Spindle Cell Lesions Of The Breast

Emad Rakha
Professor of Breast Pathology and Consultant Pathologist
The University of Nottingham, UK
* SCLs comprise a wide spectrum of diseases, ranging from reactive processes to aggressive malignant tumours.

* Overlapping clinical and morphological features, making accurate diagnosis a challenging task, particularly in biopsies.

* Important to maintain a wide differential diagnosis.

* All SCLs occurring in the soft tissue and skin can happen in the breast in addition to breast specific SCL.
REVIEW

An approach to the diagnosis of spindle cell lesions of the breast

Emad A Rakha, Mohammed A Aleskandarany, Andrew H S Lee & Ian O Ellis

Department of Histopathology, Nottingham University Hospitals NHS Trust and the University of Nottingham, Nottingham City Hospital, Nottingham, UK


SPINDLE CELL LESIONS OF THE BREAST

Benign and Malignant Spindle Cell Lesions of the Breast

Edi Brogi, MD, PhD
Spindle cell breast lesions

Epithelial cell
- Spindle cells of MBC
- Spindle cell DCIS
- Spindle cells SPC
- Spindle cells of UDH

Myoepithelial cell
- Spindle cell adenomyoepithelioma
- Myoepithelial carcinoma

Mesenchymal cell
- Fibrous scar
- Fibromatosis, PASH
- Myofibroblastoma
- Nodular Fasciitis
- SFT and SC lipoma
- Reactive SC nodule
- Neural / muscle lesions
- Vascular lesions
- Sarcoma

Others: Spindle cell component of fibroepithelial lesions, DFSP, SC melanoma and metastatic Spindle cell carcinoma
Diagnosis of Breast SCL: Approach

* **Cytonuclear atypia**: Low grade (bland) Vs high grade (malignant looking)

* **Cellularity**: low, moderate, or high

* **Component cells**: Pure spindle cells, or mixed with other cells

* **Growth pattern**: Fascicular, storiform, diffuse, or whirling

* **Margins**: infiltrating or well defined

* **Immunohistochemistry (IHC)**

* **Other features**: Such as presence of necrosis, associated lesions, entrapped normal tissue, location, patient age
**Low grade** (bland-looking)

- Fibrous scar
- Fibromatosis
- Myofibroblastoma
- PASH
- Reactive spindle cell nodule
- Nodular Fasciitis, IMT
- Benign neural lesions
- DFSP
- Fibromatosis-like metaplastic carcinoma
- Benign/borderline phyllodes tumours (stroma)

**High grade** (malignant-looking)

- SC metaplastic carcinoma
- Malignant phyllodes tumour
- Sarcoma
- Metastases /melanoma

Myofibroblasts
Fibrous scar

- More common than other SCLs of the breast
- Tissue injury (history of prior instrumentation – biopsy, surgery)
- Histological appearance depends on the elapsed time between injury and microscopy
  - *Early*: Granulation, fat necrosis, hemosiderin deposition some fibrosis,
  - *Late*: fibrosis and sclerosis
Late
Myofibroblastoma

• Benign myofibroblastic neoplasm

• Genetically related to spindle cell lipoma & solitary fibrous tumour (monosomy 13q, 16q)

• Positive expression for CD34, ER, desmin, SMA, caldesmon, vimentin, Bcl2 and CD99.

• Negative: CKs, S100 and p63, RB, STAT6

• Hormone receptor positivity may lead to resemblance of invasive lobular carcinoma (epithelioid variant)
Epithelioid
Fat component

Hemangiopericytomatous pattern

Myogenic differentiation
Myofibroblastoma

Histological variants

- Classic
- Collagenous
- Cellular
- Infiltrative (DD: MBC)
- Myxoid
- Epithelioid (DD: ILC)
- Pleomorphic
Fibromatosis

• 25-50 years old

• Palpable mass or suspicious mammographic lesion mimics breast malignancy

• Can arise within the breast or chest wall

• Locally aggressive but non-metastasizing lesion composed of fibroblasts and myofibroblasts.

• May arise in patients with familial adenomatous polyposis, Gardner’s syndrome
Fibromatosis

- Average size 2 to 4 cm
- Entraps fat and epithelial structures
- Variably low cellularity, Variably scant mitoses
- Bland tapering nuclei and little pink cytoplasm
- Long fascicles, thick bands of collagen
- Thin-walled venules,
- Lymphoid infiltrates perivascular and peripheral
Infiltrative margins
Entrapped parenchyma
Fascicular pattern

Spaced nuclei
Collagenised areas
Immunohistochemistry

- Beta catenin – 80% (nuclear)
- CD 34 negative
- CKs, p63, S100 and desmin- negative
  + \textit{CTNNB1} mutations in ~70%
Low grade spindle cell metaplastic breast carcinoma (Fibromatosis-like)

- Radiologically spiculated or well-defined
- Low grade SCL resembling fibromatosis
- Slender/wavy nuclei. Atypia: mild/focal. Low mitotic activity
- Stroma usually shows regressive changes at least focally (hyalinization, myxoid degeneration and inflammatory infiltrate).
- +/- Scattered epithelioid/glandular elements (cords/clusters)
Low-grade spindle cell metaplastic breast carcinoma (Fibromatosis-like)

- May disclose focal squamous differentiation
- Expresses epithelial diff markers: keratins (HMWCKs and to less extent LMWCKs) and p63.
- Triple negative phenotype, CD34 negative
- May be associated with papilloma and radial sclerosing lesion
- *Diagnosis change management either on core biopsy or excision:* SLN biopsy. Complete excision +/- radiotherapy
Low grade Fibromatosis-like MBC

- Excellent prognosis despite being a variant of triple negative metaplastic carcinoma (LOW GRADE)
- Local recurrence can occur
- Metastases are very infrequent
- Low genomic instability compared to other metaplastic carcinomas
Fibromatosis like MBC is not high grade
Nodular fasciitis

• Young adults, Small (<4 cm)

• More often occurs in the subcutis and deeper in the chest wall. Rare in the breast parenchyma.

• Rapid growth, may be painful / tender

• Self-limited clonal proliferation of fibroblasts and myofibroblasts

• Spontaneous regression without recurrent potential

• Translocation t(17;22) / MYH9-USP6 gene fusion
Nodular fasciitis

- Well-defined non-encapsulated but can be infiltrative
- Can be cellular with mitoses (no atypical mitosis)
- Plump stellate myofibroblasts in small whorls or fascicles and in loose matrix (tissue culture appearance)
- Red cell extravasation, may be mxoid or fibrotic
- No significant atypia or necrosis. No entrapped parenchyma or epithelioid structures
- IHC: Actin
Pseudoangiomatous stromal hyperplasia (PASH)

- Affects premenopausal women.
- Well demarcated grossly with homogeneous fibrous cut surface.
- Empty anastomosing spaces lined by myofibroblasts.
- Often incidental to other lesions.
- CD34+, PR sometimes+.
Benign neural tumours

- Schwannoma, neurofibroma
- Usually encountered in the skin of the breast
- May present as a breast lump
- S100+
Dermatofibrosarcoma protuberans

- Arises in dermal skin
- Sometimes may not manifest skin changes, presenting as a primary breast mass
- Translocation t(17;22), COL1A1 / PDGFB fusion gene
Benign & borderline phyllodes tumours

- Not usually a diagnostic problem on excision specimens as the epithelial component is visible.
- May be a challenge on core biopsy that samples only stromal elements, or in recurrent lesions that are devoid of epithelium.
Bland spindle cell lesion

- Spindle cell carcinoma: epithelioid islands, IHC+
- Scar: Fat necrosis, gran tissue, haemosiderin, IHC-
- Fibromatosis: $\beta$-catenin
- Myofibroblastoma: ER, Desmin, CD34
- Nodular fasciitis: Look for features, IHC (Actin)
- Adenomyoepithelioma and fibroepithelial lesions: Biphasic
- Remember other entities: Hamartoma, SFT ($STAT6^+$), IMT ($ALK1$), Leiomyoma, Hemangioma, DFSP,...etc
High grade spindle cell lesions

• High grade spindle cell metaplastic breast carcinoma
• Malignant phyllodes tumour
• Sarcoma
• Metastases /melanoma
High-grade Spindle cell Carcinoma

- Sarcoma like / sarcomatoid carcinoma
- Pure or often coexist with high grade conventional carcinoma (glandular or squamous)
- Variable pattern and architecture, includes carcinomas with pleomorphic-like appearances
- Typically triple negative (basal-like)
- Poor prognosis
High-grade Spindle cell Carcinoma
High-grade Spindle cell Carcinoma
High-grade Spindle cell Carcinoma

Giant cells
Diagnosis of high grade SC MBC

1- Coexistence of conventional type mammary carcinoma

2- Coexistence of an in-situ component (DCIS)

And in the absence of both

3- Molecular demonstration of epithelial differentiation using IHC with epithelial specific markers (ie CKs and EMA)
Diagnosis of MBC:

Absence of phyllodes tumour architecture (CD34-)

Thorough sampling

Clinical / previous history,

Review of the previous core biopsy
Diagnosis of MBC:

In the rare cases that lack of these feature, MBC can be considered after exclusion of:

1 - Being part of a metastatic process (ie metastatic RCC)
2 - Primary skin (ie SCC) or chest wall tumours
3 - Specific types of soft tissue tumours such as leiomyosarcoma or myofibroblastic sarcoma
Immunoprofile of metaplastic carcinomas of the breast

Emad A Rakha,1,2 Nuno D M Coimbra,3 Zsolt Hodi,1 Enaam Juneinah,4 Ian O Ellis1 & Andrew H S Lee1
1Department of Histopathology, Nottingham University Hospitals NHS Trust and the University of Nottingham, Nottingham City Hospital, Nottingham, UK, 2Department of Pathology, Faculty of Medicine, Menoufia University, Menoufia, Egypt, 3Department of Pathology, Instituto Português de Oncologia do Porto FG, Porto, Portugal, and 4Department of Pathology, Jeddah, Saudi Arabia

Table 3. (Continued)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Desmin</th>
<th>β-catenin</th>
<th>CD34</th>
<th>Bcl-2</th>
<th>AR</th>
<th>Receptor status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spindle cell</td>
<td>Fibromatosis-like</td>
<td>Matrix-producing</td>
<td>Squamous</td>
<td>Low-grade adenosquamous</td>
<td>Mixed</td>
</tr>
<tr>
<td></td>
<td>6/37 (16)</td>
<td>2/11 (18)</td>
<td>1/5 (20)</td>
<td>–</td>
<td>–</td>
<td>4/19 (21)</td>
</tr>
<tr>
<td>Desmin</td>
<td>0/3 (0)</td>
<td>0/1 (0)</td>
<td>0/5 (0)</td>
<td>0/3 (0)</td>
<td>0/1 (0)</td>
<td>0/26 (0)</td>
</tr>
<tr>
<td>β-catenin</td>
<td>0/1 (0)</td>
<td>0/1 (0)</td>
<td>0/5 (0)</td>
<td>0/3 (0)</td>
<td>0/1 (0)</td>
<td>0/26 (0)</td>
</tr>
<tr>
<td>CD34</td>
<td>0/1 (0)</td>
<td>0/1 (0)</td>
<td>0/5 (0)</td>
<td>0/3 (0)</td>
<td>0/1 (0)</td>
<td>0/26 (0)</td>
</tr>
<tr>
<td>Bcl-2</td>
<td>1/7 (14)</td>
<td>2/7 (29)</td>
<td>1/2 (50)</td>
<td>–</td>
<td>–</td>
<td>8/19 (42)</td>
</tr>
<tr>
<td>AR</td>
<td>0/11 (0)</td>
<td>–</td>
<td>2/39 (5)</td>
<td>–</td>
<td>–</td>
<td>1/4 (25)</td>
</tr>
<tr>
<td>ER</td>
<td>2/114 (2)</td>
<td>0/21 (0)</td>
<td>4/135 (3)</td>
<td>12/110 (11)</td>
<td>0/44 (0)</td>
<td>14/208 (7)</td>
</tr>
<tr>
<td>PR</td>
<td>1/106 (1)</td>
<td>0/16 (0)</td>
<td>5/122 (4)</td>
<td>13/103 (13)</td>
<td>0/18 (0)</td>
<td>13/201 (6)</td>
</tr>
<tr>
<td>HER2</td>
<td>3/110 (3)</td>
<td>0/32 (0)</td>
<td>3/122 (2)</td>
<td>7/100 (7)</td>
<td>0/31 (0)</td>
<td>3/111 (3)</td>
</tr>
</tbody>
</table>

SMA, smooth muscle actin; SMM, smooth muscle heavy myosin chain; ER, oestrogen receptor; PR, progesterone receptor; AR, androgen receptor; EMA, epithelial membrane anti-gen.
<table>
<thead>
<tr>
<th>Cytokeratins</th>
<th>Spindle cell</th>
<th>Fibromatosis-like</th>
<th>Matrix-producing</th>
<th>Squamous</th>
<th>Low-grade adenosquamous</th>
<th>Mixed</th>
<th>Non-specified</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE1/AE3</td>
<td>114/143 (80)</td>
<td>38/38 (100)</td>
<td>49/50 (98)</td>
<td>14/16 (87)</td>
<td>13/14 (93)</td>
<td>66/99 (67)</td>
<td>40/63 (63)</td>
<td>334/423 (79)</td>
</tr>
<tr>
<td>CK8/18</td>
<td>30/84 (36)</td>
<td>15/19 (79)</td>
<td>18/27 (67)</td>
<td>18/19 (95)</td>
<td>20/24 (83)</td>
<td>35/52 (67)</td>
<td>19/30 (63)</td>
<td>155/256 (61)</td>
</tr>
<tr>
<td>CK7</td>
<td>6/26 (23)</td>
<td>6/36 (17)</td>
<td>10/14 (71)</td>
<td>–</td>
<td>24/25 (96)</td>
<td>10/23 (43)</td>
<td>13/33 (39)</td>
<td>71/153 (46)</td>
</tr>
<tr>
<td>CK19</td>
<td>3/17 (18)</td>
<td>0/6 (0)</td>
<td>10/15 (67)</td>
<td>1/1 (100)</td>
<td>2/2 (100)</td>
<td>7/22 (32)</td>
<td>–</td>
<td>23/63 (36.5)</td>
</tr>
<tr>
<td>MNF116</td>
<td>52/64 (81)</td>
<td>12/12 (100)</td>
<td>15/19 (79)</td>
<td>–</td>
<td>2/2 (100)</td>
<td>13/15 (87)</td>
<td>–</td>
<td>92/110 (84)</td>
</tr>
<tr>
<td>34βE12</td>
<td>10/21 (48)</td>
<td>33/33 (100)</td>
<td>14/20 (70)</td>
<td>3/3 (100)</td>
<td>23/23 (100)</td>
<td>30/49 (61)</td>
<td>45/62 (73)</td>
<td>158/211 (75)</td>
</tr>
<tr>
<td>CK5/6</td>
<td>38/60 (63)</td>
<td>19/19 (100)</td>
<td>53/71 (75)</td>
<td>61/66 (92)</td>
<td>28/30 (93)</td>
<td>36/57 (63)</td>
<td>59/93 (63)</td>
<td>294/396 (74)</td>
</tr>
<tr>
<td>CK14</td>
<td>49/67 (73.)</td>
<td>11/11 (100)</td>
<td>54/73 (74)</td>
<td>20/22 (90)</td>
<td>5/6 (83)</td>
<td>23/38 (61)</td>
<td>–</td>
<td>162/217 (75)</td>
</tr>
<tr>
<td>CK17</td>
<td>9/14 (64)</td>
<td>–</td>
<td>7/11 (64)</td>
<td>–</td>
<td>–</td>
<td>5/6 (83)</td>
<td>–</td>
<td>21/31 (68)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Myoepithelial differentiation-specific markers</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>p63</td>
<td></td>
</tr>
<tr>
<td>SMM</td>
<td></td>
</tr>
<tr>
<td>SMM</td>
<td></td>
</tr>
<tr>
<td>CD10</td>
<td></td>
</tr>
<tr>
<td>Calponin</td>
<td></td>
</tr>
<tr>
<td>Maspin</td>
<td></td>
</tr>
<tr>
<td>S100</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Epithelial differentiation and other markers</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td></td>
</tr>
<tr>
<td>p53</td>
<td></td>
</tr>
<tr>
<td>EMA</td>
<td></td>
</tr>
<tr>
<td>E-cadherin</td>
<td></td>
</tr>
<tr>
<td>Vimentin</td>
<td></td>
</tr>
</tbody>
</table>
High grade spindle cell breast lesions

**Sarcoma**
* Angiosarcoma (commonest)
* Liposarcoma (typically part of PT)
* Chondrosarcoma and osteosarcoma (typically part of MBC but metastatic and primary chest wall should be excluded)
* Leiomyosarcoma, MPNST, myofibrobalstic & synovial sarcoma
Metastases to the breast

- Unusual histology, absence of in situ carcinoma
- Clinical history is crucial
- High index of suspicion
- Adjunctive immunohistochemistry
Spindle cell lesions on core biopsy

• Keep a broad range of differential diagnoses
• Clinicoradiological findings are important
• Benign can look malignant and malignant can look benign
• IHC is helpful, but be aware of pitfalls and limitations
• Thorough sampling
• Final diagnosis can be rendered on excision
• Important to rule out metaplastic carcinoma.
Breast SCL: additional questions

• Best immunohistochemical marker?
  • Panel approach
  • Keratins – broad spectrum, basal
  • p63
  • Markers for specific diagnoses (CD34, Alk1, B-catenin, STAT6, S100, desmin, ER, SMA, ..etc)
  • Exercise caution when staining is focal, or on limited material
  • Be aware of cross reactivities and pitfalls

• Consult a colleague with soft tissue pathology expertise
Spindle cells lesions of the breast
<table>
<thead>
<tr>
<th>Condition</th>
<th>Any</th>
<th>&gt;10% of cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myofibroblastoma, &amp; DFSP</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Fibroadenoma</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Phyllodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Borderline</td>
<td>92%</td>
<td>92%</td>
</tr>
<tr>
<td>Malignant</td>
<td>84%</td>
<td>63%</td>
</tr>
<tr>
<td>Spindle cell carcinoma</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Fibromatosis, NF &amp; Scar</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>