Renal Medullary Carcinoma: Establishing Standards in Practice

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ASSOCIATED CONTENT

See accompanying commentaries on pages 422 and 424

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Abstract

Although renal medullary carcinoma (RMC) is a rare subtype of kidney cancer, it is particularly devastating in that it is nearly uniformly lethal. No established guidelines exist for the diagnosis and management of RMC. In April 2016, a panel of experts developed clinical guidelines on the basis of a literature review and consensus statements. The goal was to propose recommendations for standardized diagnostic and management approaches and to establish an international clinical registry and biorepository for RMC. Published data are limited to case reports and small retrospective reviews. The RMC Working Group prepared recommendations to inform providers and patients faced with a low level of medical evidence. The diagnosis of RMC should be considered in all patients younger than 50 years with poorly differentiated carcinoma that arises from the renal medulla. These patients should be tested for sickle cell hemoglobinopathies, and if positive, SMARCB1/INI1 loss should be confirmed by immunohistochemistry. The majority of patients with RMC are diagnosed with metastatic disease. Upfront radical nephrectomy should be considered in patients with good performance status and low metastatic burden or after response to systemic therapy. Currently, cytotoxic, platinum-based chemotherapy provides the best, albeit brief, palliative clinical benefit. Vascular endothelial growth factor–directed therapies and mammalian target of rapamycin inhibitors are ineffective in RMC as monotherapy. Therapeutic trials of novel agents are now available for RMC, and every effort should be made to enroll patients in clinical studies.

INTRODUCTION

Renal medullary carcinoma (RMC) is a rare and particularly devastating disease that affects adolescents and young adults. In April 2016, a small international group of investigators that represented pathology, pediatric and medical oncology, urology, nephrology, hematology, cancer genomics, and therapeutic development interests in RMC gathered in Nashville, Tennessee, to discuss the status of this disease biologically and clinically to take the next steps in developing diagnostic and treatment algorithms for RMC.

EPIDEMIOLOGY AND NATURAL HISTORY

Sickle cell trait (SCT) affects 300 million people worldwide, with the largest number in sub-Saharan Africa.[1] However, prevalence rates vary widely, from 8% in African Americans to 10% to 20% in India, 20% in the Middle East, and as high as 20% to 40% in some parts of Africa.[2,3] Life expectancy with SCT has been similar to that

of unaffected individuals in American cohorts.[4] However, SCT is a risk factor for several conditions, including chronic kidney disease,[5] venous thromboembolism,[6] and sudden death.[7] The kidney is perhaps the organ most affected by SCT. In 1974, Berman[8] described six nephropathies in SCT: hematuria secondary to bleeding beneath the renal pelvic urothelium, papillary necrosis, nephrotic syndrome, renal infarction, hyposthenuria, and pyelonephritis. In 1995, Davis et al[9] described a distinctive subtype of renal cell carcinoma, RMC, that occurs almost exclusively in patients with SCT and termed it the seventh sickle cell nephropathy. Since, RMC has been recognized as a highly aggressive neoplasm almost exclusively associated with SCT (hemoglobin AS [HbAS]), although a few cases have been reported in individuals with homozygous SS disease (sickle cell anemia),[10,11] HbS/β-thalassemia,[12] and HbSC.[10,12] RMC is an extremely rare tumor and comprises < 0.5% of all renal carcinomas. However, its prevalence may be underestimated because underdiagnosis occurs as a result of difficulty in differentiating RMC from collecting duct carcinoma and other aggressive renal malignancies on the basis of standard histology evaluation (Table 1).[13] RMC is increasingly recognized in the Americas and Europe, but no information exists about its prevalence in sub-Saharan Africa, where SCT is endemic.

RMC affects primarily adolescents and young adults. Most patients present between the ages of 11 and 39 years and either already have a diagnosis of SCT or are given a diagnosis of SCT during work-up for RMC.[14] The most common presenting symptoms for RMC are gross hematuria, flank pain, and abdominal masses.[15] Males are disproportionately affected in a ratio of 2:1.[11,16] For unknown reasons, RMC has a predilection for the right-side kidney.[8,14] RMC is characterized by early and widespread metastases, and thus, most cases are diagnosed in late stages, and prognosis is poor.[16] In the initial series by Davis et al,[9] the median survival was 4 months. Even with chemotherapy and surgery, outcomes remain dismal, with a median survival of approximately 13 months.

Table 1. Differential Diagnosis of RMC

Differential Diagnosis of RMC by ISUP Classification	Molecular Diagnostics
RMC	Loss of SMARCB1/INI1
Carcinoma of the collecting ducts of Bellini	
MiT family translocation RCC Xp11 translocation RCC t(6;11) RCC	 Translocation Xp11 Nuclear immunoreactive TFE3
ALK translocation RCC (emerging tumor entity)	*VCL-ALK* translocation immunoreactive ALK
RCC, unclassified	

Abbreviations: ALK, anaplastic lymphoma kinase; ISUP, International Society of Urology Pathologists; MiT, microphthalmia-associated transcription; RCC, renal cell carcinoma; RMC, renal medullary carcinoma; TFE3, transcription factor E3; VCL, vinculin.

BIOLOGY

RMC is believed to arise from the renal papillae or calyceal epithelium and may be triggered by chronic medullary hypoxia as a result of sickled red cells in individuals with HbS and is suggested by strong expression of vascular endothelial growth factor and hypoxia-inducible factor,[17] although the mechanism has not been demonstrated conclusively. A critical finding in RMC is the loss of SMARCB1/INI1 in the switch/sucrose nonfermentable (SWI/SNF) complex, a key mediator of chromatin remodeling and modulation of transcriptional activity.[18-20] Biallelic loss of SMARCB1/INI1 is a hallmark feature in several childhood cancers, including malignant rhabdoid tumor of the kidney and atypical teratoid/rhabdoid tumor.[21-23] Furthermore, next-generation sequencing of many human neoplasms has revealed biallelic loss, loss of heterozygosity, or a high mutational frequency of various subunits of the SWI/SNF complex, which suggests a tumor suppressor role for SWI/SNF complex function.[24,25] Loss of SWI/SNF activity may be one step along the pathogenesis of RMC, but whether it is by itself sufficient for transformation remains unclear. Given the prevalence of this genomic alteration as a defining feature of the disease, the loss of SMARCB1/INI1 is almost certainly a major driving feature of this cancer.

The cell of origin of RMC remains unknown. Collecting duct carcinoma, which arises from the distal convoluted tubules,[26,27] and RMC share multiple similarities, including a predilection for the right-side kidney, the epicenter being in the renal medulla, and an aggressive clinical course.[28] Given the rarity of RMC, this similarity raises the question as to whether a small population of as yet undefined progenitor cells can potentially give rise to these tumors.

The SWI/SNF complex has an antagonistic relationship with EZH2, a subunit of the polycomb repressor complex that functions as a histone 3 lysine 27 methyltransferase.[29] SMARCB1/INI1-deficient tumors demonstrate increased

EZH2 activity, which is believed to promote tumor cell growth by repressing differentiation.[30,31] Inhibition of EZH2 activity induces cell death in SWI/SNF-deficient cell lines, which makes it a potential therapeutic target.[32] Accordingly, an ongoing phase II trial is testing the efficacy of the EZH2 inhibitor tazemetostat against SMARCB1/INI1-negative tumors, including RMC (ClinicalTrials.gov identifier NCT02601950). An ongoing phase I trial also is using the EZH2 inhibitor tazemetostat in pediatric patients with relapsed or refractory SMARCB1/INI1-negative tumors or synovial sarcoma (ClinicalTrials.gov identifier NCT02601937).

DIAGNOSIS OF RMC

Although a standard definition of RMC has not been agreed upon, one of the strongest needs identified during the panel meeting was a consensus to put forth an encompassing definition of RMC that allows for increased awareness as well as appropriate diagnosis and inclusion of patients (Tables 1 and 2).[33] Thus, RMC should always be considered in the differential diagnosis for patients younger than 50 years with SCT who present with hematuria, flank pain, weight loss, or symptoms associated with metastatic disease. Imaging in these patients commonly identifies a mass, more often in the right-side kidney, with an average size of 7 cm and associated satellite lesions with intratumoral necrosis.[14,34,35] On computed tomography imaging, RMC displays lower enhancement than the renal cortex and medulla.[36]

Table 2. Associated Features of RMC

RMC Diagnostic	Associated Features
Patient characteristics	Age < 50 years old Sickle cell trait (hemoglobin AS) Alternate hemoglobinopathies
Symptoms	Hematuria Flank pain Symptoms of metastatic disease
Gross evaluation	Right-side kidney more commonly affected than left-side kidney Average size, 7 cm Satellite lesions Intratumoral necrosis
Imaging	On computed tomography scan, tumor displays lower enhancement than renal cortex or medulla
Pathology	Infiltrative tumor extending from renal pelvis Sheets of poorly differentiated cells Reticular growth pattern Adenoid cystic component Neutrophil infiltrate predominance Loss of SMARCB1/INI1

Abbreviation: RMC, renal medullary carcinoma.

On gross pathologic review, RMC is an infiltrative tumor that extends from the renal pelvis. Histologically, these tumors comprise sheets of poorly differentiated cells commonly found to have a reticular growth pattern and adenoid cystic component with an infiltrate of neutrophils[35,37,38] (Fig 1A). Visualization of sickled RBCs in the specimen is pathognomonic for this disease. As discussed previously, a majority of RMCs has been associated with loss of SMARCB1/INI1 (Fig 1B), which may occur through chromosomal translocation or deletions that result in the loss of protein expression identifiable by immunohistochemistry.[39] Integrative analysis of larger cohorts is needed to clarify whether translocation of *SMARCB1/INI1* is a pathognomonic feature of RMC or whether other alterations such as mutations of *SMARCB1/INI1* may also be involved in the genesis of this disease. Many countries where SCT is endemic do not have access to sequencing and special testing. Therefore, creation of a standard definition that does not rely on molecular studies and where pathologic examination alone may be confirmatory for the diagnosis of RMC would be ideal. Although a majority of patients with RMC exhibit loss of SMARCB1/INI1, other subtypes of RMC exist, specifically SCT with a rare anaplastic lymphoma kinase (*ALK*) translocation that results in its fusion with vinculin.[40] Renal neoplasms that harbor this rare vinculin-ALK fusion occur in younger patients (mean age, 9 years) with SCT and arise from the renal medulla but demonstrate intact SMARCB1/INI1 and much lower proliferative activity (protein encoded by the *MKI67* gene, approximately 5%), which may represent a distinct disease process or a variant RMC. In addition, as previously mentioned, approximately 10% of collecting duct carcinomas have been reported to have SMARCB1/INI1 loss in the absence of SCT.[41] The relationship or overlap of these diseases with regard to therapeutic consideration is not yet developed.

TREATMENT OF RMC

The standard-of-care treatment for localized RMC is nephrectomy followed by close monitoring, which is based on

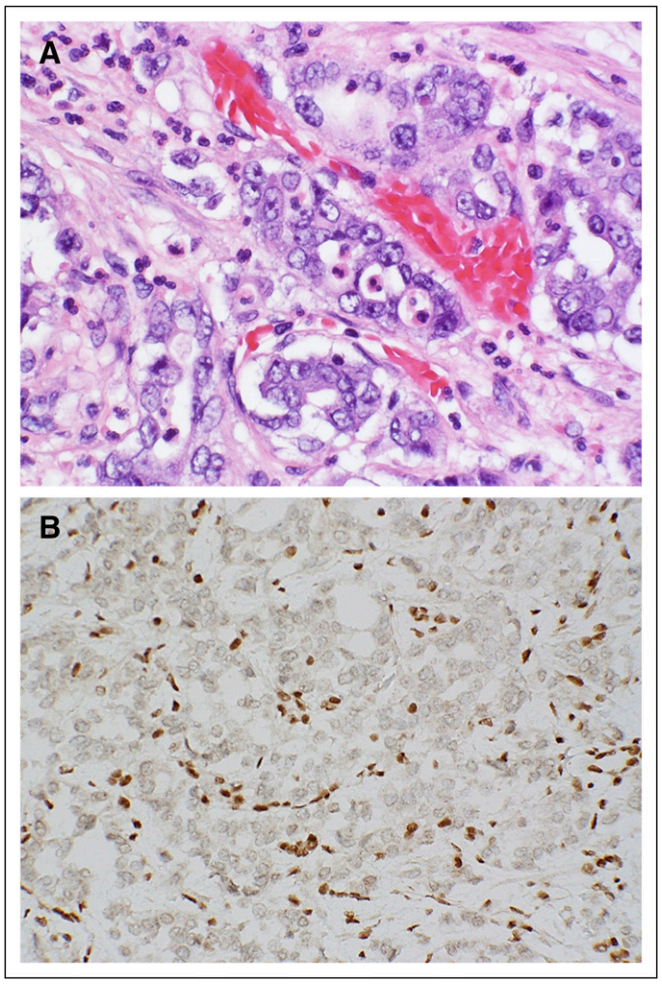

Fig 1. (A) Pathologic representation of renal medullary carcinoma. Hematoxylin and eosin stain (magnification, ×200) shows markedly atypical cells arranged in nests and cords infiltrated by abundant neutrophils. (B) Renal medullary carcinoma. Immunohistochemical stain (magnification, ×100) shows SMARCB1/INI1 loss in tumor cells, whereas expression is retained in endothelial cells.

experience gained with renal cell carcinoma (RCC),[42] although RMC rarely presents as localized disease (approximately 5% of cases).[12] Because RMC is an infiltrative tumor and arises from the renal medulla, radical rather than partial nephrectomy is the recommended operation according to the RMC Working Group's clinical experience. Cytoreductive nephrectomy, which remains the standard of care in RCC,[43] has not been studied for RMC. At the time of diagnosis, 70.8% of patients have local lymph node involvement, 71.3% have one site of metastatic disease, and 31.3% have two sites of metastatic involvement, most commonly in the lymph node, lung, liver, or contralateral kidney.[12] In a recent multicenter collaborative study that collected data from 56 patients with RMC, nephrectomy and systemic chemotherapy had superior overall survival than systemic chemotherapy alone, with a difference of 16.4 versus 7.0 months ($P < .001$).[12] If the patient's performance status is 0 or 1 and the metastatic burden is low without visceral or bone metastasis, the RMC Working Group recommends upfront nephrectomy with retroperitoneal lymph node dissection for optimal debulking to benefit patients with RMC who commonly present with advanced disease (Fig 2). Given the aggressive nature of this disease and benefit seen in the largest retrospective study in RMC to date, the panel recommends that debulking nephrectomy be considered before or after systemic chemotherapy unless the patient's comorbidities or performance status prohibit surgical intervention.[12]

When possible, pretreatment tumor samples for genomic and molecular analysis are highly encouraged to confirm the diagnosis through demonstration of loss of SMARCB1/INI1 or to provide possible insights into the biology of the RMC and inform the selection of systemic therapy. For example, pretreatment specimens could help to identify the rare subset of RMC with *ALK* rearrangements, which may respond to ALK inhibitors.[44]

Clinical trials remain the mainstay of recommended treatment of this disease, particularly those that examine a biology-driven therapeutic option. In the absence of a clinical trial, cytotoxic chemotherapy with platinum-based regimens has demonstrated partial and complete responses with clinical benefit in several case series, including the largest by Shah et al[12] that reported a 29% response rate to chemotherapy. No direct comparisons exist among the various regimens. Regimens commonly used to treat metastatic urothelial carcinoma, including dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; gemcitabine plus cisplatin; doxorubicin plus gemcitabine; and paclitaxel plus carboplatin, appear to be similarly active and would be appropriate in the management of patients with RMC.[11,42-44] Vascular endothelial growth factor–directed therapies and mammalian target of rapamycin inhibitors, in the experience of the panel, produce little benefit in patients with RMC.

An unexplored area of opportunity is the new class of immune modulating agents, such as checkpoint inhibitors, that are demonstrating antitumor activity in a variety of tumors. Given the paucity of therapeutic options for RMC, these agents may be considered, ideally in the context of a clinical trial. Pathologic evaluation of RMC occasionally reveals immune infiltrative cells,[34] a finding that has predicted response

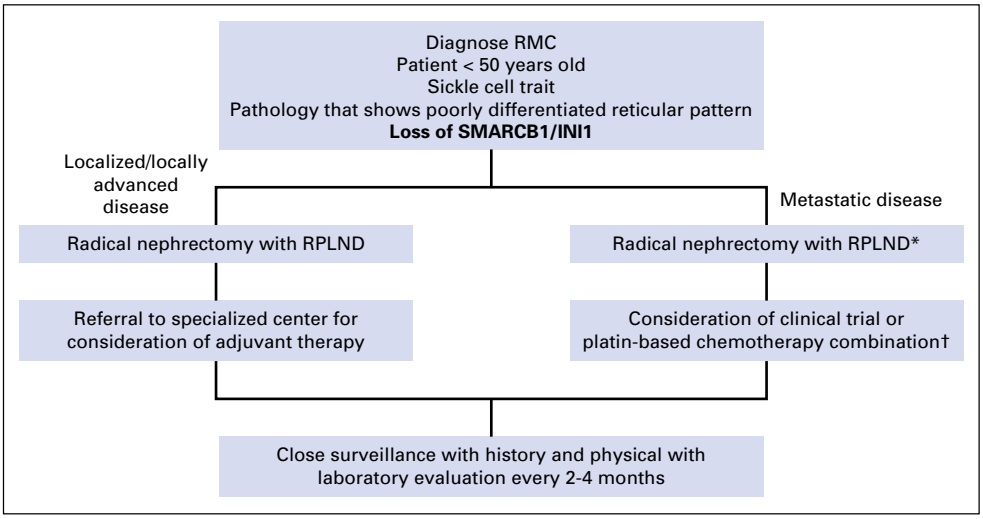

Fig 2. Renal medullary carcinoma (RMC) treatment algorithm. This flowchart represents diagnostic criteria and considerations in treating patients with RMC. *If performance status and surgical planning permit consideration. †Treatment with vascular endothelial growth factor–directed therapies or mammalian target of rapamycin inhibitors is not beneficial; single-agent chemotherapy is not encouraged. RPLND, retroperitoneal lymph node dissection.

to checkpoint inhibitors in other tumor types, such as melanoma.[45] A case report by Beckermann et al[46] has recently described a patient with RMC who developed tumor recurrence after nephrectomy and adjuvant cytotoxic chemotherapy and achieved a complete response since the start of the programmed death receptor-1 inhibitor nivolumab. A recently opened clinical trial (ClinicalTrials.gov identifier: NCT02721732) is evaluating the efficacy of the programmed death receptor-1 inhibitor pembrolizumab in patients with rare tumors, including RMC.

Finally, no evidence points to the benefit of screening individuals with SCT for RMC because currently, no feasible schedule and modality of screening would have a likelihood of identifying the presentation of disease at an early stage. In addition, no effective measures exist for the prevention of RMC.

DEVELOPMENT OF AN INTERNATIONAL REGISTRY OF PATIENTS WITH RMC AND SCT OR SICKLE CELL DISEASE

To date, our understanding of the incidence, natural history, and underlying biology of RMC is poorly defined. Reports in the medical literature are generally confined to small series or case reports, including a small number in individuals without SCT or sickle cell disease.[16,47-49] However, given the rarity of RMC coupled with its ambiguous definition and rapidly fatal clinical course, the true incidence remains unclear. In addition, although most cases of RMC have been described in association with SCT for more than two decades, our understanding of the shared biology and epidemiology between these two conditions remains limited.

We propose to develop clinical and biologic registries of patients with SCT or sickle cell disease (HbSS) and RMC through partnerships with academic institutions in the United States, Europe, Central and South America, Caribbean countries, and West Africa to accurately define the incidence, natural history, and underlying pathophysiology of RMC on a global level. To what extent the tumor microenvironment, gene interactions, epigenetic modifiers, or a combination of these factors predispose individuals with SCT and sickle cell disease to develop RMC is unclear.[17] In addition, the incidence of RMC has been described largely in individuals with SCT compared with HbSS. Because patients with HbSS now survive into later adulthood (only over the past few decades), whether the higher prevalence of RMC in individuals with SCT is a true biologic effect versus a reflection of our limited ability to diagnose the disease in individuals with HbSS as a result of premature mortality is difficult to determine. However, in a recent study of 3,596 patients registered in the Nigerian sickle cell disease registry and reviewed over a 10-year period, the prevalence of RMC in this patient group was 0.056%, with only two patients being diagnosed.[50] We anticipate that development of an international registry of patients with RMC will help to answer these questions and welcome the participation of any interested parties.

ADVOCACY

Key components to successful improvement in diagnosing and treating RMC is enhanced awareness, education, and communication. A strong advocacy program led by a network of social media sites, such as RMC Support[51] and the Chris "CJ" Johnson Foundation,[52] can help to bring this awareness to patients and caregivers and serve as a link to information for inexperienced providers. The RMC Working Group and others in the field stand committed to provide rapid communication and guidance for the treatment of this disease. Finally, the establishment of an RMC alliance that comprises experts in the field and formation of partnerships with government agencies, industry, and advocacy groups are necessary to break down barriers to early referral and diagnosis of RMC to expedite the development of novel therapeutic agents for this devastating disease.

FUTURE DIRECTIONS

In summary, RMC is a rare but devastating malignancy that most often presents in young adults with SCT and less commonly in patients with sickle cell disease or without a recognized hemoglobinopathy. The true incidence of this cancer is unknown and may be more prevalent than previously considered because individual cases can occur in geographic settings without access to tertiary care where comprehensive diagnostic and management considerations can be implemented. Unfortunately, most patients have advanced disease at presentation, and survival often is limited to months from the date of initial diagnosis. Although a renal tumor characterized by loss of SMARCB1/INI1 expression in a patient with SCT is generally agreed to be diagnostic of RMC, the need for a uniform diagnostic algorithm for this rare disease remains. This first RMC Working Group gathered and reviewed the data and reached consensus in accordance with WHO and International Society of Urologic Pathologists classification that RMC is a rapidly progressive neoplasm of the renal medulla most frequently, though not exclusively, found in patients with SCT who exhibit loss of expression in SMARCB1/INI1, although the group acknowledges additional molecular alterations that may also be associated with subtypes of RMC. The mainstay of treatment of metastatic RMC is radical nephrectomy with retroperitoneal lymph node dissection when performance status permits and consideration for enrollment in a clinical trial or for systemic platinum-based chemotherapy. We recommend the referral of patients with RMC for urgent consultation at a tertiary care center for consideration of nephrectomy as well as for enrollment in a clinical trial. The banking of tumor specimens from treatment-naïve patients is strongly encouraged for future investigations and to develop individualized targeted therapies in vitro. If enrollment in a clinical trial is not an option, we recommend that systemic combination chemotherapy with cisplatin or carboplatin, a taxane, gemcitabine, or doxorubicin. Multidisciplinary teams that comprise pediatric and medical oncologists, urologists, radiologists, and pathologists are essential to expedite experienced diagnosis and treatment of these patients.

Despite that RMC has been described in the medical literature for more than two decades, many questions remain unanswered but are critical to address to optimize the future care of this patient population. Future directions include the development of a uniform diagnostic algorithm for RMC that can be applied to areas of the world where the burden of SCT is the highest and diagnostic tools and resources are limited. Development of an international clinical registry and biorepository of blood and tumor specimens is critical for defining the incidence, natural history, and underlying pathogenesis of RMC. An increase in education about RMC and reinforcement of advocacy efforts as well as awareness of SCT status in the general population are critical to facilitate earlier diagnosis, to determine true incidence, and to increase the number of patients who receive comprehensive treatment and participate in clinical trials. JOP

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Authors' Disclosures of Potential Conflicts of Interest

Disclosures provided by the authors are available with this article at jop.ascopubs.org.

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