GUT-C
Dalal Hassan
PGY-2
09/27/2018
Case

69 yo F with a past medical history of multiple myeloma and polymyalgia rheumatica presented with right flank pain, fatigue and weight loss x 1 month. The patient had no history of asbestos exposure. No history of previous malignancy.

The only finding on physical examination was right flank tenderness. No masses were palpable.

Labs showed leukocytosis, microcytic hypochromic anemia and thrombocytosis.

Given that the patient was symptomatic, CT abdomen/pelvis was performed.
Serum CEA and CA-125 levels were within normal limits.

PET scan showed no evidence of disease elsewhere.

U/S guided biopsy of the mass suggested a poorly differentiated hepatocellular carcinoma.

Serum alpha-fetoprotein was also within normal limits.

Because the mass was localized and presumed to be HCC, the patient underwent a lap. assisted wedge resection of segment 6 of the liver, laparoscopic colectomy, omentectomy, abdominal wall resection and cholecystectomy.
Liver
Liver capsule
Tumor
Differential diagnosis?

Stains?
Epithelial markers: CEA, MOC31, Ber-EP4, HMWCK and CK19 are negative.

Tumor-specific markers:
- RCC, WT-1, PAX-8, S100, HMB45, Desmin, Myogenin, Inhibin, ERG, FLI-1, CD34 and STAT6 are all negative.

- Albumin mRNA by ISH, Arginase-1 (on 2 separate sections), and HepPar-1 (on 2 separate sections) are negative.

- INI-1 is retained in the rhabdoid areas.
IHC

AE1/AE3 (all 3 components)

Calretinin (all 3 components)
CK5/6 (all 3 components)

D2-40 (all 3 components)
CK5D3 (all 3 components)
Diagnosis?
FINAL DIAGNOSIS: Localized biphasic peritoneal mesothelioma with rhabdoid features
### 2015 WHO classification of mesothelial tumors

<table>
<thead>
<tr>
<th>Diffuse Malignant Mesothelioma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelioid</td>
</tr>
<tr>
<td>Sarcomatoid</td>
</tr>
<tr>
<td>Desmoplastic</td>
</tr>
<tr>
<td>Biphasic</td>
</tr>
</tbody>
</table>

<table>
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<th>Localized Malignant Mesothelioma</th>
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<tr>
<td>Epithelioid</td>
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<td>Sarcomatoid</td>
</tr>
<tr>
<td>Biphasic</td>
</tr>
</tbody>
</table>

- *Well-differentiated papillary mesothelioma*
Localized biphasic type malignant mesothelioma arising in the peritoneum: Report of a case

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3 Department of Pathology, Steel Memorial Yawata Hospital, Kitakyushu, Japan

Discussion

Localized malignant biphasic peritoneal mesothelioma is very rare. Localized malignant mesothelioma is an uncommon circumscribed tumor of the serosal membrane with the microscopic appearance of diffuse malignant mesothelioma but without any evidence of infiltration. Allen et al. reported spread. Localized malignant mesotheliomas should be separated from other mesotheliomas as well as their mesothelial behavior and far better prognosis.¹ Clinical reports of localized peritoneal

Because it can be surgically resected!
### TABLE 1. Demographic and Pathologic Information: 23 Localized Malignant Mesothelioma Patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Site</th>
<th>History</th>
<th>Att</th>
<th>Size (cm)</th>
<th>Type</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>52</td>
<td>M</td>
<td>Pl</td>
<td>Lineman × 16 years</td>
<td>P</td>
<td>2.2</td>
<td>E</td>
<td>Alive &gt;4.5 years after diagnosis</td>
</tr>
<tr>
<td>B</td>
<td>66</td>
<td>M</td>
<td>Pl</td>
<td>P</td>
<td>P</td>
<td>4</td>
<td>E</td>
<td>DOD &lt; 6 months after diagnosis</td>
</tr>
<tr>
<td>C</td>
<td>67</td>
<td>F</td>
<td>Pl</td>
<td>P</td>
<td>P</td>
<td>4</td>
<td>E</td>
<td>Alive &gt;2 years after diagnosis</td>
</tr>
<tr>
<td>D</td>
<td>56</td>
<td>M</td>
<td>Per</td>
<td>P</td>
<td>P</td>
<td>15</td>
<td>E</td>
<td>Alive &gt;2 years after diagnosis</td>
</tr>
<tr>
<td>E</td>
<td>78</td>
<td>F</td>
<td>Pl</td>
<td>Prior colon carcinoma</td>
<td>P</td>
<td>3</td>
<td>E</td>
<td>Alive &gt;3 years after diagnosis</td>
</tr>
<tr>
<td>F</td>
<td>76</td>
<td>F</td>
<td>Pl</td>
<td>Hemicolectomy for cecal mass</td>
<td>P</td>
<td>6</td>
<td>E</td>
<td>Alive &gt;8 years after diagnosis</td>
</tr>
<tr>
<td>G</td>
<td>76</td>
<td>M</td>
<td>Pl</td>
<td>No history of asbestos exposure</td>
<td>P</td>
<td>11</td>
<td>E</td>
<td>DOD &lt;1 year after diagnosis</td>
</tr>
<tr>
<td>H</td>
<td>83</td>
<td>F</td>
<td>Per</td>
<td>Prior bilateral mastectomy</td>
<td>P</td>
<td>7</td>
<td>E</td>
<td>Alive &gt;8 years after diagnosis</td>
</tr>
<tr>
<td>I</td>
<td>72</td>
<td>M</td>
<td>Pl</td>
<td>S</td>
<td>P</td>
<td>3.5</td>
<td>E</td>
<td>Alive &gt;6.5 years after diagnosis</td>
</tr>
<tr>
<td>J</td>
<td>61</td>
<td>M</td>
<td>Pl</td>
<td>LR 3 months; DOD 9 months after diagnosis; mets: vertebral</td>
<td>P</td>
<td>5</td>
<td>E</td>
<td>DOD 3 years after diagnosis; mets: widespread</td>
</tr>
<tr>
<td>K</td>
<td>48</td>
<td>F</td>
<td>Pl</td>
<td>D ruptured aortic aneurysm 1 month after diagnosis</td>
<td>S</td>
<td>7</td>
<td>Mi</td>
<td>Alive 18 months after diagnosis</td>
</tr>
<tr>
<td>L</td>
<td>43</td>
<td>M</td>
<td>Pl</td>
<td>Shipyard worker</td>
<td>S</td>
<td>8</td>
<td>S</td>
<td>LR 6 months; DOD 6 years after diagnosis; mets: skin</td>
</tr>
<tr>
<td>M</td>
<td>65</td>
<td>F</td>
<td>Pl</td>
<td>Shipyard worker</td>
<td>S</td>
<td>7</td>
<td>Mi</td>
<td>DOD 18 months after diagnosis</td>
</tr>
<tr>
<td>N</td>
<td>67</td>
<td>M</td>
<td>Pl</td>
<td>No history of asbestos exposure</td>
<td>S</td>
<td>8</td>
<td>Mi</td>
<td>Alive 18 months after diagnosis</td>
</tr>
<tr>
<td>O</td>
<td>72</td>
<td>M</td>
<td>Pl</td>
<td>Shipyard worker</td>
<td>S</td>
<td>2.5</td>
<td>E</td>
<td>LR; DOD 19 months after diagnosis; mets: mediastinum</td>
</tr>
<tr>
<td>P</td>
<td>37</td>
<td>F</td>
<td>Pl</td>
<td>Shipyard worker</td>
<td>S</td>
<td>8.5</td>
<td>Mi</td>
<td>DOD 15 months after diagnosis; mets: widespread</td>
</tr>
<tr>
<td>Q</td>
<td>52</td>
<td>M</td>
<td>Pl</td>
<td>Prior laryngeal carcinoma</td>
<td>S</td>
<td>3.2</td>
<td>E</td>
<td>Alive &gt;11 years after diagnosis</td>
</tr>
</tbody>
</table>

**Notes:**
- Att, attachment to serosal; M, man; F, woman; Pl, pleural; Per, peritoneal; P, pleural; S, serosal; E, epithelial; M, mixed; S, sarcomatous; ANRD, alive with no recurrent disease; DOD, dead of disease; mets, metastases; LR, local recurrence; D, dead.
LMPM: Pathogenesis

- *May be associated with asbestos exposure but not found in the majority of cases*
- Radiotherapy exposure
- Thorotrast use
- Malignant mesothelioma genetic susceptibility syndrome, associated with germline mutations of BAP1 (BRCA associated protein 1); patients develop mesothelioma in addition to uveal melanoma and other tumors.
- Somatic mutations of BAP1 observed in 23% of malignant mesotheliomas.
- Erionite exposure
- SV40; causal nature of association questioned

LMPM: Clinical Features

- Incidental finding
- Non-specific symptoms
Key Differences in Gross Findings Between Diffuse and Localized Malignant Peritoneal Mesotheliomas
LMPM: Histology

- Can be bi-phase, spindled or epitheloid
- Cells in the epithelial type can have any of the following architectural patterns: Tubulopapillary, acinar, adenomatoid/microcystic, micropapillary (associated with lymphatic invasion), solid (sheets, nests or cords/trabeculae of cells), single cells, cystic. A combination of patterns can be seen.
  - Cytology: Clear cell, signet ring, deciduoid, adenoid cystic, small cell, rhabdoid or pleomorphic with multinucleated cells, cells with foamy/vacuolated cytoplasm or hobnail cells. May have intracytoplasmic crystalline inclusions.
- Spindled cells in sarcomatoid type may form sheets or fascicles or a storiform pattern; may be associated with heterologous elements such as chondrosarcoma, osteosarcoma or rhabdomyosarcoma. Lymphohistiocytic and transitional types also forms of sarcomatoid mesothelioma.
- Stroma can be fibrotic, hyalinized, edematous, myxoid or inflammatory with lymphoid follicles or with foamy histiocytes. May have marked vascular proliferation.
- Cytologic atypia ranges from mild to moderate to severe. Mitotic activity is variable.
- May see intranuclear inclusions or nuclear grooves.
- Psammoma bodies may be present.
Differential diagnoses depend on location, gender (male/female), type of mesothelioma and clinical circumstances/past medical history of the patient. Diagnosis in specific subtypes (e.g. epithelioid) may also depend on the cytology and architecture of the neoplastic cells.

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Location</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Epithelioid mesothelioma</td>
<td>Pleura</td>
<td>Adenocarcinoma of lung, Metastatic adenocarcinoma involving pleura, Reactive mesothelial hyperplasia</td>
</tr>
<tr>
<td></td>
<td>Peritoneum</td>
<td>Serous papillary adenocarcinoma of ovary, Serous carcinoma of peritoneum</td>
</tr>
<tr>
<td>2. Sarcomatoid mesothelioma</td>
<td>Pleura</td>
<td>Sarcoma, chest wall, pleura or lung, Sarcomatoid carcinoma of lung</td>
</tr>
<tr>
<td></td>
<td>Peritoneum</td>
<td>Sarcoma, abdominal wall, peritoneum or intestine</td>
</tr>
<tr>
<td>3. Desmoplastic mesothelioma</td>
<td>Pleura</td>
<td>Fibrous pleuritis</td>
</tr>
<tr>
<td>4. Biphasic mesothelioma</td>
<td>Pleura</td>
<td>Carcinosarcoma or pulmonary blastoma of lung, Biphasic synovial sarcoma of pleura</td>
</tr>
<tr>
<td></td>
<td>Peritoneum</td>
<td>Carcinosarcoma of ovary, uterus</td>
</tr>
</tbody>
</table>
Differential Diagnosis

Epitheloid MM (ddx based on cytology):
- Clear cell: Adeno ca with clear cell features, SCC with clear cell features, RCC, clear cell melanoma, clear cell carcinoma
- Rhabdoid cell: Extrarenal malignant rhabdoid tumor, proximal type epitheloid sarcoma, rhabdomyosarcoma, oxyphilic RCC, melanoma
- Signet ring: Metastatic signet ring ca from GI tract (colon, stomach, appendix), metastatic lobular breast ca
- Deciduoid: Pseudotumoral deciduosis/ectopic decidua, HCC, adrenocortical carcinoma
- Small cell: Lymphoma, desmoplastic small round blue cell tumor, PNET, small cell melanoma, metastatic small cell ca of the lung
- Foamy/vacuolated cytoplasm: Reactive histiocytic aggregates (histiocytic nodule)
- Hobnail cells: Clear cell carcinoma
- Adenoid cystic: Female adnexal tumor of probable Wolffian origin
- Pleomorphic: Undifferentiated (pleomorphic) carcinoma of the lung
Epitheloid MM (ddx based on architecture)

- Tubulopapillary: Primary peritoneal or ovarian serous borderline tumors, primary peritoneal or ovarian/uterine/fallopian tube serous carcinomas, metastatic papillary thyroid ca

- Adenomatoid: Adenomatoid tumor (commonly seen in the genital tract but has been described in the uterus - arises from mesothelial cells – considered a type of mesothelioma)

- Acinar/Tubular: Adenocarcinoma (e.g. cholangiocarcinoma), Sertoli-Leydig cell tumors

- Solid: Well-differentiated (solid adenocarcinoma e.g. from lung, SCC) or poorly differentiated (poorly differentiated ca or lymphoma), yolk sac tumor (can also have tubulocystic and papillary growth patterns)

Epitheloid MM with myxoid stroma: Myxoid variant of epitheloid MM.

DDx: Mucinous adenocarcinoma and pseudomyxoma peritonei (grossly and histologically). Best marker for distinguishing between the two is D2-40.

DDx also includes sarcomas with epitheloid features (epitheloid angiosarcomas, epitheloid hemangioendothelioma), etc
Biphasic MM (tumors with biphasic features):

- Carcinosarcoma (MMMT from uterus or ovary)
- Metastatic pleomorphic carcinoma of lung
- Synovial sarcoma
- Melanoma
- Serosal metastases with desmoplastic reaction

Sarcomatoid MM:

- Fibrosarcoma
- Monophasic synovial sarcoma
- Extra-intestinal GIST with spindled features
- Malignant solitary fibrous tumor
- Neurogenic tumors (MPNST)
- Vasogenic tumors (poorly differentiated angiosarcomas)
- Smooth muscle tumors (leiomyosarcoma, leiomyomatosis peritonealis disseminata)

If seen with heterologous elements such as chondrosarcomatous, osteosarcomatous (metastatic chondrosarcomas, metastatic osteosarcomas)

If cells very pleomorphic (similar to pleomorphic epitheloid type), can mimic MFH/undifferentiated pleomorphic sarcoma

- Melanoma
- Spindle cell carcinomas
- Lymphohistiocytic subtype: Inflammatory pseudotumor, Hodgkin's and non-Hodgkin's lymphoma; usually sarcomatoid component present (CK +ve cells)

- Desmoplastic variant of sarcomatoid mesothelioma: Spindled cells in hyalinized collagenous stroma.

DDx: Fibrous pleurisy (in pleura)
Diagnosis of malignant mesothelioma is challenging – here the goal is to distinguish primary malignant peritoneal mesothelioma from primary peritoneal or metastatic tumors: Current recommendation is to use at least two mesothelial markers (including Pan-CK) such as calretinin and CK 5/6 and two other markers based on differential diagnosis (PAX-8, ER, Ber-EP4, MOC.31) for diagnosing epitheloid malignant mesotheliomas. In WT-1 negative cases, recommended to use at least two mesothelial markers and four other markers based on differential.

For sarcomatoid malignant mesotheliomas, the ERS/ESTS guidelines recommend the use of at least two broad-spectrum cytokeratin antibodies and two markers with negative predictive value.
Table 6. Peritoneal Malignant Mesothelioma (PMM) Versus Papillary Serous Carcinoma (PSC) and Nongynecologic Adenocarcinoma (AdCa)

<table>
<thead>
<tr>
<th>Positive Mesothelioma Markers</th>
<th>Calretinin</th>
<th>Podoplanin (D2-40)</th>
<th>CK5/6</th>
<th>WT1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Useful</strong> Positive in 85%–100% of PMM cases, but reactivity in 0%–38% PSC limits its use as a single marker.</td>
<td>Very useful. Positive in 98% of PMM and 5% of PSC.</td>
<td>Not useful. Positive in 93%–96% of PMM cases, but wide spectrum of positivity in PSC from 13%–65%.</td>
<td>Not useful. Positive in 53%–100% of PMM cases, but positive in 22%–35% of PSC cases.</td>
<td>Not useful. Positive in 43%–93% of PMM, but 89%–93% of PSC are positive.</td>
</tr>
</tbody>
</table>

**PSC markers**

<table>
<thead>
<tr>
<th>Claudin 4</th>
<th>MOC 31</th>
<th>PAX8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very useful. Positive in 98% of PMM and 5% of PSC.</td>
<td>Very useful. Positive in 98% of PSC and 5% of PMM.</td>
<td>Very useful. Positive in most Müllerian carcinomas; usually negative in PMM.</td>
</tr>
</tbody>
</table>

**BG8**

| Very useful. Positive in 3%–9% of PMM and 89% of AdCa. |

**BFEP4**

| Limited utility. Positive in 65%–100% of PSC and 0%–3% of PMM, but many cases show only trace/focal staining. |

**B72.3**

<table>
<thead>
<tr>
<th>CEA</th>
<th>Estrogen receptor</th>
<th>Progesterone receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not useful. Positive in 0%–45% PSC (average 20%) and 0% PMM, but sensitivity in PSC is too low compared with other choices.</td>
<td>Useful. Positive in 60%–93% in PSC, and negative or very low positive rate (0%–8%) in PMM.</td>
<td>Limited utility. Lower sensitivity than ER, but uniformly negative in PMM. May be valuable if positive.</td>
</tr>
</tbody>
</table>

**PMM versus nongynecologic AdCa** (biliary, pancreatic, gastric, colonic)

<table>
<thead>
<tr>
<th>Claudin 4</th>
<th>Calretinin</th>
<th>WT1</th>
<th>Podoplanin (D2-40)</th>
<th>CK5/6</th>
<th>MOCC11</th>
<th>BG8 (Lewis')</th>
<th>CEA</th>
<th>B72.3</th>
<th>BER-EP4</th>
<th>CDX2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very useful. Positive in 100% of gastric, pancreatic, colonic and biliary adenocarcinomas, and always negative in PMM.</td>
<td>Very useful. Positive in 85%–100% of PMM, but also positive in 10% of pancreatic AdCa, so limited as a single marker.</td>
<td>Very useful. Positive in 43%–93% of PMM and 3% of gastric AdCa; negative in pancreatic AdCa.</td>
<td>Potentially useful. Positive in 93%–96% of PMM; negative in pancreatic and gastric AdCa (but limited data).</td>
<td>Not useful. Positive in 53%–100% of PMM and 38% pancreatic AdCa positive.</td>
<td>Very useful. Positive in 5% of PMM and 87% of AdCa.</td>
<td>Very useful. Positive in 3%–9% of PMM and 89% of AdCa.</td>
<td>Very useful. Positive in 81% of AdCa; negative in PMM.</td>
<td>Very useful. Positive in 84% of pancreas, 89% of bile duct, 98% of colon AdCa; 0%–3% of PMM.</td>
<td>Useful. Positive in &gt;98% of pancreatic and gastric AdCa; 9%–13% of PMM.</td>
<td>Useful. Positive in 90%–100% of colon, 80% of small intestine, and 70% of gastric carcinomas; negative in PMM.</td>
</tr>
</tbody>
</table>

Abbreviations: BG8, blood group 8; CEA, carcinoembryonic antigen; CK5/6, cytokeratin 5/6; WT1, Wilms tumor-1.
References


USCAPKnowledgeHub: USCAP 2016: Gynecologic Pathology Evening Session, Case #4

Foundation Series in Diagnostic Pathology: Gynecologic Pathology