Paget disease of the nipple
Definition of the WHO

• Malignant glandular epithelial cells (Paget cells) within the squamous epithelium of the nipple
History

• first described by Sir James Paget in 1874

English surgeon and pathologist

Paget's disease of bone
Paget’s disease of the nipple
Extramammary Paget’s disease
Paget’s abscess
Paget-von-Schroetter-Syndrom
Paget disease of the nipple

• Usually associated with underlying carcinoma, mostly high grade invasive ductal carcinoma (53-60%) or DCIS (24-43%)
• Rare without underlying carcinoma (1-4-13%)
Epidemiology

- 1-4% of all breast cancers
- Can be bilateral
- Men and women
- 27-88 years
Extramammary Paget disease

Vulva:
- Primary
- Secondary (40%): Association with Adenocarcinoma from Bartholin gland, urethra, rectum

Penis, scrotum:
- Primary or secondary

Perianal, inguinal, axillary
Extramammary Paget disease

- Usually postmenopausal
- Red, eczematoid, pruritic
- Mostly non-invasive
- High recurrence rate (1/3)
- Er-, Pr-, Her2+
- Mortality <10%
- DD: Melanoma
Extramammary Paget disease

- 6.-7. decade
- Thickened red to pale plaques, scaling
- DD: Pagetoid spread of penile or urothelial carcinomas, Bowen disease, Melanoma
Paget disease of the nipple, Etiology

1. Theory:
Paget cells originate in underlying or intraepidermal lactiferous ducts, then migrate into the epidermis
Etiology

2. Theory:
Toker cells as Precursors of Paget cells
Clinical features

- Eczematous or erythematous changes
- Nipple discharge, itching, ulceration, retraction, scaling
Mammographic findings

• Skin, nipple and areolar thickening, nipple retraction, mass(es), microcalcifications, asymmetrical density, architectural distortion
Histology

• Large cells with abundant pale stained cytoplasm and large, atypical nuclei with prominent nucleoli
Histopathology

• single to numerous cells arranged in nests or tubular structures
• Contain mucin in 40%
• May contain melanin pigment
• Rarely invading the dermis
Histopathology

- Ductal carcinoma in situ in underlying lactiferous ducts
- Cytologically similar to Paget’s cells
- Frequently comedo type necrosis
Immunoprofile

- CK-7
- CAM5.2
- Her2 (80-90%)
- Er (40%), Pr (30%)
- CEA, EMA, GCDFP-15, p53 (50%)
- CA15-3, KA-93
- Underlying carcinoma usually with the same immunoprofile
Differential diagnosis

- Malignant melanoma of the skin
- Bowen disease of the skin
- Toker cells
- Breast carcinoma with invasion of the skin and nipple
Genetics

- No association with specific gene mutation
- Paget cells genetically similar to underlying carcinoma cells in 80% (Morandi et al 2003)
Therapy

- Mastectomy with or without axillary node dissection (high association of underlying breast carcinoma)
- Radiotherapy
- Chemotherapy
- Antihormonal therapy
Prognosis

Depends on underlying carcinoma and tumor stage

5-year recurrence-free survival:
• DCIS: 75-90%
• Invasive Ca: 63-75%

5-year overall survival:
• DCIS: 94-98%
• Invasive Ca: 73-93%
Toker cells

- Detectable in 10% of the nipples
- 90% cytologically bland
- 10% morphologically atypical
Toker cells

- Clear cells
- Basal layer
- Larger than keratinocytes
- Oval-shaped nuclei
- 1-2 small nucleoli
- Sometimes glandular structures, growing up to the spinous layer
Toker cells

- First described by Cyril Toker 1970

CLEAR CELLS OF THE NIPPLE EPIDERMIS

Cyril Toker, MD

Examination of 340 nipples from cancerous breasts revealed histologically benign clear-cell infiltrates in 51. Nipple-duct cancer coexisted in but a single instance. These findings suggested that the epidermal infiltrates were of non-neoplastic nature and, consequently, were to be distinguished from the infiltrate of Paget's disease. Examination of 190 nipples removed from 101 autopsy subjects disclosed, within 23, epidermal infiltrates morphologically similar to those present within the surgical specimens. Nipple-duct cancer was not encountered. Within the clear-cell aggregates, tubular structures resembling mammary ductules were observed. It is believed that the cellular complexes referred to represent nonneoplastic mammary elements within the nipple epidermis. These complexes may possibly provide an anatomical basis for the development of Paget's disease as a primary intra-epidermal malignancy. Distinction from the cancerous nipple infiltrate of Paget's disease is of both histogenetic and practical importance.
Toker cells origin

1. Abortive glandular differentiation during embryonic or postnatal life
2. Migration of ductal cells from lactiferous ducts
Toker cells

• Morphological features of TC
• Immunohistochemical characterization
• Prevalence of normal and atypical TC
• DD between normal, atypical TC and malignant cells
Toker cells

- 390 Mastectomy specimen January 1998-December 2002 retrospectively reviewed
- 40 cases with TC
- 5 cases of classical PD with underlying carcinoma
- 5 cases of primary PD
Toker cells

- TC in 10% of cases
- 60% morphologically bland
- 27% «hyperplastic TC»
- 12% «hyperplastic and atypical TC»
## Immunohistochemistry

### Table 2: Immunohistochemical features of TC as compared to those of PD

<table>
<thead>
<tr>
<th></th>
<th>Normal TC</th>
<th>Hyperplastic TC</th>
<th>Atypical TC</th>
<th>Primary PD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER</td>
<td>9/9 (100%)</td>
<td>11/11 (100%)</td>
<td>5/5 (100%)</td>
<td>2/5 (40%)</td>
<td>2/5 (40%)</td>
</tr>
<tr>
<td>PgR</td>
<td>5/7 (71%)</td>
<td>10/11 (91%)</td>
<td>5/5 (100%)</td>
<td>0/5</td>
<td>3/5 (60%)</td>
</tr>
<tr>
<td>HER2/NEU</td>
<td>0/4</td>
<td>1/9 (11%)</td>
<td>4/5 (80%)</td>
<td>5/5 (100%)</td>
<td>4/5 (80%)</td>
</tr>
<tr>
<td>CD138</td>
<td>0/4</td>
<td>0/9</td>
<td>1/5 (20%)</td>
<td>5/5 (100%)</td>
<td>2/5 (40%)</td>
</tr>
<tr>
<td>EMA</td>
<td>NA</td>
<td>9/9 (100%)</td>
<td>5/5 (100%)</td>
<td>5/5 (100%)</td>
<td>5/5 (100%)</td>
</tr>
<tr>
<td>CK7</td>
<td>NA</td>
<td>9/9 (100%)</td>
<td>5/5 (100%)</td>
<td>5/5 (100%)</td>
<td>5/5 (100%)</td>
</tr>
<tr>
<td>p63</td>
<td>NA</td>
<td>0/9</td>
<td>0/5</td>
<td>0/5</td>
<td>0/5</td>
</tr>
<tr>
<td>p53</td>
<td>NA</td>
<td>0/9</td>
<td>0/5</td>
<td>4/5 (80%)</td>
<td>2/5 (40%)</td>
</tr>
</tbody>
</table>

**NOTE:** Only 9 cases of normal TC were available for immunohistochemical studies and most of them disappeared after the very first serial sections; similarly, 2 cases of hyperplastic TC disappeared after the first serial sections.

**Abbreviations:** NA, not assessed; EMA, epithelial membrane antigen; CK7, cytokeratin 7.
Immunohistochemistry TC

- Positive for ER (100%)
- Mostly positive for PR (87%)
- HER2 mostly- (72%)*
- CD138- (95%)
- CK7+, EMA+ (100%)
- P63-, p53- (100%)
Immunohistochemistry PD

- ER mostly- (60%)
- PR mostly- (70%)
- HER2+ (90%)
- CD 138 mostly+ (70%)
- EMA+, CK7+ (100%)
- P63- (100%)
- P53 mostly+ (60%)
## Results Immunohistochemistry

<table>
<thead>
<tr>
<th></th>
<th>TC</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Her2</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>CD138</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>p53</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
Results

• TC are rare and nonneoplastic
• A few with atypical cytologic features
• Hypothesis that TC can undergo hyperplastic expansion and transformation into malignant cells
TC origin of PD?

• Rare coexistence of TC and PD in the same nipple
• Some TC and PD share similar ultrastructural features
• Some PD genetically different from underlying carcinoma
• Progressive expression of HER2 from normal to hyperplastic to hyperplastic/atypical TC
Conclusions

• TC are intraepidermal elements of mammary origin
• A fraction of them can acquire the ability to proliferate and expand
  -> Progressive increase in nuclear atypia and HER2 expression
• DD PD: absence of clinical features, clear cut cytologic features, negativity for CD138, p53