Primary angiosarcoma of the kidney: case analysis and literature review

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Abstract: Objective: To study the clinical presentation, diagnosis, treatment and prognosis of primary angiosarcoma of the kidney. Methods: We treated a patient with primary angiosarcoma, then searched the published papers with the terms of ‘primary angiosarcoma of the kidney’ and ‘primary renal angiosarcoma’ in PubMed database, found 27 patients with detailed data, and analyzed their characters in the clinical presentation, diagnosis, treatment and prognosis. Results: The primary angiosarcoma occurred mainly from 50 years old to 69 years old, predominated in male patients. The clinical presentation was flank pain and hematuria, and the nephrectomy was the mainstay of the treatment; the maximum diameter and the metastasis status at the time of diagnosis had important prognostic value. Conclusions: The primary angiosarcoma is a rare carcinoma and lacks of specific presentation. Accurate diagnosis depends on pathological examination. Surgery is the mainstay of the treatment, but the prognosis is poor.

Keywords: Primary angiosarcoma of the kidney, diagnosis, treatment, prognosis

Primary angiosarcoma of the kidney is extremely rare, with less than 40 cases reported in the literature up to date [1]. The most reports described the origin of angiosarcoma in a normal kidney. But there was a report of primary angiosarcoma of the kidney arising from a multicystic kidney [2]. We present another 52-year-old male case of primary angiosarcoma of the kidney. The standard treatment is absent, and prognosis is very poor. In order to provide helpful information to diagnose and treat it, we searched the published papers with the terms of ‘primary angiosarcoma of the kidney’ and ‘primary renal angiosarcoma’ in PubMed database, found others 27 patients with detailed data (Table 1), and made a systematic review of this disorder.

Case report

A 52-year-old male presented with a history of left lumbar and left leg pain starting one month earlier, but no macroscopic hematuria. Physical examination revealed left flank pain. The routine blood tests showed the presence of anemia, and hemoglobin was 122 g/L (normal value ranging from 131 g/L to 172 g/L). The remaining blood tests were normal. An ultrasound showed a large left renal mass with heterogeneous internal echo and no blood flow signal. Abdominal computed tomography confirmed the presence of a tumor in the middle section of the left kidney measuring 8.0 cm×5.2 cm×5.1 cm, with a low increased density after administration of contrast medium and there were multiple liver lesions (Figures 1, 2).

A radical nephrectomy was performed including the ipsilateral adrenal gland. The macroscopic appearance of the solid tumor measured 8.0 cm×5.0 cm×4.0 cm. It was located in the upper middle of the kidney, and was dark red in color with marked hemorrhage and necrosis. The tumor did not involve perinephric fatty tissue, ureter and adrenal gland. Histopathological examination showed pleomorphic tumor cells with large hyperchromatic nuclei, prominent nucleoli and clear cytoplasm (Figure 3). An immunohistochemical study showed a vascular tumor strongly and diffusely positive for vimentin, CD31, CD34 and p53, and partially positive for ki67 (about 40%), while negative for AE1/
### Table 1. Clinical data of 28 patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Author</th>
<th>Age (year)</th>
<th>Sex</th>
<th>Site</th>
<th>Clinical presentation</th>
<th>History</th>
<th>Metastasis at diagnosis</th>
<th>Treatment</th>
<th>Postoperative survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Prince [30]</td>
<td>51</td>
<td>M</td>
<td>L</td>
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<td>no</td>
<td>no</td>
<td>RT</td>
<td>A and W</td>
</tr>
<tr>
<td>2</td>
<td>Peters [18]</td>
<td>74</td>
<td>M</td>
<td>L</td>
<td>weight loss</td>
<td>no</td>
<td>lung, local invasion</td>
<td>N</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>Askari [13]</td>
<td>24</td>
<td>M</td>
<td>R</td>
<td>hematuria</td>
<td>no</td>
<td>disseminated</td>
<td>N</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>Allred [31]</td>
<td>67</td>
<td>M</td>
<td>R</td>
<td>flank pain, hematuria</td>
<td>no</td>
<td>lung</td>
<td>N</td>
<td>3</td>
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<tr>
<td>5</td>
<td>Terris [27]</td>
<td>47</td>
<td>M</td>
<td>L</td>
<td>flank pain</td>
<td>no</td>
<td>bone</td>
<td>N, RT</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>Cason [15]</td>
<td>46</td>
<td>M</td>
<td>L</td>
<td>flank pain, weight loss, nausea, low fever</td>
<td>-</td>
<td>no</td>
<td>N, CT, RT</td>
<td>10</td>
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<tr>
<td>7</td>
<td>Desai [32]</td>
<td>54</td>
<td>M</td>
<td>L</td>
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<td>-</td>
<td>no</td>
<td>N, CT</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>Adjiman [16]</td>
<td>36</td>
<td>M</td>
<td>R</td>
<td>flank pain, fever, cough, hemoptysis</td>
<td>HIV-1 infection</td>
<td>chest wall, skin</td>
<td>N</td>
<td>RP and D</td>
</tr>
<tr>
<td>9</td>
<td>Kern [14]</td>
<td>56</td>
<td>M</td>
<td>L</td>
<td>hematuria</td>
<td>-</td>
<td>lung</td>
<td>N</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>Kern [14]</td>
<td>69</td>
<td>M</td>
<td>L</td>
<td>flank pain, hematuria, weight loss</td>
<td>-</td>
<td>lung</td>
<td>N</td>
<td>1.5</td>
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<tr>
<td>12</td>
<td>Hiratsuka [22]</td>
<td>59</td>
<td>F</td>
<td>R</td>
<td>hematuria</td>
<td>-</td>
<td>no</td>
<td>N</td>
<td>A and W</td>
</tr>
<tr>
<td>13</td>
<td>Mordkin [17]</td>
<td>75</td>
<td>M</td>
<td>L</td>
<td>weight loss, fever</td>
<td>-</td>
<td>spleen</td>
<td>N, S, CT</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>Tsuda [33]</td>
<td>77</td>
<td>M</td>
<td>L</td>
<td>macromhematuria renal failure</td>
<td>unilateral kidney</td>
<td>no</td>
<td>N</td>
<td>21</td>
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<tr>
<td>15</td>
<td>Cerilli [34]</td>
<td>67</td>
<td>M</td>
<td>R</td>
<td>macrohematuria, flank pain</td>
<td>-</td>
<td>renal vein</td>
<td>N, RT</td>
<td>6</td>
</tr>
<tr>
<td>16</td>
<td>Aydulg [35]</td>
<td>77</td>
<td>M</td>
<td>L</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>N</td>
<td>-</td>
</tr>
<tr>
<td>17</td>
<td>Aksay [21]</td>
<td>55</td>
<td>M</td>
<td>L</td>
<td>spontaneous rupture</td>
<td>-</td>
<td>no</td>
<td>N, S</td>
<td>3</td>
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<tr>
<td>18</td>
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<td>50</td>
<td>M</td>
<td>L</td>
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<td>-</td>
<td>lung</td>
<td>no</td>
<td>RP and D</td>
</tr>
<tr>
<td>19</td>
<td>Akkad [36]</td>
<td>58</td>
<td>M</td>
<td>R</td>
<td>4.5</td>
<td>no</td>
<td>no</td>
<td>LN</td>
<td>A and W *</td>
</tr>
<tr>
<td>20</td>
<td>Lorenzo [23]</td>
<td>60</td>
<td>M</td>
<td>L</td>
<td>after trauma</td>
<td>smoking</td>
<td>spleen, peritonea</td>
<td>N</td>
<td>8</td>
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<tr>
<td>23</td>
<td>Zenico [1]</td>
<td>56</td>
<td>M</td>
<td>L</td>
<td>large</td>
<td>no</td>
<td>Hodgkin’s lymphoma, radiotherapy history</td>
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<tr>
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<td>Douard [26]</td>
<td>60</td>
<td>M</td>
<td>R</td>
<td>-</td>
<td>-</td>
<td>bone, lung</td>
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<td>3</td>
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<tr>
<td>25</td>
<td>Singh [37]</td>
<td>83</td>
<td>M</td>
<td>L</td>
<td>acute chest pain, dyspnea</td>
<td>colon cancer</td>
<td>-</td>
<td>CT-guided biopsy</td>
<td>-</td>
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<td>26</td>
<td>Chaabouni [38]</td>
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<td>M</td>
<td>R</td>
<td>6</td>
<td>right lumbar pain, macrohematuria</td>
<td>no</td>
<td>no</td>
<td>RT</td>
</tr>
<tr>
<td>27</td>
<td>Sabharwal [19]</td>
<td>67</td>
<td>M</td>
<td>L</td>
<td>left loin pain, malaise, appetite loss, weight loss</td>
<td>smoking</td>
<td>no</td>
<td>RN</td>
<td>A and W</td>
</tr>
<tr>
<td>28</td>
<td>Presence</td>
<td>52</td>
<td>M</td>
<td>L</td>
<td>left leg bone pain and left flank pain</td>
<td>no</td>
<td>liver, bone</td>
<td>RN</td>
<td>A and W</td>
</tr>
</tbody>
</table>

Note: A and W= alive and well at the time of publication; CT= chemotherapy; D: the maximum of diameter; F= female; LN= laparoscopic nephrectomy; M= male; N= nephrectomy; R= right; RP and D= rapid progression and death; RN= radical nephrectomy; RT= radiotherapy; S= splenectomy. *Alive and well 30 months after the surgery.
Primary angiosarcoma of the kidney

AE3, EMA, CK7, CD10 and PGM1. These findings indicated that the tumor was angiosarcoma of the kidney. The postoperative course was uneventful and the patient was discharged 10 days after surgery.

Literatures analysis

A review of the pertinent literature worldwide carried out using the search terms “primary renal angiosarcoma/primary angiosarcoma of the kidney” revealed 27 articles published with relative detailed content, up to 28 cases after adding our case. The disease arises significantly more frequent in men (27 cases) than women (1 case). Tumors presented predominantly in the left kidney than right kidney (20 left vs 8 right). Median age of patients was 59.9 ± 12.6 years, range mainly from 50 to 69 years old (Figure 4).

Symptoms were mainly flank pain (12/28, 42.9%) and hematuria (10/28, 35.7%), without
Primary angiosarcoma of the kidney

Table 4. The effect of age on prognosis

<table>
<thead>
<tr>
<th></th>
<th>death group</th>
<th>survival group</th>
<th>t value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>the age of the patient</td>
<td>56.94 ± 3.112</td>
<td>59.14 ± 2.483</td>
<td>0.417</td>
<td>0.6805</td>
</tr>
<tr>
<td>the maximum of tumor diameter</td>
<td>13.41 ± 1.296</td>
<td>8.000 ± 1.210</td>
<td>2.536</td>
<td>0.0192</td>
</tr>
</tbody>
</table>

specific presentation and similar to the sign of renal cancer. It was worthwhile to note that there were no any clinical presentation in 4 patients (4/28, 14.3%) (Table 2).

11 patients (11/28, 39.3%) did not have secondary disease at the time of diagnosis, but there were 8 patients (8/13, 61.5%) without metastasis symptom showed tumor spread. The organ most frequently involved was the lung (6 cases, 21.4% of the total and 46.2% of the metastatic group). There was bone involvement in 3 cases (10.7% of overall and 23.1% of metastatic patients). The average size of the tumors, measured along the longest axis, was 12.1 ± 6.1 cm.

As proof of the disease was of the rarity, and a standard treatment protocol was absent, treatment was necessarily heterogeneous: nephrectomy was carried out in 21 (75.0%) cases, nephrectomy and chemotherapy in 2 (7.1%) patients, nephrectomy with radiotherapy in 2 (7.1%), nephrectomy associated with radiotherapy and chemotherapy in 1 (3.6%), and 1 (3.6%) patient underwent radiotherapy alone. Median survival span after surgery was very short (6.28 ± 4.96 months).

The metastasis and the maximum diameter of renal angiosarcoma were obviously related to the prognosis; the difference was statistically significant between survival group and death group. But the age of patients was not related to prognosis (Tables 3, 4 and Figures 5 to 7). ROC curve analysis was further performed, and found that the size was a factor of prognosis, and the cutoff value was 10 cm (P<0.05) (Figure 8).

Discussion

Angiosarcoma (AS) account about 2%-3% of adult soft tissue sarcomas [3]. Despite it was rarity, AS displays remarkable clinical heterogeneity in term of presentation and behavior. These tumors can occur in any location of the body (two-thirds are cutaneous-mainly in head and neck area, one-fourth arise in soft tissue) [4]. The primary angiosarcoma of the kidney is an exceptional rare angiosarcoma. It is a very rare tumor, and very little information on this entity is available. The most primary angiosarcoma of kidney are already metastasized when the diagnosis was made [5].

Renal angiosarcoma shows no clinical presentation and patients often present with symptoms similar to renal disease (i.e., side pain, macroscopic hematuria, palpable abdominal mass) [5]. Generally, a computed tomography scan reveals a solid renal tumor with no characteristic signs and studied local and metastases extension [6].

Etiology

Certain risk factors for primary kidney angiosarcoma have not been identified [7], even if predisposing factors for angiosarcoma occurring in other tissues include exposure to arsenic, thorium dioxide (Thorotrast), vinyl chloride, radiation, and post treatment lymphedema [7, 8]. The relationship between kidney angiosarcoma and these factors is suggested by the relatively strong evidence linking several substances to the induction of hepatic angiosarcomas occurring in patients who have received thorium dioxide (Thorotrast) for cerebral angiography, in vineyard workers exposed to AsO3 containing insecticides, or blue-collar workers exposed to vinyl chloride during the production of synthetic rubber [9-12]. However our patient was a white-collar worker not subjected to any of the mentioned risk factors. Previously, Askari [13] described a kidney angiosarcoma occurring de novo in a renal allograft recipient. And Kern SB [14] reported the primary kidney angiosarcoma frequently occurred in brothers, which means that the occurrence of primary kidney angiosarcoma may be related to hereditary. However, the etiology of primary kidney angiosarcoma remains unknown, and the previous surgery in the genitourinary tract of our patient may be coincidental.

Clinical presentation

Our patient presented some clinical characters similar to the previously described cases (Table
Primary angiosarcoma of the kidney

1), such as flank pain, and more male sex. In particular, flank pain is the most common initial clinical presentation described in the cases analysis. Another clinical characteristic is represented by macrohematuria and/or microhematuria, but not present in our patient. Less common clinical presentations include low grade fever [15-17], weight loss [14, 15, 17-19], anorexia and asthenia [19, 20], hemoptysis [16], cough [16], spontaneous rupture with consequent retroperitoneal hematoma [21], and so on. Hiratsuka [22] described the only case of primary renal angiosarcoma in a female patient. The prevalence of mainly male patient may be partly related to occupational factors and smoking, although a causal role of androgens cannot be excluded either [23].

Treatment methods

Primary angiosarcoma of the kidney is highly malignant, and there seems to be no standard therapy. Therapy must be specific to each patient, with special attention on the presence of distant metastases. According to the literatures analysis, surgery is the most effective treatment for primary angiosarcoma of the kidney, particularly in the analyzed cases (Table 1), nephrectomy was not performed in only 3 cases. Radical nephrectomy must be performed in all cases because of the impossibility of making a differential diagnosis between primary angiosarcoma of the kidney and the more common renal cell cancer [1]. On the other hand, the data in the literature regarding radiotherapy and/or chemotherapy are controver-
Primary angiosarcoma of the kidney

sial. Certainly, the lack of a standard therapy is a result of the rarity of this malignancy [24-26]. According to Terris [27], postoperative adjuvant radiotherapy may contribute to local control as it did for sarcomas in other sites. According to Zenico [1], patients who had the best response also underwent radiotherapy and chemotherapy, with a median survival of 13 months (p>0.005) compared to 7 months in patients who only underwent nephrectomy. On the contrary, according to Martinez-Pineiro [20], radiotherapy does not seem to get longer survival, and systemic chemotherapy should be added. Some patients presented the only primary localization, their prognosis were similar to the prognosis of angiosarcoma metastasized at diagnosis (2-24 months), confirming that micro-metastases had already occurred at diagnosis [5]. So, according to Mordkin [17], chemotherapy could be relevant for significant palliation, although durability of the response is likely to be short. In the last years, taxanes may be more efficient than standard chemotherapy in the treatment of metastatic renal angiosarcoma [2]. With the development of molecular biology, anti-angiogenic therapy, mediated by inhibition of VEGFR-2 or VEGF capture, can be a promising therapeutic opportunity [28].

Prognosis

The prognosis of primary angiosarcoma of the kidney is uniformly fatal with widespread metastases. Metastases are found mainly in the lung, liver and bones. The most important factor determining the prognosis of primary angiosarcoma of the kidney in many studies seemed to be the size of the initial lesion [23, 24, 29]. Tumors <5 cm in diameter have a significantly better prognosis than larger lesions. Analyzing various cases of primary angiosarcoma of the kidney, Mark RJ [25] reported a 5-year survival of 32% for lesions <5 cm compared to 13% for those >5 cm. According to our data and ROC curve analysis, the cutoff value of the maximum tumor diameter should be 10 cm other than 5 cm in order to more accurately determine prognosis. Moreover, according to our analysis, it also is one of prognosis factors whether it has metastasized at the time of diagnosis. The survival of group with metastasis at the time of diagnosis was obviously shorter than the death group without metastasis at the time of diagnosis. So it maybe another prognosis factor whether it is metastasized at the time of diagnosis.

Conclusion

Primary angiosarcoma of the kidney represents a rare variant of renal parenchymal cancer. It has a high potential of malignancy, with a very short survival period. The very low incidence of this tumor and the extreme variability in its clinical course means that we are still far from defining a diagnostic and therapeutic protocol.

Disclosure of conflict of interest

None.

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References

Primary angiosarcoma of the kidney


Primary angiosarcoma of the kidney
