What’s new in breast pathology?

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Outline

• IHC markers of metastatic carcinoma of breast origin
• Uses and limitations of e-cadherin IHC
• Breast neoplasms with limited metastatic potential
• Sentinel node staging: changes in clinical management
1. IHC panels for metastatic carcinoma

- Work-up for metastatic carcinoma of unknown primary is common
  - Axillary lymph node metastasis
  - Carcinoma in other sites (liver, lung, bone marrow) with remote or no known primary
  - Breast tumors with atypical histologic features
‘Breast panel’

- CK7 +/-CK 20 –
- ER
- GCDFP-15
- Mammoglobin
- GATA3
ER

• Metastatic setting, ERα is neither sensitive or specific for breast carcinoma
• Only ~50% of metastatic breast cancers express ER
• ER is expressed in non-breast carcinomas: endometrium, ovary, PTCa, adnexal tumors of skin
• ~10-20% of lung adenocarcinomas show weak/focal ER expression
GCDFP-15

- Ab derived against secretory glycoproteins
- Expressed in ~55% primary breast carcinomas
- Sensitivity in metastatic breast carcinoma only ~11%
- Dependent on histologic subtype: highly expressed in tumors with apocrine features and in lobular carcinoma with signet ring differentiation
- Often not expressed in high grade, triple negative tumors
- Expressed in non-breast primaries: cutaneous apocrine & eccrine carcinoma, salivary gland carcinoma, 5-10% of ovarian & endometrial carcinomas; ~5% lung adenocarcinomas
Mammaglobin

- Cytoplasmic protein
- Higher sensitivity than GCDFP-15
- Expressed in non-breast primaries: cutaneous adnexal carcinomas, salivary gland carcinoma, ~5-10% ovarian, endocervical & endometrial carcinomas
- Not expressed in lung ca
GATA3

• One of the 6 members of zinc finger transcription factor family
• Binds to the DNA nucleotide sequence GATA
• Involved in the differentiation of breast glandular epithelial cells, hair follicles, T cells, adipose tissue, kidney and nervous system
• Sensitivity in breast cancer >90%
• Expressed at lower levels in ER negative/triple negative tumors
GATA3

- Expressed in non-breast primaries: urothelial carcinoma, squamous cell tumors, BCC, cutaneous adnexal carcinomas, salivary gland carcinoma, chromophobe RCC, trophoblastic tumors
- ~5% thyroid carcinomas, ~8% lung adenocarcinomas, 58% mesotheliomas, 9% cholangiocarcinomas, 37% pancreatic carcinoma
GATA3

- GATA3 expression is frequently maintained between matched primary and metastatic carcinomas, including ER negative cases (90%)
IHC panels for metastatic carcinoma

• Utilize a broad panel
• None of the markers available as yet have both high sensitivity and specificity
• All ‘breast markers’ have lower sensitivity in triple-negative breast cancers; GATA3 is the most useful in this context
• Incorporate clinical setting & imaging findings
Case 1

• 65 y.o. female
• Right axillary adenopathopathy
• Right breast mass; 2 previous core biopsies were benign
• PHx: contralateral invasive breast carcinoma 1997, invasive urothelial carcinoma, high grade, treated with radical cystectomy; no residual invasion seen cystectomy, 2009.
Case 1

• IHC positive: PR, patchy GCDFP-15
• IHC negative: CK 7, CK 20, p63, HER2, TTF-1, napsin

• Most consistent with metastatic adenocarcinoma of breast origin
Case 2

• 72 year old female
• History of stable breast mass x 10 years, now enlarging
IHC panel

• Positive markers: GATA3, actin, focal weak expression of p63, CK5/6, AE1/AE3
• Negative: ER, PR, HER2, CD34, beta-catenin
GATA3 expression in triple negative and sarcomatoid carcinomas

- GATA3 expression seen in ~43% high grade triple-negative breast cancers
- GATA3 expression seen in ~56% of metaplastic carcinomas, weak-moderate
- Stromal GATA3 expression is rare in fibroepithelial neoplasms (~3%, 1 case of malignant PT)

Malignant spindle cell neoplasms in core biopsies

• Ddx: metaplastic carcinoma, phyllodes tumor, primary/secondary sarcoma

• Pitfall: weak expression of p63, p40 and keratins can be seen in malignant phyllodes tumors!

• Include CD34 (for PT) and GATA3 in w/u, especially in core biopsy specimens
2. E-cadherin IHC: uses and pitfalls

• Commonly used to help distinguish:
  – LCIS from DCIS
  – Invasive lobular carcinoma from invasive ductal carcinoma

• Most lobular lesions have genomic and/or epigenetic alterations in the gene encoding e-cadherin, *CDH1*, resulting in biallelic silencing and loss of expression of the e-cadherin protein, therefore loss of intercellular cohesion
E-cadherin biology

• E-cadherin gene, *CDH1*, located on 16q
• Encodes a Ca2+-dependent transmembrane protein involved in intercellular adhesion and maintenance of cell polarity
• Cell-cell adhesion function resides in the extracellular domain
• E-cadherin is linked to the actin cytoskeleton via α-, β-, γ- and p120 catenins
E-cadherin

- Lobular lesions: disruption of cadherin-catenin complex and loss of membrane expression of e-cadherin and catenins
- Accumulation of p120 catenin in the cytoplasm
- Most common molecular alteration in lobular lesions is LOH at 16q; other molecular aberrations can occur (deletions, transcriptional repression)
E-cadherin IHC

• Lobular lesions typically exhibit loss of membranous expression of e-cadherin
• Ductal lesions typically retain it
• This is not always the case:
  – Related to the type of molecular inactivation of e-cadherin
  – Invasive lobular can have membranous expression (~15%)
  – ILC may have partial/fragmented membrane staining or perinuclear cytoplasmic staining
  – Invasive ductal carcinomas can have aberrant/loss of expression of e-cadherin (~7%), usually high grade
E-cadherin IHC

• In situ lesions:
• Aberrant expression of E-cadherin in LCIS cells
  – Partial/fragmented membrane staining or perinuclear cytoplasmic staining
  – Staining of admixed luminal cells
  – Consider a mixed LCIS/DCIS lesion
Case 5
Case 6
Use of e-cadherin IHC

• Not necessary in unambiguous straightforward cases; rely on morphology of ILC
• Another marker may be helpful: p120 catenin, β-catenin
<table>
<thead>
<tr>
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<th>Normal epithelium</th>
<th>LCIS and ILC</th>
<th>DCIS and IDC</th>
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<tr>
<td>E-cadherin</td>
<td>Membrane staining</td>
<td>Aberrant membrane staining</td>
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<td>p120 catenin</td>
<td>Membrane staining</td>
<td>Cytoplasmic</td>
<td>Membrane staining</td>
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<td>B-catenin</td>
<td>Membrane staining</td>
<td>Absence of membrane staining</td>
<td>Membrane staining</td>
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Use of e-cadherin IHC

• When is it more important:
  – Core biopsy diagnosis of ILC may prompt pre-op MRI
  – Diagnosis of LCIS in CB may prompt excision
  – LCIS vs DCIS e.g. margin assessment
3. Breast neoplasms with limited metastatic potential

- Encapsulated papillary carcinoma (EPC)
- Solid papillary carcinoma (SPC)
- Low grade adenosquamous carcinoma
- Low grade fibromatosis-like metaplastic carcinoma
- Borderline phyllodes tumor
- Atypical adenomyoepithelioma
Encapsulated papillary carcinoma

• Architecture
• Low-intermediate grade nuclear atypia
• ER positive; HER2 negative
• >80% completely lack a myoepithelial component
• Current consensus: EPC should be managed and staged as Tis (DCIS) disease
• Look for conventional invasive component outside of the fibrous capsule; sample well
  – pT stage based on focus of conventional invasive tumor
Encapsulated papillary carcinoma

• Tend to occur in older women
• Usually have indolent clinical course
  – LVI 3%
  – Nodal mets 3% (microscopic)
  – Chest wall recurrence 7%
    • Recurrence is associated with aggressive behaviour

High grade EPC-like carcinoma

- Rare
- Often ‘triple negative’
- High mitotic rate +/- necrosis
- Should be managed as invasive carcinoma
- Report as ‘invasive high-grade carcinoma with EPC-like features’
HER2
Solid papillary carcinoma

- Architecture
- Neuroendocrine cytology
- May not see a myoepithelial layer around all tumour nests
Solid papillary carcinoma

• Identification of frank invasion can be problematic
  – Look for ragged irregular margins and complex architecture with complete lack of myoepithelial cells
  – When in doubt, classify as pTis
• Managed/staged as Tis (DCIS) unless associated with conventional invasion
4. Sentinel lymph nodes in breast cancer

• Gross specimen handling
• Reporting/staging
• Changes to the clinical management of nodal disease
National Surgical Adjuvant Breast and Bowel Project B-32 trial

- Randomized prospective clinical trial
  - Demonstrated that in patients with T1/T2 cN0 tumors and negative SLNs, staging by SLN biopsy is equivalent to ALND
NSABP B-32 trial

CLINICALLY NEGATIVE AXILLARY NODES

STRATIFICATION
- AGE
- CLINICAL TUMOR SIZE
- TYPE OF SURGERY

RANDOMIZATION

GROUP 1
SENTINEL NODE RESECTION
FOLLOWED BY AXILLARY DISSECTION

GROUP 2
SENTINEL NODE RESECTION

Pathologically Positive Sentinel Node
Axillary Dissection

Pathologically Negative Sentinel Node
No Axillary Dissection
NSABP B-32 trial

• Mean study time 95.6 mo (~8 yrs)
  – Axillary recurrence 0.4% SLN vs 0.7% for SLN-ALND for SLN+ disease
  – Fewer side effects without ALND
  – SLN predicts burden of axillary disease in 90-99% of patients
Sentinel lymph nodes - basic recommendations

- Thin gross sections: 2mm
- Embed and examine each slice; only one H&E section required
- If levels used, evenly space sections through block (0.5mm or 0.2 mm intervals)
- IHC not required, but can be helpful especially for lobular carcinoma
Gross Examination

• Rationale: by sectioning node at 2mm intervals, there is a high probability of identifying macrometastases (≥2mm)
pN staging, 7th ed. AJCC

- Isolated tumor cells ≤0.2 mm (< 200 cells) considered pN0(i+)
  - considered node negative

- Micromets >0.2mm - ≤2mm (and/or >200 cells) are pN1(mi)

- Macromets >2mm are pN1
pN0(i+)
pN1mi
Nodal disease: breast carcinoma

- Clinical trial data has changed clinical practice
- Trend to avoid axillary dissection due to morbidities
- Limited non-palpable SLN mets may be treated with axillary radiotherapy and chemotherapy instead of axillary dissection

- Palpable nodal disease: axillary dissection
American College of Surgeons Oncology Group Z0011 trial

• Among patients with T1/T2 tumors and limited SLN metastatic disease (1-2 positive nodes) treated with BCS and tangential whole breast irradiation, the use of SLNBx alone compared with ALND did not result in inferior survival
ASOSOG Z0011 trial

• Axillary recurrence <1% at 6.3 years median f/u (0.9% in SLN group vs 0.5% in ALND group)
• Local recurrence at 5 years did not differ between the 2 groups (1.6% in SLN group vs 3.1% in the ALND group)
• No difference in DFS or OS
EORTC AMAROS trial

- Radiotherapy or surgery after a positive SLN bx
  - T1/T2 (<3 cm), clinically node negative
  - Both provide excellent comparable regional control
  - Less lymphedema with RT
EORTC AMAROS trial

• Axillary recurrence at 6.1 years median f/u (1.03% in SLN group vs 0.54% in ALND group)
• Examined the incremental benefit of adding nodal RT to ALND

• Standard breast RT vs breast RT plus regional nodal fields (including supraclav, infraclav, ipsilateral internal mammary chain)

• Inclusion:
  - SLN positive
  - High risk node negative, tumors >2cm, < 10 axillary node removed + 1 other high risk feature (gr 3, ER neg, +LVI)
MA.20

• Improved 5 yr DFS (89.7% for nodal and whole breast RT vs 84% for whole breast RT alone)
• No difference in overall survival
• More adverse outcomes in the nodal RT arm (side effects of RT)
Limitations of the trial data: Z0011 & AMAROS

- Underpowered for adverse events
- Favoured accrual of low-risk T1, ER positive cases
- Z0011 did not meet accrual goal, closed early
Limitations of the trial data: MA.20

• More patients with > 2 positive nodes and extracapsular extension
• Only 10% were node negative
• Higher risk patient population/heterogeneous group
Approach to the axilla in early stage breast cancer

• T1/T2, clinically node negative
  – BCS with:
    • SLN negative including ITC positive: breast irradiation
    • 1-3 SLN positive: breast and axillary irradiation
    • >3 SLN positive or unexpected bulky nodal disease: breast and axillary irradiation, and axillary LN dissection
  – Mastectomy with:
    • SLN negative including ITC positive: no further Rx
    • 1-3 SLN positive: consideration of axillary irradiation
    • >3 SLN positive or unexpected bulky nodal disease: axillary irradiation and axillary LN dissection
Lack of data...

- Microscopic extracapsular extension
- Use/timing of SLN biopsy in patients receiving neoadjuvant Rx
  - may be suitable for patients with cN0 disease prior to chemo
References

- Pilewskie ML, Morrow M. Management of the clinically node-negative axilla: what have we learned from the clinical trials? *Oncology* 2014
References
