Hemorrhagic Epithelioid Angiosarcoma of the Peritoneal Cavity Clinically Posing as a Dissecting Abdominal Aortic Aneurysm; A Case Report and Literature Review

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Abstract

Epithelioid angiosarcoma (EA) is a very rare, malignant, vascular neoplasm that is difficult to diagnose and treat. To our knowledge involvement of the omentum and, or mesentery has been reported in only four other cases.1-4 Angiosarcomas comprise less than 2% of all sarcomas, and sarcomas comprise less than 1% of soft tissue cancers.5-8 Among angiosarcomas, the epithelioid variant is exceedingly rare.8,9 The differential diagnosis for abdominal pain is extensive and includes abdominal aortic aneurysm (AAA), mesenteric ischemia and infarction, peritonitis, and intestinal obstruction. Based on laboratory and imaging studies, inclusion of mesenteric angiosarcoma may be warranted in this list of differentials. Since these neoplasms are readily mistaken for carcinomas and melanomas, immunohistochemical staining is vital to diagnosing these lesions. The patient's omentum and mesenteric lesions were positive with epithelial marker AE-1/AE-3; the vascular markers CD31, Factor VIII, and CD34; as well as endothelial marker Fli-1 supporting the diagnosis of epithelioid angiosarcoma. Interestingly, the human herpes virus stain was negative. This case demonstrates the importance of considering epithelioid angiosarcoma in the differential diagnosis of patients presenting with progressively worsening abdominal pain and findings reminiscent of a ruptured aortic aneurysm. Also challenging is the histopathologic diagnosis of these tumors due to the “epithelioid” features of the neoplastic endothelial cells. Utilizing appropriate immunohistochemical studies can be extremely helpful in this regard.

CASE REPORT

A 77 year old, obese, Latino male presented to the emergency department (ED) with two weeks complaint of abdominal pain, which became progressively worse. The patient was nauseous, lethargic, had a decrease in appetite but denied any hematemesis and hematochezia. Pertinent past medical history included ethanol abuse, hypertension and benign prostatic hypertrophy. Upon admission, he was hypotensive (102/70), tachycardic (110), with a respiration rate of 16 breaths per minute. He had a slightly distended, non-tender abdomen. A slight hernia was seen in the abdomen. The physical exam was otherwise normal. Initial laboratory studies revealed anemia with hemoglobin of 8.2 g/dL and hematocrit of 24.4%. CT scan showed an abdominal aortic aneurysm 5.2 X 5.0 X 7.5 cm, without evidence of hematoma. There was also questionable free fluid in the abdomen which “appeared more dense than urine suggesting…blood” and diverticulosis. Based on these findings, the patient was admitted to the intensive care unit, transfused, and seen by various specialists.

The vascular surgeon ruled out dissection of the aneurysm. An angiogram did not show active bleeding. Serial CT scans, with and without contrast, did not show leaking from the aortic aneurysm. The CT scans did show peritoneal fluid extending into the pelvis and around the liver. There was an infiltrative process involving the omental and mesenteric fat, deep to the rectus abdominus muscles, representing either blood or inflammation. Paracentesis was performed, showing blood.

Approximately one week prior to presenting to the ED, the patient underwent an outside CT without contrast. The report stated that there was no leakage from the aneurysm, no ascites nor pneumoperitoneum. Scans through the lower abdomen and upper pelvis showed irregular peritoneal densities within the anterior pelvic peritoneal fat. Multiple diverticulae were noted in the sigmoid colon located posterior and medial to the area of fatty infiltration. Findings were suggestive of diverticulitis vs other inflammatory processes. Neoplastic
involvement of the peritoneum was also in the differential diagnosis. There was rapid progression of the disease. In less than one week the patient developed free fluid (blood) in his abdominal cavity.

Following hospital admission, the patient underwent a laparotomy where approximately seven liters of blood were removed. There was extensive infiltration of the mesentery and omentum with hemorrhagic, friable, nodular implants. The nodules (Fig 3) that burst easily upon manipulation, discharging significant amounts of blood. It appeared that these nodules caused the hemoperitoneum. The omentum was excised. A portion of the mesentery, containing a large mass, with the attached mid small bowel was removed. Also, a portion of the sigmoid colon, containing a non-obstructing mass, was removed. There were no obvious liver nodules, but there was “prominence involving the right lobe of the liver”. The omentum, and portions of the small and large bowels were submitted for pathological study.

PATHOLOGY
The laparotomy specimen consisted of a portion of omentum and segments of large and small intestines. The omentum was 38 x 11 x 2 cm, conspicuously nodular and moderately firm. The sigmoid colon was 10 cm long, 3.5 cm in diameter, containing an ulcerated, sessile polyloid fungating neoplasm, situated 2 cm from the closest sutured margin, circumferentially extending along the entire circumference of the intestinal lumen and extending 2.5 cm along its longitudinal axis. The neoplasm was 3 x 2.5 cm and protruded into the lumen. Microscopic sections of the latter showed moderately differentiated adenocarcinoma arising in a villous adenoma (Figs 1 and 2). The small bowel was 7 cm long and 3 cm in diameter with an attached portion of mesentery, 2.5 cm wide and 1.0 cm thick, coursing along its entire length of small intestine. The mesentery, contiguous with the intestinal wall, contained hemorrhagic defects up to 2 cm in diameter. The omentum contained similar hemorrhagic defects arborizing throughout the specimen (Figs 3 and 4).
Figure 3
Fig 3. At surgery mesenteric and omental surfaces were covered with hemorrhagic nodular implants.

Histologic sections of the omentum disclosed extensive infiltration by rows and aggregates of malignant epithelioid cells supported by fibrovascular trabeculae associated with recent hemorrhage. The pericolic adipose tissue and mesentery associated with the small intestine were similarly infiltrated by rows and aggregates of malignant epithelioid cells. The segment of small intestine was, otherwise, benign with no grossly discernable mucosal lesions.

The fibroadipose omental tissue showed proliferation of nests and clusters of round cells with high nuclear grade and prominent nucleoli. The cellular proliferation contained numerous dilated vessels and slit-shaped spaces filled with fibrin and red blood cells. The tumor was focally necrotic. Immunohistochemically, the tumor stained positive with pancytokeratin, AE-1/AE-3, with vimentin and with the vascular markers CD31, Factor VIII, and CD34 (few). The endothelial marker Fli-1 was diffusely positive. These results support the diagnosis of epithelioid angiosarcoma. The tumor cells were negative with HHV-8 arguing against Kaposi sarcoma. Although cytokeratin was positive, the negative Ber-EP4, MOC31, EMA, CK7 and CK20 mitigate against a metastatic carcinoma. The neoplastic cells were negative with Calretinin and WT-1 arguing against a mesothelioma. The S100 was negative, ruling out melanoma.

Figure 5
Fig 5. Throughout the omentum firm arborizing hemorrhagic lesions.

Figure 4
Fig 4. Resected portion of omentum showing firm arborizing hemorrhagic lesions.

Figure 6
Fig 4. Cut surface of mesentery showing similar arborizing hemorrhagic lesions.
Angiosarcomas are rare, highly malignant, vascular mesenchymal neoplasms. The incidence is approximately 0.01 per 100,000, with older adults being primarily affected, although angiosarcomas can develop at any age, with a similar distribution between sexes. \(^{10,11}\) Our patient was a 77 year old male. The other patients’ ages were 18 months, 11 years, 13 years, and 61 years old. The three pediatric patients were female.

The presentation and behavior of angiosarcomas vary depending on location.\(^ {11}\) Angiosarcomas can be divided into the following groups: 1) angiosarcoma of the deep soft tissue, 2) cutaneous angiosarcoma (associated or not with lymphadema), 3) primary angiosarcoma of the breast and
4) angiosarcoma affecting the parenchymal tissues.\textsuperscript{5,11,12} They may also be found in a pre-existing vessel.\textsuperscript{13} They typically arise in the skin and subcutaneous tissues of the head and neck.\textsuperscript{4} The deep soft tissue variant accounts for only approximately 25% of all angiosarcomas.\textsuperscript{5} Angiosarcomas can present as several morphological variants, including a well-differentiated form, where the vascular nature of the tumor is apparent, a poorly differentiated form that resembles undifferentiated neoplasms, and an epithelioid form, where tumor cells grow in sheets and have abundant pink cytoplasm.\textsuperscript{7} Angiosarcomas of deep soft tissue frequently have an epithelioid cytomorphology, which can make differentiating them from carcinoma, melanoma, and epithelioid leiomyosarcoma\textsuperscript{2,11,14} challenging.

Angiosarcomas may arise spontaneously. Their development has also been linked to various risk factors, such as exposure to chemicals like vinyl chloride and thorium dioxide, irradiation, lymphedema and foreign bodies such as A–V shunts for dialysis.\textsuperscript{11,15,17} Radiation therapy, alone, increases the relative risk of developing secondary angiosarcomas by 10 fold; this is increased by 26.7 fold when combined with chemotherapy.\textsuperscript{2} To the best of our knowledge, our patient did not have these risk factors. Only one patient, the 13 year old, had a history of radiation exposure to treat Hodgkin lymphoma.\textsuperscript{2}

Clinical presentation varies, depending on the location of the malignancy. Deep soft tissue and visceral lesions usually present as an expanding mass associated with pain, discomfort and bleeding, and cutaneous lesions often appear as bruises.\textsuperscript{5,11,15} Intra-abdominal angiosarcomas tend to be diffuse versus discrete lesions.\textsuperscript{3} Our patient complained of abdominal pain initially and then reported nausea, anorexia, and lethargy. We cannot definitively state that these symptoms were not related to the sigmoid adenocarcinoma, although it is unlikely considering that tumors low grade and stage. Our patient was also anemic secondary to bleeding into his abdomen. Out of the other four cases, only the 18 month old was not reported to present with abdominal pain, which might be attributable to her age and language development.\textsuperscript{1,4} Also, all other patients, except for the 11 year old, were reported to have blood in their abdomens.\textsuperscript{5,4}

Diagnosing angiosarcomas is both clinically and pathologically challenging. Fine needle aspiration smears of EA are not useful for diagnosis.\textsuperscript{20} The rounded epithelioid shaped cells may exhibit a rhabdoid morphology, easily being confused with carcinoma, with epithelioid forms of sarcoma, and with malignant melanoma.\textsuperscript{19} Microscopically, angiosarcomas are infiltrative and do not have clear borders between normal and abnormal tissue. Abnormal, pleomorphic, malignant endothelial cells are characteristic of this type of soft tissue sarcoma. Mitotic figures are common, as are small clusters of erythrocytes within the cytoplasm of the abnormal endothelial cells.\textsuperscript{3} However, these characteristics are not diagnostic, making immunohistochemistry vital to the diagnosis. Vascular markers: CD31 and CD34 identify most angiosarcomas. CD31 (platelet-endothelial cell adhesion molecule) is a highly sensitive, specific antigen for endothelial differentiation.\textsuperscript{1} Nearly all vascular tumors express CD31, whereas many soft tissue tumors of nonvascular lineage do not.\textsuperscript{3} CD31 is an important marker for poorly differentiated cases.\textsuperscript{11} CD34 (human hematopoetic progenitor cell antigen) is expressed by many angiosarcomas but is also seen in some soft tissue tumors. Another endothelial marker is Factor VIII.\textsuperscript{15} Approximately one third of epithelioid angiosarcomas will express cytokeratins.\textsuperscript{5,11,15} Therefore, CD31,CD34, and Factor VIII are useful markers for identifying EA and for differentiating it from other epithelioid neoplasms.

As of October 2010, there were no randomized trials and few prospective studies on the treatment of angiosarcoma.\textsuperscript{11} Phase II studies and case reports suggest radical surgery with complete resection and adjuvant radiotherapy for local disease, and chemotherapy for metastatic disease.\textsuperscript{11} Radiotherapy, with large doses (>50 Gy), and wide treatment fields, is recommended due to the high risk of local recurrence.\textsuperscript{11} Treatment for metastatic diseases is cytotoxic chemotherapy with the main drug groups being: anthracyclines, ifosfamide, and taxanes. Specifically, low dose liposomal paclitaxel and doxorubicin, alone and in combination, have shown positive results.\textsuperscript{11,18} Mathew P., et al, effectively treated a patient with metastatic epithelioid angiosarcoma with low dose, regularly scheduled liposomal paclitaxel and doxorubicin and cisplatin who remained in remission 2 years post treatment. Research and clinical studies into antiangiogenic molecules, such as the vascular endothelial growth factor-A (VEGF-A) monoclonal antibody, bevacizumab, and the broad-spectrum tyrosine-kinase inhibitor, sorafenib, which targets vascular endothelial growth factor receptors (VEGFs), show promising results but are suggested to be utilized only in clinical trials.\textsuperscript{11} In our patient, his advanced age and the diffuse nature of the tumor made treatment difficult. While the patient was en route to receive radiotherapy, he became
hemodynamically unstable. He never received radiotherapy.

The poor prognosis for angiosarcomas parallels their rare occurrence.

EAs are highly aggressive, with a short survival expectancy. The overall 5 year survival rate, for angiosarcomas is approximately 35%. For those involving the mesentery, it is less than 10%. Accordingly, we regret to report that our patient passed away approximately one months after surgical resection and diagnosis. Like our patient, many patients reach a transfusion dependent state before death. Three of the other EA cases resulted in death. It is unknown whether or not the 13 year old is deceased, however the patient did have bone metastases 6 months after diagnosis.

It is difficult to make any conclusions about EA involving the omentum, based on these few cases. It is extremely rare, making it an unlikely addition to the differential diagnosis list. It is aggressive and rapidly progressive, making it difficult to treat with poor outcomes despite treatment. Diagnosing an angiosarcoma is a challenge, especially when there might be other sources of bleeding, such as in our case, but immunohistochemistry allows for the definitive diagnosis of epithelioid angiosarcoma.

References
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