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CASE REPORT

The Not-So-Benign Sickle Cell Trait: A Case of Renal Medullary Carcinoma

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Abstract

Sickle cell trait (SCT) has long been considered a benign carrier state with malarial protection, but carriers can be affected by increased venous thromboembolism, exercise-related injury, renal complications and very rarely a fatal renal malignancy. Renal medullary carcinoma is a very rare and aggressive renal tumor described almost exclusively in sickle cell trait. A review of the current literature provides clues to this link and describes trends expected in these cases. We report a case of renal medullary carcinoma in a 32-year-old female with known sickle trait who presented with cough, hemoptysis, left flank pain and gross hematuria. Initial presentation was concerning for pulmonary renal syndrome, but her labs did not show evidence of nephritic syndrome with negative autoimmune and infectious serologies. Abdominal CT imaging identified a large left renal mass with biopsy confirmation of renal medullary carcinoma and subsequent staging showing pulmonary and osseous metastases. Despite palliative chemotherapy, she died within 3 months of diagnosis following a protracted clinical course. Renal medullary carcinoma should be considered in patients with SCT presenting with hematuria.

Keywords: Renal medullary carcinoma, Sickle cell trait, Sickle cell, Nephropathy

1. Introduction

Sickle cell trait (SCT) by definition is the heterozygous inheritance of sickled hemoglobin, which likely evolved due to malarial protection. Population studies estimate that 6–9% of African Americans in the United States live with SCT, which translates into 2.5 to 3 million persons.[1] Globally, the prevalence rate is up to 30% in some countries with the WHO estimating global SCT prevalence of 300 million.[2] In the United States, individuals with SCT are identified through nationwide newborn screening, but unlike when sickle cell disease (SCD) is identified, widespread variability exists in how SCT results are reported, such that some individuals remain unaware. The presence of SCT may later come to light during screening by military enrollments, athletic organizations and prenatal examinations.

SCT was long considered a benign carrier state with mostly reproductive implications. There was initial concern by sports governing bodies and military recruitment committees about the potential role of SCT in causing exertional sudden death in young African American with SCT. However, robust studies by Liem et al. and Bello et al. did not find increased risk of cardiovascular disease in SCT.[3,4] A systematic review by Naik et al. of 41 observational studies did show an increased association of SCT with proteinuria, chronic kidney disease, exertional rhabdomyolysis and pulmonary embolism.[5] The potential association of SCT with renal medullary carcinoma, a very rare and aggressive renal tumor was first described by Davis et al. in 1995.[6] He published a case series of 34 patients; 33 of whom had SCT with one SCD (SC genotype), presenting with a highly aggressive renal neoplasm all with metastases on presentation with microscopic finding of sickle red blood cells (RBCs) in tumor tissue.[6] This was initially referred to as the seventh sickle cell nephropathy, the other six being hyposthenuria (inability to concentrate urine), hematuria,

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papillary necrosis, renal infarction, pyelonephritis and nephrotic syndrome.[6] Since then, a handful of cases have been described in individuals without sickle hemoglobinopathy but, the pathophysiology of the disease remains elusive and not completely understood.

The case of a 32-year-old-female with known sickle cell trait presenting with hemoptysis and hematuria is presented. The path to her diagnosis was challenging, complicated by an initial focus on a possible pulmonary renal syndrome. Her presentation is intriguing given the challenge of diagnosing this rare, aggressive malignancy with the rapidity of her decline all rooted in SCT that is largely considered a benign condition.

2. Case description

A 32-year-old-female with history of asthma and sickle cell trait presented to the Emergency Department (ED) with one-month progressive history of cough, hemoptysis, left flank pain and gross hematuria. Initially, the cough was productive of clear phlegm with subsequent hemoptysis. Evaluation at an outside hospital showed ground glass opacities on CT chest imaging. Since her symptoms started at the beginning of the COVID pandemic, there was concern for COVID-19 pneumonia, but SARS-COV-2 PCR was negative. She was treated in primary care office with antitussives, antipyretics, and antibiotics for presumed bacterial pneumonia. After some brief improvement, she presented to the ED with reemerging hemoptysis, accompanied by new onset gross hematuria, left flank pain, anorexia, and five-pound weight loss. She denied fevers, chills, night sweats, mouth sores, joint pain or rashes. History was also negative for recent travel or unusual exposures.

In the ED, her heart rate was 83/min, blood pressure 136/73 mmHg, respiratory rate of 16/min, temperature of 37 °C (98.6 ° F) and oxygen saturation of 96% on room air. Physical examination was notable for ill appearing young female, lung fields that were clear to auscultation, and left flank tenderness. Admitting labs revealed Leukocytes 7.55 x10^3/μL (4-11 × 10^3/μ L), Hemoglobin 11.9 g/dL (12.5–15 g/dL), MCV 76 fL (77-103 fL) Creatinine 0.67 mg/dL (0.5–1.00 mg/dL), ESR 40 mm/h (<20 mm/h), C-Reactive Protein 3.58 mg/dL (<0.05 mg/dL), Procalcitonin <0.09 ng/mL (<0.10 ng/mL). Urinalysis was notable for large blood, too numerous to count RBCs with 100 mg/dL proteinuria and no RBC casts. CT Angiography of chest was negative for pulmonary embolus but showed scattered ground glass and nodular opacities in lung peripheries with mediastinal and hilar adenopathy.

At this point, the clinical picture was concerning for pulmonary-renal syndrome with differentials ranging from granulomatosis with polyangiitis to anti-glomerular basement membrane disease. Bacterial pneumonia seemed unlikely with negative procalcitonin, bilateral lung infiltrates with failure to improve despite adequate antibiotic coverage for community acquired pneumonia. Allergic bronchopulmonary aspergillosis appeared unlikely with normal eosinophil count and absence of characteristic imaging. She had no history of travel, which would have led to unusual infections. The possibility of a dual diagnosis with separate lung and renal pathologies was also considered. Pulmonary consultation was obtained which led to additional testing recommendations including negative Aspergillus antibody, Anti Neutrophil Cytoplasmic Antibodies (ANCA) and anti-GBM vasculitis panel. Nephrology was additionally consulted for anticipated renal biopsy, but she had no evidence of nephritic syndrome, normal renal function, minimal proteinuria, urinalysis free of casts, and normal serum complement level. HIV and hepatitis viral serologies were also negative. CT abdomen without contrast showed large lobulated soft tissue structure in left retroperitoneum, suspected to be lymph node (Fig. 1). Follow up imaging with contrast was recommended and MRI renal mass protocol revealed an 8 cm infiltrating mass arising from the lower pole of the left kidney with multiple enlarged retroperitoneal lymph nodes compressing the left renal vein. There were additionally suspected lung nodules in the right and left lung.

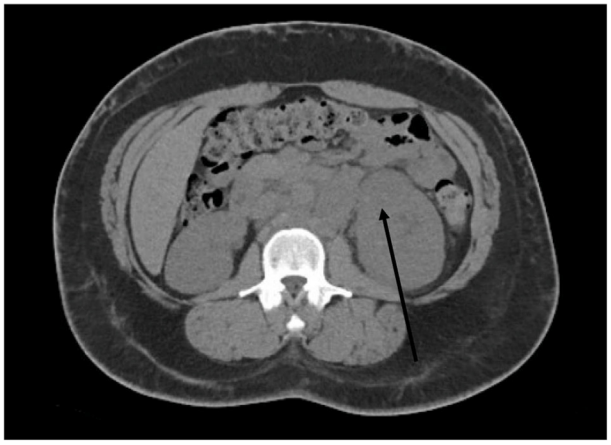

Fig. 1. CT abdomen without contrast showed large lobulated soft tissue structures in left retroperitoneum suspected to be lymph node (single arrow).

The differential diagnoses were expanded to include primary renal neoplasm and lymphoma. Urine cytology revealed fragments of non-small cell carcinoma. Renal biopsy (Fig. 2) finally confirmed malignant renal neoplasm consistent with renal medullary carcinoma. There was reported lymphovascular invasion with sickled red blood cells identified within tumor and nonneoplastic parenchyma (Fig. 2). Staging with PET CT scan disclosed multiple pulmonary and osseous metastases. She was initiated on palliative combination chemotherapy of carboplatin and paclitaxel with progression of disease. Her clinical course was complicated by severe flank pain requiring multiple hospitalizations for very high dose opiates and palliative radiation, left hydronephrosis requiring percutaneous nephrostomy. She expired three months after diagnosis due to sepsis with multiorgan failure requiring hemodialysis.

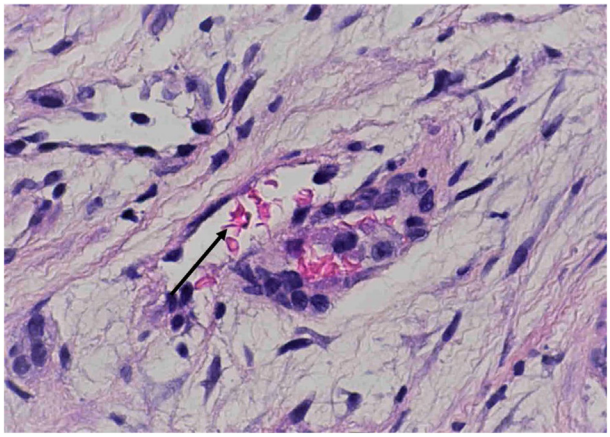

Fig. 2. Renal biopsy consistent with renal medullary carcinoma with lymphovascular invasion with sickled red blood cells (single arrow) identified within tumor and nonneoplastic parenchyma.

3. Discussion

3.1. Epidemiology

Renal medullary carcinoma is an aggressive form of non-clear cell renal carcinoma. It is extremely rare, occurring in less than 0.5% of all renal carcinomas, such that true incidence is not well defined.[7] Table 1 details nine case series of RMC that have been written that help shape our understanding of this rare disease. While RMC presents almost exclusively in SCT, a handful of cases have been described in sickle cell anemia (SS), hemoglobin SC and hemoglobin S with beta-thalassemia.[7] When the diagnosis occurs outside of sickle cell hemoglobinopathy, as has been very rarely described; the term "renal cell carcinoma, unclassified with medullary phenotype" is used.[8] Given the link with SCT, it primarily occurs in individuals with African heritage, and other populations that have a high SCT rate namely India, Middle East, Mediterranean and Latin countries.[9] Median age of onset is twenty-two years with males being affected more frequently (10, Table 1).

3.2. Pathogenesis

Exact mechanism of transformation to RMC remains unclear. One proposed hypothesis postulates the hypoxic environment of the renal medulla in SCT patients, increases expression of vascular endothelial growth factor (VEGF) and Hypoxia Inducible Factor (HIF).[7] This hypoxia, together with hypertonia of the renal medulla could create a favorable environment for breaks in the DNA strands and foster subsequent tumor development.[11]

Table 1. Case series of renal medullary carcinoma.

Study/year	Number	Age at diagnosis	Survival
Davis et al. 1995[6]	34	11–39 years	1–12 months
Swartz et al. 2002[15]	40	5–32 years	2 weeks-15 months
Simpson et al. 2005[16]	95	5–40 years	1–17 months
Watanabe et al. 2007[17]	7	8–69 years	4 days-9 months
Hakimi et al. 2007[18]	9	13–31 years	4–16 months (2 patients survived beyond)
Gatalica et al. 2011[19]	3	28–34 years	3–36 months
Gupta et al. 2012[20]	13	8–58 years	Not available
Liu et al. 2013[21]	15	8–49 years	Not available
Lacovelli et al. 2015[10]	166 (pooled analysis)	Median age 21 years	4 months (metastases) 17 months (no metastases)

Another possibility is RMC has been associated with biallelic loss of SMARCB1/INI1, a tumor suppressor gene, normally involved in chromatin remodeling that is prone to translocations and deletions.[12] While there is no direct link as to how sickled hemoglobinopathy directly contributes to the pathogenesis; the renal medulla has low oxygen tension, low pH and hyperosmolarity which promote sickling of RBCs.[10]

3.3. Presentation

The common initial symptoms are hematuria and flank pain. However, hematuria in the setting of SCT could be overlooked as it is a well-recognized complication of SCT. In our case, the initial focus in differential diagnosis was pulmonary renal syndrome. Dysuria, abdominal mass and weight loss are other common presentations with RMC. Most patients have metastatic disease by the time of diagnosis; with the frequent sites of metastases being lymph nodes, liver, lung, adrenals and bones.[11]

3.4. Diagnosis

Imaging will often be the first clue to the presence of a renal mass. There are no specific imaging findings of RMC on ultrasound, CT or MRI. The mass may have an infiltrative appearance, arising centrally from the renal medulla, and extending laterally to the renal cortex, and medially to the renal pelvis, and sinus.[10] Centrally located tumors may cause overall enlargement of the kidney while the overlying renal contour is maintained, as happened in our case. This leads to an initial unclear appearance on non-contrasted CT.[10] Tissue sampling will then confirm diagnosis. Macroscopically, the mass appears tan/gray white with necrosis and hemorrhage.[13] The tumor arises from the renal papillae or epithelium of calyx with an average size of 6 cm, and the right kidney is involved in 70% of cases.[11] Microscopically; morphology ranges from infiltrative, reticular, tubulopapillary, adenoid cystic to microcystic patterns.[11] The tumor is poorly differentiated with often marked nuclear/cytologic atypia and necrosis with sickled RBCs frequently identified within the tumor.[11] On immunohistochemical stains pax8, cytokeratin 7 and polyclonal carcinoembryonic antigen are often present.[11]

3.5. Treatment and prognosis

Given the rarity of RMC, guidelines were lacking until, the RMC working group came together in 2017 to establish the standard of care.[7] When disease is localized, radical nephrectomy with retroperitoneal lymph node dissection is recommended. In low burden metastatic disease, debulking (cytoreductive) nephrectomy with retroperitoneal lymph node dissection followed by adjuvant cisplatin therapy is pursued. For high burden metastatic disease, management options include palliative chemotherapy and radiotherapy.[7] Overall survival is improved when surgical debulking is undertaken compared to systemic chemotherapy alone. Chemotherapy is cisplatin-based with or without topoisomerase-ii-alpha inhibitor.[7] Newer treatment regimens have included Bortezomib and Tazemetostat, the latter of which targets the loss of SMARCB1/INI1.[7,14] Survival remains poor despite chemotherapy, with median survival from diagnosis of 4 months with metastases, and 17 months without metastases (10, Table 1). As of 2020, only 8 cases had been described of patients surviving beyond 24 months without evidence of active disease.[11]

4. Conclusion

While Sickle cell trait is largely benign, it is associated with a rare but fatal renal medullary cancer which can be challenging to diagnose. Renal medullary carcinoma should be considered when SCT patients present with hematuria and flank pain. Future research into pathogenesis will hopefully unlock prevention and better treatment strategies.

Conflict of interest

The authors have no conflicts of interest to declare.

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