

Case Report

Renal Medullary Carcinoma with an Aggressive Clinical Course: A Case Report and Review of the Literature

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Keywords

Renal medullary carcinoma · Metastasis · African descent · Sickle cell anemia · Sickle cell trait · Kidney tumor

Abstract

Renal medullary carcinoma (RMC) is a rare, yet aggressive malignancy of the kidney that is found predominantly in young patients with African descent and sickle cell hemoglobinopathies and most specifically sickle cell trait. Due to its aggressive nature, most cases have metastasis or local invasion at the time of diagnosis. Prognosis is extremely poor with survival less than 1 year after diagnosis. Here we present a case of metastatic RMC in a 29-year-old African female. Despite chemotherapy with cisplatin, gemcitabine, and paclitaxel, and initial shrinkage of the tumor, the patient died 5 months after diagnosis.

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Introduction

Renal medullary carcinoma (RMC) is a rare renal neoplasm and highly aggressive. This particular subtype of renal cell carcinoma, initially described by Davis et al. in 1995 [1], is

almost exclusively found in young black individuals with sickle cell trait. It has an extremely poor prognosis with most cases diagnosed later in the disease course, with metastasis often present at the time of initial presentation. Median time of survival is 4 months following surgery. We present the case of a patient at our institution diagnosed with diffuse, metastatic RMC who had an aggressive clinical course, and no response to systemic chemotherapy.

Case Report

A 29-year-old female with no medical history presented to the emergency department with 6 weeks of chronic cough and fever. Chest X-ray showed mediastinal widening concerning for lymphadenopathy.

A follow-up computed tomography (CT) scan showed multiple masses in the mediastinum, lung, liver, and retroperitoneum (Fig. 1, Fig. 2). They were measured up to 3 cm in size, and a large infiltrative mass in the lower pole of the left kidney invading the renal pelvis measured 5.7 × 5.6 × 6 cm (Fig. 3).

Admission laboratory tests revealed normocytic anemia, mildly elevated white cell count, and an elevated platelet count (Hb of 8.9 g/dL, MCV 87 fL, WBC 12,000/μL, platelets 573,000/μL). Chemistry labs revealed elevated LDH (584 U/L) with normal kidney and liver function. HIV workup was negative.

The patient underwent transbronchial endoscopic ultrasound with biopsy of station 4R. She was discharged home with short-interval outpatient follow-up. Pathology results showed atypical large cells with high nucleus-to-cytoplasm ratio, the chromatin was coarse, and nucleoli were noted with expression of CDX2 and CK7, and loss of expression of INI1. The diagnosis was most consistent with RMC. A second opinion was requested from another regional cancer center pathology department where the diagnosis was ultimately confirmed. Given this diagnosis and her anemia, Hb electrophoresis was ordered and showed HbA 59%, HbA2 21%, and HbS 38%, confirming the presence of sickle cell trait.

The patient was started on cisplatin, gemcitabine, and paclitaxel during her hospital course, and she was eventually discharged for outpatient chemotherapy over 21-day intervals. A repeat CT scan prior to cycle 3 showed improvement of the kidney mass, lung nodules, and mediastinal and retroperitoneal lesions, but progression of the liver lesions. We continued with cycle 3, which was held after day 8 due to severe cytopenia and worsening performance status. Repeat CT showed progression of disease, and the patient eventually required hospitalization due to sepsis. She passed away on day 14 of the hospital stay, 5 months after diagnosis.

Discussion

RMC is exceedingly rare and accounts for less than 1% of all renal cancers. It typically presents in young patients and the male-to-female ratio is 2:1 [1]. In comparison, the median age for renal tumors as a whole is 64 years of age, according to the National Cancer Institute [2]. We were able to retrieve 262 cases (including case reports and series) in the literature since RMC was first described in 1995 (online suppl. Table 1; see www.karger.com/doi/10.1159/000455007). This occurs almost exclusively in patients of African origin and 88–98% of cases possess sickle cell trait [3, 4]. The median age of the reported cases in the Davis study [1] was 21 years (range 11–39 years of age).

The cause of RMC is still unknown and strong correlation with sickle cell trait alone encourages discussion of potential pathophysiological mechanisms underlying this apparent pattern. In a report by Mariño-Enríquez et al. [5], they described one RMC patient with ALK rearrangement, which may provide rationale for the use of ALK inhibitors for treatment. Stahlschmidt et al. [6] have reported chromosome 9 and 22 translocation and resulting bcr/abl rearrangement. An extensive investigation into the genes that are upregulated and downregulated in RMC was conducted by Yang and colleagues [7]. The authors suggested that some genes including topo-II (upregulated by 10.79 times) could serve as potential therapeutic targets in the treatment of RMC. The upregulation and potential for treatment targeting topoisomerase II has been demonstrated by Schaeffer and colleagues as well [8].

Signs and symptoms of RMC do not differ substantially from those of other renal tumors. The most common presenting signs are hematuria, weight loss, and flank pain, as demonstrated in the report by Davis et al. [1]. The majority of these patients (70%) were metastatic at presentation. All the patients in his report succumbed to their disease with a median survival of 15 weeks following nephrectomy [1].

The diagnosis is established based on the histopathology and immunohistochemistry of the tissue specimen. Cells are generally arranged in loose sheets with a high nucleus-to-cytoplasm ratio, with rhabdoid cytology, and inflamed desmoplastic stroma, high CK7, high-molecular weight cytokeratin, and pax8 positivity [9, 10], while CK20, CEA, and p53 are mostly negative [9, 11].

CT scans with contrast is the most commonly used modality for detecting renal masses in RMC [12]. Among limited published cases, RMC is described as a heterogenous, infiltrative renal mass with associated retroperitoneal adenopathy and caliectasis with poorly defined borders [13]. The average tumor size is 7 cm, and is frequently found in the medulla of the right kidney. In comparison to surrounding medulla and cortex, RMC can be seen as an iso-intense mass on unenhanced CT and interestingly hypodense (lower enhancement) mass on enhanced CT (CT with contrast) [12–14]. Hydronephrosis and necrosis are frequently reported, while calcification is only present in a minority of cases (approximately 0–20%) on imaging [12, 13]. MRI can be helpful regarding finding concurrent liver metastases or nodal invasion [15], or detecting intratumoral hemorrhage [13]. Few studies reported failure of ultrasonography for detection of renal mass, when it was applied for investigation of hematuria [13, 15].

In adult patients being evaluated for RMC, the main differential diagnoses to consider include other high-grade kidney tumors, poorly differentiated invasive transitional cell carcinoma originating in the pelvis, collecting duct carcinoma, and other metastatic tumors. Immunohistochemistry, pathology, and certain molecular markers are helpful in making the diagnosis. Loss of SMARCB1/INI-1 protein expression and presence of OCT3/4 on immunohistochemistry in RMC can help distinguish RMC from collecting duct carcinoma [11]. “Unclassified renal cell carcinoma with medullary features” was suggested by Colombo et al. [16] for those patients who meet immunohistochemistry profile for RMC but do not have sickle cell trait.

Due to the low prevalence, there have been no well-designed clinical trials to date exclusive to this population. Thus, the current body of knowledge regarding treatments used for RMC is limited in large part to individual case reports. Platinum-based chemotherapy and MVAC regimen (methotrexate, vinblastine, doxorubicin, and cisplatin) have been used, though with limited response. Rathmell and Monk [17] used high-dose intensity MVAC regimen in 3 RMC patients, demonstrating that this is a tolerable therapy with partial responses and longer survival compared to RMC treated with conventional MVAC or other regimen.

Multiple combination chemotherapy regimens used for genitourinary cancers are available, including cisplatin, gemcitabine, methotrexate, and vinblastine. Although not statistically significant, in their review of 165 cases with RMC, Iacovelli et al. [3] found better survival in patients treated with CPG (cisplatin, paclitaxel, and gemcitabine) comparing to those treated with MVAC; 8.0 versus 1.0 months for progression-free survival ($p = 0.064$) and 12.0 versus 4.0 months for overall survival ($p = 0.058$), respectively.

The use of biologics has recently begun to be explored in the treatment of RMC, notably anti-angiogenic approaches. Among the list of molecular changes and potential targets for treatment, Lipkin and colleagues [18] report on the efficacy of maintenance everolimus therapy in the treatment of a patient with demonstrated loss of PTEN, who at the time of the report, was surviving 14 months post-diagnosis.

Response to anti-angiogenic chemotherapy has been varied. In a recent trial, concurrent everolimus (mTORC1 inhibitor) and bevacizumab (a recombinant humanized monoclonal antibody directed against VEGF-A) failed to show efficacy and increase 6-month progression-free survival against RMC [19]. However, only two patients with RMC were included in this trial. Yet some have reported longer survival with antiangiogenic therapy (bevacizumab and oral temozolomide) when used to maintain remission, after initial chemotherapy (with paclitaxel, gemcitabine, and carboplatin) and nephrectomy were successful [20]. No clinical trials exclusive to RMC have been conducted to date; future trials should be considered for this population.

RMC remains a relatively new entity within oncology, having only been formally categorized two decades ago; thus the body of knowledge that exists remains small. Investigations to date have demonstrated its aggressiveness and complex underlying pathophysiology. Further study of the molecular origin, including next-generation sequencing of RMC, may reveal new-targeted therapies against this deadly disease.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors declare that they have no relevant financial interests.

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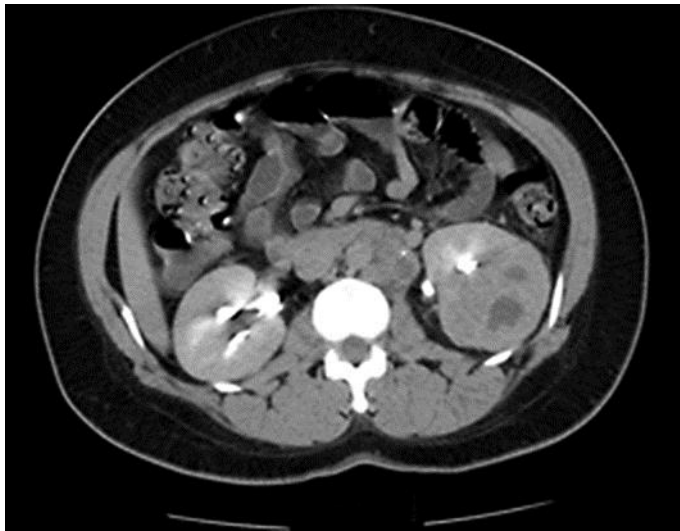


Fig. 1. CT contrast (delayed phase) showing infiltrative mass in the lower pole of the left kidney with lower enhancement compared to normal surrounding renal tissue. Left para-aortic lymph node involvement can be seen.

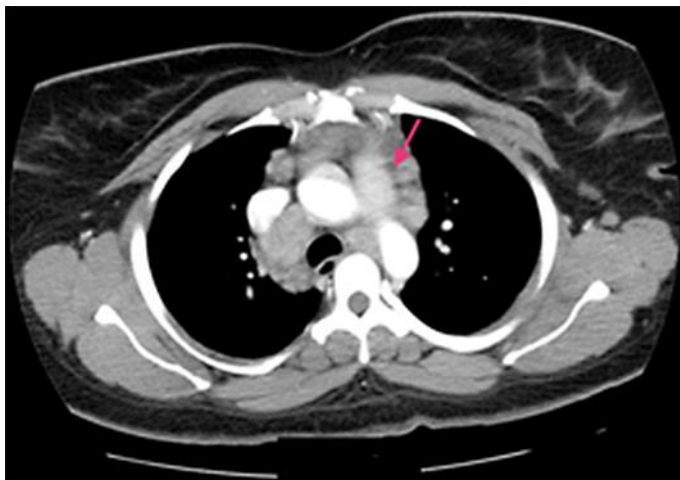


Fig. 2. CT image showing several non-calcified lung nodules and widened mediastinum due to metastasis to mediastinal lymph nodes (pink arrow).

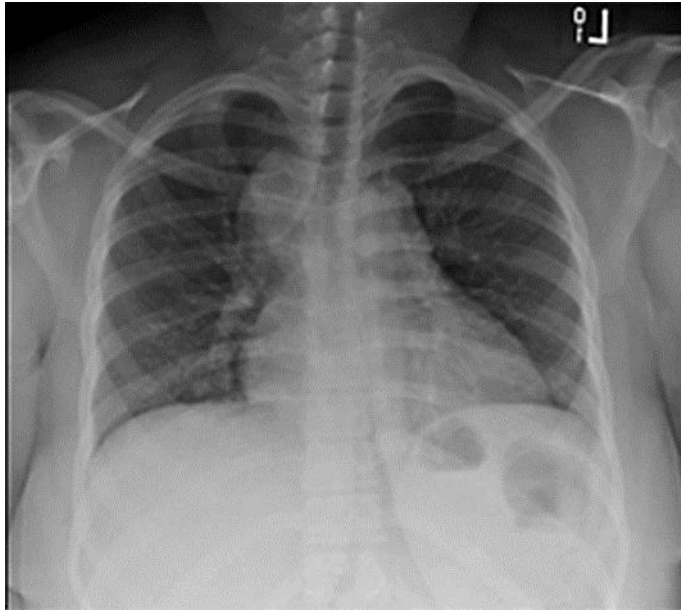


Fig. 3. Chest X-ray showing several non-calcified lung nodules and widened mediastinum due to metastasis to mediastinal lymph nodes.