Spindle Cell Conundrums in the Chest
2019 Anatomic Pathology Update
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Why a Lecture on Spindle Cell Lesions?
• Frequent problem
• Challenge on small biopsies
• Wide spectrum of possibilities
• Treatment variable
• IHC triage necessary

What do we mean by spindle cells?
• Elongate cytoplasm
• Indistinct cell borders
• Variable amounts of cytoplasm, but frequently minimal
• Cytology often deceptively bland or low grade
Outline

• Neoplastic vs. non neoplastic
• Low grade pulmonary lesions
• Metastatic lesions
• High grade pleuropulmonary neoplasms
• Approach with IHC

Are the Spindle Cells Neoplastic or Not?
Organizing Pneumonia

CT Findings in Organizing Pneumonia

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Percent (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consolidation</td>
<td>80</td>
</tr>
<tr>
<td>Bilateral</td>
<td>74</td>
</tr>
<tr>
<td>Migratory</td>
<td>12</td>
</tr>
<tr>
<td>Diffuse reticular</td>
<td>10</td>
</tr>
<tr>
<td>Mass-like</td>
<td>8</td>
</tr>
<tr>
<td>Cavitary</td>
<td>2</td>
</tr>
</tbody>
</table>

Drakopanagiotakis F et al. Chest 2011;139:893-900

Mass-like Organizing Pneumonia

- Asymptomatic – 62%
- H/O malignancy or smoking ~25%
- Contrast enhancement on CT and PET positive
- 90% idiopathic, 10% post infectious

Aspiration without Food or Particulate Matter

Histology

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organizing pneumonia</td>
<td>40</td>
</tr>
<tr>
<td>Diffuse alveolar damage</td>
<td>30</td>
</tr>
<tr>
<td>Chronic bronchiolitis</td>
<td>30</td>
</tr>
</tbody>
</table>

Yousem SY and Faber C. Am J Surg Pathol 2011;35:426-431
37 year old man with solitary lung mass

Keratin, CD34, alk negative

Non Neoplastic Inflammatory “Pseudotumor”

My Diagnosis: OP with prominent lymphoplasmacytic infiltrates

Keratin, CD34, alk negative
14 year old boy with solitary lung mass

“Neoplastic Inflammatory Pseudotumor”
Inflammatory Myofibroblastic Tumor

Alk
Inflammatory Pseudotumors

- Non-Neoplastic variants
  - Plasma cell granuloma
  - Lymphoplasmacytic/plasma cell type
  - Organizing pneumonia type
  - IgG4-related

Inflammatory Pseudotumors

- Non-Neoplastic variants
  - Plasma cell granuloma
  - Lymphoplasmacytic/plasma cell type
  - Organizing pneumonia type
  - IgG4-related

Inflammatory Pseudotumors

- Neoplastic-inflammatory myofibroblastic tumor
  - Fibrous histiocytoma
  - Inflammatory fibrosarcoma
  - Plasma cell granuloma
  - Inflammatory fibromyxoid tumor
Inflammatory Pseudotumors

- Neoplastic
  - Inflammatory myofibroblastic tumor
  - Fibrous histiocytoma
  - Inflammatory fibrosarcoma
  - Plasma cell granuloma
  - Inflammatory fibromyxoid tumor

Metastasis!

Inflammatory Pseudotumors

- Neoplastic variants more common in children
  - \textit{alk} rearranged in 40-60%
- Adult pulmonary tumors
  - \textit{alk} rearranged in 30-50%
- Specificity limited
- \textit{ROS-1, RET, ETV-6}


IgG4-Related Disease

- Major criteria: 2/3 needed for dx
  - Dense lymphoplasmacytic infiltrate
  - Fibrosis, focally storiform
  - Obliterative phlebitis
- Additional characteristic features
  - Phlebitis without obliteration
  - Increased tissue eosinophils
- Exceptions exist in lung, LN, minor salivary and lacrimal glands (fibrosis and phlebitis may be absent)
IgG4-related Disease
Radiologic Patterns of Lung Involvement
- Solitary nodule (+/- ground glass opacity)
- Consolidation, unilateral or bilateral
- Interstitial lung disease
IgG 4-related Disease
Quantitation

- Serum IgG4 concentrations normal-40%
- IgG4 + cells/IgG plasma cells > 40%
  mandatory
- > 20-50 IgG4 + cells/hpf (3-40x fields)

Deshpande V et al. Modern Pathol 2012; 1-12

History
49 year old man with posterior flank pain
Solitary Fibrous Tumor

<table>
<thead>
<tr>
<th>IHC stain</th>
<th>% Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stat 6 nuclear</td>
<td>98</td>
</tr>
<tr>
<td>Stat 6 cytoplasmic</td>
<td>96</td>
</tr>
<tr>
<td>Bcl 2</td>
<td>95</td>
</tr>
<tr>
<td>CD34</td>
<td>93</td>
</tr>
<tr>
<td>β catenin</td>
<td>88</td>
</tr>
<tr>
<td>TLE</td>
<td>14</td>
</tr>
<tr>
<td>S100</td>
<td>7</td>
</tr>
<tr>
<td>PanKeratin</td>
<td>3</td>
</tr>
<tr>
<td>CAM 5.3</td>
<td>3</td>
</tr>
</tbody>
</table>
## Predicting Recurrence in SFT

<table>
<thead>
<tr>
<th>Feature</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>&lt; 55</td>
</tr>
<tr>
<td></td>
<td>≥ 55</td>
</tr>
<tr>
<td>Size (cm)</td>
<td>&lt; 5</td>
</tr>
<tr>
<td></td>
<td>5 to &lt; 10</td>
</tr>
<tr>
<td></td>
<td>10 to &lt; 15</td>
</tr>
<tr>
<td></td>
<td>≥ 15</td>
</tr>
<tr>
<td>Tumor necrosis (%)</td>
<td>&lt; 10</td>
</tr>
<tr>
<td></td>
<td>≥ 10</td>
</tr>
<tr>
<td>Mitoses/10hpf</td>
<td>&lt; 4</td>
</tr>
<tr>
<td></td>
<td>≥ 4</td>
</tr>
</tbody>
</table>

Low risk 0-3, Intermediate risk 4-5, High risk 6-7

Domicco EG et al Mod Pathol 2017:30; 1433-1442

### Malignant SFT

- Inc. cellularity
- Necrosis
- Mitoses

### Predicting Recurrence in SFT

<table>
<thead>
<tr>
<th>Risk of metastasis at # years (%)</th>
<th>y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>0, 10 y</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>10, 10 y</td>
</tr>
<tr>
<td>High risk</td>
<td>73, 5 y</td>
</tr>
</tbody>
</table>
History

- A 73-year-old woman presented with a dominant lung mass
- Needle biopsy had been performed and diagnosed as “most consistent with epithelioid hemangioendothelioma”...but CD31 was negative
Diagnosis?
Most consistent with Metastatic Endometrial Stromal Sarcoma

Estrogen Receptor Protein

Uterus removed 20 years previously

Challenges in Dx of Metastatic ESS
• Unknown or misdiagnosis of uterine ESS
• Long tumor-free interval
• Unusual symptoms or radiologic presentation
  – Pneumothorax
  – Solitary nodule
  – Cystic lesions
  – Bilateral infiltrates mimicking interstitial ds
Metastatic ESS

- Histology parallels uterine primary
  - Spindle cells, ± smooth muscle or sex cord differentiation, hyaline fibrosis
- Immunohistochemistry
  - ER/PR/vimentin: ~ 100%
  - Actin/desmin/keratin/CD10: ~ 50%
  - Rarely positive: Inhibin, CAM 5.2, Chromogranin, HMB-45, CD34

Marked Interstitial Growth
Metastatic ESS
Differential Diagnosis

- Epithelioid hemangioendothelioma
- Other metastatic spindle cell tumors (dermatofibroma, DFSP, other sarcomas, PEComa)
- Solitary fibrous tumor
- Synovial sarcoma

Epithelioid Hemangioendothelioma

Ker

CD31
Outline

• Neoplastic vs. non neoplastic
• Low grade pulmonary lesions
• Metastatic lesions
• High grade pleuropulmonary neoplasms
• Approach with IHC
Inflammatory Sarcomatoid Carcinoma

• Variant of Sa Ca with deceptively bland morphology
• Mimics
  – Inflammatory process
  – Lymphoma, incl HD
  – Inflammatory myofibroblastic tumor
  – Fibrous histiocytoma

**Inflamatory Sa Ca**

- Occur in cigarette smokers
- Key features
  - Relatively bland spindle cells arranged in fascicles, haphazard configurations or storiform arrays
  - Assoc inflammatory infiltrate
  - Keloid-like fibrosis
  - Vascular invasion
  - Focal ordinary bronchogenic ca

Wick MR et al Hum Pathol 1995; 26:1014

**Sarcomatoid Carcinoma**

- Organizing pneumonia
- Inflammatory myofibroblastic tumor
- IgG 4-related sclerosing disease
- Lymphoma, particularly Hodgkin L.
- Malignant mesothelioma
Case History

• A 78 yr old man has a recurrent R pleural effusion for which he had talc pleurodesis.
• 1 yr later developed recurrent pleural effusion with nodularity.
• He undergoes VATS biopsy.
The single best IHC stain to order on this block is:

a. Ber EP4
b. CEA
c. CK7
d. MOC-31
e. Pan keratin
The diagnosis is:

a. Atypical/suspicious for malignancy
b. Desmoplastic mesothelioma
c. Fibrous pleurisy
d. Pleomorphic lung carcinoma
e. Solitary fibrous tumor

Sarcomatoid Mesothelioma-WHO
“Mesenchymal or spindle cell morphologic appearance.”

Sarcomatous Mesothelioma
Non-Desmoplastic Type

- No zonation
- Cellular
- Frankly malignant cytology
- May merge with epithelioid foci
- Identification of invasion not always necessary for diagnosis
Desmoplastic Mesothelioma

WHO

Dense collagenized tissue separated by malignant mesothelial cells arranged in a storiform or so-called patternless pattern, which must be present in at least 50% of the tumor.

Desmoplastic Mesothelioma

- No zonation
- Paucicellular
- Atypical cells hard to find
- Capillaries hard to find
- Invasion typically necessary
- Abrupt transitions to frankly cellular foci
- Bland infarct-like necrosis

No atypia
No capillaries
Desmoplastic Mesothelioma - Invasion

Desmoplastic Mesothelioma - Invasion

Keratin
### IHC: Sarcomatous Mesothelioma (%)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Spindle Cell Carcinoma</th>
<th>Sarcomatous Mesothelioma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratin (broad sp)</td>
<td>88</td>
<td>89</td>
</tr>
<tr>
<td>Calretinin</td>
<td>37</td>
<td>54</td>
</tr>
<tr>
<td>D2-40</td>
<td>20</td>
<td>74</td>
</tr>
<tr>
<td>WT-1</td>
<td>31</td>
<td>45</td>
</tr>
<tr>
<td>CK 5/6</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td>TTF-1</td>
<td>-17</td>
<td>4.6</td>
</tr>
<tr>
<td>CAIX</td>
<td>15 focal wk</td>
<td>100 strong diffuse</td>
</tr>
</tbody>
</table>

Stains not useful in most cases:
- CEA, CD15, MOC 31, etc.

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**Desmoplastic Meso**

![Desmoplastic Meso](image1)

**Spindle Cell Ca**

![Spindle Cell Ca](image2)

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**Marchevsky AM Hum Pathol 2017;67:160-168**

Inconclusive Immunostains?

- When the immunostains don’t fit or are inconclusive, revert to gross/radiologic findings and H+E
- Some cases are insoluble: “Malignant tumor, carcinoma favored over mesothelioma”

Sarcomatous Meso vs. Other Sarcomatous Neoplasms

- Most sarcomatous mesos ker +
- Meso specific markers not very helpful
- Other tumor specific markers may be helpful- CD31, Fli-1, Erg
- May have to rely on imaging to distinguish from sarcomatoid ca
Monophasic Synovial Sarcoma

**First Round IHC**

- Keratin-broad spectrum AE1/3, OSCAR, CAM 5.2
- **NOT** CK7/20
- Consider TTF-1
  - Primary site
  - Architecture- Is it invading lung?

Organizing Pn
IMT
Met ESS, DF,
Mesothelioma
Synovial Sarcoma
EHE
Angiosarcoma
Infectious
Pseudoneoplasm

Keratin
Benign/low
Gr
Keratin
High grade
Sarcomatoid Ca
(lung, kidney)
Mesothelioma
Carcinoid
Thymoma

Organizing Pn
Met ESS, DF,
SFT
Desm
Melan
Infect. Pseudoneoplasm

EHE
Angiosarcoma
Met ESS, DF,
DFSP
SFT
Desm
Melan
Infect. Pseudoneoplasm