Epithelial Columnar Breast Lesions: Histopathology and Molecular Markers

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Columnar Cell Lesions (CCLs)

- CCLs are characterized by the presence of tightly packed columnar cells lining distended TDLUs.

- Other morphologic features:
  - round to elongated nuclei, prominent apical snouts and intraluminal secretions or microcalcifications.
Etiology-Incidence

- Etiology unknown
- Incidence increasing due to:
  - Screening mammography
  - Improved recognition by Pathologists
Clinical profile of patients with CCLs

- Mean ages: 44 to 51 yrs
- Prevalence, demographic characteristics, distribution within the breast: unknown
- Present as nonpalpable lesions
- Calcifications in mammography
Intraepithelial breast lesions with columnar cell morphology have puzzled Pathologists for many years!!

- No new lesions

- **Other terms:** “blunt duct adenosis”, “columnar alteration with prominent apical snouts and secretions”, “enlarged lobular units with columnar alteration”, “clinging carcinoma of monomorphic type”, “atypical cystic lobules”, “well differentiated DCIS with a clinging architecture”
Classification Systems of CCLs


Two broad categories

- Columnar cell change (CCC)
- Columnar cell hyperplasia (CCH)

synthesizes and simplifies the plethora of terminology and pathological descriptions

according to the number of cell layers lining the acini
**CCC**
one to two cell layers

**CCH**
more than two cell layers
stratification, crowding, overlapping
Some CCLs show cytological atypia: round or ovoid nuclei lacking the normal perpendicular orientation to the basement membrane, variable presence of nucleoli, occasional mitotic figures and mildly increased nuclear to cytoplasmic ratio.

**CCC with cytological atypia**

**CCH with cytological atypia**
Some CCLs, especially CCH, show architectural atypia: complex architectural patterns including tufts, fronds, short micropapillae, bridge formation, early cribriform features.
Classification of Simpson PT et al, 2005

Six categories of CCLs

- **Without atypia**
  - columnar cell change (CCC)
  - columnar cell hyperplasia (CCH)

- **With atypia (architectural, cytological)**
  - CCC- cytological atypia
  - CCH- cytological atypia
  - CCH- architectural atypia
  - CCH- cytological atypia and architectural atypia
Columnar Cell Hyperplasia
-architectural and cytological atypia-
In the current WHO classification

- CCLs with cytological atypia are referred as:

  "flat epithelial atypia (FEA)"

in order to describe
“a presumably neoplastic intraductal alteration characterized by replacement of the native epithelial cells by a single or 3-5 layers of mildly atypical cells".
In the latest revision of **DIN (ductal intraepithelial neoplasia)** system, FEA is designated as **DIN1a**

<table>
<thead>
<tr>
<th>Traditional terminology</th>
<th>Ductal intraepithelial neoplasia (DIN) terminology</th>
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<tbody>
<tr>
<td>Usual ductal hyperplasia (UDH)</td>
<td>Usual ductal hyperplasia (UDH)</td>
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<tr>
<td><strong>Flat epithelial atypia</strong></td>
<td><strong>Ductal intraepithelial neoplasia, grade 1A (DIN 1A)</strong></td>
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<tr>
<td>Atypical ductal hyperplasia (ADH)</td>
<td>Ductal intraepithelial neoplasia, grade 1B (DIN 1B)</td>
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<td>Ductal carcinoma in situ, low grade (DCIS grade 1)</td>
<td>Ductal intraepithelial neoplasia, grade 1C (DIN 1C)</td>
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<td>Ductal carcinoma in situ, intermediate grade (DCIS grade 2)</td>
<td>Ductal intraepithelial neoplasia, grade 2 (DIN 2)</td>
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<tr>
<td>Ductal carcinoma in situ, high grade (DCIS grade 3)</td>
<td>Ductal intraepithelial neoplasia, grade 3 (DIN 3)</td>
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FEA is not necessarily “flat”, but rather does not form complex architectural patterns such as cribriform or micropapillary

- cases previously categorized as CCH with architectural atypia, due to the presence of cribriform spaces or micropapillae, are now proposed by several Pathologists to be classified as ADH or low grade DCIS, depending on the severity and extent of changes
Important diagnostic criteria

- CCLs are **low-grade** lesions in terms of cytological appearance

  High grade cytological atypia = should be called high-grade DCIS

- CCLs are **not so complex lesions** in terms of architectural appearance

  Cribriform or micropapillae or bridge formations = it’s better to be called ADH or DCIS depending on the severity of the findings
Biological and clinical significance

CCLs, in particular those with cytological atypia may be biologically significant, possibly representing a very early stage in the evolution of low-grade DCIS and invasive carcinoma.

- Observational studies
- Follow-up studies
- Immunohistochemical studies
- Molecular studies
Observational studies

- CCLs have been observed in association with LCIS (86.5%), ADH (60%), low-grade DCIS (42%) and with low-grade invasive carcinomas

- Low grade invasive carcinomas: tubular, tubulo-lobular and lobular carcinomas

Presence of CCLs in 90% of tubular carcinomas, 85% of tubulolobular carcinomas, 60% of lobular carcinomas

CCL with atypia merging into low-grade DCIS
CCL with atypia and coexistent LCIS
CCL with atypia associated with low-grade DCIS and invasive tubular carcinoma
“Rosen triad” has been proposed for breast lesions consisting of **CCL + LCIS + tubular carcinoma** (this co-existence has been described initially by the eponymous Pathologist P. Rosen)

Follow-up studies

*Information on the natural history of CCLs is scarce*

*Guerra-Walace M et al, Am J Surg, 2004*

- 18.3% of patients with CCLs with atypia developed invasive carcinoma (follow-up period: 5 yrs)

- *David N et al, J Radiol, 2006*

- All patients with CCLs with atypia and lesions > 10mm developed invasive carcinoma
In practice, the size of CCLs is not routinely determined by Pathologists, since it is not a safe procedure.

- Determining the size of CCLs, especially in core biopsies or determining their completeness of excision is difficult.
- Moreover, it is not known if the carcinoma that subsequently developed came from the incompletely excised CCLs or from other atypical or malignant changes that were not included in the breast tissue.

- Therefore, the management of patients based on the size of the CCLs is not practical.
Immunohistochemical/Molecular studies

- ER, PR, Bcl2, CK19 (+)
- CK5/6, CK14, p53, HER2/neu (-)
- Ki67 (- or low)

- Profile resembles that seen in ADH & low-grade DCIS

- loss on 9q, 10q, 16q, 17p
- gain on 15q, 16p, 19
- LOH at 11q, 16q, 3p

- Molecular changes analogous to that seen in low-grade DCIS & low-grade invasive carcinoma

Feeley L, Quinn CM, Histopathology, 2008
Immunohistochemistry

- ER positive
- Bcl2 positive
- CK 5/6 negative
Proposed evolutionary pathway of tubular carcinoma on the basis of the reported morphological genetic changes for each stage

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<tr>
<th>Lesions</th>
<th>Reported Genetic Changes</th>
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<tr>
<td></td>
<td>Loss</td>
</tr>
<tr>
<td>CCC</td>
<td>-16q -19q -11q</td>
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<tr>
<td>CCC with atypia</td>
<td>-16q -17p -22 -12q</td>
</tr>
<tr>
<td>CCH with atypia</td>
<td>-16q -17p -22 -12q</td>
</tr>
<tr>
<td>CCH complex architectural &amp; atypia</td>
<td>-18q -6q -17p -22 -12q</td>
</tr>
<tr>
<td>ADH</td>
<td>-16q -6q -8p -17p -22 -12q</td>
</tr>
<tr>
<td>Low grade DCIS</td>
<td>-16q -6q -8p -17p -19q -22 -12q</td>
</tr>
<tr>
<td>Tubular Carcinoma</td>
<td>-16q -6q -8p -17p -11q</td>
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Biological and clinical significance

- CCLs seems to be biologically significant lesions, since the co-existence with more advanced entities may suggest that CCLs probably represent a very early form of malignant changes.

- The concept of a family of “low-grade nuclear breast neoplasia” has been reported recently, based on the significant coexistence of precursor (ADH), in situ (DCIS, LCIS) and invasive lesions (tubular, tubulolobular and lobular carcinoma) along with CCLs.

- It has been suggested that CCLs are the earliest morphologically identifiable, non-obligate precursor lesion of low-grade nuclear breast neoplasia.

Whether the risk for subsequent development of breast cancer is due to the presence of CCLs alone or whether CCLs predict the development of higher risk lesions is not currently known.

The risk of cancer development appears to be low.

In a recent retrospective study with 1,261 pts with CCLs and a follow-up period of 17 yrs, the risk of cancer development was 1.47.

CCLs on needle core biopsy

- Whether further tissue excision should be recommended for CCLs with atypia detected in core biopsies remains controversial.

- There are limited outcome data which indicate that subsequent excision shows a more advanced lesion in 20-30% of cases when CCLs with atypia is identified in core biopsy.

Feeley L, Quinn CM, Histopathology, 2008
CCLs on needle core biopsy

- The lack of consensus and the need for guidelines in managing these lesions is highlighted by a study, which found that 21% of the pathologists would recommend excisional biopsy, when multiple ducts showing CCL with atypia

Ghofrani M et al, Virchows Arch, 2006
CCLs on excision breast specimen

- A careful search from the Pathologist with multiple levels of sectioning for more advanced lesions is very critical

- If CCLs with atypia close to resection margins - do not recommend further excision

- However in practice, most clinicians agree that close monitoring is deemed satisfactory
Conclusions

- CCLs are being identified with increasing incidence in breast tissue specimens undertaken for the assessment of mammographic microcalcifications.

- CCLs with atypia are seen frequently in relation to ADH, low-grade DCIS, LCIS and low-grade invasive carcinomas.

- Despite these associations, the risk of developing subsequent carcinoma after the diagnosis of CCLs with atypia is not exactly known; however it seems to be very low.
Conclusions

- The management of patients with CCLs with atypia remains controversial since there are very limited clinical data and therefore, their significance is still unclear.

- A multidisciplinary evaluation tailored to each patient appears to be the most feasible approach, taking account the family history, the personal history (previous breast biopsies) and the mammographic findings.
Thank you very much!

Mykonos, Greece