Aortic Intimal Sarcoma Contributes to Atherosclerotic Renovascular Hypertension: An Autopsy Case Report and Review of the Literature

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Abstract

An autopsy of a 70-year-old man with multiple bone metastases from a malignancy of unknown origin (MUO) and renovascular hypertension revealed an aortic intimal sarcoma (AIS) in the right renal artery accompanied by atherosclerotic changes. AIS appeared as aggregated mutton fat-like translucent particles arising from the intima of the branching portion of the right renal artery and was composed of undifferentiated, fine spindle cells with thicket-like proliferation. AIS was confirmed by immunohistopathology, showing the loss of the lumen lined by CD31-positive endothelium and the expression of CD31, keratin, and vimentin in the viable part of the tumor. In patients with MUO presenting with both bone metastases and an acute or sub-acute onset of renovascular hypertension, AIS in the renal artery may be responsible.

Key words: aortic intimal sarcoma (AIS), renovascular hypertension (RVHT), malignancy unknown origin (MUO)

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Introduction

Renovascular hypertension (RVHT) is one of the causes of secondary hypertension. Although the main etiologies of RVHT are atherosclerosis, fibromuscular dysplasia, and aortitis (1), Weinberg et al. reported that severe hypertension can be a prominent clinical feature associated with primary tumors of the aorta, causing obstruction of the aorta or renal artery or both (2). In fact, 10 cases of intraluminal sarcoma of the aorta resulting in RVHT have been reported to date (3-8).

In cases of malignancy of unknown origin (MUO) and RVHT, particularly cases with an acute or sub-acute onset of RVHT, it is important to consider narrowing of one or both renal arteries caused by the spread of aortic intimal sarcoma (AIS). Since AIS frequently presents with thromboembolic complications, it is commonly misdiagnosed as atherosclerotic disease (7). Therefore, it is important to rigorously search for intravascular lesions in the clinical evaluation of cases of MUO.

We herein report an autopsy case in which AIS contributed to atherosclerotic RVHT, and we review the relevant literature.

Case Report

In March 2010, a 70-year-old Japanese man was trans-
Table 1. Summary of the Investigations Performed. All Positive and Relevant Negative Results Are Shown.

<table>
<thead>
<tr>
<th>CBC on admission:</th>
<th>Uринalysis on admission:</th>
<th>Endocrinology 87 days before admission:</th>
<th>Echocardiogram 95 days before admission:</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC 9.620 /μL</td>
<td>Specific gravity 1.016</td>
<td>TSH 1.27 μU/mL</td>
<td>AOD 31.6 mm</td>
</tr>
<tr>
<td>RBC 192×10⁶ /μL</td>
<td>Protein —</td>
<td>Free thyroxine 0.95 ng/dL</td>
<td>LAD 52.1 mm</td>
</tr>
<tr>
<td>Hb 5.7 g/dL</td>
<td>Sugar —</td>
<td>Plasma renin activity 6.8 ng/mL/hr</td>
<td>LVPW 15.1 mm</td>
</tr>
<tr>
<td>Hematocrit 16.1 %</td>
<td>Occult blood —</td>
<td>Aldosteron 21.8 ng/dL</td>
<td>LVDd 52.3 mm</td>
</tr>
<tr>
<td>Platelet 16.1×10⁶</td>
<td>Keton ±</td>
<td>Metanephrine (pooled urine) 0.04 μg/day</td>
<td>Metanephrine (pooled urine) 0.12 μg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biochemistry on admission:</td>
<td>Tumor makers on admission:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total protein 6.0 g/dL</td>
<td>CEA 0.5 ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin 3.4 g/dL</td>
<td>CA19-9 9.7 U/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDH 123 U/L</td>
<td>SCC 1.3 ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALP 176 U/L</td>
<td>PSA 5.8 ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP 0.25 mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na 134 mmol/L</td>
<td>BNP series:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K 5.4 mmol/L</td>
<td>3 months before admission 334.6 pg/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CI 102 mmol/L</td>
<td>Hospital day 30 162.2 pg/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ca 8.8 mg/dL</td>
<td>IVC diameter (inspiration) 24.1 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP 6.2 mg/dL</td>
<td>IVC diameter (expiration) 14.6 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUN 157 mg/dL</td>
<td>TR-IPG 55.0 mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine 4.92 mg/dL</td>
<td>Mitral valve regurgitation severe</td>
<td></td>
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</tr>
</tbody>
</table>


ported to the emergency department of our medical center due to massive hematemesis requiring four units of blood transfusion. An actively bleeding gastric ulcer was found at the lesser curvature of the stomach and was clipped endoscopically. He then underwent further examination and treatment.

The patient had previously undergone transurethral resection of the prostate for benign prostatic hypertrophy at 57 and 62 years of age. He also received skin ablative therapy for Paget disease, which affected the base of the penis, at 66 and 62 years of age. In addition, he smoked 20 cigarettes per day between 20 and 65 years of age.

Six months prior to admission, the patient had a high prostate specific antigen level (7.0 mg/dL) at his annual health checkup by a family physician. At that time, the serum creatinine level (Scr) was 1.00 mg/dL. He was found to have hypertension for the first time and antihypertensive medication was started. Four months prior to admission, gadolinium (Gd)-enhanced pelvic magnetic resonance imaging (MRI) and bone scintigraphy at a cancer center revealed multiple abnormal lesions at the lumbar spine, pelvic bone, and both femurs, but no prostatic malignancy. A tentative diagnosis of multiple bone metastases from MUO was made at this time.

Three months prior to admission at our center, the patient, who was being treated by his family physician with amiodipine (5 mg/day) and candesartan (8 mg/day), was admitted to another medical center with acute congestive heart failure due to severe mitral valve regurgitation as evaluated by two-dimensional echocardiography (Table 1). After stopping both amiodipine and candesartan, treatment was begun with furosemide (40 to 80 mg/day) and low-dose carperitide (0.02 μg/kg/minute) and perindopril (1 mg/day). A high plasma renin activity (6.8 ng/mL/hour) was noted on hospital day 9 while under treatment with furosemide (80 mg/day). Congestive heart failure and hypertension responded to furosemide (80 mg/day), spironolactone (25 mg/day), azelnidipine (16 mg/day), and bisoprolol (5 mg/day). The patient’s clinical course concerning the blood pressure, Scr level and both hypoventilation and respiratory rate, 18 breaths/min. The conjunctivae were pale and there were no rales or heart murmur despite a history of mitral valve regurgitation, no abdominal tenderness or pretibial edema, an autodermic graft at the base of the
penis, right hip tenderness, a skin harvest scar at the right femoral area, and no superficial lymphadenopathy. A digital rectal examination revealed an elastic, hen’s egg-sized prostate that was diffusely hard without any nodular induration.

A summary of all the positive and relevant negative data is shown in Table 1. Chest radiography showed no cardiomegaly, pleural effusion, or pulmonary congestion, and the electrocardiogram was normal. We carefully reviewed the imaging findings with the radiologists obtained before admission and found on enhanced CT bilateral atrophic kidneys, renal-artery stenoses and irregular thickness of the wall of the abdominal aorta (Fig. 2). There were no abnormal accumulations of FDG in these lesions (Fig. 3). High echogenicity of the bilateral renal cortex and both stenoses and high blood flow patterns at the origin of bilateral renal arteries were detected by abdominal ultrasonography (Fig. 4). Repeated plain pelvic MRI revealed the progression of bone metastases (Fig. 5).

A pathological examination of a CT-guided fine needle biopsy of a tumor site in the left iliac bone revealed a spindle-celled tumor mixed with collagen fibers. The histological pattern of the tumor cells exhibited malignant features without any differentiation (Fig. 6).

We decided against chemotherapy because of the patient’s renal function, cardiac condition, and a life expectancy estimated to be short due to the multiple bone metastases. Additional candesartan therapy (4 mg/day) caused a marked rise in the Scr level from 1.67 mg/dL on hospital day 5 to 6.0 mg/dL on hospital day 27, although the earlier use of candesartan was not associated with this adverse effect. The Scr level improved to 1.96 mg/dL on hospital day 37 after discontinuation of candesartan. Due to right inguinal pain on walking, palliative focal radiotherapy to the right femur and oxycodone (10 mg/day) were administered. Significant oliguria, which developed on hospital day 53, and a progressively increasing blood pressure were treated with intermittent intravenous nitroglycerin (0.27 μg/kg/min), furosemide (80 mg/day), and carperitide (0.02 μg/kg/min) after hemodialysis was initiated on hospital day 59. Hemodialysis three times a week was continued and the patient was discharged on hospital day 76 on omeprazole (20 mg/day), long-acting nicardipine (40 mg/day), doxazosin (2 mg/day), and furosemide (80 mg/day).

Two months later, whole-body MRI was repeated with the use of diffusion-weighted whole body imaging with background body signal (DWIBS) and showed multiple bone metastases at the sternum, both humeri, vertebrae, pelvis, and both femurs, multiple vertebral compression fractures and a pathological right femoral neck fracture (Fig. 7), but failed to detect a primary lesion.

Unfortunately, five months later, he was readmitted to our facility with a precipitous onset of pain in the pelvis, both thighs, thoracic spine, and loin. He could not walk anymore because of severe pain due to the pathological right femoral neck fracture. Epidural block and palliative radiotherapy for the right femur were not effective for pain relief. The patient
An autopsy revealed mutton fat-like clots blocking the intravascular lumen of the right renal artery (Fig. 8). This lesion arose from the intima of the branching portion of the right renal artery. Atherosclerotic stenosis (75%) was found at the left renal artery and the media and adventitia of the aorta were intact. Moderate to severe atherosclerotic changes were seen in the luminal face of the abdominal aorta and the branching area of both renal arteries. Elastic yellow-brown colored masses were seen in the spine, ilia, and femurs. No other metastases or recurrence of Paget disease were found.

Histologically, the clots consisted of undifferentiated fine spindle-celled tumor cells with thicklet-like proliferation. Immunohistopathology (Fig. 9) of the right renal artery revealed the loss of nearly the entire lumen lined by a CD31-positive endothelium. CD31, keratin, and vimentin were expressed in the viable part of the tumor, a staining pattern similar to that of endothelial cells. The media was positive for α-smooth muscle actin (α-SMA). The mutton fat-like material occluding the right renal artery was diagnosed as AIS. Two-thirds of the clot was AIS, including coagulative necrosis, while the remainder was determined to be atherosclerosis.

According to the autopsy findings, we concluded that stenoses caused by AIS of the right renal artery and bilateral renal-artery atherosclerosis were likely to have contributed to RVHT.
Primary aortic sarcomas account for less than 1% of all sarcomas (9). Furthermore, AIS, a type of primary aortic sarcoma, is extremely rare (10). Primary aortic sarcomas are classified into the intimal type, which originates from the endothelium, and the mural type, which originates from the media or adventitia. This classification depends on both the location and immunohistochemical pattern of the tumors (11). AIS progresses insidiously and tends to spread widely along the lumen, obstructing all branches of the renal artery.

Figure 4. Two-dimensional ultrasonography shows stenosis at the origin of both the right renal artery (A: solid red arrow) and the left renal artery (C: solid white arrow), high echogenicity of both renal cortices, and bilateral renal atrophy; the long axis of the right kidney measures 90 mm and the left kidney 82 mm. The blood flow detected by color-flow Doppler ultrasonography was 154 cm/sec- ond maximum velocity at the origin of the right renal artery (B) and 51 cm/second maximum velocity at the origin of the left renal artery (D). The estimation of maximum velocity at the origin of the left renal artery was poorly-reproducible, because of sparse blood signals at the interlobar arteries of the left kidney. The dotted white arrows indicate the abdominal aorta.

Figure 5. Coronal views of both T1-weighted (A) and T2-weighted (B) magnetic resonance images of the abdominopelvic cavity show multiple abnormal low intensity lesions of the lumbar spine, pelvis, and both femurs.

Discussion

Primary aortic sarcomas account for less than 1% of all sarcomas (9). Furthermore, AIS, a type of primary aortic sarcoma, is extremely rare (10). Primary aortic sarcomas are classified into the intimal type, which originates from the endothelium, and the mural type, which originates from the media or adventitia. This classification depends on both the location and immunohistochemical pattern of the tumors (11). AIS progresses insidiously and tends to spread widely along the lumen, obstructing all branches of the renal artery. The dotted white arrows indicate the abdominal aorta.
aorta (12); the most common location is the abdominal aorta (13). An acute or sub-acute embolus and obstruction or stenosis of any vessel are indicative of AIS. On the other hand, the mural type usually extends extramurally to the para-aortic tissues and lymph nodes (11).

The prognosis for aortic intimal sarcoma is quite poor, with a mean survival period of approximately one year (14). The value of treatment for AIS with antineoplastic agents or radiation remains controversial. If metastasis is limited to one organ, however, then resection should be considered in order to achieve both an improved disease-free survival and overall survival (10). Disseminated metastases may be managed with observation or, if palliative therapy is a consideration, palliative radiation therapy including proton ther-

Figure 6. Tissue specimen obtained via a computed tomography-guided fine needle biopsy of the tumor site in the left iliac bone stained with Giemsa (A: original magnification, 40×) and silver staining (B: original magnification, 40×). Spindle cells mixed with collagen fibers are shown. The histological pattern of tumor cells shows malignant features without any differentiation.

Figure 7. Magnetic resonance imaging with the use of diffusion-weighted whole body imaging with background body signal (MRI-DWIBS) shows multiple bone metastases at the sternum, both humeri, vertebrae, pelvis, and both femurs, multiple vertebral compression fractures (dotted white arrows) and a pathological right femoral neck fracture (solid white arrow), but failed to detect any primary lesion.
Figure 8. Inner (A) and outer (B) aspects of the abdominal aorta and the branches (thick black arrow: right renal artery; thin black arrow: left renal artery; dotted black arrow: superior mesenteric artery) are shown. The intravascular lumen of the right renal artery is blocked by mutton fat-like clots (white star). Moderate to severe atherosclerotic changes are seen in the luminal face of the abdominal aorta and the branching area of both renal arteries.

Figure 9. Autopsy specimens of the right renal artery with the mutton fat-like clots immunostained with antibodies against keratin (A: original magnification, 4×), vimentin (B: original magnification, 4×), CD31 (C: original magnification, 4×), and α-smooth muscle actin antibodies (α-SMA) (D: original magnification, 4×). Immunohistochemical findings show almost an entire loss of the lumen (black arrows) lined by a CD31-positive endothelium. Positivity for keratin, vimentin, and CD31 expression is seen in the viable part of the tumor. α-SMA is positive in the media (red arrows).
Table 2. Case Reports of Renovascular Hypertension Caused by an Intraluminal Sarcoma of the Aorta.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Presentation</th>
<th>Primary tumor site</th>
<th>Renal artery involvement</th>
<th>Histopathology</th>
<th>Immunohistochemistry</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>Autopsy</th>
<th>Involvements and Metastasis</th>
<th>Reference number</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>44</td>
<td>M</td>
<td>Lumbar, Hypertension, General fatigue, Dyspnea, Intermittent claudication, Anorexia</td>
<td>Abdominal aorta</td>
<td>No record</td>
<td>High-grade epitheloid angiosarcoma</td>
<td>CD31 +</td>
<td>descending thoracic aortic intimal sarcoma, Hemodialysis, Local radiation, hemodialysis, splenectomy</td>
<td>5 months +</td>
<td>-</td>
<td>Common hepatic artery, Multiple infarcts in both kidneys, Bowel</td>
<td>6</td>
</tr>
<tr>
<td>50</td>
<td>82</td>
<td>F</td>
<td>Escalating systolic hypertension</td>
<td>Abdominal aorta</td>
<td>No record</td>
<td>High-grade epitheloid angiosarcoma</td>
<td>CD31 +</td>
<td>descending thoracic aortic intimal sarcoma, Hemodialysis, Local radiation, hemodialysis, splenectomy</td>
<td>16 months +</td>
<td>-</td>
<td>Common hepatic artery, Multiple infarcts in both kidneys, Bowel</td>
<td>7</td>
</tr>
<tr>
<td>59</td>
<td>56</td>
<td>M</td>
<td>New onset of refractory hypertension, Significant weight loss</td>
<td>Abdominal aorta</td>
<td>No record</td>
<td>High grade pleomorphic intimal sarcoma</td>
<td>No record</td>
<td>Aortic arch and upper half of the descending thoracic aortic replacement, brachiocephalic debranching, radiation, adjuvant chemotherapy</td>
<td>9 months +</td>
<td>-</td>
<td>Brain, lung, liver</td>
<td>7</td>
</tr>
<tr>
<td>41</td>
<td>70</td>
<td>M</td>
<td>Refractory hypertension, Elevated creatinine of 4.0 mg/dL</td>
<td>Abdominal aorta</td>
<td>No record</td>
<td>High grade pleomorphic intimal sarcoma</td>
<td>No record</td>
<td>Aortic arch and upper half of the descending thoracic aortic replacement, brachiocephalic debranching, radiation, adjuvant chemotherapy</td>
<td>5 months +</td>
<td>-</td>
<td>SMA, IMA, Bones (pelvis, sacrum, bilateral femoral diaphyses)</td>
<td>8</td>
</tr>
<tr>
<td>70</td>
<td>70</td>
<td>M</td>
<td>Elevated PSA, Bone metastases, Congestive heart failure, Mitral valve regurgitation, High renin hypertension</td>
<td>Abdominal aorta</td>
<td>Right</td>
<td>Aortic intimal sarcoma</td>
<td>CD31+, Vimentin +, Keratin +, a-SMA -</td>
<td>Hemodialysis, Antihypertensive therapy drugs, Oxyxodone, local radiation</td>
<td>5 months +</td>
<td>-</td>
<td>Bone (iliac fossa)</td>
<td>5</td>
</tr>
</tbody>
</table>

apy (15), chemotherapy, or palliative surgery. There are currently no combination chemotherapy recommendations for AIS. Radiation therapy with adjuvant doxorubicin and ifosfamide chemotherapy is associated with a response rate of up to 20% (14, 16). Recently, Dewaele et al. reported the potential of molecular target treatment against the genes coding for platelet-derived growth factor receptor-α (PDGFRA), epidermal growth factor receptor (EGFR), or MDM2 in AIS (17).

The clinical course of the patient herein described presents two important issues. First, AIS is difficult to diagnose. Second, AIS can cause RVHT.

The diagnosis of AIS is difficult, both because it is rare and because it is often difficult to distinguish AIS from atheromatous lesions. Though bone metastases are common with AIS, they are hard to diagnose by a bone biopsy alone, particularly in cases of undifferentiated type lesions. Thus, it is important to make an effort to detect intravascular masses through imaging studies. Recently, the advantages of MRI for diagnosing AIS have been reported by von Falck et al. who demonstrated that a pedunculated or lobulated appearance and subtle enhancement during first-pass perfusion were consistent with AIS (18). Regrettably, Gd-enhanced MRI, which was performed in our patient, did not focus upon the origins of the renal arteries, which could have detected the primary lesion at the right renal artery bifurcation area. In addition, FDG-PET/enhanced CT or MRI-DWIBS failed to yield findings indicative of AIS. The FDG uptake has been reported to be poor in intimal sarcomas (18, 19).

We performed a bone biopsy, but this was not sufficient to confirm the diagnosis due to the undifferentiated pattern seen upon the pathological examination, the lack of a highly specific immunostaining marker, and the lack of clinical information regarding the primary lesion. A three-reagent immunohistochemical panel of CD31, CD34, and von Willebrand factor is recommended, as it has a higher sensitivity and specificity in identifying endothelial differentiation than any individual marker (20). Positivity for CD31 and von Willebrand factor, but not CD34, is indicative of intravascular malignancy (20). The retrospective immunohistochemical findings of the needle biopsy specimen of this patient showed strong positive staining for CD31, vimentin, and keratin, together with negative staining for both CD34 and α-SMA. These results suggest that the bone lesions were metastases of AIS.

Our case also highlights that AIS can cause RVHT. The accelerated rise of the Scr level after the second course of candesartan therapy was suggestive of RVHT due to progressive stenosis of the renal artery (21) since the Scr level did not change after the administration of candesartan or perindopril earlier in the clinical course (Fig. 1).

RVHT caused by any intraluminal sarcoma of the aorta is extremely rare, as there have been only 10 reported cases (3-8) (Table 2) since the first description by Kattus in 1960 (3). Severe or refractory hypertension was a prominent clinical feature in all 10 cases. In our patient, the first clinical findings were prostate specific antigen elevation, hypertension and multiple bone metastases; subsequently, congestive heart failure due to severe mitral valve regurgitation developed and RVHT. Among previously reported cases, the primary sites included the thoracoabdominal aorta in four cases, aortic arch in three cases, and abdominal aorta in three cases. Hypertension with these sarcomas was attributed to the obstruction of at least one renal artery, obstruction of the aorta, or a combination of the two. The histological findings demonstrated the intimal type sarcoma in four cases, leiomyosarcoma in two cases, and one case each of fibromyxosarcoma, hemangioendotheliosarcoma, and epithelioid angiosarcoma. The histological diagnosis of case no. 5 was unknown for technical reasons. Immunohistochemistry showed no consistent patterns. Although the treatments selected were thought to be appropriate, the prognoses were extremely poor. Similar to our patient, bone metastasis was found in four cases. Therefore, in patients who develop RVHT and have a MUO, the possibility of AIS should be seriously considered.

In conclusion, although it is often difficult to identify the primary location of sarcomas in patients with a MUO, physicians should consider the possibility that RVHT could be due to AIS rather than atherosclerosis, fibromuscular dysplasia, or aortitis, and may require a thorough investigation for intravascular lesions around the renal arteries.

The authors state that they have no Conflict of Interest (COI).

References


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