Renal Medullary Carcinoma in a White Adolescent With Sickle Cell Trait

Paul Daher, MD, PhD,* Ali Bourgi, MD,* Edward Riachy, MD,* Antoine Khoury, MD,* Caline Rehayem, MD, † and Claude Sader-Ghorra, MD †

Summary: Renal medullary carcinoma (RMC) is a rare neoplasm of the kidney that has been recently described. It is almost exclusive to young patients of African descent and associated with sickle cell hemoglobinopathy, mainly sickle cell trait and hemoglobin sickle cell disease. The prognosis of RMC is very poor because of the highly aggressive behavior of this neoplasm and its resistance to conventional chemotherapy. Metastatic disease is almost universal at the time of presentation, and the malignancy is minimally responsive to a variety of regimens and/or modalities, including surgery, radiotherapy, chemotherapy, and biological immune-modulation therapy. We report the seventh case of a left RMC occurring in a white child with sickle cell trait, but with a localization of the tumor in the left kidney, considered a nonpredominant side for this type of tumor.

Key Words: renal medullary carcinoma, sickle cell trait, sickle cell disease, metastasis

(J Pediatr Hematol Oncol 2014;00:000–000)

Received for publication May 18, 2013; accepted January 14, 2014.

From the Departments of *Pediatric Surgery; and †Pathology, Hotel-Dieu de France University Hospital, Boulevard Alfred Naccache, Achrâieh, Beirut, Lebanon.

The authors declare no conflict of interest.

Reprints: Edward Riachy, MD, Department of Pediatric Surgery, Hotel-Dieu de France University Hospital, Boulevard Alfred Naccache, Achrâieh, P.O. Box 16-6830, Beirut, Lebanon (e-mail: eddyriachy@gmail.com).

Copyright © 2014 by Lippincott Williams & Wilkins.

Original Article

Renal medullary carcinoma (RMC) is a rare aggressive neoplasm of the kidney recently described with less than 100 cases reported in the literature. This entity was first characterized in 1995 by Davis et al1 and called “the seventh sickle cell nephropathy,” the others being: unilateral hematuria, papillary necrosis, renal infarct, nephrotic syndrome, inability to concentrate urine, and pyelonephritis. With the exception of 4 patients, all other reported cases have been associated with sickle cell hemoglobinopathy, mainly sickle cell trait (SCT), and less frequently sickle cell disease (SCD).2 Another characteristic finding of this tumor is the involvement of the right kidney in over 3 quarters of the cases.1

The prognosis of RMC is very poor because of the highly aggressive behavior of this neoplasm and its resistance to conventional chemotherapy. Metastases are both lymphatic and hematogenous with the liver and lungs most often involved.3 Metastatic disease is almost universal at the time of presentation, and the malignancy is minimally responsive to a variety of regimens and/or modalities, including surgery, radiotherapy, chemotherapy, and biological immune-modulation therapy. The average length of survival after diagnosis has been 4 months.1 RMC has been reported almost exclusively in individuals of African descent carrying the SCT or afflicted by SCD.1,2 We report a case of RMC occurring in a white adolescent with SCT. This is the seventh case of RMC, but is unique in the localization of the tumor in the left kidney, considered a nonpredominant side for this type of tumor.

CASE REPORT

A 13-year-old white boy presented with a 2-week history of left flank pain, gross hematuria, loss of appetite, and lack of energy. The physical examination showed no lymphadenopathy and no palpable mass or organomegaly. The rest of his physical examination was also unremarkable. Complete blood count and electrolyte values were within normal limits and kidney function appeared normal. A left renal mass was suspected on abdominal ultrasound. An abdominal computed tomographic scan with IV contrast identified a 6 × 5 cm heterogeneous infiltrative mass of the left upper renal pole, with multiple 1.0 and 1.5 cm periaortic and retrocrural lymph nodes (Fig. 1). A chest computed tomographic scan with IV contrast showed multiple left jugular, left subclavian, anterior mediastinal, right paratracheal, and bilateral hilar lymph nodes with subpleural pseudo-nodular condensation of the lower lobes with associated peribronchial wall thickening and linear interlobular septal thickening. Ultrasound-guided core biopsies of the mass revealed a RMC; the diagnosis was based on histologic features similar to those described by Davis et al (Fig. 2).1 A PET scan showed multiple fluorodeoxyglucose-avid lymphadenopathy mainly in the left lower neck, the left infra-clavicular region, the mediastinum, and the retrocrural region, as well as a large fluorodeoxyglucose-avid tumor of the left kidney, with no metastatic liver, lung, or bone disease. Although a preliminary “sickle solubility test” did not suspect a hemoglobinopathy, the electrophoresis of hemoglobin actually did demonstrate a SCT. The child had undergone an open left radical nephrectomy. Postoperative pathology confirmed the diagnosis of RMC and revealed the presence of 1 positive hilar metastatic node. One month after the surgery, an abdominal ultrasound identified a residual tumor of about 30 mL in volume. The patient received an adjuvant chemotherapy regimen combining gemcitabine and cisplatin. After 3 cycles, a repeat abdominal ultrasound showed a 50% increase in volume on the left flank mass. The patient was therefore switched to gemcitabine, carboplatin with the addition of paclitaxel, with a subsequent clear reduction in the residual left flank mass to 6 mL. Despite this transitory improvement, the mass rapidly progressed to a volume of 50 mL, in association with innumerable enlarged retrocaval and interaortocaval lymph nodes. At the time of writing this manuscript, and 10 months after his initial diagnosis, the patient is still alive, complaining of left flank pain, and receiving morphine for palliative care.

DISCUSSION

Demographics

RMC is a rare aggressive neoplasm of the kidney recently described with less than a 100 cases reported in the literature. It typically affects adolescents and young...
adults. Table 1 summarizes the demographic findings of the previously described cases.

Almost all patients described with RMC have been of African descent.\(^1,2\) Unfortunately, most described cases were referred to as “black,” and hence it would be difficult to differentiate “African American” from “African” from an epidemiologic standpoint. The first cases described in the literature regarding the occurrence of RMC in white individuals without a history of SCD or SCT were a 13-year-old child in 1997 by Kalyanpur et al\(^4\) and a 42-year-old man in 2010 by O’Donnell et al.\(^5\)

A striking finding is the higher incidence of patients with SCT than those with SCD, and one may be tempted to speculate that SCT may predispose to RMC more than SCD.\(^36\) However, according to Swartz and colleagues, both are at risk for RMC, and the greater reported incidence in patients with SCT is simply because the prevalence of SCT in the US population is 8% and that for SCD is 0.15% (for every 53 individuals with SCT, only 1 person will have SCD).\(^15,36,37\)

One of the most intriguing features of this tumor is its predilection for the right side in over 70% of the cases.\(^1,6,37\) What renders our case most unique is the occurrence of this condition in a white adolescent with an SCT in the left nonpredominant side for this type of tumor.

**Diagnosis**

The clinical presentation of RMC has been highly variable among the reported cases, but most patients presented with at least 1 component of the “classic renal tumor triad” (flank pain, hematuria, and flank mass), but rarely with the complete triad.\(^37,38\) Some patients may present with symptoms of metastatic disease. The sites of metastasis include the regional lymph nodes, adrenal glands, lung, liver, inferior vena cava, and the peritoneum.\(^1\)

Radiologic findings of RMC are nonspecific and include an infiltrative renal mass with necrosis, caliectasis, and regional adenopathy.\(^23\) The association of those findings in the clinical setting of a young adult, with gross hematuria, hemoglobinopathy, and a right-sided involvement, should suggest the diagnosis of RMC. Our patient did not have any palpable abdominal mass on presentation, and his mass was left-sided on imaging, making the diagnosis of RMC less likely in our differential. We could have been misled further had the hemoglobin electrophoresis not been done.

On the basis of the patient demographics described in the literature, we recommend that a search for hemoglobinopathy be conducted in adolescent and young patients with a renal mass and gross hematuria, particularly if it is associated with one of the following: a family history of hemoglobinopathy, an African descent, a right-sided tumor, a central renal mass with lymphadenopathy, or metastasis on presentation. The diagnosis of a hemoglobinopathy should not be based on the “sickle solubility test,” and hemoglobin electrophoresis should be considered the test of choice.

**Histopathology**

A distinctive characteristic of this neoplasm is that it arises in the medullary portion of the kidney, whereas renal cell carcinoma (RCC) and Wilms’ tumor, rare in the second to fourth decades of life, tend to arise more peripherally in the cortical areas.\(^39\) In addition, RMC typically has a fair amount of inflammatory infiltrate and reactive stromal elements, unlike most types of RCC.\(^3\) Other renal neoplasms that present with central location and infiltrative
pattern are: transitional cell carcinoma invading renal parenchyma, renal lymphoma with trans-sinus invasion, and collecting duct carcinoma. Those malignancies can be differentiated from RMC considering its typical clinical findings (age, ethnicity, and hemoglobinopathy). RMC has been previously thought to be a subgroup of collecting duct carcinoma because of their similar pathologic features. However, immunohistochemical studies confirm that those malignancies can be distinct entities, with RMC lacking the expression of the 

<table>
<thead>
<tr>
<th>References</th>
<th>N</th>
<th>Disease</th>
<th>Ethnical Origin</th>
<th>Age (y)*</th>
<th>Laterality</th>
<th>Survival†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davis et al</td>
<td>34</td>
<td>33 SCT; 1 SCD</td>
<td>33 AA; 1 C</td>
<td>11-39</td>
<td>8 L; 23 R</td>
<td>4 mo</td>
</tr>
<tr>
<td>Dimashkieh et al</td>
<td>2</td>
<td>1 SCT; 1 SCD</td>
<td>AA</td>
<td>21-40</td>
<td>1 L; 1 R</td>
<td>5 mo; 1 LTF</td>
</tr>
<tr>
<td>Watanabe et al</td>
<td>7</td>
<td>5 SCT; 1 SCD; 1 NA</td>
<td>4 AB; 1 C; 2 NA</td>
<td>8-69</td>
<td>2 L; 5 R</td>
<td>4 mo; 1 alive 8 y +</td>
</tr>
<tr>
<td>Kalyanpur et al</td>
<td>1</td>
<td>None</td>
<td>C</td>
<td>13</td>
<td>R</td>
<td>4 mo</td>
</tr>
<tr>
<td>O’Donnell et al</td>
<td>1</td>
<td>None</td>
<td>C</td>
<td>42</td>
<td>L</td>
<td>Alive 9 mo +</td>
</tr>
<tr>
<td>Khan et al</td>
<td>1</td>
<td>SCT</td>
<td>AA</td>
<td>19</td>
<td>L</td>
<td>Alive</td>
</tr>
<tr>
<td>Stahlschmidt et al</td>
<td>1</td>
<td>SCT</td>
<td>African</td>
<td>14</td>
<td>L</td>
<td>12 mo</td>
</tr>
<tr>
<td>Figenhau et al</td>
<td>2</td>
<td>SCT</td>
<td>AA</td>
<td>30</td>
<td>R</td>
<td>4 mo</td>
</tr>
<tr>
<td>Herring et al</td>
<td>1</td>
<td>SCT</td>
<td>AA</td>
<td>18</td>
<td>L</td>
<td>2 mo</td>
</tr>
<tr>
<td>Friedrichs et al</td>
<td>1</td>
<td>SCT</td>
<td>AA</td>
<td>27</td>
<td>R</td>
<td>5 mo</td>
</tr>
<tr>
<td>Adsay et al</td>
<td>1</td>
<td>SCT</td>
<td>AA</td>
<td>37</td>
<td>R</td>
<td>0 mo</td>
</tr>
<tr>
<td>Warren et al</td>
<td>1</td>
<td>SCT</td>
<td>AA</td>
<td>18</td>
<td>R</td>
<td>1 mo</td>
</tr>
<tr>
<td>Pirich et al</td>
<td>1</td>
<td>SCT</td>
<td>AA</td>
<td>12</td>
<td>R</td>
<td>15 mo</td>
</tr>
<tr>
<td>Wesche et al</td>
<td>1</td>
<td>SCT</td>
<td>AA</td>
<td>10</td>
<td>R</td>
<td>1 mo</td>
</tr>
<tr>
<td>Coogan et al</td>
<td>3</td>
<td>SCT</td>
<td>AA</td>
<td>29</td>
<td>R</td>
<td>3 mo</td>
</tr>
<tr>
<td>Mathur et al</td>
<td>1</td>
<td>SCT</td>
<td>AA</td>
<td>33</td>
<td>R</td>
<td>0 mo</td>
</tr>
<tr>
<td>Qi et al</td>
<td>1</td>
<td>SCT</td>
<td>AA</td>
<td>14</td>
<td>L</td>
<td>Alive</td>
</tr>
<tr>
<td>Selby et al</td>
<td>1</td>
<td>SCT</td>
<td>AA</td>
<td>21</td>
<td>L</td>
<td>Alive 2 y +</td>
</tr>
<tr>
<td>Larson et al</td>
<td>1</td>
<td>SCT</td>
<td>AA</td>
<td>18</td>
<td>R</td>
<td>2 mo</td>
</tr>
<tr>
<td>Rodriguez-Jurado et al</td>
<td>1</td>
<td>SCT</td>
<td>NA</td>
<td>12</td>
<td>R</td>
<td>NA</td>
</tr>
<tr>
<td>Diao et al</td>
<td>1</td>
<td>SCT</td>
<td>NA</td>
<td>38</td>
<td>L</td>
<td>Alive 8 mo +</td>
</tr>
<tr>
<td>Chatelain et al</td>
<td>1</td>
<td>SCT</td>
<td>AA</td>
<td>NA</td>
<td>L</td>
<td>Alive 2 mo +</td>
</tr>
<tr>
<td>Blitman et al</td>
<td>6</td>
<td>SCT</td>
<td>4 AA; 2 Hispanic</td>
<td>15-27</td>
<td>R</td>
<td>NA</td>
</tr>
<tr>
<td>Baig et al</td>
<td>1</td>
<td>SCD</td>
<td>AA</td>
<td>36</td>
<td>R</td>
<td>0 mo</td>
</tr>
<tr>
<td>Noguera-Irizarry et al</td>
<td>1</td>
<td>SCD</td>
<td>Hispanic</td>
<td>19</td>
<td>R</td>
<td>12 mo</td>
</tr>
<tr>
<td>Khabir et al</td>
<td>1</td>
<td>NA</td>
<td>NA</td>
<td>40</td>
<td>L</td>
<td>6 mo</td>
</tr>
<tr>
<td>Simpson et al</td>
<td>3</td>
<td>SCT</td>
<td>AA</td>
<td>12-22</td>
<td>R</td>
<td>5 mo</td>
</tr>
<tr>
<td>Assad et al</td>
<td>3</td>
<td>SCT</td>
<td>1 A; 2 AA</td>
<td>20-33</td>
<td>2 L; 1 R</td>
<td>2 mo</td>
</tr>
<tr>
<td>Milhoua et al</td>
<td>1</td>
<td>SCT</td>
<td>AA</td>
<td>13</td>
<td>R</td>
<td>7 mo +</td>
</tr>
<tr>
<td>Leitão et al</td>
<td>1</td>
<td>SCT</td>
<td>AA</td>
<td>26</td>
<td>R</td>
<td>4 mo</td>
</tr>
<tr>
<td>Rathmell et al</td>
<td>1</td>
<td>SCT</td>
<td>AA</td>
<td>17-48</td>
<td>R</td>
<td>8 mo; 1 alive 1 y +</td>
</tr>
<tr>
<td>Thomas et al</td>
<td>1</td>
<td>SCT</td>
<td>Afro-Caribbean</td>
<td>17</td>
<td>L</td>
<td>Alive</td>
</tr>
<tr>
<td>Hakimi et al</td>
<td>9</td>
<td>SCT</td>
<td>8 AA; 1 Hispanic</td>
<td>13-27</td>
<td>1 L; 8 R</td>
<td>10 mo; 2 alive</td>
</tr>
<tr>
<td>Gatalica et al</td>
<td>3</td>
<td>1 SCD; 2 None</td>
<td>1 AA; 2 C</td>
<td>28-34</td>
<td>R</td>
<td>18 mo</td>
</tr>
<tr>
<td>Sathyamoorthy et al</td>
<td>1</td>
<td>SCD</td>
<td>AA</td>
<td>36</td>
<td>R</td>
<td>5 mo</td>
</tr>
<tr>
<td>This study</td>
<td>1</td>
<td>SCT</td>
<td>C</td>
<td>13</td>
<td>L</td>
<td>Alive</td>
</tr>
</tbody>
</table>

*Age range.
†Median length of survival from time of diagnosis.
AA indicates African American; AB, African Brazilian; C, Caucasian; L, left; LTF, lost to follow-up; NA, no available data information; N, number of patients; R, right; SCD, sickle cell disease; SCT, sickle cell trait.

Pathophysiology

The origin and pathogenesis of RMC are not completely understood. Accumulated experience with radiographic and pathologic findings suggests that RMC probably originates in the calyceal epithelium in or near the renal papillae, which could be the result of the chronic ischemic damage of the epithelium of the renal papillae related to sickled erythrocytes. Positivity for vascular endothelial growth factor (VEGF) and hypoxia-inducible factor (HIF1α) supports that chronic hypoxia secondary to the hemoglobinopathy may be involved in the pathogenesis of RMC. However, given that a large number of the population has hemoglobinopathy while RMC is fortunately rare, this suggests that other factors (such as genetic or environmental) are also involved.

To date, no single chromosomal numerical or structural nor molecular anomalies are considered specific to RMC. Interestingly, a few but inconsistent reports of cytogenetic studies revealed monosomy of chromosome 11, suggesting that the short arm of chromosome 11, where the gene for the β-globin is also found, may be involved in the pathogenesis of this tumor. In contrast, a BCR-ABL translocation of chromosomes 9 and 22 by fluorescence in situ hybridization analysis has been found by some, whereas others demonstrated only an ABL amplification but no translocation. Additional authors described an absence of SMARCB1 protein expression suggesting that inactivation of the SMARCB1, a tumor-suppressor gene, may play an important role in the pathogenesis of RMC. A different cohort of RMC patients found an over-expression of topoisomerase IIα protein (TOP2A), a nuclear enzyme that controls DNA topological structure.
and cell-cycle progression, but not an overexpression of the TOP2A gene, implying not only a possible cause for RMC but also a potential therapeutic role of TOP2A inhibitors.44

A recent review on the pathogenesis of RMC advocates that there is a common underlying hypoxic cellular environment favoring the activation of a well-known carcinogenic pathway: the HIF1α. This can arise from conditions that either favor “hypoxia” such as the case of SCT and SCD, or “pseudo-hypoxia” such as the case of genetic mutations such as biallelic inactivation of fumarate hydratase gene or the absence of functional VHL tumor-suppressor protein (von Hippel-Lindau) both of which affect the hypoxia-sensing pathway.34

Treatment

Several methods of treatment, encompassing surgery, different chemotherapeutic regimens, and palliative radiation therapy, have been tried, but no regimen has shown significant effects on disease progression to date.

An initial aggressive surgical resection with regional lymph node dissection has been advocated in the literature using either using standard or laparoscopic approaches.25,29,33 There are, however, no reports in the literature regarding resection of residual disease of RMC, particularly that the tumor is rapidly aggressive. However, it would seem reasonable to attempt a resection of residual intra-abdominal metastatic disease after 3 cycles of chemotherapy. If complete resection is not feasible, then we recommend either continuing or changing chemotherapy and reassessing for the feasibility of resection after 3 additional cycles.

Regarding adjuvant chemotherapy, many options are currently available. Although not published, I treatment option that certain centers offer is actually “no treatment,” given the really poor prognosis and the absence of known effective therapy. Others centers would offer the patient to be involved in a phase I trial, given the already poor prognosis such as trying a novel treatment such as the ones mentioned below (targeted therapeutic options). We chose the third option, the “standard therapy,” as this is what has been mainly described in the literature. The 2 most commonly used standard regimens have been the high-dose intensity MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin)31 and PCG (paclitaxel, carboplatin, and gemcitabine),13,44,45 with the latter considered by most as the preferred regimen. On the basis of global gene expression profiling, Yang et al46 found that RMC resembled transitional cell carcinoma, and suggested that it should not be treated as a conventional RCC. As a result, and because a remission has been reported,31 we initially offered our case a gemcitabine-cisplatin combination. As this did not turn out to be effective to our patient, we eventually added paclitaxel to his regimen, as PCG has shown good response in previous reports.33,44,45

Newer targeted therapeutic options are being considered recently: In a phase II study evaluating “bortezomib,” a proteasome inhibitor, in patients with advanced RCC, one of those patients actually had an RMC. An updated follow-up on this specific patient revealed that after receiving a total of 7 months of bortezomib therapy, he achieved complete remission, and remained without evidence of disease after more than 27 months.47,48 In contrast, Simpson et al27—who found ABL amplification in their RMC cases—raised the notion that “imatinib,” a tyrosine-kinase inhibitor, may have activity in this disease, as it has been shown to be beneficial in patients with chronic myeloid leukemia. As previously mentioned, a TOP2A inhibitor such as doxorubicin may also play a potential therapeutic role.5,44 Because of the association of RMC to the hypoxia-sensing pathway and HIF1α activation, a VEGF-targeted therapy could be another valuable future therapy.34

In agreement with most other authors, we did not offer radiotherapy to our patient as earlier reports have not shown that it had any positive effect on the course of the disease.42

Prognosis

Metastatic disease is almost universal at the time of presentation, making the prognosis dismal with a median survival after diagnosis of about 4 months.37 However, there are a few exceptions such as an 8-year-old African Brazilian patient with a medullary carcinoma who has been alive and free of recurrence 8 years after diagnosis and surgery.3 In addition, Selby et al18 reported a case diagnosed at an early stage with a nonaggressive behavior. The common reasons that lead to an early identification of those cases was a more aggressive hematuria workup and imaging. In fact, gross hematuria is a frequently encountered symptom in patients already known to have hemoglobinopathy, is self-limiting and benign, and traditionally did not require any further workup but observation. However, given the better outcome in those early diagnosed cases, many authors now advocate that a screening for RMC (at least beginning with an abdominal ultrasonography), particularly in young patients with gross hematuria and known abnormalities of the hemoglobin gene, could result in an early diagnosis and treatment, and consequently a better survival.3,15,18,35

CONCLUSIONS

RMC is a rare aggressive malignancy that can present in all age groups. It typically occurs in young patients of African descent with SCT or SCD, with a predilection to the right side. However, this condition has been described in whites even without SCT or SCD, and it is necessary to recognize that this group of patients may also be susceptible to this aggressive neoplasm. At the current stage, early prevention by screening those at risk (young patients afflicted with SCT or SCD and presenting with gross hematuria) seems reasonable. A better understanding of the molecular and genetic factors implicated with this rare disease is progressively opening doors to promising targeted therapies.

REFERENCES


