The Diagnosis of Malignant Mesothelioma

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The individual below has disclosed the following financial relationship with commercial interest:

Andrew Churg, MD, serves as a consultant to various law firms in asbestos litigation.
Histologic Patterns of Malignant Mesothelioma*

- Epithelial
- Sarcomatous
- Mixed Epithelial and Sarcomatous
  - Also called Biphasic

* Classification in Series 4 Fascicle and WHO 2004
Names Not to Be Used for Different Forms of Epithelial Mesothelioma

- "Epithelioid" (Sheet-like)
- Tubulopapillary
- Microcystic/Adenomatoid
- Deciduoid
- Unnamed patterns
- Every possible mixture of above
- However, high grade (= pleomorphic) perhaps should be named
  - Recent reports suggest pleomorphic has a very poor prognosis, similar to sarcomatous
  - (Ordonez Mod Path 2012; Kadota JTO 2011)

No reproducibility among pathologists
Mixtures of types common (problem with small bx)
Thus far only 1 claimed correlation with survival (has not been confirmed (Mod Path 2011))
Histologic Patterns of Malignant Mesothelioma

- Epithelial
- Sarcomatous
- Mixed Epithelial and Sarcomatous
  – Also called Biphasic

Good concordance among pathologists
This classification correlates with survival
Sarcomatous forms do not respond to radical triple therapy
Epithelial mesothelioma

Tubulopapillary pattern (Do NOT mention in report!!)

Deciduoid pattern (Do NOT mention in report!!)
Adenomatoid patterns—Do not mention in report

Epithelial Mesotheliomas
Immunohistochemical Staining Patterns in Carcinoma and Mesothelioma

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Mesothelioma</th>
<th>Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broad spectrum keratin</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Vimentin</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>EMA</td>
<td>+ (membrane)</td>
<td>+ (cytoplasmic)</td>
</tr>
<tr>
<td>CEA</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LeuM1</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>B72.3</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>BEREP4</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>MOC31</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>HM16</td>
<td>+ (membrane)</td>
<td>+ (cytoplasmic)</td>
</tr>
<tr>
<td>Lewis blood group antigens (Bg8)</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Thrombomodulin</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Calretinin</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Cytokeratin 5/6</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>HBME1</td>
<td>+ (membrane)</td>
<td>-</td>
</tr>
<tr>
<td>WT-1</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>D2-40/Podoplanin</td>
<td>+ (membrane)</td>
<td>-</td>
</tr>
<tr>
<td>Mesothelin</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Napsin A</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>


Mesothelioma: Expected staining
Referred in case: Mesothelioma - Aberrant Staining for CD15

Referred in case: Aberrant Staining for MOC-31

Which Antibodies Should You Use?

- If unsure whether mesothelioma or carcinoma select 2 "mesothelioma" markers and 2 "carcinoma" markers
- Modify your markers to account for likely primary site
- If pretty sure you are dealing with one or the other, 3 of one and 1 of the other might be another choice
- You need to know how these markers behave in your lab!
- *The more markers you use, the more anomalous results you can expect!*
- Remember that most sarcomatous mesotheliomas only stain with pan-keratin
Recommended Antibodies for Separating Mesothelioma from Adenocarcinoma  
(From Ordonez 2007; Churg 2006)

<table>
<thead>
<tr>
<th>Mesothelioma Markers</th>
<th>Carcinoma Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calretinin</td>
<td>CEA^3</td>
</tr>
<tr>
<td>Cytokeratin 5/6</td>
<td>B72.3</td>
</tr>
<tr>
<td>WT-1^2</td>
<td>LeuM1</td>
</tr>
<tr>
<td>D2-40^2</td>
<td>MOC-31</td>
</tr>
<tr>
<td></td>
<td>TTF-1^4</td>
</tr>
<tr>
<td></td>
<td>p63 (for squamous ca)</td>
</tr>
</tbody>
</table>

^1 Positive in many squamous carcinomas  
^2 Stains 75% of lung adenocarcinomas

Dealing with Morphologically High Grade Epithelial Tumors ? Mesothelioma

- There are several hundred thousand malignant pleural effusions/yr in the US
- There are 2500 mesotheliomas (and not all are pleural)
- The odds are overwhelming that a high grade epithelial tumor that stains only with keratin is a carcinoma and not a mesothelioma
- The diagnosis of pleomorphic mesothelioma requires exactly correct IHC
Cautions Re Diagnosing Epithelial Mesotheliomas

• Value of names is for pathologic recognition
  – Morphologic subtypes (apart from pleomorphic) have no clear prognostic significance—differentiation is not a concept easily applied to mesotheliomas
  – Avoid use of "well-differentiated" in diagnosis of malignant mesotheliomas because it causes confusion with "well differentiated papillary mesothelioma," a generally benign tumor
• Don’t get hung up on IHC results if the morphology fits and the IHC mostly fits
  – High grade epithelial tumors are more likely carcinoma than mesothelioma—here IHC critical for diagnosis

Subtypes of Sarcomatous Mesothelioma

• Sarcomatous NOS (like fibrosarcoma or MFH)
  – With heterologous elements
• Lymphohistiocytoid (probably a form of epithelial mesothelioma)*
• Transitional
• Desmoplastic

*Galateau-Salle et al: AJSP 2007
Sarcomatous mesothelioma

Pan-Keratin  WT-1  Calretinin

IHC in Sarcomatous Mesos
93% Keratin + (Klebe Mod Path 2010)
31% Calretinin + (−)
30% WT-1 +
84% Podoplanin + (?)(Padgett AJSP 2008)

Mesothelioma with heterologous differentiation

Keratin
Cautions re Diagnosing Sarcomatous Mesotheliomas

• There is more agreement on nomenclature than is true of epithelial forms
• Sarcomatous forms less often show mixtures
• Pleomorphism/cytologic atypia common in sarcomatous mesotheliomas
• Desmoplastic mesotheliomas are frequently misdiagnosed
• Most sarcomatous mesotheliomas only show pan-keratin staining (save your money and don’t get upset when nothing else stains!)
• Avoid the term “fibrous mesothelioma” for sarcomatous forms because the same term has been used for benign solitary fibrous tumors
Differential Diagnosis: Diffuse Pleural/Peritoneal Tumors

- Metastatic carcinoma or sarcoma (including direct spread)
- Primary serous papillary carcinoma
- Angiosarcoma
- Synovial sarcoma
- ? Chondrosarcoma & osteosarcoma in pleura (may all be mesotheliomas)

Squamous cell ca of lung mimicking mesothelioma

Papillary Serous Carcinoma of Peritoneum
Separation of Benign vs Malignant Mesothelial Proliferations

US-Canadian Mesothelioma Reference Panel Data
Total circulated cases 1994-1998 217

Percent of cases with disagreement about benign vs malignant 22%

Distribution of Proliferating Mesothelial Cells and Malignancy In a Thickened Pleura
Mesothelioma: full thickness spread in a thick pleura

Mesothelioma: expansile stromal nodule
Stromal Invasion and Mesothelioma

- Stromal invasion is the most useful single criterion for separating benign from malignant mesothelial proliferations.
- Deciding what is invasion and what is entrapment can be difficult.
Separating Invasion from Entrapment

- Be cautious diagnosing invasion in the presence of a major inflammatory reaction
- Linear arrays tend to be entrapped
- Sharply circumscribed mesothelial proliferations tend to be entrapped
- *En face* cuts are a major problem in small biopsies
- If in doubt it’s better to report the process as “atypical mesothelial hyperplasia”
The Concept of Mesothelioma in Situ

D Whitaker, DW Henderson, KB Shilkin

Sem Diag Pathol 1992; 9: 151-161

- Seven cases
- All had areas of invasive mesothelioma
- In situ mesothelioma = single layer of surface cells
Recommendation:
The best time to diagnose mesothelioma in situ is never.
Criteria for the Diagnosis of Desmoplastic Mesothelioma

- Bulk of lesion is paucicellular and shows a storiform or "patternless" pattern plus
- Stromal invasion or
- Bland necrosis or
- Overtly sarcomatous foci or
- Nodular stromal expansions or
- Distant metastases
Desmoplastic mesothelioma

Desmoplastic mesothelioma: downward invasion of fat

Keratin
Desmoplastic mesothelioma: invasion of fat

Keratin

Invasion of fat

DMM – Sarcomatous Focus
Features of Organizing Pleuritis *

- Cellularity greatest immediately under effusion
- Progressively fibrotic and paucicellular away from effusion (“zonation”)
- Capillaries perpendicular to surface
- Cells immediately under effusion can be very atypical, particularly when mesothelial cells are mixed with fibrin
  - Examine areas away from fibrin
- All active mesothelial proliferations are keratin +
- Fibrosis can extend into fat (but usually keratin negative)!

* Also called fibrosing pleurisy, organizing pleurisy
Organizing pleuritis
Pan-keratin: sharply demarcated line of positivity—no keratin positive cells in fat

Pan-keratin (hydrocoele): lamellar arrays
<table>
<thead>
<tr>
<th>Marker</th>
<th>Proposed Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pankeratin</td>
<td>Seen in both benign and malignant mesothelial processes</td>
</tr>
<tr>
<td>EMA</td>
<td>Claimed to be marker of malignancy</td>
</tr>
<tr>
<td>p83</td>
<td>Claimed to be marker of malignancy</td>
</tr>
<tr>
<td>Desmin</td>
<td>Claimed to be marker of malignancy</td>
</tr>
<tr>
<td>GLUT-1</td>
<td>Claimed to be marker of malignancy</td>
</tr>
<tr>
<td>K-linked inhibitor of apoptosis</td>
<td>Claimed to be marker of malignancy</td>
</tr>
<tr>
<td>IMP-3</td>
<td>Claimed to be marker of malignancy</td>
</tr>
</tbody>
</table>

Abbreviations: EMA, epithelial membrane antigen; GLUT-1, glucose transporter-1.
Authors’ conclusions: “Immunohistochemistry is of limited value… The diagnostic importance of histological features seen on plain tissue sections is emphasized.”
**Conclusions Re IHC for Separating Benign from Malignant Mesothelial Proliferations**

- Pan-keratin is very useful because it tells you where the proliferating cells are located (*but all proliferating mesothelial cells are pan-keratin positive*).
- Other markers may work in a statistical sense but aren’t suitable for an individual case.
- Combinations of markers might be a potential approach, but require exacting control of IHC.
Benign Reaction

Mesothelioma

Chromosome 9
centromere---
green

p16 probe---red

M with pleural
effusion, pleural
thickening. Clinically
suspicious for
malignancy. Biopsy
shows only surface
proliferation
Problems with p16 FISH for Diagnosing Mesothelioma vs Reactive Proliferation

- Preparation technically time consuming/difficult
- Interpretation of homozygous deletion in tissue section can be a problem
  - Works well if groups of cells present, but difficult if lines of cells are the only finding
  - Cutoff value needed because in tissue section some fraction of cells tend always appear to have homozygous deletion
  - FISH homozygous deletions often don’t correlate with protein staining by IHC
- NB: 30% of pleural mesotheliomas and 25-50% of peritoneal mesotheliomas do not show homozygous p16 deletion
Suitable Specimens for Diagnosing Mesothelioma

• Needle biopsy
  - Low yield (literature values about 25%)
  - Rarely useful for desmoplastic mesothelioma
• Thoracoscopic biopsy
  - High yield (literature values about >90%)
• Open biopsy/Pleural stripping
  - High yield
  - May be particularly useful for desmoplastic mesothelioma
• Cytology
  - Low yield (literature values about 25%)
  - Often hard to tell reactive from malignant mesothelial cells
  - When definitely malignant, often hard to separate carcinoma from mesothelioma (IH results may be strange in cell blocks)

Survival in Pleural Mesothelioma by Histologic Type
(Flores: J Thoracic Oncol 2007)

Survival in Pleural Mesothelioma by Treatment
(Flores: J Thoracic Oncol 2007)
Survival in Peritoneal Mesothelioma after Debulking and Hot Intraperitoneal Chemotherapy (Cao: J Oncol 2012)

Female N=135

Male N=159

It’s probably a good idea to include a comment in your report indicating that with proper therapy survival in peritoneal mesothelioma is 50% or better and provide a reference.

Don’t confuse epidemiology with diagnosis