Case Report

Renal Medullary Carcinoma, A Rare But Aggressive Sickle Cell Nephropathy: A Case Report

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Abstract

Renal Medullary Carcinoma (RMC) is a highly aggressive cancer that typically affects adults in second to third decades of life with male preponderance and dismal prognosis. As the name indicates, it is medulla centric and is almost exclusively associated with sickle cell hemoglobinopathy. Tumor shows SMARCB1 /INI-1 deficiency and hence called SMARCB1 deficient renal medullary carcinoma. As there are only around 600 cases been reported worldwide till date, we report this case as an eye opener for having high degree of clinical and pathological suspicion in renal cancer patients of younger age, especially if there is no known history of hemoglobinopathy. Prompt diagnosis and treatment is warranted to prolong survival. Our case is that of a 36yr old male who presented with hematuria and loin pain of six months without any significant past history. Radiological evaluation showed right renal mass with extensive metastatic disease. Palliative right radical nephrectomy was done which on thorough histomorphological and immunohistochemical examination was diagnosed as renal medullary carcinoma. Tumor cells showed loss of INI 1 expression which is a surrogate marker for SMARCB1 deficient status. High performance liquid chromatography was done which revealed sickle cell trait. He was started on immunotherapy and chemotherapy, following which he had a favorable treatment response.

Keywords:

Renal medullary carcinoma, Sickle Cell Trait, Hemoglobinopathy, Prognosis

Introduction

Renal medullary carcinoma (RMC) primarily affects African males in the second and third decades with sickle cell hemoglobinopathy. Tumor is mainly centered in renal medulla and patients usually present with pain and hematuria and are found to have metastatic disease at diagnosis. [1] Prognosis is extremely poor with a dismal course and means survival is measured in months (1month - 26months) in most cases. RMC constitutes less than 1 percent of renal cell carcinomas. The first case was described by Davis et al. in 1995. [2, 3] We present a case of RMC including radiological and pathological findings, treatment, and outcome. A brief review of the literature is also presented, with an emphasis on its association with sickle cell trait, which was an unknown diagnosis in our patient at presentation.

Case Report

Our case was a 36-year-old male, evaluated from outside hospital for right loin pain and hematuria for 3 months. USG abdomen and pelvis showed right renal hypoechoic lesion possibly neoplastic. Splenomegaly was also noted. Computed tomography (CT) scan of Thorax with Abdomen showed right renal lesion, enlarged intra-abdominal and intra thoracic lymph nodes. PET CT showed a lesion in the mid cortical and lower pole of the right kidney with enlarged left supraclavicular, mediastinal, abdominal retroperitoneal and pelvic lymph nodes [Fig 1]. The marrow lesion in the head of right humerus and consolidatory changes in bilateral lung fields were also reported. Renal biopsy was done elsewhere which was reported as high-grade urothelial carcinoma. The slides were reviewed at our centre. We gave a descriptive report of scattered atypical cells in the background of necroinflammation with neutrophilic microabscess. As our patient was clinically diagnosed as having stage 4 renal cell carcinoma, palliative right radical nephrectomy was performed. We received a right kidney measuring 13.0 x 7.0 x 6.0 cms. On the cut section there was an infiltrating grey, white tumor measuring 8.5 x 5.0 x 7.0 cms seen predominantly at renal medulla involving pelvis and renal sinus and extending into cortex. The cut surface of tumor was grey, white with areas of necrosis and hemorrhage. The tumor was pushing into perirenal fat.

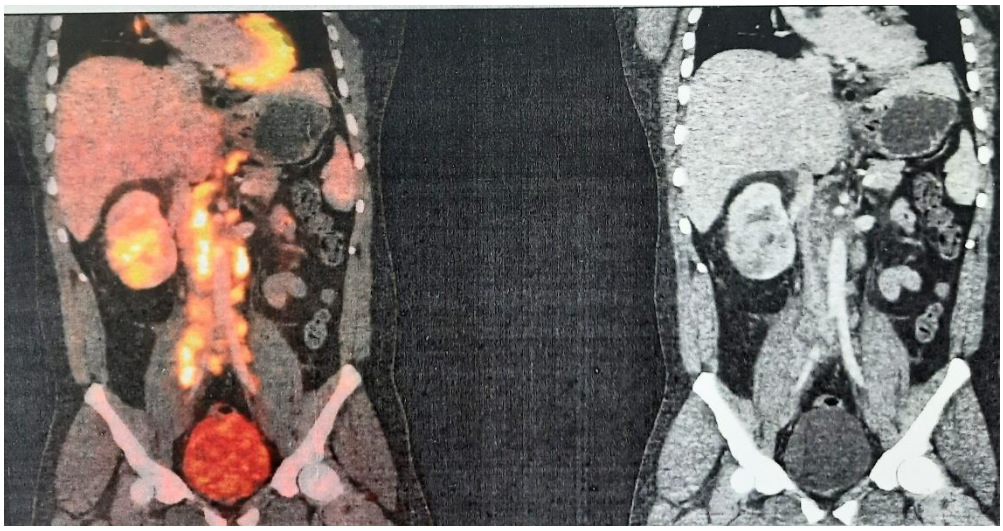

Figure 1: PET CT showed mid cortical and lower pole tumor of the right kidney with enlarged abdominal, retroperitoneal and pelvic lymph nodes.

Microscopy showed a widely infiltrating neoplasm mixed with extensive areas of necrosis and hemorrhage. Tumor was arranged as solid nests, sheets, microcytic spaces with dyscohesive tumor cells within it and cribriforming in areas [Fig 2]. Cells had moderate to abundant eosinophilic cytoplasm with vesicular nucleus and prominent nucleoli. Numerous mitoses and apoptosis were seen. Tumor cells were studded with neutrophil rich inflammatory infiltrate forming abscess like collection at multiple foci. Numerous sickled RBCs were seen within tumor and within adjacent renal vasculature and glomeruli [Fig 3]. No urothelial dysplasia was seen. Considering the primary diagnosis of renal medullary carcinoma, we proceeded with immunohistochemical studies. Tumor cells were patchy strong positive for CK7 and PAX 8, patchy weak positive for GATA3 with loss of INI 1. HMWCK and p63 were negative. IHC for ALK D5F3 was done which was negative. High performance liquid chromatography was done for the patient which revealed Sickle cell trait (HbS – sa q36.9%) [Fig 4]. Peripheral smear examination was within normal limits. This IHC profile excluded the differentials of collecting duct carcinoma, high grade urothelial carcinoma and VCL:

ALK fusion RCCs with sickle cell trait. The patient was started on pembrolizumab with gemcitabine and carboplatin. Follow up PET CT done after 3 months, showed favorable response to treatment with no evidence of clinically significant abnormal hyper metabolism anywhere in the body.

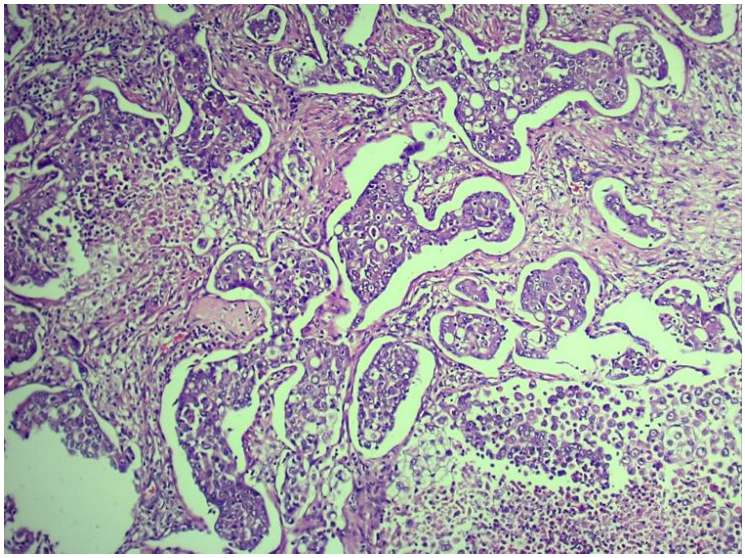

Figure 2: Tumor arranged as solid nests and dyscohesive cells within microcystic spaces in desmoplastic stroma. H&E-stained sections at 100X magnification

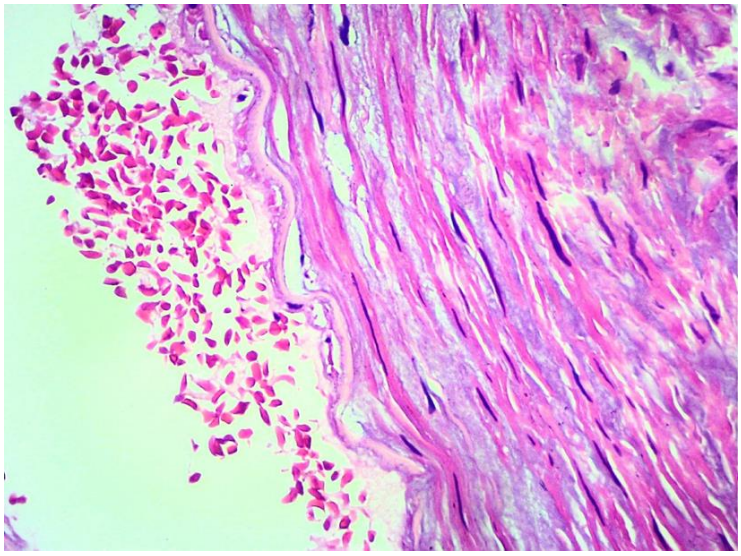

Figure 3: Hematoxylin and eosin-stained section shows numerous sickled RBCs within vessel at 1000X magnification.

Discussion

RMC is a rare but aggressive renal cell carcinoma described by Davis et al as the "seventh sickle cell nephropathy in 1995. Later two large, pooled reports were published. The first was by Iacovelli et al., which included 166 patients (1995–2013). [4] The second, by Alvarez et al., describing 217 patients (1995–2014) which included at least 154 (93%) of the Patients from the Iacovelli report. [5] These were the two main cohort studies describing this entity. Most reported cases were in blacks with 7-10%

prevalence in African American and 30% in Sub Saharan American population with a smaller proportion in Hispanic and Brazilian patients .A few cases were found in Whites .[6] It presents almost exclusively in patients with sickle cell trait (SCT), although it has also been reported in individuals with sickle cell anemia, hemoglobin S with Beta-thalassemia, and hemoglobin SC .[1–6] This explains why African population, where sickle cell hemoglobinopathy is highly prevalent is the most affected. Although the prevalence of SCT in India is up to 13%, case reports of RMC from India are sparse after thorough literature search.

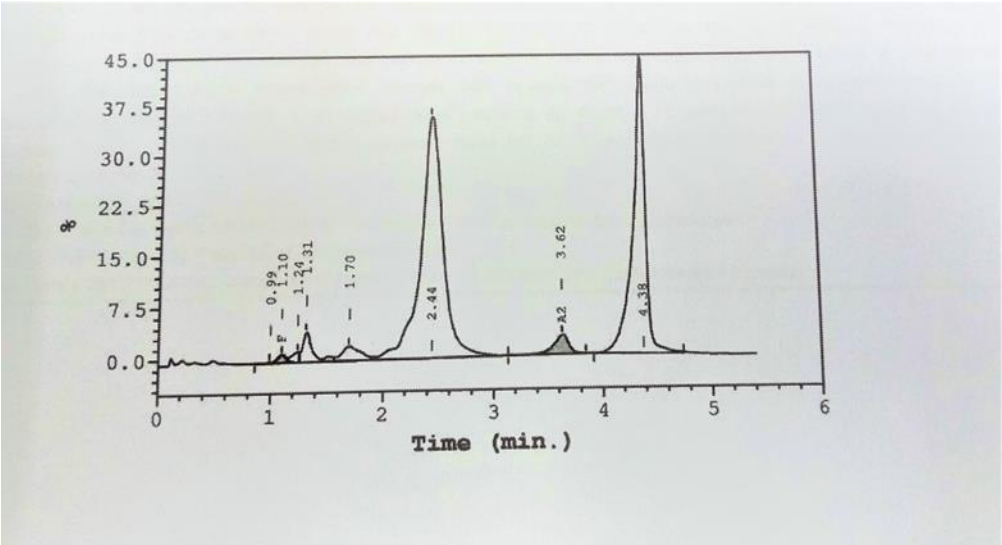

Figure 4: HPLC chromatogram showing increased HbS of 36.9 % (retention window - 4.3 to 4.7)

Virtually all patients were presented with hematuria and flank pain. Weight loss and abdominal masses were the other reported presenting manifestations. Metastatic disease was present in 80.5% of the patients just as in our case. Common metastatic sites are lymph nodes, lung, liver, adrenal glands, and bone. Brain was an uncommon site [7, 9]. Ultrasonography, CT imaging, and magnetic resonance imaging do not provide findings specific for RMC [8]

The exact pathogenesis of RMC is unclear, but new data and concepts are emerging. Key predisposing features thought to interact include the hypoxic and hypertonic environment in the renal medulla, the vulnerability of the SMARCB1 gene to translocations and deletions, and the sickling hemoglobinopathy. RMC occurs in medulla where there is a hypoxic microenvironment created by hyperosmolarity, low pH and stasis which in turn enhances sickling and causes ischemic damage. [2,7,9] Renal artery being longer promotes stasis and hypoxia and hence 70% of the tumors are right sided like our case.

RMC is an infiltrative tumor with tubules, tubulopapillary configuration, reticular pattern and microcystic spaces in a desmoplastic and necroinflammatory stroma. Sometimes an entirely solid architecture with rhabdoid morphology is also seen. A myxoid stroma with neutrophilic micro abscess and sickled RBCs in microvasculature are the diagnostic clues. Marked cytological and nuclear atypia seen reflecting its high-grade behavior. [10, 11] In view of poorly differentiated morphology and medulla centricity, guided biopsy from cortex usually precludes definite diagnosis as it was in our case. Immunohistochemically tumor cells are positive for PAX8, CK7, CEA and CAM 5.2. Loss of INI 1 correlating with loss of SMARCB1 gene and acquisition of OCT ¾(POU5F1), a stem cell factor is diagnostically helpful.

SMARCB 1 (SWI / SNF related, matrix associated, actin dependent regulator of chromatin subfamily B member) located on

chromosome 22q11.2, is a tumor suppressor gene, which is actively involved in the regulation of gene expression. Its codes for protein INI1 (hSNF5/SMARCB1/BAF47) which is present in all normal tissues from yeasts to humans. It is involved in transcriptional activation and repression by chromatin remodeling and also interacts with other cancer associated pathways like WNT signaling pathway and hedgehog signaling pathway. [11, 12,13] Mutation of this gene resulting in loss of expression is seen in RMC which is hence also called SMARCB 1 deficient renal medullary carcinoma. SMARCB1/ INI1 loss and rhabdoid histology have independent association with aggressive tumor behavior and at the same time make targeted therapy feasible.

Conclusion

Definite treatment protocols have not been validated for RMC. Prompt diagnosis and treatment regimen based on combined immunotherapy and chemotherapy had resulted in favorable outcome in our case. This case emphasizes the importance of considering renal medullary carcinoma in the differential diagnosis of young patients with sickle cell trait or disease who presents with hematuria. Also screening for this neoplasm in SCT patients and family could result in an early diagnosis and better survival. We hope that this era of targeted therapy may improve the outcome in young patients who are in the most affected group. This may later on help in formulating definite treatment protocols.

Abbreviations

RMC	*Renal Medullary Carcinoma*
SCT	*Sickle Cell Trait*
Hb	*Hemoglobin*
HPLC	*High Performance Liquid Chromatography*
IHC	*Immunohistochemistry*
SMARCB1	*SWI / SNF related, matrix associated, actin dependent regulator of chromatin subfamily B member*

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