COMMON CONSULTATION
CONUNDRUMS IN BREAST PATHOLOGY

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DISCLOSURE

- NONE
Weill Cornell Comprehensive Breast Pathology Consultation Service

Excellence in Academic and Diagnostic Breast Pathology

Weill Cornell Comprehensive Breast Pathology Consultation is a leading-edge consultation service provided by three expert breast pathologists—Dr. Sandra J. Shin, (Left), Dr. Paul Peter Rosen, (Center), and Dr. Syed A. Hoda, (Right).

Established more than 10 years ago with an annual consultation rate in excess of 2,500 cases, it is the leading choice of pathologists, clinicians and patients who seek an expert opinion in breast pathology. The breast consultation service offers referring pathologists, clinicians and patients the speed and accuracy of results that can make a life-saving difference.

Referring physicians and their patients benefit from:

- Consultation and case review with a diagnostic expert in breast pathology
- A state-of-the-art, full service laboratory
- Rapid turnaround time with final report faxed immediately
- Utilization of a large array of immunohistochemical markers including estrogen receptor, progesterone receptor and HER-2/neu

Services

- Routine H and E Interpretation
- Comprehensive Immunohistochemistry including prognostic markers
- Fluorescent In-Situ Hybridization (FISH) for HER-2/neu
- Chromogenic In-Situ Hybridization (CISH) for HER-2/neu
- Electron Microscopy

Reports

All reports are autofaxed. A hard copy is returned with the slides.

Protein overexpression of HER-2

Gene amplification of HER-2

Our expert breast pathologists have consistently been recognized in New York Magazine’s Best Doctors in New York issue as well as Castle Connolly’s renowned America’s Top Doctors—New York Metro Area Edition.
CONSULTATION CONUNDRUMS

THE VAST MAJORITY OF CONSULTATION CASES REPRESENTS THE PROBLEMATIC AREAS IN BREAST PATHOLOGY COMMON TO ALL PATHOLOGISTS
CONSULTATION CONUNDRUMS

- UNUSUAL, UNEXPECTED OR AMBIGUOUS HISTOLOGIC FEATURES AND/OR IMMUNOHISTOCHEMICAL RESULTS
- UNCLEAR REPORTING GUIDELINES
- LACK OF INTRADEPARTMENTAL CONSENSUS OF DIAGNOSIS
- RARITY OF LESION
CONSULTATION CONUNDRUMS

- Unusual, unexpected or ambiguous histologic features and/or immunohistochemical results
- Unclear reporting guidelines
- Lack of intradepartmental consensus of diagnosis
- Rarity of lesion
CHALLENGING AREAS IN BREAST PATHOLOGY

- PAPILLARY LESIONS
- FIBROEPITHELIAL LESIONS
- SMALL GLANDULAR PROLIFERATIONS
- SPINDLE CELL LESIONS (includes VASCULAR)
TOPIC 1 OF 4
PAPILLARY LESIONS
NO ONE’S FAVORITE BREAST LESION

- COMPLEX AND HETEROGENEOUS
- DO NOT FOLLOW A STEPWISE PROGRESSION OF INCREASING PROLIFERATIVE CHANGES AND “ATYPIA”
- GROSS TUMOR SIZE / CLINICAL SIGNS/SX NOT HELPFUL
- IMMUNOHISTOCHEMISTRY LESS HELPFUL IN CLASSIFYING THESE LESIONS (i.e. INVASIVE VS. IN-SITU)
HISTOLOGIC COMMONALITY OF PAPILLARY LESIONS

PAPILLARY, ARBORSCENT EPITHELIAL PROLIFERATION SUPPORTED BY FIBROVASCULAR STALKS WITH OR WITHOUT AN INTERVENING MYOEPITHELIAL CELL LAYER
SPECTRUM OF PAPILLARY LESIONS

- PAPILLOMA WITH/WITHOUT PROLIFERATIVE CHANGES
- PAPILLOMA WITH ATYPIA
  - AKA…ATYPICAL PAPILLOMA, PAPILLOMA WITH ADH, ATYPICAL PAPILLARY LESION
- PAPILLOMA WITH DCIS
- PAPILLARY (IN-SITU) CARCINOMA
  - PAPILLARY DCIS
  - ENCAPSULATED (INTRACYSTIC) PAPILLARY CARCINOMA
  - SOLID PAPILLARY CARCINOMA
- INVASIVE PAPILLARY CARCINOMA
PROBLEM AREAS

- Papilloma vs. Papillary DCIS
- Papilloma with (Florid DH vs. ADH vs. DCIS)
- Papilloma with Florid DH vs. Solid Papillary Carcinoma
- Encapsulated (Intracystic) Papillary CA
- Papillary Lesions in Needle Core Bxs
- In-Situ vs. Invasive Papillary CA
PROBLEM AREAS

- PAPILLOMA VS. PAPILLARY DCIS
- PAPILLOMA WITH (FLORID DH VS. ADH VS. DCIS)
- PAPILLOMA WITH FLORID DH VS. SOLID PAPILLARY CARCINOMA
- ENCAPSULATED (INTRACYSTIC) PAPILLARY CA
- PAPILLARY LESIONS IN NEEDLE CORE BXES
- IN-SITU VS. INVASIVE PAPILLARY CA
PAPILLOMA VS. PAPILLARY DCIS

- HISTOLOGIC OVERLAP
  - WELL-FORMED PAPILLAE WITH FIBROVASCULAR CORES THROUGHOUT LESION
  - LOW NUCLEAR GRADE
  - INTRADUCTAL/INTRACYSTIC GROWTH PATTERN WITH POINT OF ATTACHMENT
  - VARIABLE SIZE
<table>
<thead>
<tr>
<th></th>
<th><strong>INTRADUCTAL PAPILLOMA</strong></th>
<th><strong>PAPILLARY DCIS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CELL TYPE</strong></td>
<td>EPITHELIAL AND MYOEPITHELIAL</td>
<td>EPITHELIAL</td>
</tr>
<tr>
<td><strong>CELL ORIENTATION</strong></td>
<td>HAPHAZARD</td>
<td>UNIFORM, ⊥ TO FVC</td>
</tr>
<tr>
<td><strong>NUCLEI</strong></td>
<td>NORMOCHROMATIC</td>
<td>HYPERCHROMATIC</td>
</tr>
<tr>
<td><strong>STROMA OF PAPILLAE</strong></td>
<td>PROMINENT; FIBROSIS</td>
<td>DELICATE</td>
</tr>
<tr>
<td><strong>APOCRINE MET</strong></td>
<td></td>
<td>ABSENT</td>
</tr>
<tr>
<td><strong>PROLIFERATION IN ADJ DUCTS</strong></td>
<td>HYPERPLASIA</td>
<td>DCIS</td>
</tr>
</tbody>
</table>
Diagnostic evaluation of papillary lesions of the breast on core biopsy

Nirmala Pathmanathan1,2,3,4,6, Ann-Flore Albertini1,4,6, Pamela J Provan1,4,6, Jane S Milliken1, Elizabeth L Salabury4,5, A Michael Bileus1,4, Karen Byth3 and Rosemary L Balleine3,4,5

1Department of Tissue Pathology, Institute of Clinical Pathology and Medical Research, Sydney West Area Health Service, Westmead, NSW, Australia; 2BreastScreen Greater Western Sydney, Westmead, NSW, Australia; 3Westmead Millennium Institute, Westmead, NSW, Australia; 4Sydney Medical School—Western, University of Sydney, Westmead, NSW, Australia and 5Translational Gastroenterology, Sydney West Area Health Service and Westmead Institute for Cancer Research, Westmead, NSW, Australia
OTHER “SOFT” FINDINGS OF PAPILLOMAS

- MYOEPITHELIAL HYPERPLASIA
- APOCRINE METAPLASIA
- INFARCTION
- SQUAMOUS METAPLASIA
<table>
<thead>
<tr>
<th></th>
<th>WITHIN PAPILLAE</th>
<th>PERIPHERY</th>
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<tbody>
<tr>
<td>PAPILLOMA</td>
<td>PRESENT</td>
<td>PRESENT</td>
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<tr>
<td>PAPILLOMA WITH ADH/DCIS</td>
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</tr>
<tr>
<td>SOLID PAPILLARY CA</td>
<td>ABSENT</td>
<td>PRESENT OR ABSENT</td>
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Collins LC and Schnitt SJ, Histopathol 2008
POSSIBLE PITFALLS OF MYOEPTHELIAL CELL MARKERS

- MEC MARKERS VARY IN SENSITIVITY AND SPECIFICITY - PANEL
- MISTAKEN FOR MEC
  - PERICYTES
  - MYOFIBROBLASTS IN THE STROMA
  - NEOPLASTIC CELLS
- DISPLACED CARCINOMA CELLS CAN BE NEGATIVE FOR ME MARKERS
PROBLEM AREAS

- Papilloma vs. Papillary DCIS
- Papilloma with (Florid DH vs. ADH vs. DCIS)
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- Papillary Lesions in Needle Core BXS
- In-Situ vs. Invasive Papillary CA
PAPILLOMA WITH FLORID DUCT HYPERPLASIA

SOLID PAPILLARY CARCINOMA
# DISTRIBUTION OF MYOEPITHELIAL CELLS

<table>
<thead>
<tr>
<th>Within Papillae</th>
<th>Periphery</th>
</tr>
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<tbody>
<tr>
<td>Papilloma (+/-FDH)</td>
<td>Present</td>
</tr>
<tr>
<td>Papilloma with ADH/DCIS</td>
<td>Present/absent</td>
</tr>
<tr>
<td>Papillary DCIS</td>
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<tr>
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<td>absent</td>
</tr>
<tr>
<td>Solid Papillary Carcinoma</td>
<td>absent</td>
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<tr>
<td></td>
<td>Papilloma</td>
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<tr>
<td><strong>Hmwck</strong></td>
<td>Diffuse or mosaic</td>
</tr>
<tr>
<td>(CK5/6; K903)</td>
<td></td>
</tr>
<tr>
<td><strong>Er</strong></td>
<td>Few pos</td>
</tr>
<tr>
<td><strong>Ne markers</strong></td>
<td>Neg</td>
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<tr>
<td>(Synaptoto, CD56)</td>
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OTHER USEFUL IMMUNOSTAINS

<table>
<thead>
<tr>
<th>PAPILLOMA</th>
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<th>SOLID PAP</th>
<th>CARCINOMA</th>
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<tbody>
<tr>
<td>+ FDH</td>
<td>+ ADH/DCIS</td>
<td></td>
<td></td>
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<tr>
<td>HMWCK</td>
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<td>FEW POS</td>
<td>NEG/POS</td>
<td>POS</td>
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<tr>
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NEUROENDOCRINE MARKERS

- MOST COMMONLY POSITIVE IN SOLID PAPILLARY CARCINOMA
- ALSO POSITIVE IN PAPILLARY DCIS AND ENCAPSULATED PAPILLARY CARCINOMA (LESSER EXTENT)
- SYNAPTOPHYSIN, CHROMOGRANIN, CD56
- NEURON SPECIFIC ENOLASE – NOT RECOMMENDED
PROBLEM AREAS

- PAPILLOMA VS. PAPILLARY DCIS
- PAPILLOMA WITH (FLORID DH VS. ADH VS. DCIS)
- PAPILLOMA WITH FLORID DH VS. SOLID PAPILLARY CARCINOMA
- ENCAPSULATED (INTRACYSTIC) PAPILLARY CA
- PAPILLARY LESIONS IN NEEDLE CORE BXs
- IN-SITU VS. INVASIVE PAPILLARY CA
### DISTRIBUTION OF MYOEPITHELIAL CELLS

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ENCAPSULATED (INTRACYSTIC) PAPILLARY CARCINOMA

- ? IN-SITU OR LG INVASIVE CA
  + MORHOLOGICALLY SIMILAR METASTATIC FOCI
- PRECURSOR TO MUCINOUS CARCINOMA BUT ALSO OTHER TYPES OF INVASIVE DUCT CA
- INDOLENT BEHAVIOR WITHOUT CONCURRENT INVASIVE COMPONENT
- EVEN WITH INVASION, PROGNOSIS IS FAVORABLE COMPARED TO INVASIVE DUCT CA OF COMPARABLE SIZE
PROBLEM AREAS

- PAPILLOMA VS. PAPILLARY DCIS
- PAPILLOMA WITH (FLORID DH VS. ADH VS. DCIS)
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- PAPILLARY LESIONS IN NEEDLE CORE BXS
- IN-SITU VS. INVASIVE PAPILLARY CA
DIAGNOSTIC PROBLEMS MAGNIFIED IN NEEDLE CORE BXs

- MORPHOLOGIC PITFALLS DUE TO SMALL SAMPLE SIZE
  - ENTRAPPED GLANDS OF A SCLEROSING PAPILLARY LESION MIMICK INVASIVE DUCT CARCINOMA
- ATYPPIA, IF PRESENT, CAN BE FOCAL
- TISSUE FRAGMENTATION
- RENDERING A FINAL DX OF A PAPILLARY LESION ON NCB IS VIRTUALLY IMPOSSIBLE
CONCLUSIONS - SHAH ET AL STUDY

- With IHC, accuracy of diagnosis increased for all 4 observers
  - PPV 78-88%
  - NPV 100%
  - Accuracy 91-95%
- IHC most helpful to least experienced observer
- IHC permitted reclassification of all B3a cases into one of two more clinically useful categories (B2 or B3b/4/5)
Cytokeratin 5 and Estrogen Receptor Immunohistochemistry as a Useful Adjunct in Identifying Atypical Papillary Lesions on Breast Needle Core Biopsy

Andrea Grin, MD,* Frances P. O’Malley, MB, FRCP,*† and Anna Marie Mulligan, MB, FRCP†


82 PAPILLARY LESIONS WITH EPITHELIAL PROLIFERATION BETWEEN FIBROVASCULAR CORES
52 CASES-TEST  30 CASES-VALIDATION (ALL WITH EXBX)
ER-high/CK5-low immunoprofile identifies atypical papillary lesions at a sensitivity of 93% and specificity of 100%

ER-low/CK5-high immunoprofile identified non-atypical papillary lesions at a sensitivity of 100% and specificity of 93%
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TOPIC 2 OF 4
SMALL GLANDULAR PROLIFERATIONS
HISTORY

- 59 YEAR-OLD FEMALE
- BREAST NODULE - RETROAREOLAR
- NO OTHER SIGNIFICANT CLINICAL HX
- NEEDLE CORE BIOPSY PERFORMED
DIFFERENTIAL DIAGNOSIS

- INVASIVE WELL-DIFFERENTIATED DUCT CARCINOMA
  + TUBULAR FEATURES
- SYRINGOMATOUS ADENOMA
- LOW-GRADE ADENOSQUAMOUS CARCINOMA
- RADIAL SCLEROSING LESION
- COMPLEX SCLEROSING LESION
- SCLEROSING ADENOSIS
- SKIN ADNEXAL CARCINOMA
HOW WE LEARN PATHOLOGY

- Most didactic lectures are focused around specific entities.
- Pattern – based learning may be more useful, esp in certain settings such as core needle biopsies.
  - Pathologic findings are fragmented.
  - Diagnostic features are missing.
- The spectrum of benign, atypical and malignant entities can have the same pattern.
ARRIVING AT THE CORRECT DX

- PATTERN RECOGNITION - DDX
- ALGORITHM
- WHEN WE GET STUCK....
  + USE ADJUNCTIVE TOOLS (IHC)
  + CONSULT A COLLEAGUE
  + BOTH
ADJUNCTIVE DIAGNOSTIC TOOLS

- IMMUNOHISTOCHEMISTRY
- SPECIAL STAINS
- MOLECULAR CHARACTERIZATION
  - FISH
  - GENE PROFILING
- ELECTRON MICROSCOPY
SMALL GLANDULAR PROLIFERATIONS OF THE BREAST (SGPB)

- MALIGNANT-APPEARING BUT BENIGN
- BENIGN-APPEARING BUT MALIGNANT
- MALIGNANT-APPEARING BUT MALIGNANT OF A DIFFERENT TYPE
CASE 1 continued…
DIAGNOSIS RENDERED

- INVASIVE DUCT CARCINOMA, WELL-DIFFERENTIATED
- RE-REVIEWED AT INSTITUTION WHERE SURGERY WAS PLANNED
- NEW DIAGNOSIS: SYRINGOMATOUS ADENOMA
- NO SURGERY PERFORMED
5 YEARS LATER…2011

- BREAST MASS GROWN 5 CM LARGE; NEEDS MASTECTOMY IF MALIGNANT

- NEEDLE CORE BIOPSY PERFORMED
LOW-GRADE ADENOSQUAMOUS CARCINOMA
[187] Immunohistochemical Staining Patterns of Low-Grade Adenosquamous Carcinoma (LGASC) Different from Other Small Glandular Proliferations of the Breast (SGPB).

Kathy Kawaguchi, Sandra J Shin. Weill Cornell Medical College, New York, NY

- 29 CASES OF LGASC
- MYOEPITHELIAL MARKERS (p63, SMM, CD10, CALPONIN, SMA)
- CYTOKERATINS (CKAE1/3, CK7, Cam 5.2, CK5/6, K903)
- GLANDULAR EPITHELIUM AND ADJACENT STROMA STUDIED
RESULTS - MYOEPITHELIAL MARKERS

GLANDULAR EPITHELIUM
CIRCUMFERENTIAL STAINING IN MOST (>80%) CASES WITH EITHER COMPLETE (~75%) OR WEAK, DISCONTINUOUS (~35%) STAINING USING ANY ONE STAIN. OCCASIONALLY GLANDS ARE NEGATIVE

ADJACENT STROMA
LAMELLAR STAINING ~45% OF CASES USING ANY ONE STAIN
DIFFUSE STROMAL POSITIVITY IN >50% (CALPONIN, CD10, SMA); ~12.5% (SMM); 0 (p63)
RESULTS- CYTOKERATIN MARKERS

GLANDULAR EPITHELium
POSITIVE FOR ONE OR MORE STAINS IN ALL CASES
DIFFUSE WITH EITHER UNIFORM OR VARIABLY
INTENSE INTENSITY IN >75% OF CASES

CORE STAINING IN 25% TO 67% USING ANY ONE STAIN

ADJACENT STROMA
UNIFORMLY NEGATIVE IN ALMOST ALL CASES
OTHER SGPB TO CONSIDER IN CORE NEEDLE BIOPSIES

- INVASIVE DUCT CARCINOMA (WELL-DIFFERENTIATED, TUBULAR TYPE)
- RADIAL SCLEROSING LESION
- ADENOSIS/SCLEROSING ADENOSIS/ADENOSIS TUMOR
- MICROGLANDULAR ADENOSIS
MORPHOLOGIC FEATURES

IFDC (TUBULAR) VS LGASC

- WELL-FORMED GLANDS
- HAPHAZARD, INFILTRATIVE ARRANGEMENT
- ROUND, OVAL, OR TEAR DROP-SHAPED GLANDS
- LOW NUCLEAR GRADE
- ELASTOTIC STROMA

- WELL-FORMED GLANDS
- HAPHAZARD, INFILTRATIVE ARRANGEMENT
- ANGULATED GLANDS +/- SQUAMOUS DIFFERENTIATION
- LOW NUCLEAR GRADE
- PERI-GLANDULAR SPINDLE CELL METAPLASIA IN STROMA
- LYMPHOCYTIC AGGREGATES
IMMUNOHISTOCHEMICAL FEATURES

IFDC VS LGASC

- NEGATIVE FOR MYOEPITHELIAL MARKERS (P63, SMM, CALPONIN)
- POSITIVE FOR ER/PR (STRONG, DIFFUSE)
- STROMA - NEGATIVE

- CIRCUMFERENTIALLy POSITIVE (VARIABLE) FOR MYOEPITHELIAL MARKERS; OCCASIONAL NEGATIVE GLAND(S)
- “LAMELLAR” POSITIVITY FOR MYOEPITHELIAL MARKERS (SMM) IN SPINDLE CELL STROMA
- P63 ALSO POSITIVE IN EPITHELIUM WITH SQUAMOUS DIFFERENTIATION
- POSITIVE (DIFFUSE, VARIABLE INTENSITIES) FOR MOST CYTOKERATINS
- CORE STAINING FOR SOME CYTOKERATINS (HMWCK)
- ER/PR NEGATIVE
**MORPHOLOGIC FEATURES**

**IFDC (TUBULAR) VS RSL**

- WELL-FORMED GLANDS
- HAPHAZARD ARRANGEMENT
- ROUND, OVAL, OR TEAR-DROP SHAPED GLANDS
- LOW NUCLEAR GRADE
- CO-EXISTING CCL, ADH, LOBULAR LESIONS
- ELASTOTIC STROMA

- WELL-FORMED GLANDS
- CENTRIFUGAL ARRANGEMENT
- ANGULATED OR SLIT-LIKE GLANDS
- LOW NUCLEAR GRADE
- OTHER FCC ELEMENTS PARTICIPATING
- ELASTOTIC STROMA
- +/- HEAVY SCLEROSIS IN NIDUS
MORPHOLOGIC FEATURES

IFDC (TUBULAR) VS SA

- WELL-FORMED GLANDS
- HAPHAZARD ARRANGEMENT
- ROUND, OVAL, OR TEAR-DROP SHAPED GLANDS
- ELASTOTIC STROMA

- WELL-FORMED GLANDS
- LOBULOCENTRIC BUT MAY NOT BE APPARENT ON CNB
- PSEUDOINFILTRATIVE GROWTH PATTERN WITH INCREASING SCLEROSIS
- CAN BE SECONDARILY INVOLVED BY ALH, LCIS, ADH, DCIS
- ASSOCIATED CALCS; MASS FORMING IF ADENOSIS TUMOR
IS THIS TUBULAR CARCINOMA ARISING IN A RADIAL SCLEROSING LESION?
IMMUNOHISTOCHEMICAL FEATURES

IFDC VS RSL/SA

- NEGATIVE FOR MYOEPITHELIAL MARKERS (P63, SMM, CALPONIN)
- POSITIVE FOR ER/PR (STRONG, DIFFUSE)

- POSITIVE FOR MYOEPITHELIAL MARKERS (P63, SMM, CALPONIN)
  BUT CAN BE VERY ATTENUATED OR ABSENT IN AREAS OF MARKED SCLEROSIS
- ER/PR POSITIVE BUT NOT DIFFUSELY
NOT ALL MYOEPITHELIAL MARKERS ARE CREATED EQUAL

- DIFFER IN SENSITIVITIES AND SPECIFICITIES
  - SOME ALSO STAIN MYOFIBROBLASTS (i.e. SMOOTH MUSCLE ACTIN, CD10)
- SOME ARE LESS ROBUST IN AREAS OF HEAVY SCLEROSIS; FALSE NEGATIVITY
- RECOMMEND USING A PANEL OF MYOEPITHELIAL MARKERS
  - P63, SMOOTH MUSCLE MYOSIN, CALPONIN
INVASIVE CARCINOMA WITH TUBULAR AND LOBULAR FEATURES

BIOMARKER STAINS PENDING
MICROGLANDULAR ADENOSIS GIVING RISE TO INVASIVE CARCINOMA
MORPHOLOGIC FEATURES
IFDC (TUBULAR) VS MGA

- Infiltrative well-formed glands
- Round, oval or tear-drop shaped glands
- Low nuclear grade
- Elastotic stroma
- In-situ component is absent or ADH/LG DCIS
- Co-existing CCL and/or lobular lesions

- Infiltrative well-formed glands
- Round glands
- Low nuclear grade
- Bright eosinophilic luminal secretions
- Stroma is unaltered
- No in-situ component unless atypical
IMMUNOHISTOCHEMICAL FEATURES

IFDC VS MGA

- NEGATIVE FOR MYOEPITHELIAL MARKERS (P63, SMM, CALPONIN)
- POSITIVE FOR ER/PR (STRONG, DIFFUSE)
- NEGATIVE FOR MYOEPITHELIAL MARKERS (P63, SMM, CALPONIN)
- NEGATIVE FOR ER/PR
- POSITIVE FOR BASEMENT MEMBRANE MARKERS (RETICULIN, LAMININ, COLLAGEN TYPE IV)
- POSITIVE FOR S-100 PROTEIN
INVASIVE LOBULAR CARCINOMA FOCALLY INVOLVING A RADIAL SCLEROSING LESION
RADIAL SCLEROSING LESION (RSL)

- Occurrence of invasive or in-situ carcinoma involving RSL or in close proximity of RSL is well known
- Rates 0-34%
- Easily underdiagnosed on NCB since involvement by carcinoma of a RSL is focal or peripheral
TOPIC 3 OF 4
FIBROEPITHELIAL LESIONS
FIBROEPITHELIAL LESIONS

- Fibroadenoma (FA)
  - Variants (cellular, juvenile, complex, giant)
- Phyllodes Tumor (PT)
  - Grades (benign, borderline, malignant)
- Fibroadenomatoid Mastopathy
  (Sclerosing Lobular Hyperplasia)
MANAGEMENT

- FIBROADENOMAS
  - Simple enucleation
  - Clinical follow-up if small

- PHYLLODES TUMOR
  - Wide local excision (1cm or more?) for PT (all grades?) compliance by surgeons?
  - Residual PT at margins is a strong predictor of local recurrence; re-excision is recommended
BENGIN PT CALLED FA ON CNB

Clinical F/U only

- EXBX if clinically worsening
  - Potentially higher grade PT in unsampled areas; less favorable cosmetic result if large

Enucleation (unoriented specimen)

- Positive undesignated margins in the EXBX
  - Re-excision of undesignated margin(s)
    - Potentially more tissue excised

Psychological +/- physical morbidity of pt
PHYLLODES TUMORS

- Rare compared to FA (2-3% of FEL tumors of the breast)
- Age 35-55 females
- Breast mass +/- rapid growth
- Size at presentation larger than that of FA but difference is shrinking due to screening
  - 1.3cm (PT) vs. 1.0cm (FA) [Komenaka et al. Arch Surg 2003]
- Clinically and radiologically indistinguishable from FA
- Local recurrence rates: Benign (8%), BL (29%), HG (36%)
- Metastatic potential: Benign (0%), BL (<4%), HG (<22%)
MORPHOLOGIC FEATURES

- Leaf-like growth pattern
- Stroma (cellularity, atypia, overgrowth)
- Interfield variability of gland to stroma ratio
- Tumor border (invasive)
- Stromal mitotic figures
- Pseudoangiomatous stromal hyperplasia
- Excessive epithelial hyperplasia (micropapillary)
Jacobs, et al.  
AJCP 2005;124:342-354

- 29 pts with NCB containing FEL with cellular stroma who had subsequent EXBX
- “cellular stroma” = 2x normal perilobular stroma
- Surgical outcome:
  - 16 (55%) were FA
  - 12 (41%) were PT (5-benign, 6-LGM, 1-HG)
10 HISTOLOGIC FEATURES

- Stromal cellularity
- Stromal nuclear atypia
- Stromal mitotic count
- Stromal proportion to epithelium
- Stromal overgrowth

- Enhancement of stromal cellularity adjacent to epithelium
- Infiltrative tumor border
- Epithelial hyperplasia
- Overall growth pattern
- Multinucleated giant cells
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Histological features useful in the distinction of phyllodes tumour and fibroadenoma on needle core biopsy of the breast

A H S Lee, Z Hodi, I O Ellis & C W Elston
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Date of submission 22 September 2006
Accepted for publication 20 February 2007

Lee A H S, Hodi Z, Ellis I O & Elston C W
Seven histologic features significantly different b/t FA and PT

- Stromal cellularity >50% of core
- Marked stromal pleomorphism
- Stromal overgrowth (x10 field)
- Edge-infiltrative (only when edge can be adequately assessed in ncb)
- Fragmentation
- Adipose tissue in stroma (invasive tumor border vs lipomatous metaplasia)
- Stromal mitoses
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Analysis of histological features in needle core biopsy of breast useful in preoperative distinction between fibroadenoma and phyllodes tumour

J Mike Morgan, Anthony G Douglas-Jones¹ & Sanjeev K Gupta²
Department of Histopathology, University Hospital of Wales, Cardiff, ¹Cardiff University, Heath Park Campus, Cardiff, UK, and ²Institute of Medical Sciences, BHU, Varanasi, India

112 NCB of FEL
(21 PT AND 91 FA ; ALL WITH EXBX)
RECEIVER-OPERATING CHARACTERISTIC (ROC) ANALYSIS

- Objective method for determining optimal cut-off values in frequency distributions for 2 datasets with one variable (tumor type).

- CUT OFF VALUES FOR PT OVER FA
  - AGE (50-55)
  - PERCENT STROMA (85-90)
  - MITOSES ($\geq 1$ PER 2.2 MM$^2$)

- CONFIRMED FINDINGS OF LEE, et al.
Predictors of phyllodes tumours on core biopsy specimens of fibroepithelial neoplasms

Ana Richelia Jara-Lazaro, Meenakshi Akhilesh, Aye Aye Thike, Philip Chi-Wai Lui
Gary Man-Kit Tse & Puay Hoon Tan
Department of Pathology, Singapore General Hospital, Singapore, and 1Department of Anatomical and Cellular Pathology, Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, SAR, China

261 NCB OF FEL
98 (37%) FEL CANNOT EXCLUDE PT
57/98 (58%) UNDERWENT EXBX
MORPHOLOGIC FEATURES

- EXCLUSIVE FEATURES OF PT
  - MARKED STROMAL CELLULARITY
  - MARKED STROMAL ATYPIA
  - MITOSES $\geq 2 / 10$ HPF
  - ILL-DEFINED LESIONAL BORDER

- HIGH CORRELATION WITH PT ON EXBX
  - MODERATE STROMAL CELLULARITY
  - STROMAL OVERGROWTH
  - MODERATE STROMAL ATYPIA
  - PASH
SUMMARY OF STUDIES

- MORPHOLOGIC FEATURES OF PT
  - STROMAL CELLULARITY (MODERATE TO MARKED)
  - STROMAL ATYPIA
  - STROMAL MITOSES (AT LEAST 1)
  - STROMAL OVERGROWTH
  - INFILTRATIVE TUMOR BORDER
SPINDLE CELL LESIONS

- SIMILAR TO SMALL GLANDULAR PROLIFERATIONS, SPINDLE CELL LESIONS CONSISTS OF A SPECTRUM OF BENIGN TO MALIGNANT ENTITIES WHICH SHARE AN OVERALL SIMILAR MORPHOLOGIC APPEARANCE

- FORMULATING AN ACCURATE DX ON CORE NEEDLE BIOPSIES CAN BE DIFFICULT IF NOT IMPOSSIBLE
CELLS OF ORIGIN

- FIBROBLASTS, MYOFIBROBLASTS
  - INTRA- AND INTERLOBULAR MAMMARY STROMA
  - POSITIVE VIMENTIN, BCL-2, CD-99
  - MYOFIBROBLASTS ALSO \(\alpha\)-SMOOTH MUSCLE ACTIN, DESMIN, HORMONE RECEPTORS
- EPITHELIAL
- MYOEPITHELIAL
- HISTIOCYTES
- ENDOTHELIAL CELLS
SPINDLE CELL LESIONS

- CYTOLOGICALLY BLAND-APPEARING LESIONS
  - BENIGN
  - MALIGNANT

- CYTOLOGICALLY ATYPICAL LESIONS
  - MALIGNANT
CYTOLOGICALLY BLAND SPINDLE CELL LESIONS DIFFERENTIAL DIAGNOSIS

- PASH
  - FASICULAR
  - TUMOROUS
- MYOFIBROBLASTOMA
- BENIGN PHYLLODES TUMOR (STROMA ONLY)
- SCAR
- REACTIVE SPINDLE CELL NODULE
- ADENOMYEOEPITHELIOMA
- SPINDLE CELL LIPOMA
- NEUROFIBROMA
- LEIOMYOMA

- SARCOMA
  - LOW-GRADE (including well-differentiated angiosarcoma)
- METAPLASTIC SPINDLE CELL CARCINOMA
  - LOW-GRADE FIBROMATOSIS-LIKE
CYTOLOGICALLY ATYPICAL SPINDLE CELL LESIONS: DIFFERENTIAL DIAGNOSIS

- NODULAR FASCIITIS
- PHYLLODES TUMOR (STROMA ONLY)
  - BORDERLINE, HIGH GRADE
- METASTASES
  - MELANOMA
- SARCOMA
  - PRIMARY (HIGH-GRADE ANGIOSARCOMA)
  - METASTATIC
OTHER CO-EXISTING CELLS

- RED BLOOD CELLS - ANGIOSARCOMA
- MIXED INFLAMMATORY INFILTRATE & RED BLOOD CELLS – NODULAR FASCIITIS
- LYMPHOCYTES
  - PERIPHERAL AGGREGATES – FIBROMATOSIS
  - DISPERSED IN BACKGROUND – SPINDLE CELL METAPLASTIC CARCINOMA, REACTIVE SPINDLE CELL NODULE
- UNINVOLVED BREAST TISSUE OR ADIPOSE TISSUE PRESENT?
CLINICAL AND RADIOLOGIC CORRELATION

- PAST CLINICAL HISTORY
  - RECENT HISTORY OF TRAUMA/NEEDLE BX (SPINDLE CELL NODULE)
  - BREAST CARCINOMA AND STATUS POST RADIATION THERAPY (POST-RADIATION ANGIOSARCOMA)
  - OTHER MALIGNANCIES (I.E. MELANOMA)
  - FAMILILAR ADENOMATOUS POLYPOSIS OR GARDNER’S SYNDROMES (FIBROMATOSIS)
  - “BRUISE” ON BREAST SKIN (ANGIOSARCOMA)
TUMOR CHARACTERISTICS

- SOLITARY (PHYLLODES TUMOR, MYOFIBROBLASTOMA, MYOEPITHELIOMA, TUMOROUS PASH)
- WELL-CIRCUMSCRIBED (MYOFIBROBLASTOMA, ADENOMYOEPI THELIOMA)
- INFILTRATIVE BORDERS (FIBROMATOSIS, SOME PHYLLODES TUMORS)
- SMALL SIZE (NODULAR FASCITIS, REACTIVE SPINDLE CELL NODULE)
- SUPERFICIAL LOCATION (SPINDLE CELL LIPOMA, DFSP, DF)
- NIPPLE LOCATION (LEIOMYOMA)
MYOFIBROBLASTOMA

- Circumscribed +/- lipomatous differentiation
- Short fascicles of uniform spindle-shaped cells with round to oval nuclei; mitoses very rare
- Hyalinized collagen bands
- Mast cells, myxoid change, chondroid or smooth muscle metaplasia
- Variants exist…most impt, epithelioid confuse with infiltrating carcinoma
- CD 34 POSITIVE +/- SMOOTH MUSCLE ACTIN, DESMIN; S-100 NEG (unlike spindle cell lipoma)
- ER, PR, BCL-2, VIMENTIN
FIBROMATOSIS

+ Painless, slowly growing mass
+ Stroma vary from keloidal to myxoid/fasciitis like
+ SMA positive; +/-desmin, S-100
+ High rate of local recurrence
+ Difficult or impossible to distinguish between fibromatosis and scar in re-excision
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*POSITIVE STAINING CAN BE VERY FOCAL*

*p63 IS DIFFUSELY POSITIVE IF ONE CK IS ALSO*

*ALWAYS PERFORM A PANEL OF CK MARKERS TO RULE IN/OUT THIS ENTITY*

*A NEGATIVE IMMUNOPANEL ON A CNB DOES NOT EXCLUDE THIS DX*
SPINDLE CELL METAPLASTIC CARCINOMA

- MORPHOLOGIC CLUES BEFORE IHC
  - ADMIXED INVASIVE DUCT CARCINOMA, NOS
  - PRESENCE OF DCIS
  - SPINDLE CELLS THAT AGGREGATE AND CONTAIN MORE CYTOPLASM/LARGER NUCLEI (“EPITHELIOID”)
  - AREAS OF SQUAMOUS DIFFERENTIATION
  - SCATTERED CHRONIC INFLAMMATION IN THE BACKGROUND (“DIRTY BACKGROUND”)
LOW-GRADE FIBROMATOSIS-LIKE SCMC

- Composed of bland spindle cells similar to those seen in fibromatosis
- Can see areas that are more epithelioid +/- squamous differentiation
- High rate of local recurrence
- Metastasis is rare
Hemangiomas and Angiosarcomas of the Breast

Diagnostic Utility of Cell Cycle Markers With Emphasis on Ki-67

Sandra J. Shin, MD; Martin Lesser, PhD; Paul Peter Rosen, MD

Context.—Vascular tumors comprise a minor subgroup of tumors arising in the breast and represent variants of hemangiomas and angiosarcomas. Diagnostic challenges may arise when differentiating hemangiomas from types I and II angiosarcomas. Ki-67 expression has been used as an adjunct to distinguish between benign and malignant lesions exhibiting histologic overlap at various anatomic sites.

Objective.—To investigate the utility of Ki-67 and other cell cycle regulatory proteins (S-phase kinase-associated protein 2 [Skp2], p27, and cyclin D1) in the differential diagnosis of mammary vascular lesions.

Design.—Thirty-four vascular tumors (21 hemangiomas and 13 angiosarcomas) of the breast were studied. The Ki-67 index and immunoreactivity for Skp2, p27, and cyclin D1 were determined in each case. Appropriate statistical methods were used.

Results.—The mean value of Ki-67 index was statistically different when comparing hemangiomas and angiosarcomas (P < .001). Angiosarcomas were typically positive for Skp2, whereas hemangiomas were negative (P < .001). Sensitivity and specificity cutoffs for Ki-67 index to distinguish hemangiomas from angiosarcomas showed a candidate cutoff point of 175. The mean values of Ki-67 of low-grade angiosarcomas were significantly different from all hemangiomas (P < .001) and also different from the subset of atypical hemangiomas (P = .02). Sensitivity and specificity cutoffs for Ki-67 index to distinguish all hemangiomas from low-grade angiosarcomas showed a candidate cutoff point between 150 and 175. Among angiosarcomas, positivity for Ki-67 was inversely related to that of p27 but not to Skp2 or cyclin D1. This was also true among hemangiomas.

Conclusions.—Ki-67 index can be used as a diagnostic tool to distinguish between benign and malignant vascular lesions of the breast. This can be particularly helpful in cases of histologic overlap such as low-grade angiosarcoma and hemangioma.

(Arch Pathol Lab Med. 2007;131:538–544)
THANK YOU!

For consultation submissions, http://www.cornellpathology.org