ATYPICAL GLANDULAR CELLS ON PAP SMEARS: CYTOMORPHOLOGICAL CORRELATION AND DIAGNOSTIC CHALLENGES

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THE PAP TEST

• Has stood the test of time

• CHALLENGES IN DIAGNOSES OF GLANDULAR LESIONS
  – Diversity in presentation and in origin of both benign and malignant entities,
  – Existence of non-glandular lookalikes,
  – Reduced accuracy in predictive value and in sensitivity when compared with squamous prediction

“The reports of my death have been greatly exaggerated.”
Mark Twain
‘ATYPICAL’ GLANDULAR CELLS (AGCS)

• Cells that demonstrate changes beyond those encountered in benign reactive processes, but not sufficient for diagnosis of adenocarcinoma

• Origin of AGCs – uterine and extra-uterine

• Frequency of AGCs - 0.1 to 2.1% in literature

• Significance AGCs on Pap - Close association with premalignant and malignant diseases of genital or less commonly extragenital origin
HOW TO REPORT ‘AGCs’?

- 2001 Bethesda System removed ‘AGUS’ & ‘ASCUS’

- ‘Atypical glandular cell’ (AGC) category
  - Focuses on neoplastic diagnoses
  - Indicates potential for malignancy
  - ? Classify cells by their source (endometrial/cervical)
STUDY

• **Aim:** To evaluate the underlying pathology in women who had AGCs on Pap smears (should we sub-classify)

• **Design:** Retrospective cross-sectional study

• **Patients and Methods:**
  – Clinicopathological data of patients with AGC on Pap smears (Jan 2015 - Dec 2017) retrieved
  – Exclusion: prior history of CIN or gynecological cancer
Patients with AGCs on PAP

53

Primary cases with AGCs

49

Previous history of gynecological cancer or cervical pre-invasive disease

4

Patients lost to follow-up

2

Cases with clinical follow-up

47

Inadequate follow-up with PAP only

7

Valid cases with histological follow-up

40
PATIENT EVALUATION

• Liquid-based cytology

• Following AGC result, patients underwent
  – Colposcopy with biopsy
  – Endocervical curettage, and
  – Endometrial biopsy

• Patient’s age, symptoms, menopausal status, Pap test findings (with subclassifications), biopsy results analyzed
CLINICAL FEATURES ($n=40$)

- The median age at diagnosis: 49 years (range 28–79)

- No. of postmenopausal women: 16 (40%)

- No. of women with gynecological symptoms: 28 (70%)
# HISTOPATHOLOGIC RESULTS IN AGCs

<table>
<thead>
<tr>
<th>Histopathologic results</th>
<th>n (%)</th>
</tr>
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<tbody>
<tr>
<td>Nonsignificant genital lesion</td>
<td>27 (67.5%)</td>
</tr>
<tr>
<td><strong>Significant pathological lesion</strong></td>
<td>13 (32.5%)</td>
</tr>
<tr>
<td>CIN III</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Cervical squamous carcinoma</td>
<td>1 (2.5%)</td>
</tr>
<tr>
<td>Cervical adenocarcinoma</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Endometrial adenocarcinoma</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Ovarian carcinoma</td>
<td>2 (5%)</td>
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<tr>
<td>Metastatic tumor (Krukenberg)</td>
<td>2 (5%)</td>
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<tr>
<td><strong>Total</strong></td>
<td>40 (100%)</td>
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<tr>
<td></td>
<td>AGC-NOS (n=5)</td>
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<tr>
<td>--------------------------------</td>
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</tr>
<tr>
<td>Cervical squamous lesion</td>
<td></td>
</tr>
<tr>
<td>CIN III</td>
<td>1</td>
</tr>
<tr>
<td>Sq cell ca</td>
<td></td>
</tr>
<tr>
<td>Cervical Glandular lesion</td>
<td></td>
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<tr>
<td>Adenocarcinoma</td>
<td></td>
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<tr>
<td>Endometrial lesion</td>
<td></td>
</tr>
<tr>
<td>Serous Ca</td>
<td>1</td>
</tr>
<tr>
<td>Endometrioid Ca</td>
<td></td>
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<tr>
<td>Ovarian lesion</td>
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<tr>
<td>Serous Ca</td>
<td>1</td>
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<tr>
<td>Mucinous Ca</td>
<td></td>
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<tr>
<td>Metastatic tumor (Krukenberg)</td>
<td>1</td>
</tr>
<tr>
<td>TOTAL</td>
<td>4</td>
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</tbody>
</table>
Cluster of Atypical cells showing small hyperchromatic nuclei and high N:C ratio. The histologic follow-up showed CIN III
Atypical glandular cells in a tight cluster and with visible nucleoli. The histologic follow-up showed Endometrial Serous Carcinoma.
Atypical glandular cells reported initially as NOS but showed mucin on special stains and histological follow-up revealed Mucinous carcinoma of the ovary
HPE CORRELATION FOR AGC-NOS

- CIN III – 1
- Endometrial serous ca – 1
- Ovarian mucinous ca – 1
- Metastatic ovarian ca - 1
AGC - EC

A pseudo-stratified strip of endocervical cells showing cigar-shaped nuclei and high N:C ratio. The histologic follow-up showed CIN III.
Hyperchromatic crowded cluster of relatively uniform sized nuclei. Thick crowded centre and thinner disorderly periphery. HPE – Endometrioid ca
Cluster of atypical cells with moderate nuclear pleomorphism and occasional neutrophils. The histologic follow-up showed Serous endometrial carcinoma
A loosely cohesive population of atypical cells showing nuclear pleomorphism, abundant cytoplasm and ‘tadpole cells’. The histologic follow-up showed Squamous cell carcinoma.
HPE CORRELATION FOR AGC-FN

• Cervical squamous cell carcinoma – 1

• Cervical Adenocarcinoma – 1

• Endometrioid ca – 1

• Ovarian serous ca - 1
Three dimensional cluster of pleomorphic cells some with large punched out vacuoles and nuclei pushed to the periphery of the group giving a scalloped edge. Note small nuclear size compared with adjacent intermediate cells. HPE – Krukenberg tumor of the ovary (Mets from gastric primary)
<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>AGC-NOS</th>
<th>AGC-EC</th>
<th>AGC-EM</th>
<th>AGC-FN</th>
<th>AGC Ex</th>
<th>TOTAL</th>
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<tr>
<td>Cervical squamous</td>
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<td>3</td>
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<tr>
<td>lesion</td>
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<td>CIN III</td>
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<tr>
<td>Sq cell ca</td>
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<td>1</td>
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<tr>
<td>Cervical Glandular</td>
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<td>1</td>
<td>1</td>
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<td>lesion</td>
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<td>Adenocarcinoma</td>
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<tr>
<td>(Krukenberg)</td>
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<tr>
<td>TOTAL</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>13</td>
</tr>
</tbody>
</table>
BENIGN MIMICS

**Tuboendometrioid metaplasia (TEM).**
Hyperchromatic crowded group of glandular cells with well formed cytoplasmic borders and terminal bars (×60, Thinprep)

**Lower uterine segment sampling (LUS).**
Parallel sided tube of crowded epithelial cells with peripheral palisading (×40, Thinprep)

Inset: Accompanying stromal cells (×60, Thinprep)
REACTIVE CELLS

A sheet of reactive endocervical cells showing nuclear enlargement and prominent nucleoli, reported initially as atypical glandular cell-not otherwise specified; later revised to negative for any intraepithelial lesion or malignancy (Pap, ×40); (HPE: Chronic cervicitis)

Cluster of reactive endometrial cells showing nuclear enlargement, smudgy chromatin, and small nucleoli, reported initially as atypical glandular cell-not otherwise specified; later revised to negative for any intraepithelial lesion or malignancy (Pap, ×40), (HPE: Simple hyperplasia without atypia);
CGIN vs Invasive adenocarcinoma of the endocervix: Pseudostratified nuclei with scanty wispy basal cytoplasm and fused “common border” at upper surface of cell group. Feathering with apparently bare nuclei protruding at upper end of strip. Cytological features of early adenocarcinoma of the endocervix and CGIN overlap and invasion cannot always be predicted cytologically. ×60 SurePath.
PRACTICAL POINTS FOR INTERPRETATION OF MALIGNANT GLANDULAR CELLS

• Appearance of adenocarcinoma is neither type nor site specific

• Raised N/C ratio cannot be relied upon for prediction or exclusion of invasion

• Prediction of site depends on presence of other features such as recognizable CGIN adjacent to clusters of malignant glandular cells

• Discuss at multidisciplinary team meeting
Is it really abnormal? Yes

Is it really glandular? Uncertain

Yes

Non-glandular neoplastic lookalikes
- Hyperchromatic crowded groups
- Squamous microbiopsies
- Crypt involvement in CIN
- Papillary pattern in CIN3

No

Non-glandular report as appropriate

Cytologically difficult glandular lesions to predict
- Type II CGIN
- Mixed squamous and glandular lesions
- Poorly differentiated carcinoma
- SMILE (adenosquamous carcinoma in situ)
- Adenosquamous carcinoma

Report: ?Glandular neoplasia
Quality: Endocervical glandular neoplasia
  Non-cervical glandular neoplasia
  - Endometrial
  - Exteruterine
  - Uncertain origin

Report – with indication of difficulty in interpretation
CONCLUSIONS

- Questions on cytology - Are the cells in question really glandular, and if so, are they really abnormal?

- With LBC, nuclear details tend to be more pronounced and architectural features more subtle

- Diagnosis: ?Glandular neoplasia (UK) or AGC favour neoplasia (Bethesda) reasonable for subjecting the patient to a thorough clinical work-up and follow-up
CONCLUSIONS

• Univariate analysis showed that prognostically significant outcome was associated with
  – postmenopausal status ($P < 0.001$),
  – age >50 years ($P < 0.001$),
  – symptomatic ($P = 0.04$) and
  – AGC ‘favor neoplasia’ smear results ($P = 0.04$)

• Patients with AGCs on Pap smears need a thorough clinical and histological workup, especially if they are older than 50 years, postmenopausal or symptomatic
As I slowly grow wise I briskly grow cautious

- Mark Twain
THANK YOU

Jaisalmer Fort, Rajasthan (India)