Renal medullary carcinoma: a nearly fatal malignancy specifically affecting patients with a so-called benign condition

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Abstract

Renal medullary carcinoma (RMC) is a highly aggressive and rare malignancy found almost exclusively in young patients with sickle cell trait (SCT). Metastatic disease is commonly present at diagnosis. There is very limited experience treating disseminated disease and the prognosis is dismal. We report the case of a young 9-year-old boy with SCT, who presented with 4 months' progression of abdominal pain, nausea and vomiting associated with cough spells, dysphagia, and weight loss. Upon evaluation, he was underweight, pale, and in mild respiratory distress. Cervical lymphadenopathy was evident and abdomen was diffusely tender. A whole-body CT scan showed a left kidney lesion with associated cervical, mediastinal, and retroperitoneal lymphadenopathy. Biopsy of a cervical lymph node revealed metastatic RMC. Patient was started on combination chemotherapy with paclitaxel, carboplatin, and gemcitabine followed by left adrenalectomy. In spite of having advanced disease, our patient achieved an excellent response with a progression-free survival of 17 months. Although SCT is thought to be a “benign” condition, RMC is one devastating complication associated with it. Considering its rarity, the near uniform associated fatality should prompt the question of whether clinical practice should change regarding proper counseling of these patients and raise awareness in the medical community.

Keywords Renal medullary carcinoma · Sickle cell disease · Sickle cell trait · Sickling · Hematuria · Kidney medulla · Hemoglobinopathies

Introduction

Approximately 1 in 12 African Americans in the United States have SCT. Worldwide, the prevalence of SCT is estimated to be around 300 million people. SCT is regarded as a benign carrier condition, usually with none of the symptoms of sickle cell anemia (SCA). However, recent reports have challenged this notion, since some complications of

SCT have been consistently described, the most notorious of which are venous thromboembolism and renal disease [1].

Among the renal complications of SCT, renal medullary carcinoma (RMC) is, although rare, the most devastating of all. It was initially described by Davis and colleagues over 2 decades ago as the seventh sickle nephropathy [2]. The mean duration of life after surgery was 15 weeks. In 2015, Alvarez et al. [3] published the first systematic review of the 217 RMC cases reported to date, 88.6% of which were associated with SCT. Median overall survival was 10 months. The mean age of presentation was 24 years, with a male-to-female predominance, and 70% of the tumors arose in the right kidney. The primary tumor mean diameter at diagnosis was 6.8 ± 3 cm. The most common presenting signs reported in literature include: hematuria, abdominal/flank pain, palpable abdominal mass, and weight loss. Importantly, 94% of the cases presented as metastatic disease, with most common sites being the regional lymph nodes, adrenal glands, and lung. Most case reports to date have had prolonged duration of symptoms before diagnosis, with an average of 5 months [3].

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An initial aggressive surgical resection with regional lymph node dissection has been advocated followed by adjuvant chemotherapy. Several studies have been published describing the role of surgery, chemotherapy, immunotherapy, stem cell transplant, or radiation in the treatment of RMC but have found unfavorable outcomes with an overall mortality of 95% [3, 4]. The two most commonly used chemotherapy regimens have been the high-dose intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) and paclitaxel, cisplatin or carboplatin, and gemcitabine (PCG). MVAC is a standard first-line option for metastatic urothelial carcinoma based on the results of randomized clinical trials demonstrating improved survival outcomes [5, 6]. Toxicity is a major concern with MVAC therapy. Myelosuppression, neutropenic fever, sepsis, mucositis, and nausea and vomiting are common [6]. PCG has similar efficacy and less toxicity compared with MVAC [5–9]. Scant data regarding RMC show that PCG is considered by most the preferred regimen [10]. There are no prospective trials of treatment for RMC, in part because it is rare and has only recently been recognized as a distinct entity. Treatment plans have, therefore, been extrapolated from those used for advanced malignancies of the uroepithelium of children and adults. Comparably, there have been limited reports of success with anthracyclines and the proteasome inhibitor bortezomib [11]. In addition, topoisomerase II inhibitors may be of benefit due to the overexpression of topoisomerase II alpha in this tumor [12]. Since neovascularization both precedes and is necessary for tumor progression and metastasis, angiogenesis inhibition with agents such as everolimus and bevacizumab has become an attractive approach. However, data assessing their effectiveness in this type of malignancy have not been studied [13]. The lack of data on specific agents of this kind makes it difficult to comment on their efficacy with confidence. To date, there is no proven effective therapy for treating RMC.

In the current paper, we describe a 9-year-old boy with SCT, diagnosed with metastatic RMC. Despite advanced disease at presentation, he had an excellent response to aggressive cytotoxic chemotherapy with a tumor-free survival of 17 months.

Case description

9-year-old previously healthy Hispanic boy, presented to our institution with worsening dyspnea, dysphagia, and cough spells associated with nausea and persistent vomiting. Patient had a 10-pound weight loss, progressing over 4 months. Upon the initial evaluation, patient was in mild respiratory distress using accessory muscles for breathing and a low oxygen saturation breathing at room air (87%). Supraclavicular and cervical lymphadenopathy was evident

upon palpation, most prominent in the left cervical region. His chest auscultation was significant for decreased breath sounds bilaterally with dullness to percussion. Abdomen was diffusely tender in four quadrants, with diminished bowel sounds. The initial routine laboratory investigation was significant for normal cell counts and relatively normal chemistry except for a hypochloremic metabolic alkalosis with a central bicarbonate in 31 and chloride in 88. Lactate dehydrogenase levels were slightly elevated to 455. Liver function tests, uric acid, renal function, and urine analysis were unremarkable. Arterial blood gases were remarkable for hypoxemia with PO₂ of 50 and metabolic alkalosis with pH 7.461.

With a working diagnosis of an esophageal mass an upper endoscopy was performed, which was unremarkable. Subsequently, a cervical computed tomography (CT) scan showed multiple, enlarged, necrotic lymph nodes, the larger of which measured 9 cm transverse, and no evidence of aerodigestive tract lesions. This prompted a chest CT scan (Fig. 1a), which showed innumerable pulmonary parenchymal nodular radiopacities, mediastinal and bilateral hilar lymphadenopathy, as well as bilateral small pleural effusions. An abdominopelvic CT scan (Fig. 1c) showed asymmetric enlargement of the left kidney (11.9 cm long vs right kidney measuring 8.8 cm) with associated mild hydronephrosis. A left kidney mid-pole rounded hypodense lesion with central fluid attenuation measuring ~1.8 × 1.9 cm was also noted. In addition, multiple, confluent, large, retroperitoneal paraaortic lymph nodes some with central necrosis were seen centered in the left renal hilum with associated encasement of the left renal artery and mass effect upon the left renal vein. One of the aforementioned left retroperitoneal lymph nodes was seen abutting the left adrenal gland suspicious of a left adrenal metastatic deposit.

Incisional biopsy of a left cervical lymph node revealed metastatic renal medullary carcinoma (Fig. 2). The neoplastic cells stained positive for epithelial membrane antigen, cytokeratin 8/18, cytokeratin 19, cytokeratin 7, and vimentin on immunohistochemical analyses. The cells stained negative for RCC, HMWK, CEA, INI-1, CD10, and PAX8.

Due to the extensiveness of the tumor burden, decision was made to defer surgery until a more suitable clean resection could be made. We choose PCG over other chemotherapy regimens for various reasons. First of all, he had bilateral significant pleural effusions and methotrexate's elimination is documented to be reduced in patients with pleural or pericardial effusions resulting in prolonged half-life and increased toxicity. In addition, cisplatin is associated with severe cumulative nephrotoxicity and ototoxicity which is more pronounced in children and can be associated with deafness. On the other hand, carboplatin has limited potential for nephrotoxicity, unless administered concomitantly with aminoglycosides or other nephrotoxic agents. For this

Fig. 1 CT scans. **a** Chest. Innumerable pulmonary parenchymal nodular radiopacities with thickening of lobular pulmonary septae in some regions as well as mediastinal and bilateral hilar lymphadenopathy. Small bilateral pleural effusions, **b** near complete resolution of previously described bilateral pulmonary nodules, **c** asymmetric enlargement of the left kidney (right kidney measured 8.8 cm long

and left 11.9 cm long) with associated mild hydronephrosis. A left kidney mid-pole rounded hypodense lesion with central fluid attenuation measuring $\sim 1.8 \text{ cm} \times 1.9 \text{ cm}$ with adjacent lymphadenopathy was also noted; **d** there has been interval resolution of the previously visualized left interpolar renal lesion, now only showing renal scarring and a small residual mass in the left adrenal gland

reason, we explored other treatment regimens for malignancies of the genitourinary system that does not include methotrexate or cisplatin. Thus, we decided to use PCG substituting cisplatin for carboplatin to minimize further ototoxicity and nephrotoxicity in a patient that would most likely be dependent on a single kidney in a long run.

The patient began treatment with paclitaxel 80 mg/m^2 and gemcitabine 1000 mg/m^2 on days 1, 8, and 15, and carboplatin 4 mg/ml/min on day 1. This was repeated every 21 days for a total of nine cycles.

After his first course of chemotherapy, his dysphagia and cough improved significantly. A repeated CT scan after the fourth course demonstrated dramatic improvement of the primary left kidney lesion and the pulmonary, and lymphatic metastatic disease. However, the hyperenhancing nodularity within the anterior aspect of the superior pole of the left kidney was still noted. After the seventh cycle, a repeated CT scan showed complete resolution of the mediastinal

lymphadenopathy and the bilateral pulmonary nodules (Fig. 1b). It showed interval resolution of the left interpolar renal lesion and decrease in size of the previously visualized left adrenal gland metastatic deposit (Fig. 1d). The patient underwent an additional two cycles (nine total) of combination chemotherapy. For the fourth and seven cycles, the day 15 chemotherapy doses were held due to thrombocytopenia (platelet count $< 50,000$) and severe neutropenia (ANC < 500) requiring platelet transfusions and filgrastim.

The patient tolerated the chemotherapy relatively well without major infection, bleeding, ototoxicity, or nephrotoxicity. His major complaints were mild nausea and vomiting which were treated with ondansetron. After the ninth cycle, a whole-body PET/CT Scan was performed. The study demonstrated no evidence of abnormal F-18 FDG accumulation involving both lung fields or interpolar region of the left kidney that suggested neoplastic involvement or recurrence of disease. However, it demonstrated

Fig. 2 Pathology. **a** Sheet of tumor cells replacing lymph node, H&E $\times 10$, **b** high magnification of tumor cells with abundant eosinophilic cytoplasm and large pleomorphic vesicular nuclei with prominent

nucleoli, H&E $\times 40$, **c–e** positive immunoreaction to cytokeratins CK7, CK8/18, and CK19, **f** EMA positivity $\times 20$, **g** Vimentin positive cells, $\times 20$

an increased F-18 FDG accumulation involving the left adrenal gland measuring 1.27 cm $\times$ 1.62 cm with an SUV of 5.46. This finding was compatible with residual neoplastic involvement.

After count recovery, the patient underwent left adrenal-ectomy. The pathology analysis from the left adrenal gland showed margins negative of disease. In view of these findings, our patient did not receive any chemotherapy after surgery. At the time of writing this manuscript, the patient is disease-free 28 months from diagnosis.

Discussion

What renders our case most unique is the occurrence of this condition in a 9-year-old boy (the youngest of all cases reported to date) located in the left non-predominant side for this type of tumor, making the diagnosis of RMC less likely in our differential. In addition, our patient did not have any of the signs of the “classic renal tumor triad” (flank pain, hematuria, and flank mass). We could have been misled further had the history of SCT not been pursued.

Currently, the pathogenesis of this tumor is not well understood. Some studies suggest that hypoxia and acidosis, more pronounced in the renal medulla as compared to cortical areas where Renal Cell Carcinoma and Wilms tumor arise, lead to increased expression of hypoxia inducible factor, tumor protein 53, and vascular endothelial growth factor. This in turn leads to angiogenesis and tumor development [14, 15]. However, these conditions which promote sickling of erythrocytes are also present in the renal environment of SCA individuals, but these patients do not exhibit a higher incidence of RMC than the general population. Therefore, other unknown contributors must be playing important roles. Liu Q, et al. suggested in 2013 that SMARCB1, a tumor suppressor protein, is not detectable in renal medullary carcinoma by immunohistochemistry. Thus, inactivation of the SMARCB1 gene may play a role in the pathogenesis as well as *ALK* re-arrangements [16]. These all are promising findings in a path toward understanding this rare malignancy. Molecular studies as well as prospective trials are needed to further describe this aggressive tumor and improve the clinical outcomes by targeting it in an effective manner.

PCG has been described in the literature as an effective regimen for metastatic urothelial cancer in patients who have good performance status [5, 7]. This is probably one of the reasons why in our patient was very effective. In addition, our patient, despite having metastatic disease, had a very small primary tumor compared to the bigger tumors reported in literature. It is probable that this is another factor that contributed to the favorable response. In our institution, there are two other cases of diagnosed metastatic RMC with similar presentation which have responded favorably to PCG with a long overall survival (more than 4 and 15 months, respectively), yet another reason why we can definitely support the effectiveness of this regimen for this type of malignancy.

For nearly 4 decades, screening for sickle cell disease and related hemoglobinopathies has been part of state-public health newborn screening programs in the U.S, Canada, and Europe. However, the current guidelines only include counseling regarding conception. Due to the well-defined association between RMC and SCT, the widespread prevalence of SCT, and RMC's nearly uniform fatality when diagnosed in its metastatic form, early diagnosis is critical for survival. In this globalized world, changing immigration patterns are causing increased prevalence of this condition in countries previously thought to be spared due to genetic background. Thus, we think that the medical community, especially primary care physicians, should be aware of this malignancy and its most common presenting forms. In addition, it is possible that individuals with SCT might benefit from a thorough orientation about all the implications of SCT, so they too can be attentive and act accordingly. Screening for RMC in SCT patients might be an overreach, but current

screening programs could be extended as a simple intervention and preventive strategy to improve clinical outcomes.

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Compliance with ethical standards

Conflict of interest All the authors have declared no competing interest.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

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