr>
<td>EMC</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>wt&gt;M</td>
<td>M&gt;wt</td>
<td>M&gt;wt</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>PTEN and MMR loss</td>
</tr>
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<td></td>
<td>Presence of endometriosis</td>
</tr>
<tr>
<td>CCC</td>
<td>+</td>
<td>-</td>
<td>-/+</td>
<td>wt</td>
<td>M&gt;wt</td>
<td>wt</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Napsin A, HNF1β, AMACR</td>
</tr>
<tr>
<td>MC</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>wt&gt;M</td>
<td>wt</td>
<td>wt</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-/+</td>
<td>Presence of teratoma or Brenner tumour</td>
</tr>
<tr>
<td>SMT</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>wt</td>
<td>M&gt;wt</td>
<td>wt</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Presence of endometriosis</td>
</tr>
<tr>
<td>GCT/SCST</td>
<td>-/+</td>
<td>+</td>
<td>+/-</td>
<td>wt</td>
<td>wt</td>
<td>wt</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Inhibin, SF1, FOXL2 mut (GCT), DICER1 mut (SCST), EMA</td>
</tr>
<tr>
<td>SCC-HT</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>M</td>
<td>wt</td>
<td>wt</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>SMARCA4 (BRG1) loss</td>
</tr>
</tbody>
</table>
WT-1 – is most sensitive and specific marker of serous histiotype.\(^{(2)}\)

- It can be used to discriminate serous from other histiotypes.
- Nuclear expression of WT-1 (muellerian marker)
- This marker is consistently nuclear expressed in normal tubal epithelium; thus coherently expressed in HGSC and LGOC
- Recently a practical approach to use IHC in classification of primary ovarian carcinoma using IHC algorithm. Basically the four markers WT-1, P53, Napsin a and progestrone receptors (PR). A modified IHC ALGORITHM that includes interchangeable markers, namely HNF1BETA and AMACR (racemase or p504s) for CCC. Fig 1a and fig 1b \(^{(1)}\)
- ER and vimentin for endometroid carcinomas

**Endometroid versus HGSC**

- HGSC with glandular and cribriform may closely resemble endometroid
- WT-1, 60-70% OF THE HGSC. \(\text{p53}\) is overexpressed, and diffusely and intensely nuclear staining of \(\text{p53}\) \(^{(3)}\). 30% of high grade endometroid may have \(\text{p53}^+\)ve.
- \(\text{P16}^+\) is mosaic in endometroid whereas diffuse intense or completely blank in HGSC
- ENDOMETROID - 50% express the beta catenin
- 52% downregulation ARIDIA
- 42% downregulation pten
• HGSC - PTEN downregulation
• CCNE1 overexpression, absent in endometroid

CLEAR CELL VERSUS HGSC-
• HGSC with morphology of cytoplasmic clearing from CCC or vice versa CCC with eosinophilic cytoplasm from HGSC
• WT-1 and ER chiefly expressed in HGSC, along with aberrant p53, as well as nuclear HNF1 beta
• Cytoplasmic napsin and AMACR POSITIVE IN CCC(4)

• ARID1A can be negative in 57% cases of CCC

ADVANCED OVARIAN VERSUS UTERINE SEROUS CARCINOMA
AND SYNCHRONOUS PRIMARY OF ENDOMETRIUM AND OVARY
• WT-1 – is diffusely positive in MAJORITY HGSC, whereas in uterine serous carcinoma upto one third of cases
• WT-1 negative in both points to primary endometrium
• If staining in different patterns at two different sites, suggest two synchronous primary.(4-6)

Peritoneal serous carcinoma versus epitheloid mesothelioma
• The most reliable recent marker loss of BRCA – associated protein 1(BAP-1), deletion of P16 BY FISH for mesothelioma
• Mesothelioma - calretinin, keratin5/6, D2-40 positive
• Serous carcinoma - Pax-8, ER, claudin -4, MOC31 and Ber-EP4 positive in serous carcinoma(7-8)

MUCINOUS ADENOCARCINOMA - PRIMARY/METASTATIC
• There is a overlap of ihc between primary and metastatic gastrointestinal tumors
• CDX-2, CK20 and SATB2 are diffusely expressed and strongly positive in colorectal adenocarcinoma,
• Where as ,the above markers are less intense and weak, in comparison to CK-7 in Primary ovarian carcinomas, with exception of rare intestinal type mucinous ovarian tumors from teratomas
• Primary ovarian- positive for CA125, pax-8
• Ca125- BREAST, lung, pancreas, cervix and uterine carcinomas and mesothelioma , although, CK20+/CK7- VE IS PROTO TYPICAL OF METASTATIC ADENOCARCINOMA HENCE SPECIFIC MARKERS pax-8 and sat-b2(9-10) both highly specific, but sensitivity is low.
• ER AND PR are negative in both intestinal type and metastatic carcinoma, cdx2 is a site unspecific
• marker of intestinal differentiation
• Smad4 (DPC4)- is lost in half pancreatic cancer
• Small cell carcinomas of hypercalcemia versus other mimic(HGSC and adult granulosa)
• specific is loss of SMARCA4(BRG1) expression(11)

CCC VERSUS YOLK SAC TUMOR
Both share similar morphology- glycogen rich clear cells
CCC- is usually arises in a background of endometriosis, or clear cell adenofibroma and positive AMACR, CK-7, EMA and Napsin-a but negative for AFP and GLYPICAN as opposed to yolk sac tumor(12,13,14)
SALL-4 is the germ cell marker positive in yolk sac tumor(14)

FIG-3  ihc staining  image of staining of the metastaic and primary ovarian carcinoma

IHC OF NON-EPI THELIAL TUMORS-
  ihc of primitive germs cell malignancies
dysgerminoma- sall4+, OCT3/4+, SOX-2-VE
YST- SALL4+, OCT3/5 -VE
EC- SALL4+, OCT3/4+VE,SOX2+VE
SCST- AMBIGUOUS CASES – ALONG WITH F0XL2,CALRETININ/OR INHIBIN ALPHA
FISH - FOXL2(402C-G) TO DIAGNOS AGCT(14)
Fig-4 YOLK SAC COMPONENT OF A MIX GERM CELL TUMOR
Fig -5 EMBRYONAL CELL OF MIX GERM CELL TUMOR
Fig. 6: IMMATURE AND MATURE TERATOMA IN MIX GERM CELL TUMOR
Photomicrographs showing immunohistochemical detection of podoplanin in nongerminomatous GCTs. In immature teratomas, positive staining for podoplanin (brownish color) is limited to basal layers of immature squamous epithelium (a) and immature columnar epithelial cells (b). Embryonal carcinoma (c), yolk sac tumor (d), and choriocarcinoma (e) are negative for podoplanin. Bar 10 μm
Hcg +ve in giant syncytotrophoblast (A)
© cd-30+ve
(d) oct-4+ve embyronal component
Ovarian small cell carcinoma of hypercalcemic type (OSCCHT) is a rare neoplasm with an aggressive behavior, broad differential diagnosis, and unknown histogenesis. d/d of small round cell tumors

Scst, small cell morphology, small round blue cell tumor, neuroendocrine small cell, small cell carcinoma of pulmonary type, this may be a component of atypical ovarian surface epithelial – stromal tumor (14). In addition to pnet, rhabdomyosarcoma, neuroblastoma, sexcord-stromal-tumor, metastatic pulmonary small cell carcinoma
Fifteen OSCCHTs (including four of the "large cell" variant) were stained with a range of antibody
Cases were stained with AE1/3, EMA, BerEP4, CK5/6, calretinin, WT1, chromogranin, CD56, synaptophysin, CD99, NB84, desmin, S100, CD10, alpha inhibin, TTF1, and p53.

Staining was classified as 0 (negative), 1+ (<5% cells positive), 2+ (5% to 25% cells positive), 3+ (26% to 50% cells positive), or 4+ (>50% cells positive).

All cases were positive with p53 (two 1+, five 3+, eight 4+),

14 of 15 cases were positive with WT1 (one 1+, thirteen 4+),

14 of 15 with CD10 (three 1+, four 2+, two 3+, five 4+),

13 of 15 with EMA (three 1+, three 2+, two 3+, five 4+),

11 of 15 with calretinin (nine 1+, one 3+, one 4+), 9 of 15 with AE1/3 (eight 1+, one 2+),

4 of 15 with CD56 (one 1+, two 2+, one 4+),

3 of 15 with BerEP4 (two 2+, one 4+),

2 of 15 with synaptophysin (two 1+), and 1 of 15 with S100 (4+). This was a study done in an institute in Japan.
• SLCT-FOXL2 –VE TUMORS , AT LEAST CALRETININ/OR ALPHA INHIBIN IS POSITIV
• RECNTLY DICER1 MUTATION
• SCCOHTs (small cell carcinoma of ovary hypercalcemic type)
• SMARC4 IHC SENSITIVE AND SPECIFIC IN DIAGNOSIS OF SCCOHT( THERE IS LOSS OF EXPRESSION OF SMARC4(BRG1))
• POORLY DIFFERENTIATED TUMORS, RESEMBLING SMALL CELL OR ROUND CELL IN MORPHOLOGY
• D/D adult granulosa cell tumors, metastatic melanoma, ewings sarcoma, dysgerminoma and undifferentiated carcinoma.
• SMARC4 – IS USEFUL
**Fig-12 (ihec markers of small round cell tumors)**

**FALLOPIAN TUBE IHC**
- Serous tubal intraepithelial carcinoma vs other mimics (HGSC)
- Stics – Marked cytological atypia with a high Ki-67>10% proliferation index and P53 ihec mutant form (16)

**ENDOMETRIAL IHC**
- The dualistic pathogenetic model has been proposed for endometrial cancer
- Type I- Endometroid variety
- Type II- USC, CCC, Malignant mixed muellerian tumor, undifferentiated
- The glandular cribriform USC, papillary endometroid carcinoma and endometroid carcinomawith clear cells, there distinction needs IHC
- Endometriod are ER and PR positive, whereas USC AND CCC and _ve
- P53 and mutant A POSITIVE IN CCC (17)
- Arias stella raetion and some endometroid carcinomas exHNF1 beta

Fig-13 (IHC of mesenchymal tumors of uterine tumors)

Table 3: Immunohistochemical (IHC) markers in the differential diagnosis of endometrial carcinomas

<table>
<thead>
<tr>
<th></th>
<th>vimentin (vim)</th>
<th>ER</th>
<th>PR</th>
<th>ARID1A</th>
<th>β-catenin</th>
<th>AMACR</th>
<th>HNF1α</th>
<th>Nap103A</th>
<th>p53</th>
<th>p16</th>
<th>Specific</th>
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</thead>
<tbody>
<tr>
<td><strong>Endometrial tumors</strong></td>
<td></td>
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<tr>
<td>EMC</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>M&gt;wt</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>PTF1 and MMR loss</td>
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<td>USC</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>wt</td>
<td>-</td>
<td>-/+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>CCNE1 amplification</td>
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<tr>
<td>CCC</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>wt</td>
<td>+/-</td>
<td>+/-</td>
<td>wt&gt;M</td>
<td>-</td>
<td>-</td>
<td>MMR loss</td>
</tr>
<tr>
<td>UC</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>M&gt;wt</td>
<td>NA</td>
<td>NA</td>
<td>M&gt;wt</td>
<td>-</td>
<td>+/-</td>
<td>E-cadherin and MMR loss</td>
</tr>
<tr>
<td>MMMT</td>
<td>+/+</td>
<td>-/+</td>
<td>-/+</td>
<td>wt&gt;M</td>
<td>wt</td>
<td>NA</td>
<td>NA</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>WT1, desmin, CD10, h-caldesmon, myogenin, S100, Myo-D1. Biphasic pattern</td>
</tr>
</tbody>
</table>

p53 M corresponds to intense and diffuse positivity in ≥60% of cells or complete negativity; p53 wt is the presence of rare cells weakly positive or positivity in <6% desm, desmin; h-caldesmon; HGESS, high-grade endometrial stromal sarcoma; LGESS, low-grade endometrial stromal sarcoma; LM, leiomyoma; LMS, leiomyosarcoma; MUT, mutant pattern; wt, wild-type pattern.

Table 4: Immunohistochemical markers in the differential diagnosis of endometrial mesenchymal tumors

<table>
<thead>
<tr>
<th></th>
<th>vimentin (vim)</th>
<th>ER</th>
<th>PR</th>
<th>p53</th>
<th>p16</th>
<th>CD10</th>
<th>desm</th>
<th>h-caldesmon</th>
<th>Specific</th>
</tr>
</thead>
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<tr>
<td><strong>Endometrial mesenchymal tumors</strong></td>
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<tr>
<td>HGESS</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>wt</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>JAG1-SUZ12 fusion</td>
</tr>
<tr>
<td>HGESS</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>wt</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>YWHAE-NUTM2A/B fusion, cyclin D1, c-KIT, K5-67 high</td>
</tr>
<tr>
<td>LM</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>wt</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>Actin</td>
</tr>
<tr>
<td>LMS</td>
<td>+</td>
<td>-/+</td>
<td>-/+</td>
<td>M&gt;wt</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>K5-67 high</td>
</tr>
</tbody>
</table>
UNDIFFERENTIATED –are negative or focal positive for CKS(AE1/AE3,8,18,8/18), vimentin, EMA, ER, PR, chromogranin, synaptophysin, E-cadherin and CTNNB1, TP53, AND MMR in 30%, 30% and 50% (18).

CD 34 +ve in 29% of undifferentiated, loss of expression of SMARCA4 AND SMARCA2 (18).

MMMT - high P53/wt-1 and low ER AND PR.

Muellerian adenosarcoma vs endometrial polyp.

Ki-67 +ve in adenosarcoma.

ENDOMETRIAL STROMAL SARCOMA

LGESS - CD10 +VE, ER and PR +VE.

HGESS - CD-10, ER, PR –VE, WHEREAS STRONGLY NUCLEAR POSITIVE FOR CYCLIN D1 AND MEMBRANOUS/ CYTOPLASMIC REACTIVITY FOR C-KIT.

UNDIFFERENTIATED – VARIABLE EXPRESSION OF CD-10, ER, PR mostly diagnosed by exclusion of leiomyosarcoma, undifferentiated carcinoma, rhabdomyosarcoma and diffuse B-LARGE LYMPHOMA. (19) IHC(REQUIRED FOR UDEC).

CK- CK-(ae1/ae3,8,18) is frequently positive, CK- 18 more frequently positive (1).

CAM5.2 (2)

EMA- usually focally positive, very rarely diffusely positive.

special emphasis should be give to intensity of staining of keratin AND EMA than the percentage of staining (3).

IHC(REQUIRED FOR UDEC)

CK- CK-(ae1/ae3,8,18) is frequently positive, CK- 18 more frequently positive (1).

CAM5.2 (2)

EMA- usually focally positive, very rarely diffusely positive.

special emphasis should be give to intensity of staining of keratin AND EMA than the percentage of staining (3).

ER/PR- CONFLICTING DATA (1)

Relative frequency loss of SMARC4 and SMARC2.

Vimentin –ve or may be focally positive, Focally positive CD-10(2).

Focal positivity for S-100, CD- 56.

Recently CD-34 expression.

UEC- is completely negative SMA, desmin, HMB-45.

OTHER IHC MARKERS FOR UEC

Synaptophysin, chromogranin, CD56- usually –ve, may be focally positive (4,5).

P-16 is diffusely / strongly positive +/- ve.

P53 wt- weakly nuclear positivity seen.

SPECIFIC UEC- NEARLY HALF HAVE LOSS OF ONE MMR PROTEIN, E- CADHERIN (4,5).
Figure 4. Cytokeratin MIF immunostain showing focal intense reactivity (original magnification ×20).

Figure 5. The tumor is focally positive for vimentin immunostain (original magnification ×40).

Figure 6. Cohesive growth of the solid component of the poorly differentiated endometrioid adenocarcinoma, FIGO (International Federation of Gynecology and Obstetrics) grade 3 (hematoxylin-eosin, original magnification ×20).

Figure 7. Cytokeratin MNF immunostain showing diffuse and strong reactivity in poorly differentiated endometrioid adenocarcinoma, FIGO International Federation of Gynecology and Obstetrics, grade 3 (hematoxylin-eosin, original magnification ×20).

FIG 14

EMA

Uec and iha stainind of EMA FIG15
FIG-16 UEC AND p-16. p53 IHC

Fig-17 endometrial carcinoma with lynch syndrome
• ENDOMETRIAL HYPERPLASIA VS ENDOMETRIAL INTACT EPITHELIAL CARCINOMA VS ENDOMETROID CARCINOMA
• EIN- loss of PAX-2(20), NUCLER BETA CATENIN, MLH1 OR PTEN LOSS
• ENDOMETROID – ADDITIONAL LOSS OF ARIDIA and increased expression of Ki-67(21)
• Endometrial stromal vs uterine smooth muscle tumor
• cellular leiomyomas
• Smt are h- caldesmon desmin NOT CD 10
### Immunoprofiles of Similar Spindle Cell Neoplasms

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Myogenin</th>
<th>Desmin</th>
<th>SMA</th>
<th>H-caldesmon</th>
<th>S100</th>
<th>GFAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC-RVS</td>
<td>++</td>
<td>++</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>-</td>
<td>+/-</td>
<td>++</td>
<td>+/-</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>Low-grade myofibroblastic sarcoma</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>Malignant peripheral nerve sheath tumor with rhabdomyoblastic differentiation</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Desmoplastic melanoma</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>++</td>
<td>+/-</td>
</tr>
</tbody>
</table>

Abbreviations: GFAP, glial fibrillary acidic protein; SC-RVS, spindle cell rhabdomyosarcoma; SMA, smooth muscle actin; +, positive; ++, strongly positive; +/-, occasionally positive; ++/-, occasionally positive, more often negative; -, negative.

**Fig-12**

D/D UEC (SPINDLE CELL MORPHOLOGY)

**Fig-19**

POORLY DIFFERENTIATED CARCINOMA OF ENDOMETRIAL CARCINOMA

http://dx.doi.org/10.29322/IJSRP.9.09.2019.p9346
POORLY DIFFERENTIATED CARCINOMA OF ENDOMETRIUM OF SPINDLOID CELL MORPHOLGY FIG 20

SPINDLE CELL CARCINOMA IS A POORLY DIFFERENTIATED CARCINOMA. BASICALLY A DIAGNOSIS OF EXCLUSION -

GRADE 3 endometroid adenocarcinoma – Spindle cell pattern firstly -the low grade endometroid carcinoma immature squamous differentiation

Solid pattern of serous cancer – CARCINOSARCOMA

• Rhabdomyosarcoma
• Lymphoma
• Melanoma
• Secondly- those woman on hormonal therapy may show spindle pattern
uec/endometroid (7)

Morphology   UEC

ENDOMETROID

• Growth     Diffuse
  solid and glandular

• Glands     absent
  present in 1-4% of
uec/endometroid (7)

Morphology UEC
ENDOMETROID

• Growth Diffuse
  solid and glandular

• Glands absent
  present in 1-4% of

UEC/SEROUS(8)
  • Morphology - pappilary formation, psammo--bod ies
  Solid pattern of serous cancer – ihc –p53 ,+,shows a diffuse ck positivity

Carcinosarcoma / uec(SPINDLE CELL MORPHOLOGY)(8)
  • there is disinct compartmentalisation of the carcinoma and sarcomatous component.there are presence of heterologous elements.
  • Morphological features is enough for diagnosis
  • High +VE WT-1/P53 is helpful indifferentiating from spindle carcinoma(9)

RHABDOMYOSARCOMA / UEC (SPINDLE CELL MORPHOLOGY)(10)
  • Uniform spindle cell with a herring bone pattern
  • Negative or else focal reactive FOR CK
  • SMA +VE
  • DESMIN+VE, MYOGLOBIN+, CALDESMON
  • +ve in spccBAF-47(INI-1 ) this protein is lost in rhabdoid tumor,
    nuclear expression of is maintained in UEC
  • IHC PANEL SPINDLE CELL CARCINOMA-
    • Specific panel KERATIN(AE1/AE3) AND EMA
    • This panel helps differentiating the SPCC from sarcoma
    • Some cases of spcc show CEA and P63 positive(x3. neville etal elseveir pathology)
    • These two above markers are additional epithelial markers may be done in few spcc, cytokeratin negative, with
      mesenchymal metaplasia and vimentin +.(5)
    • Very rarely SPCC , may be SMA +VE THEN A KI-67. 60% IN SARCOMATOUS regions, 40% in ccarcinomatous
      regions(6)

CERVICAL CANCERS IHC
• cervical squamous neoplasia vs bening mimic(reactive or metaplastic squamous changes, atrophy and cytologic atypia artefact)
• P 16- HPV INTEGRATION is STRONGLY diffusely positive both nuclear and cytoplasm , involving the basal third of epithelial cells(block staining’)
• P-16 block sensitivity posite for HSIL,AND ONE THIRD OF LSIL
• ALTHOUGH HSIL(cin3) is almost invariably positive for p16 the other extremity lsil(cin2) is negative
• P16 positive LSIL progresses whereas negative LSIL regresess

• Ki-67 – positive HSIL
• SCJ MARKERS(ck-7,ck17,mmp7)
• Ck-7 is widely used
• Positive lsil likely to be progressive (21)

IHC FOR SYNDROMIC GYNAECOLOGICAL CANCER
• Lynch syndrome- IHC MLHI , MSH2, MSH6,PMS2
• HBOC -REAL TIME PCR FOR BRCA ANTIBODIES

unexpected immunostains – some organ specific ihc not properly muellerian have also been described in gynaecological tumors (22)

CDX2 - colonic, intestinal. oesphagesl. biliopancreatic, positive in ovarian mucinous carcinomas 36%-94%
cervical adenocarcinokas- 39%
endometrial carcinomas -6-44%

ovarian endometroid carcinoimas- 0-

D2-40 (ALSO KNOWN AS -PODOPLANIN), is a mesothelial and lymphatic endothelial marker
• Besides gynaecological adenomatoid tumors, peritoneal mesothelioma, vascular tumors variable portion of ovarian carcinomas
• 10%-60% of serous carcinomas
• 0-16% mucinous carcinomas
• 0 -55%-CCC
• It is used to differentiate dysgerminoma from other germ cell malignancies, because invariably positive in dysgerminoma

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• **GATA-3** - IS COMMONLY USED IN BREAST AND UROTHELIAL DERIVATION

GATA-3 IS FOCALLY POSITIVE IN ENDOCERVICAL, ENDOMETRIAL, OVARIAN ADENOCARCINOMAS IN UP TO 18%, 23%, 10%

Brenner diffusely GATA-3 POSITIVE

all GTN and totality of mesonephric carcinomas 95% express Gata-3 positive

• **TTF-1** Thyroid Transcription factor-1 - is primary marker of lung and thyroid

Ovarian(3%-39%, endometrial carcinoma(2%-23%), cervical adenocarcinoma(4%) (23)
Fig 22 (IHC STAINING OF RARE GYNAECOLOGICAL MALIGNANCIES)

ABBREVIATIONS – UEC- UNDIFFERENTIATED ENDOMETRIAL CANCER
EIN-ENDOMETRIAL INTRAEPITHELIAL NEOPLASIA
SPCC – SPINDLE CELL CARCINOMA

CONCLUSION
Whenever the morphology or diagnostic dilemma, we should consider frequency of primary and metastasis at the site. There should be a hierarchy in use of markers and then to specific marker panel. The immunochemistry also help in providing knowledge about the progression of lesion e.g. P16, p53 in EIN

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