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KIDNEY DISEASES (G CIANCIO, SECTION EDITOR)

Renal Medullary Carcinoma: a Report of the Current Literature

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Abstract

Purpose of the Review We present an updated report of renal medullary carcinoma (RMC), a rare and aggressive condition.

Recent Findings There is a majority of male patients, of African descent, in the second or third decade of life. In differential diagnosis, other tumors, such as malignant rhabdoid tumor (MRT), vinculin-anaplastic lymphoma kinase (VCL-ALK) translocation renal cell carcinoma, and collecting duct carcinoma, may present difficulties. Abnormalities of tumor suppressor gene SMARCB1 have been found in RMC. Reported symptoms were hematuria, pain, weight loss, respiratory distress, palpable mass, cough, and fever. Most patients present with metastases at diagnosis. There is no definite recommended treatment, and protocols are extrapolated from other malignancies, with nephrectomy and systemic therapies being most frequently used. Response to treatment and prognosis remain very poor.

Summary RMC is a rare and aggressive tumor. Definitive diagnosis requires histological assessment and the presence of sickle-cell hemoglobinopathies.

Keywords Renal medullary carcinoma · Kidney cancer · Sickle cell

Introduction

Renal medullary carcinoma (RMC) is a very rare and aggressive neoplasm that occurs mostly in the second and third decades of life, with male preponderance, in persons of African descent with sickle cell trait or sickle cell disease [1, 2••]. First described by Davis in 1995 [3•], RMC develops within the renal medulla, in locations in the kidney with pronounced sickling, the calyceal epithelium of the renal pelvis or near the renal papillae [4]. RMC grows rapidly, presenting with hematuria, flank pain, or palpable mass, referred as the components of the "renal cancer triad", and weight loss; the initial clinical evidence may be marked by metastatic deposits [4, 5]. Although this tumor comprises < 0.5% of renal carcinomas, its prevalence could be underestimated because of difficulty in differentiating it from collecting duct carcinoma (CDC) and other renal malignancies [6]. It is important that clinicians be aware of this rare and aggressive complication in patients with sickle cell trait to act promptly. We present an updated report of this devastating condition.

Materials and Methods

We conducted a search on Medline and PubMed databases to identify recent (2013–present) clinical cases of RMC. Search terms used were (kidney OR renal) AND (medulla*) AND (cancer OR carcinoma OR malignancy). References of included manuscripts were assessed to identify additional studies. Case reports and series published as full texts were included. Thirty-five case reports and case series were selected, and all relevant information was extracted into a database. No language restrictions were applied. In addition, 19 reviews were identified to construct an overview. Two reviewers screened all titles, abstracts, and full texts identified by the search with discrepancies on eligibility criteria resolved by consensus and/or discussion and extracted data from the included reports using standardized and piloted forms. Prespecified data items determined a priori included patient

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demographics (sex, age, race, history, clinical features, location, lymph node, metastases at presentation, size, treatments, follow-up, relapse/progression, secondary treatment, response, overall survival, and time to death, amongst others). Findings from cases and the overview were then integrated into a narrative review.

Epidemiology

Thirty-five case reports and case series were included [2••, 7–38, 39••, 40], with a total of 374 patients, 105 (28%) were females, 256 (68%) males, and 13 (4%) with sex information not available. Table 1 shows main characteristics of recently published cases of RMC.

In the reviewed cases, we found a majority of male patients, the mean age at presentation was 26.1 (range, 6–72 years). In 292 cases, race was reported, 84% (246/292) were African-Americans followed by 6% (16/292) Caucasians. RMC usually presents in teenagers or young adults, with the majority of cases in their 20s or early 30s, although some patients can be younger [1, 41, 42]. There is a twofold male predominance, and it has also been reported that the majority of patients are of African descent [1, 43]. The vast majority of patients with RMC have sickle cell trait or other associated hemoglobinopathy [42–46]. Although Nigeria reports the highest global burden of sickle cell disease, in a multicenter national survey for renal tumors in individuals with this condition, two RMC cases were reported in 3596 patients, a prevalence of 0.056% for RMC with sickle cell disease over a median follow-up of 10 years [47]. Evidence supports that there were very few patients who had small tumors and non-metastatic disease at presentation and who survived and, therefore, screening is not recommended [4].

Etiology

A total of 178/374 (48%) cases were assessed with the presence of sickle cell trait or hemoglobinopathy, 96% (171/178) of patients showed sickle hemoglobinopathies (including sickle cell trait) with diagnoses performed before or after tumor resection. RMC has been referred to as the seventh sickle cell nephropathy along with hematuria, hyposthenuria, renal papillary necrosis, proteinuria, renal tubular disorders, acute and chronic kidney injury, and sickle-cell glomerulopathy [3]. Sickle cell trait affects about 300 million people worldwide, and although their life expectancy has been shown to be similar to those without the trait, this is a risk factor for various conditions [6].

RMC is believed to be triggered by chronic hypoxia in the medulla as a result of sickle cells [6]. Since the identification of gene SMARCB1 mutation in malignant rhabdoid tumors, abnormalities of this gene have also been identified in other malignant neoplasms, mainly epithelioid sarcoma and RMC [48]. Gene SMARCB1 (SWI mating–type switching/SNF-related matrix-associated, actin-dependent regulator of chromatin, subfamily B, member 1) is a tumor suppressor gene from chromosome 22 at position 11.23 (22q11.23), functioning as part of the actin-dependent regulator of chromatin remodeling complex, which is important in gene regulation [45, 48]. The loss of SMARCB1 in the switch/sucrose nonfermentable (SWI/SNF) complex, a mediator of chromatin remodeling and modulation of transcriptional activity, in several neoplasms is suggestive of the tumor suppressor role for this complex [6]. Calderaro et al. observed that RMC has a simple and stable genome; SMARCB1 is genetically inactivated, and, in patients with sickle cell disease, the second hit occurs by a balanced translocation [49•]. The SWI/SNF complex is antagonistic to EZH2 (enhancer of zeste 2), a subunit of the polycomb repressor complex, a histone-lysine N-methyltransferase; in fact, tumors with deficiency of SMARCB1 demonstrate increased EZH2 activity, possibly promoting tumor cell growth through the repression of differentiation [49•]. The inhibition of EZH2 activity is a current line of research [6].

A recent model postulates that extreme hypoxia and hypertonicity in the renal medulla as well as regional ischemia induced by red blood cell sickling activate DNA repair mechanisms to produce deletions and translocations in SMARCB1, located at a hotspot for de novo deletions and translocations [50•]. This results in perturbations of interstitial osmolarity that reactivate DNA double strand break repair; under hypoxic conditions, cells must utilize the low-fidelity classical nonhomologous end joining repair pathway instead of pathways associated with high-fidelity homologous recombination [50•]. Moreover, the right-sided predilection may be due to differences in vascular anatomy as the right renal artery is longer, resulting in reduced blood flow in the right medulla vasa recta compared with the left, further exacerbating regional microinfarctions and predisposing to RMC [50•].

Differential Diagnosis

In differential diagnosis, other tumors may present difficulties, and these include malignant rhabdoid tumor (MRT), vinculin-anaplastic lymphoma kinase (VCL-ALK) translocation renal cell carcinoma, and CDC. Indeed, MRT can be morphologically and immunohistochemically similar to RMC but with a different clinical setting; MRT occurs in children under 3 years whereas RMC is very unusual in children less than 5 years [6, 15, 42]. Also, if the patient has a history of sickle cell hemoglobinopathy or if sickle cells are found, the diagnosis would more probably be RMC [6, 15, 42]. On the other hand, VCL-ALK renal cell carcinoma, a newly described entity, has occurred in patients with sickle cell trait, and both VCL-ALK

Table 1 Characteristics of case reports

First author	Year	Sex	Age	Clinical features	Type of treatment	Overall survival, in months	Mortality
Di Stefano [7],	2018	F	42	Hematuria	Surgery, systemic, radio	22	No
Carden [8],	2018	M	17	Hematuria	Surgery, systemic	192	No
Lai [9],	2018	M	76	NA	Surgery, systemic	3	No
Goenaga-Vazquez [10],	2018	M	9	Pain, nausea, vomiting, cough, dysphagia, weight loss.	Systemic, surgery	28	No
Ahmad [11],	2017	F	17	Hematuria, pain, left loin swelling	Surgery, systemic	10	Yes
Sodji [31],	2017	F	24	Hematuria, pain	Surgery, systemic	25	No
Sodji		M	57	Hematuria, pain	Surgery, systemic	3	No
Heng [12],	2017	M	24	Pain	Surgery, systemic	11	Yes
Ibilibor [13],	2015	M	20	Hematuria, pain	Palliative	1	No
Çalişkan [14],	2017	M	36	Hematuria	Surgery, systemic	15	No
Beckermann [15],	2017	M	29	Hematuria	Surgery, systemic	32	No
Carter [32],	2016	M	38	Hematuria	Surgery, radiotherapy, systemic	5	Yes
Carter		F	22	Pain	Systemic	15	Yes
Kalavar [16],	2017	F	29	Fever, cough	Systemic	5	Yes
Carden [33],	2017	F	10	Weight loss, lethargy, respiratory distress	Systemic	91	Yes
Carden		M	14	Hematuria, pain, weight loss.	Surgery, systemic	23	No
Colombo [17],	2015	M	23	Pain	Surgery, systemic	10	Yes
Batra [18],	2016	M	20	Hematuria, pain, shortness of breath	Systemic, surgery	42	No
Rabener [19],	2015	M	29	Pain	Surgery, systemic	NA	No
Lipkin [20],	2015	M	27	Hematuria, pain	Surgery, systemic	14	No
Mast Vilaseca [21],	2015	M	20	Hematuria, pain	NA	NA	NA
Sandri [22],	2014	F	29	Hematuria, pain, mass	Surgery, systemic	27	Yes
Tripathy [23],	2014	M	12	Hematuria, pain, weight loss, tenderness right loin region	NA	NA	NA
Amjad [24],	2014	F	23	Pain, weight loss, poor appetite	Systemic, surgery	16	Yes
Shetty [25],	2014	F	25	Pain	Surgery, systemic	32	Yes
Daher [26],	2014	M	13	Hematuria, pain, poor appetite	Surgery, systemic	10	No
Lam [27],	2013	M	66	Hematuria	Surgery, systemic	6	Yes
Maroja [28],	2013	M	23	Pain, disnea, weight loss	Systemic	2	Yes
Maroja		M	24	Pain	Surgery, systemic	8	Yes
Maroja		F	24	Pain, weight loss.	Systemic	5	Yes
Maroja		M	30	Hematuria, pain	Surgery, systemic	26	Yes
Maroja		M	24	Pain, weight loss.	Systemic	6	Yes
Marsh [29],	2013	M	13	Hematuria, pain	Surgery, systemic, radiotherapy	20	Yes
Anne [30],	2013	F	34	Breast bilateral masses	Systemic	12	Yes
	Number of patients			Clinical presentation	Treatment	Survival, in months	
Liu [34],	2013 15	5, F; 11, M	26 (8–49)	NA	NA	3–6	

Table 1 (continued)

First author	Year		Sex	Age	Clinical features	Type of treatment	Overall survival, in months	Mortality
Geller [35],	2015	13	NA	NA	NA	NA	NA	
Shi [36]	2015	6	3, F; 3,M	50 (22–72)	NA	Surgery, systemic	3	
Shah [2••],	2016	52	15, F; 37, M	28 (9–48)	Hematuria, pain, weight loss	Systemic only ($n = 14$); surgery, systemic ($n = 28$)	13	
Sandberg [37],	2017	25	6, F; 19, M	13 (6–21)	Abdominal pain, hematuria, weight loss	NA	NA	
Carlo [38],	2017	36	9, F; 27, M	28 (12–72)	Pain, hematuria	Surgery, systemic	5.8	
Ezekian [39••],	2017	159	47, F; 112, M	24 (20–31)	NA	Surgery ($n = 96$), Systemic ($n = 103$), Radiotherapy ($n = 19$)	7.7	
Ohe [40],	2018	33	9, F; 24, M	27 (10–63)	NA	NA	10.3	

Studies with > 5 patients

F, female; *M*, male; *NA*, not available

renal cell carcinoma and RMC can contain polygonal tumor cells, vesicular nuclei, and prominent eosinophilic cytoplasm; however, VCL-ALK renal cell carcinoma does not demonstrate loss of SMARCB1 [42]. CDCs occur in middle-aged to older adults; therefore, high-grade adenocarcinomas with loss of SMARCB1 expression in children or teenagers with sickle cell hemoglobinopathy would best be diagnosed as RMC [42]. It has been suggested to use the term "unclassified renal cell carcinoma with medullary phenotype" for high-grade renal adenocarcinomas with morphological, immunophenotypic, and molecular features similar to RMC but in patients with no evidence of hemoglobinopathy [45, 51].

Clinical Features

In 135/374 cases, symptoms were reported: hematuria was found in 44% (60/135), pain in 44% (59/135), weight loss in 26% (36/135), respiratory distress in 14% (19/135), and more rarely palpable mass, cough, and fever. Out of the 171/374 cases reporting which kidney was affected, 67% (114/171) were from the right kidney and 33% (57/171) from the left. Average size at diagnosis was 6.9 cm (1.9–16.0 cm). A total of 219/374 cases were assessed with the presence of lymph nodes; 87% (191/219) of patients presented abnormal lymph nodes, mostly involving multiple regions. The majority (81%) of the 125 cases reporting location of lymph node at diagnosis presented with regional nodes, of which 26% (32/125) were mediastinum and, less frequently, 4% cervical nodes (6/125). In those cases in which presentation at diagnosis was reported (279/374), 75% (210/279) of patients presented with metastases in the lungs, liver, bone, and, less frequently, adrenal gland, peritoneum, ovarium, breast, thyroid gland, or eye. Stage was reported in 211/374 cases, only 9% (18/211) were stage I–II and 92% (193/211) were stage III–IV.

As found in the literature, patients usually present with abdominal pain, gross hematuria, weight loss, and a palpable abdominal mass [45]. Initial symptomatic metastases may include neck nodes, cerebral metastases, or hemoptysis from lung metastases [45]. It has been suggested that the high incidence of metastasis may be due to aggressiveness of RMC, the delay in diagnosis caused by typical nonspecific symptoms, or a more aggressive form of the disease [39••]. The tumor tends to occupy a central location in the kidney infiltrating and replacing adjacent kidney tissue; also common are retroperitoneal lymphadenopathy and metastasis [41].

Pathology

RMC is a poorly circumscribed firm or soft, white to gray mass, ranging in size from 4 to 12 cm with a median of 7 cm, often originating in the kidney medulla and, in most

cases, showing hemorrhage and necrosis [42, 45]. .At the macroscopic level, invasion of the renal sinus, perirenal fat, renal vein, or collecting system is observed with dilatation of the pelvicalyceal system and, less frequently, the tumor infiltrating around and encasing the renal pelvis [45]. The histologic appearance of RMC is high-grade and architecturally variable, with growth patterns ranging from a resemblance of yolk sac tumor to reticular, cribriform, adenoid, and solid [42, 52]. Tumors consist of sheets of poorly differentiated epithelial cells, arranged as ducts or infiltrating tubules [45]. Most tumors demonstrate at least focal rhabdoid features, with eccentrically placed large nuclei, prominent nucleoli, and eosinophilic cytoplasm, with atypical bizarre mitotic features [42, 52]. Sickled erythrocytes can often be seen, and desmoplasia may be prominent [42]. Rhabdoid-, squamoid-, or spindle-shaped cells, neutrophils within the tumor, or microabscesses at its periphery, as well as intracytoplasmic mucin, are found [52]. There is usually a brisk neutrophil infiltrate and a cuff of lymphocytes and macrophages around the periphery of the tumor [45]. As with CDC, satellite nodules of RMC are common in the renal cortex especially in the immediate subcapsular zone [45].

Apart from the loss of SMARCB1 staining, cells of renal medullary carcinoma stain with AE1/AE3, CK7, CK20, Cam5.2, EMA, and vimentin, although results of high molecular weight keratin staining have been found to be variable. About 70% show nuclear OCT3/4 staining, a possible cause of confusion with yolk sac tumor [1, 45, 52]. To differentiate RMC from CDC, RMC shows loss of nuclear expression of INI-1 and expression of OCT3/4; also, most of the RMC cases show high P53 expression and Ki67 index [52].

Treatment

There is no standard treatment for managing RMC, and plans have been extrapolated from protocols for urothelial cell carcinoma or primary renal tumors [6, 15, 39••]. For localized RMC, which presents in just 5% of cases, the recommended treatment is nephrectomy followed by close monitoring [6]. In 249/374 cases (67%), type of treatment was reported, 71% (177/249) received some type of systemic therapy or chemotherapy and 69% (162/249) received a radical nephrectomy, mostly associated with some type of lymphadenectomy. With regard to systemic therapy, multiple schemes were used: (a) gemcitabine/bevacizumab/paclitaxel; (b) MVAC (methotrexate, vinblastine, Adriamycin, and cisplatin); (c) sunitinib/everolimus or doxorubicin; (d) etoposide/ifosfamide; (e) bevacizumab/everolimus; (f) monotherapy with nivolumab; (g) monotherapy with ipilimumab; and (h) bortezomib/pazopanib. In most cases, a partial response followed by an increase in the spread of the disease was observed. Radiotherapy was used in 9% (22/249) of cases to treat adenomegalies or in some bone metastases with acceptable local results. The most common relapse or progression sites were the lung, pleura, mediastinum nodes, and bone.

For localized non-metastatic tumors, surgery with partial nephrectomy has been shown to be effective; whereas, upfront radical nephrectomy can be considered in those cases with good performance status and low metastatic burden or after response to systemic therapy [6, 15]. Ezekian et al. in a large report of 159 patients from the US National Cancer Database showed a longer overall and disease-free survival in patients who underwent a nephrectomy but cautioned that the benefit was probably influenced by selection bias, because those with more advanced disease were less likely to receive a nephrectomy [39••]. Cytoreductive nephrectomy is a viable option to prolong survival of RMC patients [52]. A combination of surgery and chemotherapy is often used, with the following chemotherapy combinations most commonly reported in the literature: gemcitabine, paclitaxel and cisplatin or carboplatin, or the MAVC regimen [4]. Additionally, the topoisomerase II inhibitor etoposide may be of benefit due to the overexpression of topoisomerase II alpha in this tumor [52]. Other potential new drugs are histone deacetylase inhibitors, having shown activity against malignant rhabdoid tumor cell lines and the ALK inhibitor crizotinib [4]. Cytotoxic, platinum-based chemotherapy provides a brief palliative clinical benefit; vascular endothelial growth factor–directed therapies and mammalian target of rapamycin inhibitors are ineffective in RMC as monotherapies [6, 15]. In a report with 159 patients with RMC, Ezekian et al. identified that 60% of patients underwent surgery and 65% chemotherapy, with only 12% of patients receiving radiation [39••].

Prognosis

RMC is a highly aggressive cancer, with poor response to treatment, with a survival of 4–5 months in those cases with metastatic disease at the time of initial presentation [1, 53], and a mortality rate of 95% [4, 31]. In the last 31 case reports published, the median survival was 14 months. Notable cases were reported by Carter et al., who published the successful cure of a case of a 17-year-old male with relapse and metastasis, using high-dose chemotherapy with autologous stem-cell transplant (survival of 192 months), another patient who was disease free for 23 months from diagnosis, and a third patient who survived 7 years after initially receiving platinum plus bortezomib therapy [8, 33]. Also, Batra et al. reported a 20-year-old who has survived for 42 months and was treated with chemotherapy (gemcitabine, carboplatin), nephrectomy, and mainlining antiangiogenic therapy [18].

It has been shown that an advanced stage at diagnosis increases the risk of death by about threefold whereas patient age and tumor size did not impact survival [39, 54]. Common

sites of metastases are the lymph nodes, lung, liver, and brain [52]. In a multicenter study with 53 patients, Shah et al. reported that those patients who underwent nephrectomy had superior overall survival compared to patients treated with systemic therapy only; seven patients (13%) survived for > 24 months [2••]. In a report of 159 patients with RMC, Ezekian et al. identified that 60% of patients underwent surgery and 65% chemotherapy, with only a 12% of patients receiving radiation. They also found that those patients with metastatic disease had a significantly worse median survival (4.7 vs. 17.8 months, $P < 0.001$) and were less likely to receive surgery (42% vs. 91%, $P < 0.001$) [39••].

Conclusion

Renal medullary carcinoma is a very rare tumor with a dismal outcome that is presented mostly in young males, of African descent. It is highly aggressive, and most patients present with metastases at diagnosis. It should be considered as a differential diagnosis of CDCs upon imaging. Definitive diagnosis requires histological assessment and the presence of sickle cell hemoglobinopathies. The poor clinical outcomes despite conventional therapy indicate that there remains a pressing need for further research into molecular and genetic drivers of RMC that might help in the design of novel-targeted therapies.

Compliance with Ethical Standards

Conflict of Interest Leandro Blas, Javier Roberti, Jorgelina Petroni, Liliana Reniero, and Federico Cicora each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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