Spindle cell lesions of the breast

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Disclosures

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Outline and Learning Objectives

1. Describe the general differential diagnosis of spindle cell tumors of the breast, including the specific entities of metaplastic carcinoma, phyllodes tumor, myofibroblastoma, fibromatosis and nodular fasciitis

2. Characterize the histologic spectrum and associated prognoses of metaplastic (sarcomatoid) carcinoma subtypes

3. Recognize the classification criteria for and diagnostic features of phyllodes tumor subtypes

4. Identify potential diagnostic pitfalls of spindle cell tumors of the breast on core needle biopsy
Spindle cell lesions of the breast:
Take home messages

• Always consider and exclude metaplastic or spindle cell carcinoma
• Always consider the possibility of a phyllodes tumor
• Immunostains are frequently needed to evaluate spindle cell tumors on core needle biopsy
• Definitive classification of a spindle cell tumor on core needle biopsy may not be possible
Spindle cell lesions of the breast: Take home messages

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Differential Diagnosis of Spindle Cell Lesions
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MAIN ENTITIES TO CONSIDER AND EXCLUDE

• Metaplastic (sarcomatoid, spindle cell) carcinoma
• Metaplastic (sarcomatoid, spindle cell) carcinoma
• Metaplastic (sarcomatoid, spindle cell) carcinoma
• Phyllodes tumor
• Other

Atypical spindle cells
• Metaplastic carcinoma
• Malignant phyllodes tumor
• Sarcoma
• Metastatic carcinoma, sarcoma or melanoma
• Nodular fasciitis

Less common atypical entities:
• Angiosarcoma, dermatofibrosarcoma protuberans, etc.

Bland spindle cells
• Fibromatosis
• Myofibroblastoma
• PASH
• Nodular fasciitis
• Scar
• Adenomyoepithelioma
• Benign phyllodes tumor

Less common bland entities:
• Nerve sheath tumor, leiomyoma, dermatofibroma, etc.

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LESIONS WITH ATYPICAL SPINDLE CELLS

Metaplastic carcinoma

Metaplastic carcinoma: Clinical Features

• Account for <1% of breast carcinomas
• Patients with metaplastic carcinoma (as a whole) have a worse overall survival than patients with conventional triple negative mammary/ductal carcinoma
• Metaplastic carcinomas are less likely to metastasize to axillary lymph nodes, but more likely to present with distant metastatic disease.

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• Metaplastic carcinomas are less likely to metastasize to axillary lymph nodes, but more likely to present with distant metastatic disease.
• Typically triple negative for ER, PR and HER2
• Improved treatment options are required—patients are currently treated with traditional chemotherapy, but with poor response rates.

Metaplastic carcinoma: Pathologic Features

• Metaplastic carcinoma is defined as a carcinoma with divergent or heterologous differentiation
• Varying histologic patterns:
  - Spindled
  - Squamous
  - Osseous
  - Chondroid
  - Pleomorphic
  - Adenosquamous
• Can de “de novo” or have an associated conventional invasive or in situ mammary carcinoma component
Chondroid metaplastic carcinoma

Spindled-rhabdoid metaplastic carcinoma

Pleomorphic metaplastic carcinoma
Metaplastic carcinoma: Prognosis varies with histologic type, to a degree

- The presence of high grade spindled or pleomorphic components has been associated with aggressive behavior such as metastasis.
- Low-grade, fibromatosis-like metaplastic carcinomas and adenosquamous carcinomas have high risk of local recurrence but minimal to no risk of distant spread.
- However, there is otherwise no widely accepted prognostic value to subtyping the metaplastic component or to histologic grading in metaplastic carcinoma.
Spindle cell metaplastic carcinoma: Pathologic Features

- Spindle cells vary from cytologically bland to markedly atypical and pleomorphic
  - The differential diagnosis of the bland lesions includes fibromatosis, scar, myofibroblastoma, nodular fasciitis
  - The differential diagnosis of the atypical lesions includes phyllodes tumor, nodular fasciitis, melanoma
- Spindle cells may display “fibromatosis-like,” fascicular, storiform, fasciitis-like growth, or patternless pattern
- Spindle cells irregularly infiltrate fat and benign lobules

If present, epithelial differentiation is the most helpful diagnostic feature (such as DCIS, conventional IDC, epithelioid aggregates)
Low Grade Spindle cell Carcinoma
The presence of overt epithelial differentiation can be a helpful diagnostic feature.

Here is a largely necrotic and spindled tumor...
The presence of overt epithelial differentiation can be a helpful diagnostic feature:
- Here is a largely necrotic and spindled tumor...
- With regions of markedly pleomorphic cells...
- And areas of overt epithelial/squamoid differentiation

DIAGNOSIS: METAPLASTIC CARCINOMA
(no immunostains needed)
However, if no overt epithelial differentiation is evident, cytokeratin immunostains may be necessary

Spindle cell carcinoma: Immunostains

• A panel cytokeratin approach is often necessary
• Antibodies to high molecular weight cytokeratins are the most sensitive. Panel could include:
  - CK903 (34b12)
  - CK5/6
  - Cam5.2 (CK8/18)
  - Pancytokeratin MNF116
  - Pancytokeratin AE1/AE3
• Also label for p63 (but not specific for carcinoma), variably positive for actins, and 50% label for SOX10 (?myoepithelial/basal-like differentiation?)
• Negative for: CD34
Atypical spindle cell lesion on core needle biopsy

CK903 + (34b12)

Atypical spindle cell lesion on core needle biopsy

CAM5.2 +

P63 +
Spindle cell carcinoma: Potential Immunohistochemical Pitfalls

- Spindle cell carcinomas CAN label for **nuclear beta-catenin** → mimicking fibromatosis
- Phyllodes tumors CAN label for **p63 and cytokeratins** → mimicking spindle cell carcinoma
- A broad differential diagnosis and panel approach to immunostains is necessary

Phyllodes tumors

- Common tumors
- Benign
- Rare tumors
- Three categories:
  - Benign
  - Borderline (formerly “low grade”)
  - Malignant
- How different from fibroadenomas?
  - Prominent leaf-like architecture → often cystic
  - Atypical and malignant categories

Fibroepithelial lesions of the breast

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<th>PHYLLODES TUMORS</th>
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Phyllodes tumors: Clinical features

- Rare tumors comprising <1% of all breast tumors and ~2.5% of fibroepithelial lesions
- Mainly in middle aged women in their 40's-50's (older than women with fibroadenomas; but both can occur in any age)
- Typically large painless masses, on average 4-5 cm (larger than fibroadenomas)
- Radiology is often, but not always, cystic
Fibroepithelial lesions: Pathogenesis

- Overall, phyllodes tumors appear to arise de novo
- Many studies have explored relationship between fibroadenomas and phyllodes tumors
- No definitive evidence for direct linear progression from fibroadenoma to phyllodes tumor, however various associated genetic changes are seen

Fibroepithelial lesions harbor MED12 mutations

- Recent evidence points to recurrent MED12 (mediator complex subunit 12) exon 2 mutations in stromal cells of fibroadenomas (59%) and phyllodes tumors (62.5%) across grades (Ng CC, et al. J Clin Pathol. 2015 Sep;68(9):685-91.)
- Suggests a close genetic relationship
- Tumors with MED12 mutations have longer disease-free survival
- MED12 mutations are linked to aberrant estrogen signaling, perhaps this is related to survival?

Phyllodes tumors: General behavior

- The primary risk with phyllodes tumor is local recurrence
  - Overall recurrence rate up to 21% (WHO)
  - Most recurrences occur within 2-3 years
  - Recurrence can be higher in malignant phyllodes
  - A low percentage (< 2%) of phyllodes tumors metastasize - almost all are malignant phyllodes
  - Up to 25% malignant phyllodes tumors metastasize
Phyllodes tumors: Pathologic features

- Fibroepithelial lesions with *hypercellular stroma* and *leaf-like architecture*
- Subclassified into:
  - Benign
  - Borderline (formerly “low grade”)
  - Malignant
- The distinction between these categories is based on a variety of pathologic features
- The benign ones have features that overlap with fibroadenomas
- The malignant ones have features that overlap with other cancers

Malignant phyllodes tumor: Gross pathologic features

In contrast to the homogenous, whorled appearance of the fibroadenoma, the malignant phyllodes tumors show varying colors and textures from fleshy to hemorrhagic and cystic.

*Rosen’s Breast Pathology, 3rd Ed.*
"φύλλον" means "leaf" in Greek

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<td><strong>Stromal hypercellularity</strong></td>
<td>Mild-moderate</td>
<td>Moderate</td>
<td>Marked</td>
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<tr>
<td><strong>Pleomorphism</strong></td>
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<tr>
<td><strong>Heterologous elements</strong></td>
<td>Absent</td>
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<td>May be present</td>
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Stromal overgrowth in phyllodes tumors

- Defined as one low power field (4x objective) comprised entirely of stroma without an associated epithelial component
- Seen primarily in malignant phyllodes tumors
- Implies that the stroma can proliferate and survive without the associated growth signals from the epithelium (…risk of metastatic spread…)

Benign phyllodes tumor

Borderline phyllodes tumor
Malignant Phyllodes Tumor (1): Leaf-like architecture with cellular stroma

Malignant Phyllodes Tumor (1): Leaf-like architecture with variably cellular stroma

Malignant Phyllodes Tumor (1): Leaf-like architecture with cellular and atypical stroma
Malignant Phyllodes Tumor (2): hypercellular stroma with atypia

Malignant Phyllodes Tumor (2): Markedly atypical, malignant stromal cells

Malignant Phyllodes Tumor (2): Infiltrative growth with entrapment of fat
Malignant phyllodes tumor (3): Low power field (4x) entirely comprised of spindle cell lesion

Malignant phyllodes tumor (3): Abrupt transition to a low grade component

Differential diagnosis of fibroepithelial lesions
The primary differential diagnosis of phyllodes tumors varies along spectrum from benign to malignant.

**Benign Phyllodes**
- Cellular fibroadenoma

**Malignant phyllodes**
- Metaplastic carcinoma
- Sarcoma
- Other spindle cell lesions

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**Remember: Overall Differential Diagnosis of Spindle Cell Lesions**

**Atypical spindle cells**
- Metaplastic carcinoma
- **Malignant phyllodes tumor**
- Sarcoma
- Metastatic carcinoma, sarcoma or melanoma
- Nodular fasciitis

*Less common atypical entities:*
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**Bland spindle cells**
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- **Benign phyllodes tumor**

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**Differential diagnosis 1:**
Cellular fibroadenoma versus benign phyllodes tumor
Cellular fibroadenoma versus benign phyllodes tumor: histologic features

- Benign phyllodes tumors have:
  - More cellular stroma
  - More pronounced cystic areas and leaf-like architecture
- But, these are subjective measures on a histologic continuum

Cellular fibroadenoma versus benign phyllodes tumor: interobserver variability

- There is high interobserver variability in classification of cellular fibroadenoma versus phyllodes tumor even among breast pathology experts (although distinction of fibroadenoma/benign phyllodes versus borderline/malignant phyllodes is better)


Features that favor phyllodes tumor over fibroadenoma on core biopsy

- Marked stromal hypercellularity
- Stromal overgrowth
- Infiltrative border/fat within lesion
- Tissue fragmentation of cores (suggests cystic/prominent leaf-like architecture)

Features that favor phyllodes tumor over fibroadenoma on core biopsy

- Marked stromal hypercellularity
- Stromal overgrowth
- Infiltrative border/fat within lesion
- Tissue fragmentation of cores (suggests cystic/prominent leaf-like architecture)

If the diagnosis is not clear on core biopsy, best to classify as “cellular fibroepithelial lesion” or with an explanation as to why there is uncertainty and defer final classification to excision.


Differential diagnosis 2:
Malignant phyllodes tumor versus spindle cell (metaplastic) carcinoma

Metaplastic carcinomas display various patterns of heterologous differentiation, and “spindle cell carcinomas” are purely spindled.
If present, overt epithelial differentiation (in situ or invasive) is a helpful diagnostic feature to support classification as a metaplastic carcinoma.

Likewise, if present, overt leaf-like epithelial areas are a helpful diagnostic feature to support classification as a phyllodes tumor.
The most useful aid to definite classification of a spindle cell neoplasm on excision might be **taking additional sections**

Immunohistochemistry can be helpful, but there is substantial overlap between spindle cells lesions

**Phyllodes tumors:**
**Immunohistochemistry**

- Positive for:
  - CD34
  - BCL-2
  - Actin
  - Desmin
  - Nuclear beta-catenin *(note: diagnostic pitfall with fibromatosis)*

- What about cytokeratin and p63?
The “traditional” view of immunolabeling in spindle cell carcinoma versus phyllodes tumor:

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<th>Phyllodes tumor</th>
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But the stromal cells of malignant phyllodes tumors *can label* for p63, p40 and cytokeratins.

This is a potential diagnostic pitfall, particularly on core needle biopsy.

*Gimino-Mathews A. Am J Surg Pathol. Dec 2014*

**Case Example:**
Malignant phyllodes tumor with focal p63 labeling
Low grade areas within a malignant phyllodes tumor

Abrupt transition from hypo- to hyper-cellular areas

Stromal hypercellularity with atypia and brisk mitotic rate
Many of the original studies that evaluated cytokeratin or p63 expression in phyllodes tumors included very small number of tumors, particularly small numbers of *malignant* phyllodes tumor.

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<td>Metaplastic Carcinoma</td>
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<td>62%</td>
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<th>% p40 Positive</th>
<th>% Cytokeratin Positive</th>
<th>% CD34 Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metaplastic Carcinoma</td>
<td>13</td>
<td>62%</td>
<td>46%</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>Malignant Phyllodes</td>
<td>14</td>
<td>57%</td>
<td>14%</td>
<td>21%</td>
<td>57%</td>
</tr>
<tr>
<td>Benign Phyllodes</td>
<td>10</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>100%</td>
</tr>
<tr>
<td>Benign</td>
<td>10</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>100%</td>
</tr>
</tbody>
</table>


p63 labeling is also observed in sarcomas and reactive proliferations

- Including: benign and malignant peripheral nerve sheath tumors, angiosarcoma, leiomyosarcoma, epithelioid sarcoma, rhabdomyosarcoma, synovial sarcoma, Ewing’s sarcoma/PNET, and others
- In addition, p63 is positive in a subset of lymphomas


In summary, focal cytokeratin or p63 labeling alone should not be used to diagnose a spindle cell carcinoma, particularly on core biopsy
Myofibroblastoma

Myofibroblastoma: Clinical Features

• Benign proliferations of breast stromal myofibroblasts
• Originally described as a tumor of the male breast, they also occur equally in adult females and can be palpable or screen detected
• Typically treated with excision and are not known to recur
Myofibroblastoma: Pathologic Features

- Classically comprised of bland spindled to epithelioid cells with amphophilic cytoplasm and oval nuclei, associated eosinophilic collagen matrix, and variable amounts of fat
  - Also have a wide range of variant histologic features
- Lack necrosis or frequent mitotic figures
- Usually do not entrap mammary ducts/lobules
- May contain mast cells and perivascular lymphocytes
- Share genetic alterations with spindle cell lipomas, including loss or rearrangements in 13q and 16q
Myofibroblastoma: Histologic variants

- Cellular
- Collagenous/fibrous
- Lipomatous/fat-rich
- Epithelioid
- Chondroid metaplasia
- Myoid metaplasia (leiomyomatous)
- Deciduoid-like
- Infiltrative
Caution: epithelioid myofibroblastomas can mimic invasive lobular carcinomas
Myofibroblastoma: Immunostains

- Cells positive (may be variable/focal) for:
  - CD34
  - ER
  - PR
  - AR
  - BCL-2
  - Actin
  - Desmin
  - CD99

- Negative for: cytokeratins, S-100 protein
Pseudoangiomatous stromal hyperplasia (PASH)

PASH: Clinical Features

- Detected as incidental finding on screening (“non-mass like enhancement” on MRI) or as discrete, palpable or screen-detected firm mass
- Hormonally-driven myofibroblastic proliferation most commonly seen in pre-menopausal women
- Incidentally discovered or uncomplicated, nodular PASH does not require excision
PASH: Pathologic Features

- “Pseudo-angiomatous” because bland myofibroblasts form slit-like spaces mimicking vascular channels
- Occasionally can form fascicular bundles
- Unlike classic myofibroblastomas, PASH may intercalate between ducts/lobules
- Immunolabeling similar to myofibroblastomas
  - Positive for: CD34, ER, smooth muscle actin
  - Negative for: other vascular markers (CD31, ERG) and cytokeratin
Fibromatosis (desmoid tumor)

Fibromatosis: Clinical Features

- Fibromatosis in the breast is most commonly non-syndromic (i.e., not related to Gardner’s syndrome)
- Can be seen in patients with history of prior breast surgery, or in association with implant capsule
- Clinically and radiographically mimics carcinoma
- As in other body sites, fibromatosis in the breast is locally infiltrative and aggressive, requiring complete excision to negative margins

Fibromatosis: Pathologic Features

- Identical features to fibromatoses elsewhere
- Fascicles of bland spindled cells with an associated collagenous stroma
- Infiltrative with peripheral lymphoid infiltrates
- Rare mitoses, but no atypical mitoses
- Minimal cytologic atypia
- Vessels appear to “stand out” at low power because the lesional spindle cells are hypochromatic relative to the endothelial cells
Fibromatosis: Immunostains

• Cells are immunoreactive for:
  - Nuclear beta-catenin (75%)
  - Actin
  - Desmin (variable)
• Negative for: cytokeratins, CD34, S-100 protein, ER

NOTE: Nuclear beta-catenin is not specific for fibromatosis and can be seen in spindle cell carcinomas (23%) as well as phyllodes tumors (72%). Include a cytokeratin if carcinoma is in the differential.

Nodular fasciitis: Clinical and Pathologic Features

- Typically rapidly growing and painful mass
- Histologically resemble nodular fasciitis elsewhere
- Typically circumscribed but can be infiltrative proliferation of bland spindled to stellate cells with pale cytoplasm and vesicular nuclei
- Can show frequent mitoses
- Stroma varies from loose, microcystic and myxoid to fibrous (may show zonation) and displays lymphocytes and extravasated red blood cells

Immunohistochemistry:
- Positive for: actin, calponin, (rarely desmin)
- Negative for: cytokeratin, CD34, S-100, ER, beta-catenin
SPECIAL CONSIDERATIONS
ON CORE NEEDLE BIOPSY
Case Example:
48 year-old female with spindle cell neoplasm on core needle biopsy

Atypical spindle cell neoplasm

Focal benign duct wall
Brisk mitotic rate

Immunohistochemistry: AE1/AE3 focally positive

Immunohistochemistry: focally positive for CK7 and AE1/AE3, and negative for CD34, S100 protein, ER and PR.

Diagnosis:
Malignant spindle cell neoplasm, favor metaplastic carcinoma on the basis of cytokeratin expression. However, a malignant phyllodes tumor cannot be entirely excluded. A complete excision is recommended.
Subsequent mastectomy showed...

Leaf-like architecture and cytologic atypia

Multiple zones of stromal overgrowth (4x low power field)
Stromal atypia and atypical mitotic figure

Stromal hypercellularity and atypia

Focal AE1/AE3 positivity in stromal cells
Final Diagnosis

**Malignant phyllodes tumor** (5 cm) with aberrant cytokeratin and p63 labeling

Use caution in definitive classification of breast spindle cell lesions on core needle biopsy.
Definitive diagnosis of spindle cell lesions on core biopsy can be difficult

- Limited sample of a larger lesion
- Definitive features might not be present (such as conventional invasive carcinoma or leaf-like architecture)
- Morphologic overlap between spindle cell lesions
- Immunophenotypic overlap between lesions

However, the distinction is crucial as neoadjuvant therapy may be considered for metaplastic carcinoma but has no role in phyllodes tumors.

Potential diagnostic pitfalls of spindle cell tumors of the breast on core biopsy

- **Focal p63 and cytokeratin** labeling can be seen in malignant phyllodes tumors
  - Mimics spindle cell carcinoma
- **ER labeling** can be seen in myofibroblastomas
  - Mimics lobular carcinoma
- **Nuclear beta-catenin labeling** can be seen in spindle cell carcinomas and phyllodes tumors
  - Mimics fibromatosis
Potential diagnostic pitfalls of spindle cell tumors of the breast on core biopsy

- **Focal p63 and cytokeratin** labeling can be seen in malignant phyllodes tumors
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  - Mimics lobular carcinoma
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  - Mimics fibromatosis

Immunolabeling with any of these markers alone should not be used to classify a spindle cell lesion on core needle biopsy

"To split or to lump?"

In the absence of definitive histologic or immunohistochemical evidence to support either a metaplastic carcinoma or a malignant phyllodes tumor, malignant spindle cell neoplasms on core needle biopsy should be **lumped** as “spindle cell lesion” or “malignant spindle cell neoplasm” to prevent unnecessary treatment if misclassified.

"To split or to lump?"

With examination of the overall histologic features with a targeted immunohistochemical panel on complete resection, if possible, malignant spindle cell neoplasms should be **split** into “metaplastic carcinoma,” “malignant phyllodes tumor,” or “other” to enable proper classification, treatment and prognosis.
TAKE HOME MESSAGES

Spindle cell lesions of the breast:
Take home messages

- Always consider and exclude metaplastic or spindle cell carcinoma
- Always consider the possibility of a phyllodes tumor
- Immunostains are frequently needed to evaluate spindle cell tumors on core needle biopsy
- Definitive classification of a spindle cell tumor on core needle biopsy may not be possible

Questions?