Primary Adrenal Angiosarcoma: A Rare and Potentially Misdiagnosed Tumor

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Summary: A man aged 69 years presented with acute right flank pain secondary to a hemorrhagic large adrenal tumor. En bloc resection was performed to repair the inferior vena cava. Immunoperoxidase levels in the tumor were positive for factor VIII and CD31 and negative for S100, protein Melan-A, CD34, synaptophysin, chromogranin, desmin, muscle specific actin, ETFA (EMA), KRT20 (CK20), CDX2, TTF1, LNPEP (PLAP), inhibin, α-fetoprotein, CD30, hepatocyte paraffin, and aberrant expression of cytokeratin 7 and pankeratin. The pathological diagnosis was consistent with adrenal angiosarcoma. Obtaining appropriate immunoperoxidase stains and multidisciplinary evaluation helped make the diagnosis of this rare adrenal tumor and determine its management. The patient had an uneventful postoperative course and completed 4 cycles of adjuvant chemotherapy with doxorubicin/ifosfamide and adequately tolerated the treatment. However, positive surgical margins were found, so he was referred to radiation oncology specialists for possible adjuvant radiotherapy to the surgical bed. Weeks after the first initiation of therapy, the patient presented to the emergency department complaining of shortness of breath, fatigue, and generalized weakness for 3 days. He was admitted and found to have new-onset anemia and a new-onset, large, right pleural effusion. Thoracentesis performed showed sanguinolent fluid that, after microscopic evaluation, was suggestive of recurrent malignancy. Thoracic aortography performed with subselective catheterization to several arteries (right bronchial, right phrenic, and right renal arteries) did not show any active bleeding. However, the right inferior intercostal and adrenal arteries were presumed to be the reason for the bleeding event, so they were embolized until stasis. The patient remained hemodynamically unstable but eventually experienced multiorgan failure. In spite of aggressive measures, he died 10 days after admission to the hospital.

Background
Adrenal masses are incidentally found on computed tomography (CT) of the abdomen (so-called “incidentalomas”) approximately 4% of the time and in 8% in autopsy series.1 Up to 80% are benign adenomas.2 Patients in whom a high suspicion of malignancy exists due to the clinical picture or the presence of clinically evident overt adrenal disease are excluded from the definition of incidentaloma and should be thoroughly evaluated. It is important to distinguish benign from malignant processes, especially differentiating functioning vs nonfunctioning tumors.1 Patients with benign adenomas can be clinically followed, whereas patients with entities such as adrenocortical carcinoma, pheochromocytoma, primary aldosteronism, and cortisol-producing tumors (Cushing syndrome), will require surgical evaluation.1 In 2002, a consensus of the National Institutes of Health recommended excision in all masses larger than 6.0 cm and to observe clinical judgement in those between 4 and 6 cm in size.1,3 All adrenal masses larger than 1.0 cm in size (excluding myelolipomas, hemorrhages, and cysts) should undergo thorough clinical, radiological, and hormonal testing at the patient’s initial presentation to distinguish malignant and hyperfunctioning masses from benign masses. Those that are hyperfunctional or indicative of malignancy (attenuation value < 10 HU by CT) should be evaluated for surgical removal. Percutaneous adrenal biopsy has high false-negative rates and puts patients at risk for complications.4 The only role this procedure plays is confirmation of metastatic disease in patients with known cancer or confirmation of the diagnosis of adrenal cortical carcinoma when resection is not feasible.5

Angiosarcomas make up less than 1% of soft-tissue sarcomas; they are malignant tumors that arise from the endothelium of blood vessels and, in addition to soft tissue, commonly occur in the breast, skin, spleen, bone, and liver.6,7 The survival rate at 5 years is 24% to 31%.6,7 Twenty-two cases of adrenal angiosarcomas
Pathological diagnosis is difficult because the aberrant expression of cytokeratin (CK) can lead physicians to misdiagnose metastatic carcinoma of the adrenal gland. Immunohistochemical staining for vascular markers with CD34, FLI1, CD31, factor VIII, and CD34 are necessary for the diagnosis.7

In 1988, Kareti et al8 described the first case of adrenal angiosarcoma in a 54-year-old man with long-term left upper quadrant pain. Although angiosarcomas are generally aggressive, long-term survival has been recorded.9 Adrenalectomy is the only treatment available, but the benefits of resection, the role of adjuvant radiotherapy, and the timing of radiotherapy have not yet been determined.

Case Report
A US veteran aged 69 years with a medical history significant for controlled hypertension and diabetes mellitus (diagnosed in 2003) presented to the emergency department in May 2015 due to acute right flank pain. He explained that he had been having vague discomfort for the last 2 months and recently acute-onset, right flank pain several hours before his presentation. He said that the pain did not resolve with bed rest and acetaminophen. He rated the pain as being an 8 on a scale of 0 to 10 in intensity (with 10 being the worst), and it radiated to his right inguinal area and worsened upon ambulation. In the past 2 months, he had been unintentionally losing weight. He denied flushing, dizziness, bouts of hypertension, nervousness, palpitations, diarrhea, nausea/vomiting, change in bowel habits, diaphoresis, headache, or any other complaints. He was employed as a driver and denied any occupational exposure to toxic substances. He also denied any use of alcohol or tobacco. He had no personal or family history of cancer.

On physical examination, he was alert, oriented, cooperative, and was in acute pain. His blood pressure was 145/74 mm Hg (no postural changes) and his pulse was 100 beats/minute (regular). His lungs were clear, no murmur was heard, and visceromegaly was absent. He had right-sided abdominal pain on deep palpation but experienced no rebound tenderness. Peristalsis was adequate. Findings on the neurological examination were unremarkable. Electrocardiography was obtained, the findings of which revealed sinus tachycardia.

Abdominal CT was performed and showed a right adrenal mass lesion 16.4 × 9.1 × 9.5 cm in size with adjacent retroperitoneal hematoma, reaching the right kidney and right renal vein. The mass had attenuation values higher than the liver (39 HU). He had no intra-abdominal adenopathy (Fig 1). The Table includes a list of the laboratory values obtained.

The patient’s pain improved after he was treated with analgesics. After negative findings following a workup for a hyperfunctioning tumor, he underwent exploratory laparotomy in June 2015 because of the size of the lesion and its radiographical appearance as well as the manifestations of unintentional weight loss and pain. During exploratory laparotomy, a large, right adrenal mass was found that rounded the inferior vena cava, with preserved right kidney artery and vein. En bloc resection was performed to repair the inferior vena cava.

Findings on pathology were consistent with a right hemorrhagic mass 10.0 cm in size with positive margins and associated hematoma and mitosis (Fig 2A). Results on immunohistochemistry were positive for factor VIII and CD31 (Fig 2B) and negative for S100, protein Melan-A, CD34, synaptophysin, chromogranin, no rebound tenderness. Peristalsis was adequate. Findings on the neurological examination were unremarkable. Electrocardiography was obtained, the findings of which revealed sinus tachycardia.

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<table>
<thead>
<tr>
<th>Study</th>
<th>Value</th>
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<tbody>
<tr>
<td>Norepinephrine</td>
<td>464 pg/mL (normal range, 112–658)</td>
</tr>
<tr>
<td>Free metanephrines</td>
<td>&lt; 25 pg/mL (normal &lt; 57)</td>
</tr>
<tr>
<td>Total metanephrines</td>
<td>48 pg/mL (normal &lt; 148)</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>6 ng/dL (normal &lt; 28 [upright])</td>
</tr>
<tr>
<td>Plasma renin activity</td>
<td>0.34 ng/dL (normal range, 0.25–5.82)</td>
</tr>
<tr>
<td>Adrenocorticotropic hormone</td>
<td>15 pg/mL (normal range, 6–50)</td>
</tr>
<tr>
<td>Cortisol</td>
<td>23 μg/dL</td>
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desmin, muscle specific actin, 
ETFA (EMA), KRT20 (CK20), 
CDX2, TTF1, LNPEP (PLAP), in-
hibin, α-fetoprotein, CD30, he-
patocyte paraffin, and aberrant 
expression of cytokeratin 7 and 
pankeratin (Fig 2C).

Results from the immuno-
peroxidase study excluded mel-
anoma, pheochromocytoma, 
adrenal cortical carcinoma, and 
metastases with a pulmonary, 
gastrointestinal, liver, and germ 
cell origin. The final patho-
logical diagnosis was a cystic, 
malignant, epithelioid, mesen-
chymal neoplasm consistent 
with adrenal angiosarcoma 
(Figs 2D and 2E).

The patient had an un-
eventful postoperative course 
and completed 4 cycles of ad-
juvant chemotherapy with 
doxorubicin/ifosfamide with 
adequate tolerance. Positron 
emission tomography/CT per-
formed 3 and 6 months after 
surgical resection did not iden-
tify any significant flurodeox-
yglucose-avid lesions. Positive 
surgical margins were found, 
so he was referred to radiation 
oncology specialists for pos-
sible adjuvant radiotherapy to 
the surgical bed. Thoracic and 
abdominopelvic CT performed 
1 year following the resection 
did not show any evidence of 
disease recurrence. He was 
then evaluated again by radia-
doncology specialists and 
consented to undergo adjuvant 
radiotherapy.

Some weeks after the ini-
tiation of therapy, the patient 
presented to the emergency de-
partment complaining of short-
ness of breath, fatigue, and 
generalized weakness with a 
duration of 3 days. He was ad-
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with subselective catheterization to several arteries  
(right bronchial, right phrenic, and right renal) and did 
not show any active bleeding. However, the right infe-
rior intercostal and adrenal arteries were suspected to 
be the cause of the bleeding event, so they were embo-
lized until stasis. The patient remained hemodinamically unstable, but he experienced multiorgan failure. Despite undertaking aggressive measures, he died 10 days after his admission to the hospital.

**Discussion**

Diagnosing primary angiosarcomas of the adrenal gland can be challenging to the clinician because of the rarity of these soft-tissue sarcomas. Few cases have been reported (22 in the English-language literature between 1988 and 2013), and most have been single-case reports. The largest series (9 cases) comes from Wenig et al of the Armed Forces Institute of Pathology.

The etiology of adrenal angiosarcoma is unknown, but it has been associated with exposure to arsenic-containing insecticides. Another report concerns a person aged 68 years who was employed at a factory and had been exposed to vinyl chloride for 15 years. No case, including ours, had a history of multiple endocrine neoplasia syndrome. Our patient also had no known history of toxic exposure.

Adrenal angiosarcoma occurs more frequently in men in the sixth and seventh decades of life than in younger men or women of any age. The most commonly reported symptom is pain combined with the finding of an abdominal mass.

None of the reported cases had hyperfunctioning tumors. Tumors ranged in size from 5 to 10 cm and were solid to cystic in appearance, similar to our case. Initial microscopic examination of nearly all relevant cases in the medical literature revealed an epithelioid appearance. Most immunohistochemical findings were positive for keratins, making it difficult to confirm our diagnosis. Obtaining a wide immunohistochemical panel is required for a successful pathological diagnosis.

Adrenal angiosarcomas are high-grade tumors that have the capacity to infiltrate and metastasize to distant organs. The data are limited in the use of adjuvant therapy after surgical resection. Surgical eradication appears to have a good outcome in more than 50% of patients. Due to their aggressive biology, use of adjuvant therapy for the management of adrenal angiosarcomas has been advised. For example, Rodriguez-Pinilla et al reported in 2002 on 5 cases with disease that had metastasized to the bone, liver, lung, and pleura.

Diagnosing primary angiosarcomas of the adrenal gland is made difficult for pathologists and other health care professionals for several reasons. Necrosis and hemorrhage associated with cystic changes make it challenging to identify the primary focus. In addition, other neoplasias, including pheochromocytomas and cortical adenomas, have been associated with cystic components. Thus, an experienced clinician must pay detailed attention to the gross specimen and take into account identification of the solid component of the angiosarcoma. By contrast to most angiosarcomas with a histological vasoformative pattern, most primary adrenal gland angiosarcomas have a solid epithelioid pattern. Positive immunoreactivity to cytokeratins, a marker of epithelial tumors, can lead to an incorrect diagnosis of metastatic epithelial tumor. For a definitive diagnosis, in addition to the clinical and radiographical presentation, the pathologist must perform a wide immunohistochemistry panel to establish the diagnosis. A definitive diagnosis also requires immunohistochemical staining for vascular markers such as CD31, CD34, FLI1, and factor VIII.

**Conclusions**

Our case report illustrates the need for multidisciplinary evaluation by clinicians, radiologists, surgeons, and pathologists in order to diagnose primary adrenal angiosarcomas and provide these patients with adequate therapy. Surgical excision is the treatment of choice. The irregular, histological attributes of these angiosarcomas, as well as their low incidence rate, can lead to an incorrect diagnosis. The diagnosis should be confirmed by immunohistochemistry panels after clinical suspicion is prompted by the patient's clinical and radiographical presentation.

**References**