Case #4
Ruth L. Katz, MD

64 year old female
FNA biopsy of mediastinal mass
Strike Out

- This 64 year old lady had a history of Waldenstrom’s macroglobulinemia diagnosed 14 years previously, papillary thyroid carcinoma, Hashimoto’s thyroiditis, shingles, and mixed connective tissue disorder.
- In 2007 she was diagnosed with a stage I papillary renal cell carcinoma, Fuhrman nuclear grade 3, for which she underwent a left sided radical nephrectomy. The tumor measured 2.0x1.5x1.0cm.
- Later she developed persistent pain in the area of the nephrectomy, and poor performance status with shortness of breath and recurrent pleural effusions requiring multiple thoracentesis.
- PET/CT scan showed a large mediastinal mass, and left pleural lesion extending into the right paratracheal lymph nodes, and around the level of the carina.
- A mediastinal biopsy was performed via endoscopic ultrasound guidance.

CT Thorax showing infiltrative mediastinal mass and pleural effusion

Called Metastatic Carcinoma C/W Papillary Renal Cell Carcinoma

Cytoplasm vacuole

Lymph node, 4R, FNA, DQ
Metastatic Carcinoma C/W Renal Cell Primary Neoplasm

Cytoplasm vacuole

Lymph node, 4R, FNA, DQ

Papillary renal cell carcinoma

Papillary renal cell carcinoma
Papillary renal cell carcinoma

Morphologic Similarity between present FNA and Papillary renal cell carcinoma

Papillary renal cell carcinoma

CD10  PAX-2  CK7

Vimentin  P504S
The Dilemma

- Called metastatic renal carcinoma. Comment: Morphology of the metastatic lesion resembled the original renal carcinoma.
- The diagnosis was subsequently queried!
- Clinician questioned the likelihood that a completely resected small renal papillary carcinoma with negative margins could metastasize?

Further morphologic examination of the FNA revealed features suggestive of a vascular neoplasm, and additional immunohistochemical workup of the specimen revealed positive staining for several vascular markers. The diagnosis was revised to suggest a vascular tumor.

- More tissue was requested to evaluate the mediastinal tumor and biopsy of 4R was performed via endoscopic bronchial ultra-sound guidance (EBUS).
- At the time of the procedure the pulmonologist noted submucosal infiltration from distal third of trachea into both bronchial trees.
- Again called consistent with metastatic renal carcinoma by a second cytopathologist, based in part on a positive pan-cytokeratin stain, and lack of total familiarity with the revised diagnosis and immunocytochemistry workup.
- The diagnosis was subsequently revised to a vascular neoplasm, encompassing epithelioid hemangioma (EH) after repeating the vascular marker for CD34 which was diffusely positive.

Metastatic Malignant Vascular Neoplasm

Entrapped intact and degenerating erythrocyte

Lymph node, 4R, FNA, DQ
Metastatic Malignant Vascular Neoplasm

entrapped intact and degenerating erythrocyte

Lymph node, 4R, FNA, DQ

Cytoplasm vacuole contained entrapped intact and degenerating erythrocyte

Lymph node, 4R, FNA, PAP

Lymph node, 4R, FNA, CD34
Metastatic Malignant Vascular Neoplasm

Lymph node, 4R, FNA, CD34

Metastatic Malignant Vascular Neoplasm

Lymph node, 4R, FNA, pan-keratin

Metastatic Malignant Vascular Neoplasm

Cell block, H&E
Metastatic Malignant Vascular Neoplasm

- CD31-positive (strong, diffuse)
- CD34-positive (strong, diffuse)
- Factor 8-positive (strong, focal)
- Pan-keratin-positive (weak to moderate, focal)
• Subsequently the patient developed a large bloody pleural effusion which showed metastatic malignant vascular neoplasm and concurrent low grade lympho-plasmacytic lymphoma.
• Shortly after this she expired.
Metastatic Malignant Vascular Neoplasm in a background of Lymphoplasmacytic Lymphoma

Metastatic Malignant Vascular Neoplasm

Metastatic Malignant Vascular Neoplasm
Pulmonary Epithelioid Hemangioendothelioma With Prominent Signet Ring Cell Features Mimicking Metastatic Adenocarcinoma


Pulmonary Epithelioid Hemangioendothelioma Mimicking Mesothelioma.

Armita Bahrami, 1 Timothy C. Allen 2 and Philip T. Cagle 3 1 Baylor College of Medicine and Methodist Hospital, Houston, Texas, USA
Methodist Hospital, Weill’s Medical College of Cornell University, Houston and 2 University of Texas Health Center at Tyler, Tyler, Texas, USA
Pathol Int. 2008 Nov;58(11):730-4

<table>
<thead>
<tr>
<th>Case</th>
<th>Clinical Findings</th>
<th>Cause</th>
<th>Final Diagnosis</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Abdominal pain</td>
<td>EP</td>
<td>EHE</td>
</tr>
<tr>
<td>2</td>
<td>Nausea, vomiting</td>
<td>EP</td>
<td>EHE</td>
</tr>
<tr>
<td>3</td>
<td>Tachycardia</td>
<td>EP</td>
<td>EHE</td>
</tr>
<tr>
<td>4</td>
<td>Jaundice</td>
<td>EP</td>
<td>EHE</td>
</tr>
<tr>
<td>5</td>
<td>Hypertension</td>
<td>EP</td>
<td>EHE</td>
</tr>
<tr>
<td>6</td>
<td>Hematemesis</td>
<td>EP</td>
<td>EHE</td>
</tr>
<tr>
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<td>Hemoptysis</td>
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<td>EHE</td>
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<td>8</td>
<td>Hematuria</td>
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<td>13</td>
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<tr>
<td>14</td>
<td>Hematochezia</td>
<td>EP</td>
<td>EHE</td>
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</table>

In case 1, the patient initially had a hysterectomy and bilateral salpingo-oophorectomy for uterine leiomyomas. At that time, sections of the serosal surface of the uterus showed a few unusual subserosal cell clusters, which were interpreted as mesothelial hyperplasia by two consultants. In the year following the hysterectomy, the patient developed recurrent bloody ascites. An exploratory laparotomy revealed diffuse peritoneal tumor involving the omentum, cul-de-sac, colon, cecum, and appendix.

EAD, epithelioid angiosarcoma; EA, epithelioid hemangioendothelioma; NA, not available. *With disease at 6 months’ follow-up

Table 2

### Table 3. Results of immunohistochemical studies

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Collagen IV</th>
<th>VWF</th>
<th>UEA-I</th>
<th>CD34</th>
<th>CD31</th>
<th>Keratin</th>
<th>Vimentin</th>
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<tbody>
<tr>
<td></td>
<td>12/14</td>
<td>12/14</td>
<td>7/14</td>
<td>11/14</td>
<td>11/14</td>
<td>14/14</td>
<td>14/14</td>
</tr>
<tr>
<td>No. of reactive cases</td>
<td>14</td>
<td>13</td>
<td>12</td>
<td>11</td>
<td>10</td>
<td>9</td>
<td>8</td>
</tr>
</tbody>
</table>

1. UEA-1, Ulex europaeus agglutinin-1; VWF, von Willebrand factor; +, positive; -, negative; +/-, focal positive
Case #4 History

“The Strike Out”

This 64 year old lady had a history of Waldenstrom’s macroglobulinemia diagnosed 14 years previously, papillary thyroid carcinoma, Hashimoto’s thyroiditis, shingles, and mixed connective tissue disorder.

In 2007 she was diagnosed with a stage I papillary renal cell carcinoma, Fuhrman nuclear grade 3, for which she underwent a left sided radical nephrectomy. The tumor was small and measured 2.0 x 1.5 x 1.0 cm.

Shortly after this she developed persistent pain in the area of the nephrectomy, and poor performance status with shortness of breath and recurrent pleural effusions requiring multiple thoracentesis. She was shown by PET/CT scan to have a large mediastinal mass, and left pleural lesion extending into the right paratracheal lymph nodes, and around the level of the carina.

A mediastinal biopsy was performed via an endoscopic ultrasound guidance procedure. The specimen was originally called metastatic renal carcinoma, with a comment that the morphology of the metastatic lesion resembled the original renal carcinoma. However the diagnosis was subsequently queried after the clinician questioned the likelihood that a completely resected small renal papillary carcinoma with negative margins could metastasize.

Further morphologic examination of the FNA revealed features suggestive of a vascular neoplasm, and additional immunohistochemical workup of the specimen revealed positive staining for several vascular markers. The diagnosis was revised to suggest a vascular tumor.

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Again it was called consistent with metastatic renal carcinoma by a second cytopathologist, based in part on a positive pan-cytokeratin stain, and lack of total familiarity with the revised diagnosis and immunocytochemistry workup mentioned above.

The diagnosis was subsequently revised again to a vascular neoplasm, encompassing epithelioid hemangioma (EH) after repeating the vascular marker for CD34 which was diffusely positive.

Subsequently the patient developed a large bloody pleural effusion which showed metastatic malignant vascular neoplasm and concurrent low-grade lymphoplasmacytic lymphoma.
Shortly after this she expired.

**Final Diagnosis**

Malignant vascular tumor consistent with epithelioid hemangioma or angiosarcoma

**Discussion**

The patient who had a history of multiple different neoplasms, presented with a mediastinal mass, lung lesions and pleural effusions. She presented with acute dyspnea and compressive symptoms due to her rapidly progressive tumor which had an aggressive course which terminated in death. Her diagnosis was complicated due to her previous recent history of papillary renal carcinoma, and the nature of the epithelioid mediastinal tumor that resembled a metastatic carcinoma and was called on two occasions consistent with metastatic papillary renal cell carcinoma. Subsequently the diagnosis was questioned based on the atypical presence of metastases from a small papillary renal tumor, and further immunohistochemistry workup with a panel of endothelial markers was confirmatory for an epithelioid hemangioendothelioma (EH). EHS are rare vascular tumors that may occur in the liver, bone, breast, brain and lymph nodes.

They may also occur in the lung where they show a tendency to invade pulmonary vessels and small airways similar to bronchioloalveolar carcinomas. David Dail described this tumor as “intravascular bronchioloalveolar tumor of the lung” as it may present similar to BAC with multiple lung nodules.

Primary epithelioid hemangioendothelioma (PEH) of the mediastinum is a rare entity. Suster et al reported 12 cases that occurred with a mean age of 49 years (range from 19 to 62 years). Seven patients were symptomatic due to compression of the surrounding structures, while the remaining were asymptomatic and found incidentally on routine chest x ray. Tumors ranged in size from 4.5 to 13.5cm, they were mostly encapsulated however there were five cases where the tumor was locally infiltrative. The biological behavior of most of these tumors was low grade and were controlled by surgical excision.

Histologically there was a spectrum of features from low grade epithelioid cells with abundant eosinophilic cytoplasm with prominent vacuolization and intra cellular lumen formation to more pronounced cytologic atypia.

The histological and cytological appearance of EH may cause it to be frequently confused with other types of tumors. Because of its epithelioid nature and rarity, confusion with metastatic carcinoma occurs. Hristova et al encountered a case of EH with a plasmacytoid appearance and prominent cytoplasmic vacuoles which was mistaken for a case of metastatic signet ring carcinoma from the gastrointestinal tract or pancreaticobiliary tract.

Similarly EH involving the pleura may be mistaken for mesothelioma.
The table below (Table 1) is taken from Lin et al who described 14 patients with endothelial neoplasms either EH or epithelioid angiosarcoma (EA) involving the pleural, peritoneal or pericardial cavities resulting in a clinical and histological appearance resembling mesothelioma. The histological appearance showed a diffuse sheet like pattern with a tubulo-papillary growth pattern in 4 cases. Nine cases showed a variable number of spindle cells, some neoplastic, others reactive, focally producing a biphasic growth pattern, further suggesting mesothelioma. Initial interpretations included mesothelioma, and adenocarcinoma. Immunohistochemically, strong vimentin staining and negative or weak to moderate cytokeratin staining were observed in all 14 cases. The tumor cells co-expressed at least two of four endothelial markers (CD31, CD34, von Willebrand factor, and Ulex europaeus agglutinin-I [UEA-I]). Clinically, these endothelial tumors were highly aggressive; (see table below). Twelve patients presented with disseminated disease, and most died within months of the initial presentation.

Endothelial sarcomas arising from or secondarily involving the serous membranes are rare. Some have features of EH, whereas others exhibit a higher histological grade but similar epithelioid features. In all cases, immunohistochemical studies are essential in confirming the endothelial origin of the neoplasm.

**Immunohistochemistry**

An endothelial marker panel comprising CD31, CD34, and Factor VIII related antigen should be run. In addition epithelial markers such as EMA, Cytokeratin 7 (CK7) CK20, CK 5/6, calretinin, WT-1, thrombomodulin, D2-40, BER-EP4, CEA, TTF-1, renal cell carcinoma marker and SMA should be tested and all should be negative. However pan-cytokeratin, as in the case presented may be focally positive.

Recently it has been demonstrated that immunohistochemical expression of FL1-1 protein, a nuclear transcription factor and a marker for Ewing’s sarcoma is a highly sensitive and specific marker for benign and malignant vascular tumors. The diagnosis of an endothelial neoplasm can be suspected by the presence of epithelioid cells with intra-cytoplasmic Lumina or vacuoles (sometimes containing red blood cells) and by the strong expression of vimentin, with absent or low-level expression of cytokeratin. The demonstration of immunoreactivity for two or more endothelial-associated markers is essential in confirming the diagnosis.

**Cytology**

There have been a few reports describing the cytological features of EH of lung, bone and soft tissue and liver. Similar to our present case Mhoyan et al describe a case of EH presenting as a hilar mass that was diagnosed by endoscopic US .FNA. The cytology showed loosely cohesive sheets and clusters of epithelioid cells, large irregular nuclei with nucleoli and a moderate amount of vacuolated cytoplasm. Rare cells suggested cytoplasmic lumen formation. Cell block showed some cells with red blood cells in cytoplasmic vacuoles or lumens. Endothelial cells stained positive with factor VIII and CD34.
Malignant Vascular Tumors of the Serous Membranes Mimicking Mesothelioma; A Report of 14 cases.*

<table>
<thead>
<tr>
<th>Case</th>
<th>Clinical Findings</th>
<th>Outcome</th>
<th>Final Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Recurrent hemorrhagic ascites; Diffused peritoneal tumor infiltrate</td>
<td>DOD</td>
<td>EA</td>
</tr>
<tr>
<td>2</td>
<td>Pleural thickening with effusion</td>
<td>DOD</td>
<td>EHE</td>
</tr>
<tr>
<td>3</td>
<td>Diffuse peritoneal tumor infiltrate</td>
<td>DOD</td>
<td>EHE</td>
</tr>
<tr>
<td>4</td>
<td>Multiple nodules in the left upper lobe and pleura</td>
<td>Recent</td>
<td>EA</td>
</tr>
<tr>
<td>5</td>
<td>Solitary pleural tumor</td>
<td>DOD</td>
<td>EA</td>
</tr>
<tr>
<td>6</td>
<td>Diffuse peritoneal tumor infiltrate</td>
<td>DOD</td>
<td>EA</td>
</tr>
<tr>
<td>7</td>
<td>Pleural thickening with recurrent effusion</td>
<td>DOD</td>
<td>EA</td>
</tr>
<tr>
<td>8</td>
<td>Pleural and pericardial thickening</td>
<td>DOD</td>
<td>EA</td>
</tr>
<tr>
<td>9</td>
<td>Pleural thickening with recurrent effusion</td>
<td>NA</td>
<td>EHE</td>
</tr>
<tr>
<td>10</td>
<td>Thoracic outlet syndrome and pleural thickening</td>
<td>DOD</td>
<td>EHE</td>
</tr>
<tr>
<td>11</td>
<td>Pleural effusion and solitary pleural tumor</td>
<td>Alive</td>
<td>EHE</td>
</tr>
<tr>
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<td>Pleural and pericardial thickening with effusion</td>
<td>DOD</td>
<td>EHE</td>
</tr>
<tr>
<td>13</td>
<td>Pleural thickening with effusion</td>
<td>DOD</td>
<td>EHE</td>
</tr>
<tr>
<td>14</td>
<td>Pericardial tamponade</td>
<td>NA</td>
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</tr>
</tbody>
</table>

DOD, dead of disease; EA, Epithelioid Angiosarcoma; EHE, epitheloid hemangioendothelioma;

BIBLIOGRAPHY


