Pathologic Diagnosis and Grading of Malignant Pleural Mesothelioma

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Guidelines for Pathologic Diagnosis of Malignant Mesothelioma: 2017 Update in Consensus Statement from the International Mesothelioma Interest Group


Arch Pathol Lab Med 2018;142:89-108
Outline

• General recommendations
• Benign v malignant
• Histology
• Immunohistochemistry (IHC)
• Molecular markers
• Grading
• Updates since the paper
General recommendations

• Adequate biopsy in the appropriate context of clinical and radiological findings
• **XXX** History of asbestos exposure **XXX**
• Location, gender, morphology will direct differential diagnosis and IHC panels
• Specific antibody information evolves
• Molecular testing where applicable
Separating benign from malignant mesothelial proliferations

- Start with morphology, use adjunctive techniques as necessary
- Do not start with adjunctive techniques!
“Traditional” Immunohistochemical Stains

<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>p53</td>
<td>Claimed to be marker of malignancy</td>
</tr>
<tr>
<td>Desmin</td>
<td>Claimed to be marker of benign mesothelial cells</td>
</tr>
<tr>
<td>GLUT-1 X-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.
Biphasic mesothelioma?
BAP-1 stain pitfalls

Cytoplasmic staining: irrelevant

Retained BAP-1: non-diagnostic

Background cells: BAP-1 retained
Atypical mesothelial proliferation, favor benign

BAP-1
P16/CDKN2A

Homozygous deletion

Normal

Courtesy of Dr. S. Dacic
Problems with p16 FISH for Diagnosing Mesothelioma vs Reactive Proliferation

• As with BAP1, only loss of p16 is diagnostic
• Roughly 30% of pleural mesotheliomas and at least 50% of peritoneal mesotheliomas do not show homozygous p16 deletion
• p16 loss can be seen in many types of malignancies
• Run BAP1 IHC first – it’s much cheaper, faster and has similar sensitivity as p16 FISH
MTAP

• *Methylthioadenosine phosphorylase*
• Located in the 9p21.3 locus and co-deleted with *p16*

Hida T et. al: Immunohistochemical detection of MTAP and BAP1 protein loss for mesothelioma diagnosis: Comparison with 9p21 FISH and BAP1 IHC. Lung Cancer104:98-105, 2017
Courtesy of Dr. Nabeshima
Benign v malignant mesothelioma

- Morphology
- Keratin IHC to determine invasion
- BAP1 (IHC) loss (nuclear)
- MTAP (IHC) loss (cytoplasmic)
- p16 (FISH) homozygous deletion (IHC for p16 not recommended)
Male w pleural tumor on imaging.
No invasion seen in biopsy

Courtesy of Dr. A. Churg
Malignant mesothelioma in situ

• Churg et. al. Histopathology. 2018 May;72(6):1033-1038. PMID: 29350783

• 2 cases of surface mesothelial proliferation (one pleural, one peritoneal)

• Both with loss of BAP1 and p16 deletion
Cytologic diagnosis of malignant mesothelioma

- Exfoliative cytology: epithelioid MM
- Sarcomatoid and biphasic MM: tissue diagnosis
- IHC panels: similar to those in tissue
- BAP-1 IHC and molecular tests including FISH for p16 homozygous deletions can be reliably applied to cytologic material

Key histologic features of pleural and peritoneal malignant mesothelioma

- Major subtypes (epithelioid, sarcomatoid, biphasic) in final diagnosis
- Patterns of epithelioid MM (in a comment)
- Multiple patterns usually present
- Biopsy vs. resection
Trabecular

Epithelioid MM

Tubulo-papillary

Pleomorphic > 10%

Solid

Micropapillary

Tubulo-papillary
Invasive epithelioid mesothelioma  
(architectural patterns)

- Tubulopapillary
- Trabecular
- Adenomatoid
- Solid
- Micropapillary

Cytologic variants

- Pleomorphc
- Transitional
- Rhabdoid
- Deciduoid
- Small cell
- Clear cell
- Signet ring

Sarcomatoid mesothelioma

- Desmoplastic
- With heterologous differentiation

Biphasic mesothelioma

Any combination of patterns of epithelioid and sarcomatoid mesothelioma (at least 10% of each component)

Stromal variants

- Myxoid
- Lymphohistiocytoid
Use of histochemical and IHC stains in the diagnosis of MM

Epithelioid morphology:
• Cytokeratin plus two mesothelial and two carcinoma markers are recommended
• Mesothelial markers with best sensitivity and specificity are calretinin, cytokeratin 5 or 5/6, WT-1, and D2-40 (podoplanin)
• Carcinoma markers with best sensitivity and specificity are Claudin-4, MOC-31, CEA, B72.3, Ber-Ep4, CEA and BG8
Claudin-4 in adenocarcinoma
New markers

Lung adenocarcinoma

Pleuritis

Courtesy of Dr. Nabeshima
GATA3

MUC4

- Amatya VJ et al. MUC4, a novel immunohistochemical marker identified by gene expression profiling, differentiates pleural sarcomatoid mesothelioma from lung sarcomatoid carcinoma. Mod Pathol. 2017 May;30(5):672-681. PMID: 28128276
PD-L1
If clinically indicated
Nuclear grading in pleural EMM also correlates with prognosis

A nuclear grading system is a strong predictor of survival in epitheloid diffuse malignant pleural mesothelioma

Kyuichi Kadota¹,², Kei Suzuki¹, Christos Colovos¹, Camelia S Sima³, Valerie W Rusch¹, William D Travis⁴ and Prasad S Adusumilli¹,⁵
### Nuclear Atypia & Mitotic Score

<table>
<thead>
<tr>
<th>Nuclear Atypia</th>
<th>Description</th>
<th>No. of mitoses/10 HPF</th>
<th>Mitotic count score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Mild</td>
<td>Nuclei uniform in size and shape</td>
<td>0-1</td>
<td>1</td>
</tr>
<tr>
<td>2 Moderate</td>
<td>Nuclei intermediate in size with variation in shape</td>
<td>2-4</td>
<td>2</td>
</tr>
<tr>
<td>3 Severe</td>
<td>Nuclei bizarre, variably size nuclei, some 2x larger than others</td>
<td>≥ 5</td>
<td>3</td>
</tr>
</tbody>
</table>

Kadota K et al: Mod Pathol 2012, 25:260-271
Nuclear Grade

- Nuclear atypia and mitotic scores were combined into one composite score from which nuclear grade was assigned.

<table>
<thead>
<tr>
<th>Composite Score</th>
<th>Nuclear Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-3</td>
<td>I</td>
</tr>
<tr>
<td>4-5</td>
<td>II</td>
</tr>
<tr>
<td>6</td>
<td>III</td>
</tr>
</tbody>
</table>

Kadota K et al: Mod Pathol 2012, 25:260-271
Grade III: Worst median overall survival

Kadota K et al: Mod Pathol 2012, 25:260-271
Aims of Current Study

- To determine the usefulness of this grading system in predicting overall survival in pleural EMM in a multi-institutional setting

- To evaluate additional prognostic pathologic parameters
Clinical and pathologic data from patients diagnosed with EMM between 1998-2014 were collected from 17 institutions worldwide:

- University of Chicago, USA
- Cedars-Sinai Medical Center, USA
- Duke University, USA
- Memorial Sloan Kettering, USA
- University of Pennsylvania, USA
- University of Vermont, USA
- Veterans Affairs Pittsburgh, USA
- Barts Health NHS Trust, UK
- Basildon & Thurrock University Hospital, UK
- Centre Leon Berard, France
- Fukuoka University, Japan
- Medical University of Graz, Austria
- Tokyo Women’s Medical Center, Japan
- University of Leicester, UK
- University of Wales, UK
- Royal Brompton & Harefield Hospitals, UK
- University Hospital Zurich, Switzerland
Nuclear Atypia

1. Mild
2. Moderate
3. Severe
Mitotic Count

- Mitotic count per 10 high power fields (HPF)
- Areas with highest tumor cellularity
- Necrotic areas avoided
- Apoptotic bodies/pyknotic nuclei excluded
Demographics

- Total of 776 patients
- Age: Mean 65 years, range 29-91
- Gender: 611 males & 165 females (3.7M:1F)
- Procedure
  - Decortication/pleurectomy: 269
  - Pneumonectomy: 253
  - Surgical biopsy: 206
  - Other: 48
Nuclear grade significantly associated with overall survival

Nuclear Grade I: 37
Nuclear Grade II: 19
Nuclear Grade III: 12
Presence of necrosis is associated with worse OS

Without necrosis: 28 months
With necrosis: 17 months
Necrosis stratifies OS within nuclear grade groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients (%)</th>
<th>Mean OS (months)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td></td>
<td></td>
<td>0.1 (NS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without necrosis</td>
<td>221 (91%)</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>With necrosis</td>
<td>21 (9%)</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Grade II</td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without necrosis</td>
<td>191 (63%)</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>With necrosis</td>
<td>114 (37%)</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Grade III</td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without necrosis</td>
<td>32 (34%)</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>With necrosis</td>
<td>63 (66%)</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>
Necrosis stratifies OS within nuclear grade groups
Solid pattern of growth is significantly associated with worse OS

- Solid: 20 months
- Non-solid: 28 months
Summary of Results

- Nuclear grade correlates with overall survival
- Presence of necrosis and predominately solid growth are associated with worse outcome
- Addition of necrosis stratifies prognosis in all patients with epithelioid mesothelioma (I, II and III grades)
Limitations

- Retrospective study
- Pre/post-operative chemotherapy status known in under 50%
- Follow-up limited by electronic medical records
- Atypia score: subject to inter-observer variability
- Mitotic score: subject to tumor cellularity
Strengths

- Large multi-institutional (multiple pathologist) study
- Majority is pleurectomy/pneumonectomy
- Scoring performed on whole sections not on tissue microarrays
Nuclear grade and necrosis predict prognosis in malignant epithelioid pleural mesothelioma: a multi-institutional study


Mod Pathol 2018; 31:598-606
Grade in biopsy v. resection

- In this study we compared nuclear grade and necrosis between biopsies which were followed by resection in both pleural and peritoneal epithelioid MM
- 48 had a biopsy followed by resection
Results

- 48 epithelioid MM cases:
  - 36 had same nuclear grade (75%) in biopsy versus resection
  - 12 cases had different grades (25%)
- 11 of 12 (95%) were upgraded in the resection, either from grade I to II or III, or grade II to III
- Only one case was downgraded from grade II on biopsy to grade I on resection
Results

• Overall, in 43 cases (89%), presence or absence of necrosis was concordant in biopsy and subsequent resection

• Limitations of this study: cases from a single center and that mainly one pathologist (ANH) did all the grading

• A multicenter study is ongoing
Conclusion 2

- In this study, there was good correlation between biopsy and resection specimens in nuclear grading and presence of necrosis.
- Nuclear grading and assessment of necrosis can be performed easily on H&E stained sections of both biopsy and resection specimens.
- These factors can be incorporated into a mesothelioma synoptic to be included in the pathology report, and may help clinicians to decide on clinical management.
Grading of Epithelioid Malignant Mesothelioma

*Nuclear Grade (for Epithelioid only):* of III

Nuclear atypia score: _____ (1 for mild, 2 for moderate, 3 for severe)

Mitotic count: _____ (1 for low (1/10), 2 for intermediate (2-4/10), 3 for high (5+/10))

Sum: _____ (2 or 3 = grade I, 4 or 5 = grade II, 6 = grade III)

*Prognostic features:*

Necrosis (for Epithelioid only): Present / Absent

Pattern: Favourable (trabecular, tubulopapillary, acinar, myxoid and less than 50% solid)

Unfavourable: Transitional, pleomorphic, more than 50% solid or more than 10% rhabdoid

BAP-1, nuclear expression lost/retained (for epithelioid)
Summary: Update in pathologic diagnosis of MM

• Benign v malignant: BAP-1 by IHC and 9p21 homozygous deletion (loss of p16 (CDKN2A) gene by FISH)
• Mesothelioma in situ
• Newer markers: MTAP and HEG1
• GATA3 and MUC4
• Histological subtyping/patterns
• Nuclear grading (and necrosis) of epithelioid MM for prognosis
Thank you