

Renal Medullary Carcinoma in an Adolescent With Sickle Cell Trait

Katherine E. Warren, MD*; Vinod Gidvani-Diaz, MD; and Bertrand Duval-Arnould, MD

ABSTRACT. We describe the complex presentation of a patient with renal medullary carcinoma, a newly described entity primarily affecting young patients with sickle cell trait. Renal medullary carcinoma is an aggressive, rapidly destructive tumor associated with a delayed diagnosis and a poor outcome. The most common presenting signs and symptoms include hematuria, abdominal or flank pain, and weight loss. Sickle cell trait as the sole cause of hematuria in young black patients is a diagnosis of exclusion. Hemoglobin electrophoresis, intravenous pyelography, and computed tomography scans should be the minimal studies performed in young black patients with hematuria. *Pediatrics* 1999;103(2). URL: <http://www.pediatrics.org/cgi/content/full/103/2/e22>; sickle cell trait, hematuria, renal medullary carcinoma, renal tumors.

ABBREVIATION. CT, computed tomography.

Renal tumors represent 7.8% of all pediatric malignancies in the United States.¹ Most of these are Wilms' tumors affecting children <5 years of age. Recently, a new entity, renal medullary carcinoma, has been described in young people, including children, with sickle cell disorders.² Many of the reported cases have been diagnostic challenges with poor prognoses. It is unclear whether earlier diagnosis and earlier treatment will result in a better prognosis, but awareness of this newly described entity is most important. We describe an 18-year-old female with sickle cell trait who was diagnosed with renal medullary carcinoma after a complex presentation.

CASE PRESENTATION

W.B. was an 18-year-old black female with known sickle trait, who was in good health until 6 months before admission when she developed swelling and stiffness in her metacarpophalangeal and knee joints. Her initial evaluation was significant for microscopic hematuria and a positive antinuclear antibody test with a titer of 1:640 and a diffuse pattern. She was treated with oral salicylates and naproxen sodium in the 2 months before this admission, but she took them infrequently.

Two months after her initial presentation, she developed daily nausea and bilious vomiting, resulting in a 20-lb weight loss (15% of total body weight) over a 3-week period. She sought medical care when she developed worsening right-sided flank pain and gross hematuria. She was admitted with a presumptive diagnosis of papillary necrosis. Her review of systems at the time of admis-

sion was also significant for fever, sharp intermittent periumbilical pain, midline back pain, right scapular pain, urinary frequency with nocturia, gross hematuria with clots, loose stools, and night sweats. She denied dysuria. The patient had a past medical history of hypertension of unknown cause (untreated), epistaxis, easy bruising, and vaginal yeast infections. She had been sexually active for 4 years.

At the time of physical examination, the patient was well developed and appeared well nourished despite her weight loss. She was bent over, secondary to pain. Her vital signs were significant for a blood pressure of 158/87 mm Hg. She had two café au lait spots, 1 × 2 cm on her left forearm and 1 × 1 cm on the left thigh. Lymph node examination was noteworthy for bilateral enlarged, matted, tender inguinal nodes. Chest examination revealed decreased bibasilar breath sounds. The abdomen was soft, but tender in the right lower quadrant, with no palpable masses and no organomegaly. She had tenderness over her lumbar-sacral spinous processes and bilateral costovertebral angles. Her metacarpal phalangeal joints were enlarged.

A complete blood count was normal with a white blood cell count of 4900/mm³, hemoglobin of 13.7 g/dL, hematocrit of 40.7%, and platelets of 221 000/mm³; the differential consisted of 71% neutrophils, 12% lymphocytes, 13% monocytes, and 4% eosinophils. Serum creatinine was 0.7 mg/dL. Additional laboratory values included an erythrocyte sedimentation rate of 61, a positive antinuclear antibody test at 1:640 with a diffuse pattern (negative SSA/B, negative anti-double-strand DNA, RNP, and antismooth muscle antibodies), hemoglobin electrophoresis consistent with sickle trait, and urinalysis noteworthy for brown color, presence of red and white blood cell casts, protein of >300 mg/dL, white blood cell count of 116/high-power field, and red blood cell count of 91/high-power field, with positive nitrites and ketones. The urine culture was negative.

Abdominal flat plate and upright films were normal. An intravenous pyelography study showed a large filling defect on the right, involving the ureter with irregularity of the right lower pole calyx and infundibulum, suggestive of papillary necrosis. A renal ultrasound revealed mild hydronephrosis on the right, with no ureteral dilatation, and was otherwise normal. A vesicourethrogram did not show any reflux; a glucoheptonate scan demonstrated photopenia at the upper and lower poles of the right kidney. Computed tomography (CT) scan showed a 4 × 2.5 × 2.5-cm enhancing mass in the right collecting system, with extensive retroperitoneal and mesenteric adenopathy, liver metastases, bilateral inguinal adenopathy, external compression of the inferior vena cava presumably from adenopathy, a thick and inflamed large bowel wall, a right adrenal mass, an enlarged cervix, and free fluid in the peritoneum (Fig 1). On ureteroscopy, an irregular right pelvic urothelium with no definite exophytic mass was noted. Gynecologic examination was noteworthy for diffuse vaginal nodularity. Other studies included a normal head CT scan, normal chest CT scan, normal chest radiograph, and normal bone scan.

Transurethral, cervical, vaginal, and left inguinal node biopsies were obtained. The initial pathologic diagnosis was transitional cell carcinoma, but after further review, this was amended to renal medullary carcinoma. The patient received one course of methotrexate (1 g/m²)/leukovorin (10 mg/m²), vinblastine (3 mg/m²), doxorubicin (30 mg/m²), and cisplatin (70 mg/m²). Complications related to her chemotherapy included pleural effusions, transient renal insufficiency, and severe mucositis. She had a partial response to chemotherapy, as judged by improvement on CT scan, but died 4 weeks after the start of her therapy. Autopsy findings included a thrombus arising from the wall of the right atrium,

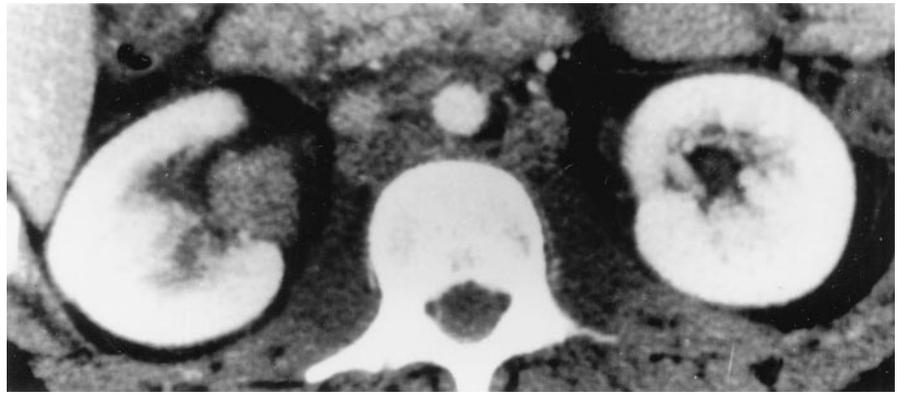
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Fig 1. CT scan of abdomen. Note the enhancing mass in the right collecting system and extensive retroperitoneal adenopathy.



which was presumed to be the immediate cause of death, and extensive widespread malignant disease.

DISCUSSION

Tumors of the kidney are the fifth most common pediatric malignancies in the United States. More than 80% of these are Wilms' tumors, with most occurring in children <5 years of age. Most of these patients present with a painless abdominal mass. In contrast, renal cell carcinoma, the most common renal malignancy in adults, represents only 1.8 to 6.3% of malignant pediatric renal tumors³; patients generally present with painless microscopic hematuria. Wilms' tumor and renal cell carcinoma generally grow by expansion, rather than infiltration, and involve the cortex of the kidney, rather than the medulla. Tumors that invade the renal pelvis and medulla are extremely rare, particularly in children.

In contrast to the rarity of pediatric renal tumors, sickle cell disease and sickle cell trait are very common in the United States. A frequent manifestation of these is nephropathy. In 1974, Berman⁵ described six nephropathies seen in patients with sickle cell disease or trait. These include 1) gross hematuria, 2) papillary necrosis, 3) nephrotic syndrome, 4) renal infarction, 5) isosthenuria, and 6) pyelonephritis. These sickle cell nephropathies can present clinically as hematuria, proteinuria, renal insufficiency, concentrating defects, or hypertension.⁶ Patients with sickle cell trait have a higher incidence of gross hematuria than patients with sickle cell disease.² The gross hematuria can be painless and is thought to arise from bleeding immediately beneath the renal pelvic epithelium² or as a result of papillary necrosis.⁶ It involves the left kidney in >80% of patients.⁶

Recently, a new entity, renal medullary carcinoma, suggested to be the seventh sickle cell nephropathy, has been described by Davis et al² at the Armed Forces Institute of Pathology. They reviewed 55 cases of "renal pelvic carcinoma" diagnosed over a 22-year period. Two distinct tumor types emerged. Twenty-one of the fifty-five cases were typical transitional cell carcinoma. The remaining thirty-four cases were highly aggressive, infiltrating, poorly circumscribed, renal tumors occurring primarily in young black patients with sickle trait. These tumors occurred in patients ranging in age from 11 to 39 years. Macroscopically, the tumors occupied primarily the renal medulla and invaded the calyces; satellite lesions



Fig 2. CT scan of abdomen. The upper pole of the right kidney is visualized. Of note is the intact cortex and satellite lesion (hypodensity). An adrenal mass and liver metastasis are also seen.

were often present on the renal cortex (Fig 2). Most (23 of 31) involved the right kidney and all demonstrated lymphatic and/or vascular invasion. Histologically, the tumors demonstrated a distinctive reticular growth pattern with some transitions to a more adenoid cystic appearance (Fig 3). Acute inflammation and stromal proliferation was present. Nine patients had known sickle trait; one patient had SC disease. The sickle cell disease status of the remaining patients was unknown, but all patients had sickled cells identified microscopically within the tumor or adjacent renal parenchyma.

All patients had prolonged duration of symptoms before diagnosis, ranging from 2 to 12 months, with an average of 4.7 months.⁷ The most common presenting signs and symptoms included gross hematuria (60%), abdominal or flank pain (50%), and significant weight loss (25%).² At the time of diagnosis, all patients for whom the information was known had metastatic disease. Frequent sites of metastases included lymph nodes, adrenal glands, liver, lungs, and retroperitoneal nodes.² The tumors were very aggressive and rapidly destructive, despite several different methods of treatment. No known patient has survived the disease. The mean survival after diagnosis was 3 months.⁷

The relationship of renal medullary carcinoma to

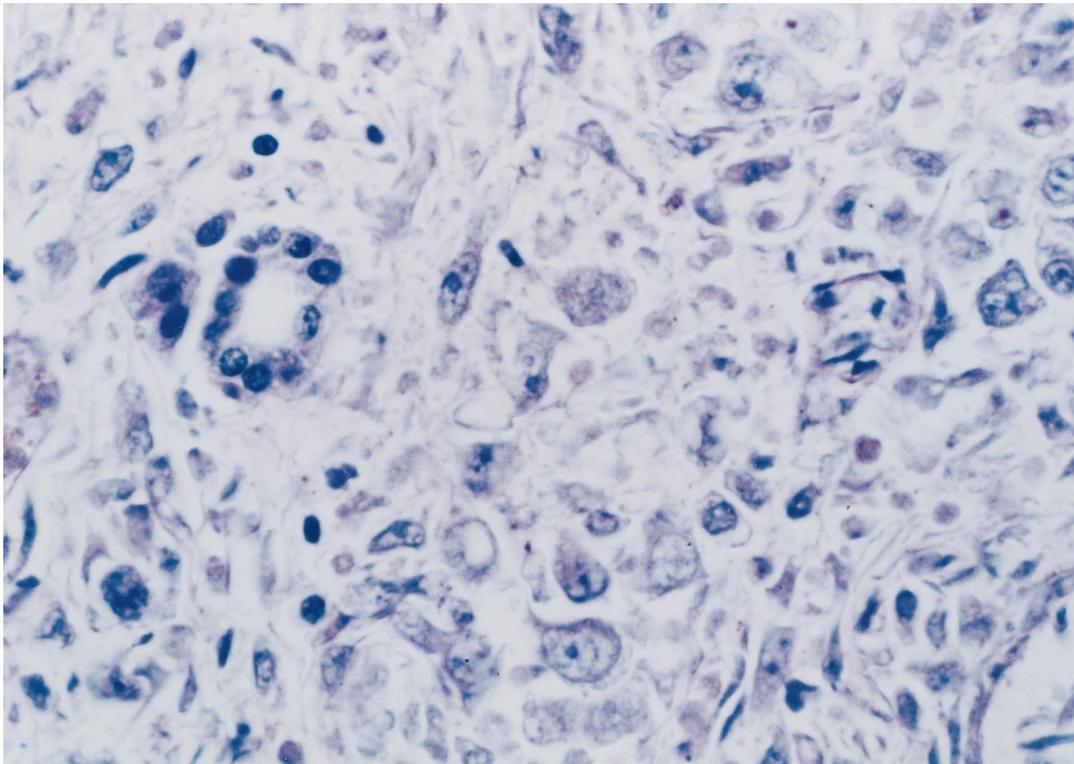


Fig 3. Focus of renal medullary carcinoma adjacent to a normal renal tubule. The tumor cells demonstrate a squamoid appearance and high mitotic rate.

sickle cell trait is unclear. It is not uncommon for patients with sickle cell trait to develop renal insufficiency in the second to fourth decades of life,⁶ but sickle cell nephropathy in a patient with hematuria should be a diagnosis of exclusion. The differential diagnosis includes papillary necrosis, renal infarction, and renal medullary carcinoma. Radiographically, renal medullary carcinomas are generally centrally located, infiltrative, and associated with pelvic encasement.⁴ These findings are not specific for renal medullary carcinoma but suggest the diagnosis in patients with sickle cell trait. Renal infarction can deform the renal calyx and cause scarring, but this does not usually manifest itself as a mass.⁸ Papillary necrosis can cause overlying scarring of the renal parenchyma with depression of the capsular surface over the injured lobe.⁶

A combination of hemoglobin electrophoresis, intravenous pyelography, and a CT scan should be the minimal studies in young black patients with hematuria. Further investigations, particularly in patients diagnosed with renal infarction or papillary necrosis

who do not respond as expected to standard therapy, may need to be undertaken. Several radiologic studies may be needed to exclude tumors of the renal pelvis. Sickle cell trait, as a sole cause of hematuria, should be a diagnosis of exclusion.

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