RESIDENT'S CORNER

Renal angiosarcoma: a case report and literature review

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Purpose: *In adults renal cell carcinoma (RCC) accounts for over 85% of all diagnosed renal cancers. A much more rare and aggressive malignant tumor of the kidney is angiosarcoma (AS) with less than 25 cases described internationally. Both RCC and AS have similar radiological appearances and thus require histological evaluation for definitive diagnosis. We present a case of renal AS in a 63-year old male who was initially radiologically diagnosed as RCC, and review the current renal AS literature.*

Methods: *The current English literature from 1981 and onwards on renal AS was reviewed and compared to our current case.*

Results: *The median age and sex of patients with renal AS at presentation was 63 years old (mean 61 years) and common in males with a left kidney predominance. Symptoms included flank pain, palpable mass, and hematuria with imaging suggestive of RCC. Hematogenous metastatic spread often occurred with median survival time of 3.5 months from time of diagnosis (mean 5.8 months). Histologically, the tumors have classical features of angiosarcoma with numerous blood-filled vascular spaces lined by plump pleomorphic endothelial cells with CD31 and CD34 staining positivity. Overall treatment was radical nephrectomy with radiation therapy for local control and metastases. The use of chemotherapy was not consistent.*

Conclusion: *Although RCC accounts for the majority of malignant renal tumors, the poor prognosis of AS and its similar radiological appearance to RCC imparts the importance of histological evaluation and the potential radiological mimicry of AS.*

Key Words: renal cell carcinoma, renal angiosarcoma

Introduction

In adults renal cell carcinoma (RCC) accounts for over 85% of all diagnosed renal cancers. A much more rare and aggressive malignant tumor of the kidney is angiosarcoma (AS) with approximately 25 cases described internationally.[1,2]

The prognosis of AS is uniformly fatal with widespread metastases and World Health Organization (WHO) reported mean survival of 7.7 months.[2] Since RCC and AS both have similar computed tomographic (CT) radiological appearances,[3] histological evaluation is required for definitive diagnosis and subsequent treatment.[4]

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We present a case of AS in the kidney in a 63-year old male, which was initially thought to be a RCC, and provide a brief comparison and review of the current literature on renal AS.

Methods

An exhaustive literature search, including a Medline search from 1942 to July 2006 was done for "renal angiosarcoma". Since the histological diagnosis and pathogenesis of renal AS has changed with the advent of immunohistochemistry and with changing epidemiological factors (such as occupational chemical exposure), only English articles from 1981 were included in an attempt to represent a more balanced current view of renal AS. Our current case was included to provide a general review of renal AS in terms of patient demographics, clinical presentation, tumor size/side, histology, initial diagnosis, metastasis, treatment, and survival time.

Results

Case history

A 63-year old male initially presented with a pathological fracture of the left clavicle, Figure 1a, and left abdominal mass. He denied left flank pain and hematuria. He has no smoking or occupational history of chemical exposure. Nuclear bone scan showed non-specific findings of the left clavicle. Follow up CT studies revealed an approximately 18 cm mass in the upper pole of the left kidney, Figure 1b, multiple bony metastases to the right petrous apex and clivus, thoracic spine, multiple ribs bilaterally, possible lung metastases, and hepatic metastatic disease. His INR was 1.2, PTT 31, and platelets were elevated at 287. Na 133, K 4.3, Cl 96, HCO_3 31, and Cr 88. Clinical diagnosis of RCC was concluded and the patient underwent a left radical nephrectomy. Histological examination of the kidney mass revealed angiosarcoma. The patient received radiation therapy for painful bone metastases, and

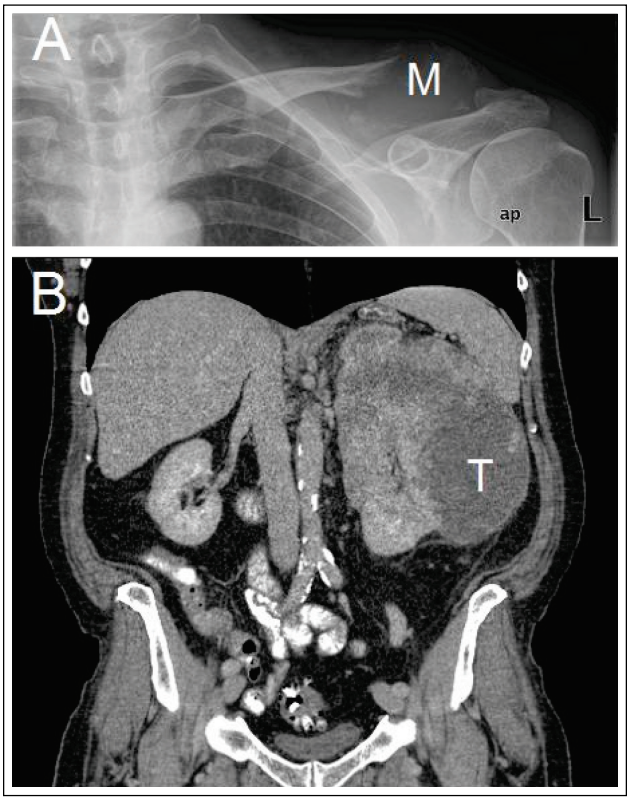

Figure 1. a) Radiograph of left clavicle showing metastatic bone lesion (M) in distal clavicle. b) CT coronal slice of abdomen and retroperitoneum showing left renal tumor (T) (18 cm). Note normal right kidney and calcified abdominal aorta.

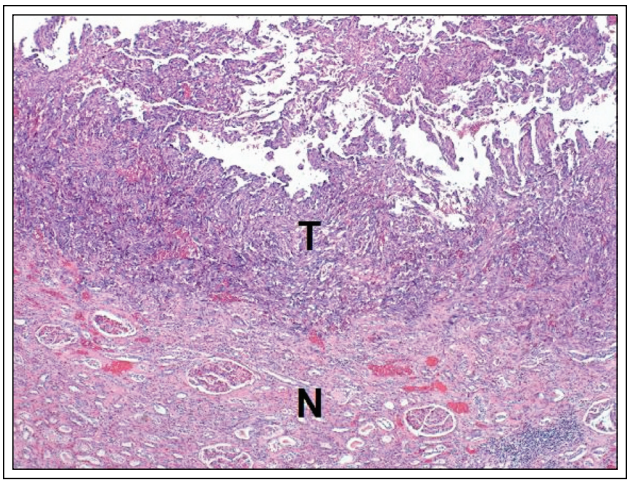

Figure 2. Low power photomicrograph of the renal tumor (T) showing features of AS, note the complex anastomosing blood-filled vascular spaces involving the normal renal cortex (N) (H&E, x88)

died approximately 4 months after diagnosis with enlarging metastases and new colonic spread. No chemotherapy was given. Autopsy was not performed.

Pathological findings

The left nephrectomy specimen weighed 2792 g and measured 23.0 cm x 15.0 cm x 14.0 cm in greatest dimension. On gross examination the outer surface

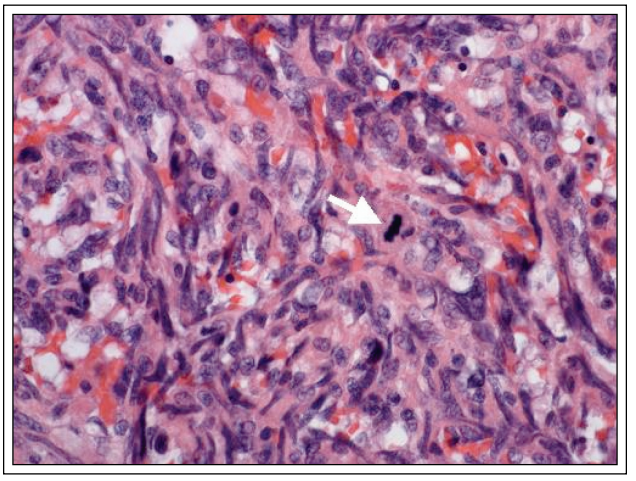

Figure 3. High power photomicrograph of the renal tumor showing features of AS, with solid poorly-differentiated areas of plump endothelial cells. Tumor cell nuclei were spindle-shaped with moderate nuclear pleomorphism and frequent mitoses (arrow). (H&E, x880)

had hemorrhagic adhesions. On cut section, a large hemorrhagic mass measuring 15.0 cm x 14.0 cm x 11.0 cm occupied the upper and mid-portion of the left kidney. The centre of the mass was yellow to grey-tan and soft. The mass extended into the perinephric fat. The uninvolved renal parenchyma was unremarkable except for a single unilocular cyst measuring up to 4.5 cm in diameter.

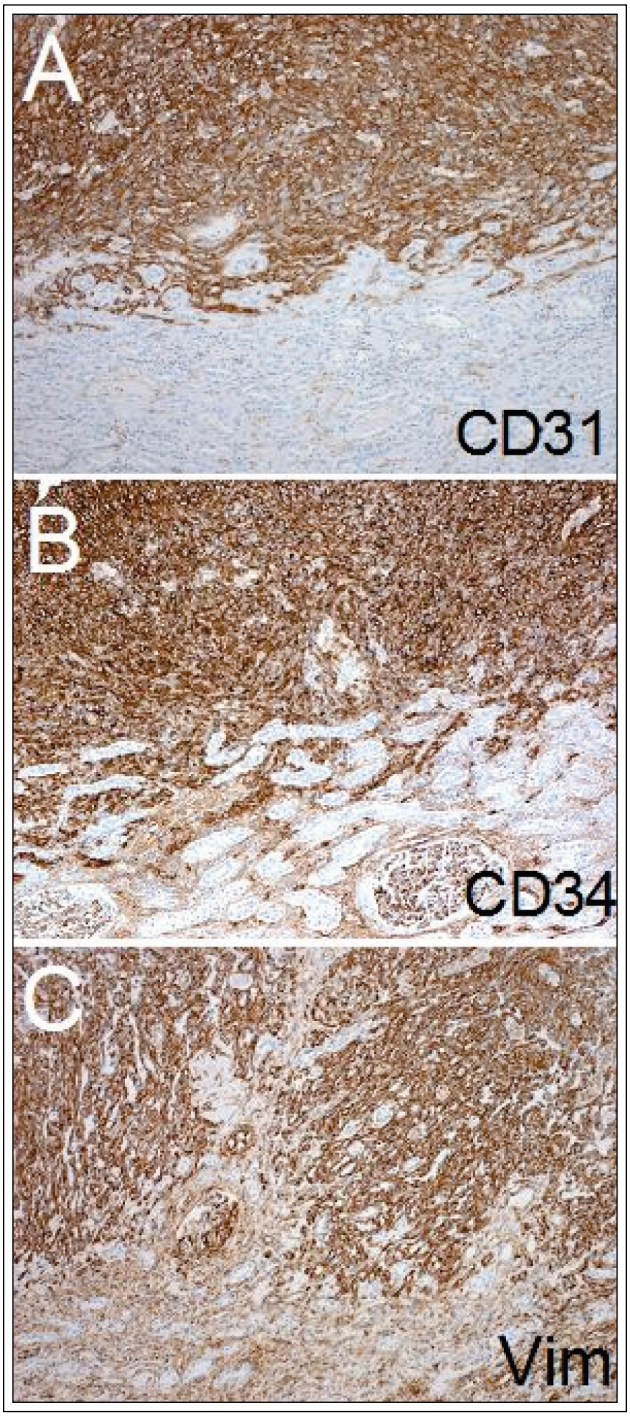

Figure 4. High power photomicrograph IHC staining of the renal tumor. A) Strongly positive tumor immunoreactivity for CD31. B) Strongly positive tumor immunoreactivity for CD34. C) Strongly positive immunoreactivity for vimentin. (IHC, x880)

Histological evaluation of the tumor revealed features of AS which involved the renal cortex, medulla, and perinephric fat. The tumor showed predominately typical angiomatous differentiation with numerous complex anastomosing blood-filled vascular spaces lined by plump endothelial cells, Figure 2. In focal areas, solid poorly differentiated spindle cell pattern was identified, Figure 3. The tumor nuclei were spindle-shaped with moderate nuclear pleomorphism and showed frequent mitoses. Areas of necrosis and hemorrhage were seen. The tumor cells were positive for CD31, Figure 4a, and CD34, Figure 4b, confirming its vascular origin, and strongly positive for vimentin, Figure 4c. The tumor was negative for AE1/AE3, S100, and HMB45 staining. Some capsular muscular vessels showed atypical endothelial proliferation. The non-tumorous kidney showed mild nephrosclerosis and a simple cyst.

Electron microscopy of the tumor revealed vascular spaces lined by endothelial cells with elongated cytoplasmic processes with a few junctions between the tumor cells. No convincing Weibel-Palade bodies were identified.

Histological evaluation of a biopsy from a left rib lesion confirmed metastatic AS involving the marrow, Figure 5.

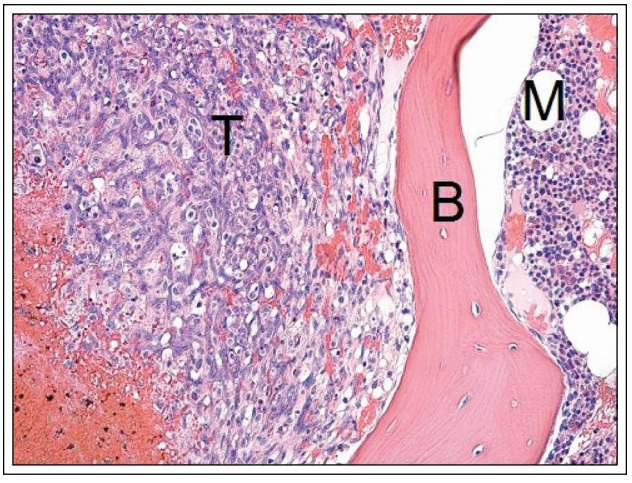

Figure 5. Photomicrograph of metastatic tumor (T) showing features of AS within a left rib biopsy. Note the uninvolved marrow (M) separated from the AS by bone trabeculae (B). (H&E, x440)

Discussion

In adults, RCC accounts for over 85% of all diagnosed renal tumors. Other renal tumors commonly seen include oncocytoma, angiomyolipoma, and metanephric adenoma. A much more rare and aggressive malignant tumor of the kidney is AS, with approximately less than 25 cases of renal AS described internationally.[1,2]

In 1917, Funke reported the first three cases of "endothelioma" of the kidney in the English literature,[5] but it was not until 1942 when one of the first well substantiated cases of renal AS was described.[6] The term AS is a sarcoma showing endothelial differentiation. AS can occur at any location but tends to predominately occur in the skin and superficial soft tissue.[7] Angiosarcoma is a rare highly malignant neoplasm that accounts for 1%-2% of all soft tissue sarcomas.

According to the WHO (see review[2]), the mean presentation age of renal AS is 58 years old (30-77) with a male predominance (ratio 19 male:4 female). Unlike AS of the skin, no relationship to arsenic, polyvinyl chloride, radiation, or Thorotrast with renal AS has been identified.[2] Review of the current renal angiosarcoma cases also showed no patient history of chemical/carcinogen exposure. The etiology of renal AS remains unknown, but an androgen factor has been suggested due to the male predilection.[2] Renal AS tend to occur near the renal capsule and may present with flank pain, hematuria, palpable mass, and weight loss.[2]

The definitive diagnosis of AS is dependent on antibodies specific for endothelial cells. The antibody for CD31 is positive in 80%-100% of AS[8] whereas the antibody for CD34 is positive in almost all malignant vascular tumors.[9] The use of factor VIII-related antigen and UEA-1 lectin antibodies show variation in AS staining.[10]

Tsuda et al[10] previously summarized 16 cases of renal AS up to the year 1997, and found that it predominated in the left kidney (with left to right kidney ratio of 11:5) and had a mean size of 11.9 (5-21) cm in diameter.

We reviewed the current English literature from 1981 and onwards on renal AS, and compared the results to our current case, Table 1. From the current literature review, including our case, the median patient age at presentation is 63 years old and is commonly a male with left kidney predominance. Common symptoms include flank pain, palpable mass, and hematuria with concomitant imaging suggestive of RCC. In some cases initial metastases were not seen at time of diagnosis, but only appeared near/at time of death. Hematogenous metastatic spread occurred with multiple lesions in bone, lung, spleen, liver, and with a few cases of bowel involvement. The median survival time from diagnosis is poor at 3.5 months (mean 5.8 months).

Generally, treatment was radical nephrectomy with radiation therapy for local control and painful bone metastases. The use of chemotherapy was not consistent, as 1) no standardized treatment is present and 2) was contraindicated due to the patients' deteriorated clinical condition. The chemotherapy strategy has drawn on the experience from the soft tissue sarcomas. Most often used agents in treatment of the soft tissue sarcomas, mostly in phase I and phase II trials, have been anthracyclines and ifosfamide often with G-CSF support.[11-13] Kern et al[14] reported no response with their renal AS chemotherapy strategy (mesna, adriamycin, ifosphamide, and dacarbazine). Berretta et al[15] found that their palliative chemotherapy responses were rapid but short-lived and inactive with prolongation of life rarely for several months. They used full doses of epirubicin 60 mg/m^2 (days 1 and 2), ifosfamide 3000 mg/m^2 (days 1-3) every 21 days, and with G-CSF 300 mg sc daily from day 5 until blood recovery. Sasaki et al[16] suggest the use of adjuvant recombinant Interleukin-2 immunotherapy as a promising treatment strategy in AS of the face and scalp and at other sites.

Current adjuvant treatment is not overtly effective, thus the possible future use of immunotherapy and anti-angiogenic agents may hold more promise as an effective treatment and require further study.[17]

Conclusion

Although the less aggressive RCC accounts for the majority of malignant renal tumors, the poor prognosis of AS and its similar symptoms and radiological appearance to RCC imparts the importance of histological evaluation and the potential mimicry of AS. It has been suggested that AS should be considered when imaging studies show a renal mass with a dominant capsular blood supply and no associated renal vein or inferior vena cava involvement.[4] Thus, early histological diagnosis and surgical intervention with adjuvant radiation therapy[18,19] appears to be the consensus of treatment for renal AS patients. The use of chemotherapy is not consistent. □

TABLE 1. **Summary of current angiosarcoma case reports in the English literature (1981-2006)**

Authors (Year)	Age/ Sex	Clinical presentation	Tumor size (cm)/side	Histo & immuno markers	Initial Dx	Metastatic involvement	Tmt	Survival time from Dx (months)
Our case Lee et al (2006)	63/M	Bone pain, mass	15x14x11/Lt	CD34, CD31	RCC	Bone, liver, lung, colon	Sx, R/T	4
Souza et al (2006)[20]	75/M	Hematuria, flank pain	15x3x10/Lt	CD34, CD31, VIII	Renal tumor	None	Sx	2 wks
Leggio et al (2006)[21]	60/M	Mass, flank pain	12/Lt	CD34 CD31	—	Spleen, peritoneum	Sx	8
Berretta et al (2006)[15]	67/M	Pain, fever asthenia,	10x6/Rt	CD31, VIII	Renal tumor	Spleen, liver, peritoneum	Sx, C/T	8
Pauli et al (2005)[1]	57/M	Unwell, cough	15x10x9/Lt	CD34, CD31, VIII	Renal tumor	Bone, vertebrae	Sx R/T	2
Johnson et al (2002)[22]	50/M	Hemoptysis, flank pain, mass	9x9x7/Lt	CD34, VIII	RCC	Lung, liver	N/A	0 (few days after Dx)
Cerilli et al (1998)[23]	67/M	Hematuria, flank pain	10.9/Rt	CD34, CD31	—	Bone, vertebrae, lung, liver, left kidney	Sx, R/T	8
Tsuda et al (1997)[10]	77/M	Hematuria	10x5/Lt	CD34, CD31, thrombo-modulin	Renal tumor	Liver, retroperitoneum bone, bowel,	Sx	21
Hiratsuka et al (1997)[24]	59/F	Hematuria	4.5x3.5x2/Rt	VIII	RCC	None	Sx, R/T	A & W
Kern et al (1995)[14]	52/M	Cough	8/Lt	Reticulin, VIII	RCC	Lung, bowel, intraperitoneal	Sx, R/T	3
Kern et al (1995)[14]	69/M	Flank pain, mass	3/Lt	Reticulin, VIII	Urine extra-vasation	Widespread hematogenous, lung	Sx, CT	6 wks
Martinez-Pineiro et al (1995)[25]	66/M	Mild LUQ tenderness	11.5/Lt	VIII	Epithelial tumor	Bone, lung, liver	Sx	3
Cason et al (1987)[26]	46/M	Flank pain, weight loss, fever	13x9x9/Lt	— (H&E)	Renal tumor	Bone, liver muscle	Sx, R/T, C/T	10
Terris et al (1986)[27]	47/M	Flank pain	13x9x9/Lt	— (H&E)	Renal tumor	Bone, liver	Sx R/T	10
Allred et al (1981)[28]	67/M	Flank pain, hematuria	13/Rt	Reticulin, (H&E)	Renal tumor	?lung liver	Sx	2

Rt - right; Lt - left; (—) - none reported; RCC - renal cell carcinoma; ? - likely via diagnostic imaging; Sx - surgery; R/T - radiation therapy; C/T - chemotherapy; A&W - alive and well at publication

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