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# Renal Medullary Carcinoma

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# Renal Medullary Carcinoma

Temidayo Adebisi

## Overview

In 1974, Berman described six sickle cell nephropathies: gross hematuria, papillary necrosis, nephrotic syndrome, renal infarction, isosthenuria, and pyelonephritis.<sup>1</sup> In 1995, Davis et al described what has been suggested to be the seventh sickle cell nephropathy, renal medullary carcinoma (RMC)<sup>2</sup>. RMC is a malignant tumor originating from the collecting duct.<sup>3</sup>

## Epidemiology

RMC is found almost exclusively in patients of African descent with sickle cell hemoglobinopathies, although it has been rarely reported in Caucasians (<10 cases)<sup>4-9</sup>. It is a rare disease with an estimated 150 reported cases to date, mostly in patients with sickle cell trait or more rarely sickle cell disease.<sup>10</sup> It appears to be more common in males with a 2:1 ratio observed in adults.<sup>10</sup> In the pediatric population, the difference is more pronounced with a 5:1 male to female ratio reported.<sup>5</sup>

## Pathophysiology

The pathophysiology of RMC is incompletely understood. Swartz et al., using immunohistochemical analysis, reported that in a subset of the overall 40 cases they analyzed, the tumors expressed TP53 (tumor protein 53), VEGF (vascular endothelial growth factor), and HIF (hypoxia-inducible factors). Therefore they proposed that hypoxia in the kidney leads to increased expression of HIF and VEGF in the absence of normal p53 leading to neovascular network formation and tumor development.<sup>11</sup> Other studies have found that SMARCB1, another tumor suppressor protein, is not detectable in renal medullary carcinoma by immunohistochemistry, suggesting that inactivation of the SMARCB1 gene may play a role in the pathogenesis.<sup>12</sup>

RMC usually presents in the right kidney (>75% of cases) as a solitary poorly circumscribed mass (Table 1).<sup>10</sup> On sectioning, there is often evidence of necrosis and hemorrhage.

Microscopic examination often shows a microvesicular pattern, reminiscent of testicular yolk sac tumors. Sickled erythrocytes are often found within the tumor and adjacent tissues.<sup>5,13</sup>

#### Clinical presentation

Patient age at presentation ranges from 5 to 69 years with a mean of 19.<sup>5</sup> RMC commonly presents with flank pain and hematuria. Other symptoms include dysuria, abdominal mass and weight loss.<sup>3-5</sup> By the time of presentation, 95% of patients have evidence of metastasis.<sup>5</sup> The most common sites for metastasis are the regional lymph nodes, adrenal glands, lung, liver, inferior vena cava, and peritoneum.<sup>4</sup>

#### Differential diagnosis

Other causes of flank pain and hematuria in a patient with sickle cell trait include papillary necrosis and renal infarction. Patients with sickle cell trait often develop renal insufficiency by the fourth decade of life, but gross hematuria due to sickle cell nephropathy is unusual and should be a diagnosis of exclusion. Renal infarction and papillary necrosis can lead to scarring and deformity but usually do not present as a mass.<sup>4</sup> The differential diagnosis for flank pain and hematuria with a mass include high grade invasive urothelial carcinoma and collecting duct carcinoma. Neither urothelial carcinoma nor collecting duct carcinoma have an association with sickle cell hemoglobinopathies. Urothelial carcinoma has a mean age of presentation > 50 and adjacent typical urothelial carcinoma or carcinoma in situ is usually seen. Collecting duct carcinoma has a mean age of presentation between 50 and 55. On pathology, it has predominantly tubular and papillary features.<sup>14</sup>

## Diagnostic evaluation

RMC should be considered in a patient with sickle cell hemoglobinopathy who presents with flank pain and hematuria.<sup>4</sup> Imaging is the first step to determine whether a mass is present. This is usually done with CT scan, intravenous pyelography, or MRI. This typically reveals a tumor within the renal parenchyma involving the renal sinus and pelvis. The lesion's growth is infiltrative resulting in an increase in overall kidney size without changing its overall shape.<sup>5,14</sup> On imaging, evidence of metastasis will often be present. Tissue sample is needed to make the diagnosis. On pathology in addition to the features mentioned above, there is usually neutrophilic infiltrate, intraluminal mucin, and perinephric extension. Immunohistochemical profile is usually positive for vimentin and CK7 and negative for CK20, Ksp-cadherin, and Pax2.<sup>14</sup>

## Treatment and Prognosis

RMC has a very poor prognosis with mean survival time being less than one year and median survival time of 15 months after diagnosis. One option would be nephrectomy. However, this is usually not pursued as most patients present with evidence of metastasis. In addition, even in cases, where there is no evidence of metastasis, and the kidney is removed with clear margins and negative lymph nodes, nephrectomy bed and distant metastasis have occurred. Radiation therapy is also not efficacious. Multiple chemotherapy agents such as cyclophosphamide, doxorubicin, cisplatin, topotecan, methotrexate, vinblastine, and alpha interferon have not been successful in treating RMC.<sup>4,10</sup> Kondagunta et al. studied the use of bortezomib in metastatic renal cell carcinoma. Bortezomib is a proteasome inhibitor approved for treating multiple myeloma and mantle cell lymphoma. One patient in this trial had metastatic RMC. This patient received 1.3 mg/m<sup>2</sup> of the drug twice a week for two weeks, followed by one week without the medication, for a total of 7 months. This patient went into remission and had no evidence of

disease for 27 months of follow up.<sup>10,15</sup> However, more studies are needed to identify the most effective therapy.

Table 1. Case Series of RMC.

Study-	Age at diagnosis	Male to Female ratio	Ethnicity	Survival	Location and Tumor size	Further Notes
Liu et al. 2013 n = 15	8-49 yrs median 26 yrs	2:1	NR	NR	73% (11/15) right kidney; 27% (4/15) left kidney;  Size: 1.1-15 cm (av 5.9 cm)	9 of 10 RMC showed loss of heterozygosity of the SMARCB1 gene located on chromosome 22q.
Gupta et al. 2012 n = 13	8-58 yrs mean 24 yrs	10:1	8 = AA or African Brazilian  1= Caucasian	Median 17 weeks.	62% right kidney  Size: 4.1-12 cm (av 7cm)	*Includes patients from Watanabe et al.
Gatalica et al. 2011 n =3	28-34 yrs	All male	2 = Caucasian  1= AA	3-36 months	100% right kidney  Size: NR	All 3 cases showed increased hypoxia-inducible factor 1 $\alpha$ expression
Hakimi et al. 2007 n = 9	13-31 yrs	3.5:1	8 = AA  1= Hispanic	4-16 months (2 patients still living at last follow-up visit)	89% right kidney  Size: 4-12 cm	All presented with at least one component in the triad of: Hematuria, flank pain, or palpable mass.  Renal ultrasound is not sufficient and can miss the diagnosis.
Watanabe et al. 2007	8-69 yrs mean 22 yrs	All male	5= African-Brazilian	4 days- 9 months	71% right kidney	The youngest patient (8 yrs of age)

n= 7			1= Caucasian		Size: 4-12 cm (av 7 cm)	treated with radical nephrectomy alive with no recurrence 8 years after diagnosis
Simpson et al. 2005 n = 95*	5- 40 yrs (mean 19 yrs)	1.9:1	88%= Black  7%= Caucasian  5%= Hispanic	1-17 months	74% right kidney	Expression of ABL protein increased, but no evidence of BCR-ABL translocation.
Swartz et al. 2002 n =40	5-32 yrs (mean 14.8 yrs)	1.7:1	28= AA  3= Brazilian  3= Caucasian	2 weeks- 15 months (average 4 months)	75% right kidney  Size 1.9- 19 cm (av 7.4 cm)	No genetic gain or loss identified in 9 of 10 tested. One with loss of chromosome 22.
Davis et al. 1995 n=34	11-39 yrs	3:1	All Black	1-12 months	74%  Size 4-12 cm (av 7 cm)	First study to identify RMC with Sickle cell trait.

\* All cases reported in the English literature using Medline from 1995- 2003 plus 3 additional subjects from the author's institution.

Abbreviations: av= average; RMC= renal medullary carcinoma; yrs= years.

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