Renal Papillary Necrosis in a Patient with Sickle Cell Trait

GINO ZADEII and JAMES W. LOHR
Department of Medicine, State University of New York at Buffalo, Buffalo, New York, and the Veterans Affairs Medical Center, Buffalo, New York.

Abstract. A patient with sickle cell trait who presented with gross hematuria and was subsequently found to have renal papillary necrosis is presented. The hematuria resolved with conservative therapy consisting of bed rest and hydration with hypotonic intravenous fluids. The pathophysiology of renal abnormalities associated with sickle cell trait is described. The management of the primary clinical manifestations of this disorder, hematuria and papillary necrosis, are discussed. (J Am Soc Nephrol 8: 1034–1040, 1997)

A variety of renal abnormalities have been described in patients with sickle hemoglobinopathies (1–5). Most of the literature has dealt with patients with homozygous sickle cell anemia (HbSS), although the incidence of heterozygous sickle cell trait in the United States has been estimated to be 40 times as great (1).

We report a case of a patient with sickle cell trait presenting with gross hematuria, who was subsequently found to have papillary necrosis on intravenous pyelography. A discussion of the renal abnormalities associated with sickle cell trait and the approach to management of these disorders is presented.

Case Report

An African-American man 66 yr of age presented to the Buffalo Veterans Affairs Medical Center with a 2-d history of gross hematuria. He denied having experienced fever and chills, dysuria, or flank pain. He had no history of recent trauma or nephrolithiasis. Past medical history was significant for hypertension, hypercholesterolemia, and benign prostatic hypertrophy, which had been evaluated in the previous year and found not to be causing any urinary tract obstruction. He also had sickle cell trait, diagnosed by AS pattern on hemoglobin electrophoresis in 1986. The patient was taking lisinopril and colestillip. He denied taking any nonsteroidal inflammatory drugs.

The physical examination revealed a well-developed man in no acute distress. Blood pressure was 140/70 mmHg, pulse was 76 beats/min, and temperature was 36.5°C. Examination of the abdomen showed no evidence of hepatosplenomegaly. No costovertebral tenderness was noted. The physical examination was otherwise unremarkable except for a symmetric, mildly enlarged prostate gland. Laboratory tests showed normal complete blood cell counts, clotting studies, and electrolytes. Blood urea nitrogen was 12 mg/dl, and serum creatinine was 1.3 mg/dl. Urine dipstick revealed a specific gravity of 1.020, pH 5.5, 3+ blood, 3+ protein, and was negative for glucose, ketones, and leukocyte esterase. The microscopic exam showed many red blood cells (RBC), but no RBC casts or white blood cells were seen. Urine culture showed no growth.

The patient was evaluated by a urologist, and an intravenous pyelogram was performed that showed bilateral papillary necrosis (Figure 1). The patient was placed at bed rest and given intravenous half-normal saline at a rate of 150 ml/h. The hematuria cleared on day 4. Before discharge, he had cystoscopy that was unremarkable. Retrograde urogram could not be completed due to patient discomfort.

The patient has not had any recurrent hematuria in the 9 mo since discharge.

Discussion

Several renal abnormalities have been described in patients with sickle cell disorders. These vary depending on whether the patient has sickle cell disease or sickle cell trait. In sickle cell disease, there are two abnormal genes related to hemoglobin production, with at least one being the gene for hemoglobin S. These include sickle cell anemia, sickle cell-hemoglobin C disease, sickle cell-thalassemia, and some less common disorders. Nephropathy associated with sickle cell disease has been well reviewed (1–4). In sickle cell trait, there is a normal gene, along with the gene for hemoglobin S. This is the most common hemoglobinopathy in the United States, present in more than 2 million people. This discussion will be restricted to renal findings in sickle cell trait, with only a mention of the contrasting features of sickle cell anemia.

Pathophysiology

The renal medullary interstitium may achieve an osmolarity of 800 to 1200 mosmol/kg based on the countercurrent mechanism, which involves the loops of Henle and the blood supply of the midcortical juxtamedullary nephrons. The medullary interstitium is made hypertonic by reabsorption of sodium chloride without water in the ascending limb of the loop of Henle. Solute is transferred from the tubular lumen into the medullary interstitial fluid, raising the osmotic concentration of the interstitial fluid relative to tubular fluid. The hyperosmotic
medullary interstitium causes removal of water from the descending limb of the loop of Henle and raises the osmolality of the tubular fluid as it approaches the tip. Urea also contributes to the hyperosmolality of the medullary interstitium by diffusion from the inner medullary collecting tubule. The vasa recta are vessels with hairpin-like construction that lie near the loops of Henle and carry blood through the medullary tissue at a much slower rate than cortical vessels. Thus, this blood comes into contact with the hypertonic medullary interstitial fluid through the capillary wall.

In patients with sickle cell trait, the hyperosmolar interstitial fluid draws water from the cells, resulting in an increased concentration of sickle cell hemoglobin, the most important determining factor for sickling (Figure 2). Another factor that may contribute to red blood cell sickling is the low oxygen tension present in the medulla. Along with the fact that the medulla receives less than 10% of the renal blood flow, the configuration of the vasa recta capillaries results in a loss of oxygen as the blood enters the medulla with subsequent uptake by the opposing ascending capillaries leaving the medulla. This can result in oxygen tensions of 20 mmHg or less in the medulla, with sickling often occurring at less than 45 mmHg due to polymerization of sickle cell hemoglobin. This hypoxia, along with the acidic medullary pH, also promotes sickling of RBC (6). As sickling occurs, there is an increase in blood viscosity, which may further slow the blood flow in the medullary capillaries.

Initially, capillaries become engorged with erythrocytes. Subsequently, RBC sickling in the vasa recta causes formation of microthrombi, infarction, and formation of collateral vessels (7). Capillaries develop increased permeability, allowing RBC to leak into the collecting system. This results in a reduced number of vasa recta and loss of the normal medullary architecture as revealed by microangiographic studies (7).

Eventually, these events may lead to papillary necrosis. The papillary necrosis usually involves the tip of the papilla, with no involvement or destruction of the fornices. Gross pathologic exam shows one or more papillae with areas of necrosis, usually involving one-third of the papilla (8). Calcification may be seen in old areas of necrosis. Microscopic examination reveals total or partial necrosis of tubular and collecting duct epithelium in the area of necrosis. There may be evidence of expansion of the interstitial space with fibrosis.

The functional renal changes (Table 1) that are seen in sickle cell trait are primarily due to the loss of vasa recta, which disrupts the countercurrent exchange system. This results in an impaired ability to concentrate the urine in patients with sickle cell trait (9–12). This appears to be reversible early in life, but there is a continual gradual decrease throughout life, which then becomes fixed. In patients over 50 yr of age, maximum urine osmolality generally will not exceed 450 mosmol (9). The ability to dilute the urine has been found to be normal in patients with sickle cell trait (12).

Patients with sickle cell trait have been found to have a normal ability to excrete acid in response to ammonium chloride loading (10). This is in contrast to those with sickle cell disease who frequently have an incomplete distal renal tubular acidosis (10). Potassium excretion has also been studied and was found to be normal in patients with sickle cell trait, whereas it was frequently impaired in those with sickle cell anemia (13,14). Sodium handling is thought to be normal in patients with sickle cell trait, although this has not been well.
stressed (1). The tubular reabsorption of phosphate is normal in patients with sickle cell trait, but increased in those with sickle cell anemia (10). In some studies, the fractional excretion of uric acid does not differ between sickle cell anemia, sickle cell trait, and control subjects (15), whereas others show increased rate of uric acid clearance in sickle cell anemia (16).

In contrast to sickle cell disease, in which there is an early increase in glomerular filtration rate in younger patients with a subsequent decrease in later life, glomerular filtration rate has been found to be normal in patients with sickle cell trait (10). However, the filtration fraction is decreased as it is in sickle cell disease. This is due to a small increase in renal plasma flow (10).

Clinical Presentation

Hematuria. Patients with sickle cell trait will most commonly present with gross hematuria in the third or fourth decade, although microscopic hematuria may be picked up on routine urinalysis (1). The hematuria is generally painless, although patients may present with flank or abdominal pain due to sloughing of papilla. The left kidney appears to be involved approximately 80% of the time because of increased venous drainage into the left renal vein, which may elevate the venous pressure and lead to stasis (17).

Recurrent episodes of hematuria in affected people are common (8,17). Hematuria due to sickle cell trait must be considered a diagnosis of exclusion, particularly in patients presenting with hematuria for the first time. Thus, the work-up should include urinalysis and urine culture, urinary acid-fast bacilli, urinary cytology, hematologic work-up for coagulation abnor-

malities, intravenous pyelogram, and cystoscopy. Hemoglobin electrophoresis should be performed in all patients with hematuria of unknown etiology, as sickle cell trait is not exclusively seen in African-American patients (18).

Papillary Necrosis. Renal papillary necrosis may occur in up to 50% of patients with sickle cell trait who present for evaluation (19,20). It is generally discovered during evaluation of hematuria. It must be differentiated from the other common causes of papillary necrosis listed in Table 2. Various patterns of papillary abnormalities have been described on excretory urography (intravenous pyelogram and/or retrograde pyelogram) (19–22). The most common pattern seen in sickle hemoglobinopathies is a medullary type of partial papillary necrosis, which appears as a cavity within the papilla (20,21).

Papillary necrosis is most commonly identified in sickle cell trait at 30 to 40 yr of age, but initial presentation in older patients, such as in this case report, is not uncommon. There does not seem to be a sex predominance in the incidence of the disease.

The clinical presentation of papillary necrosis in sickle cell trait is quite variable (22). It may appear as gross hematuria with or without renal colic. Patients may have symptoms of urinary tract infection or sepsis. There may be minor episodes of hematuria with years of asymptomatic periods. The patients may be totally asymptomatic with the papillary necrosis found incidentally during radiographic studies. Urinary findings may include the presence of white blood cells in addition to red blood cells. The urine should be strained and examined for the presence of sloughed papillae.

Other Renal Abnormalities. An increased incidence of pyelonephritis during pregnancy has been well demonstrated in sickle cell trait (23). Patients have presented with perinephric hematoma thought to be associated with bleeding into the renal capsule after cortical infarction. Other findings that have been reported in patients with sickle cell trait in which causality has not been proven include nephrotic syndrome, renal vein thrombosis, and chronic renal failure.

Treatment

Hematuria. Although usually responsive to conservative measures, treatment of gross hematuria in patients with sickle hemoglobinopathies may be quite challenging. A number of different approaches have been tried in the past.

One early approach involved the administration of distilled water intravenously along with oral bicarbonate solution (24). This was found to be effective in stopping the hematuria. Although one might expect intravascular hemolysis to occur, this was not observed. Treatments such as vitamin K, vasopressin, and hyperbaric oxygen have been used with varying degrees of success. Urologic interventions have included irrigation of the renal pelvis with sodium oxychlorosene, silver nitrate, or aminocaproic acid and use of ureteral catheters in an effort to tamponade the bleeding.

Table 3 outlines the current approach to management of hematuria in sickle cell trait involving measures designed to eliminate the underlying pathophysiologic conditions leading to sickling (25). Thus, an effort is made to reduce the tonicity,
Table 1. Renal features of sickle cell trait (SCT) and sickle cell anemia (SCA)\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>Type</th>
<th>Control</th>
<th>SCT</th>
<th>SCA</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physiologic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR (inulin clearance) (ml/min per 1.73 m(^2))</td>
<td>99 ± 5</td>
<td>95 ± 9</td>
<td>125 ± 11</td>
<td>10</td>
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<tr>
<td>renal plasma flow (PAH clearance) (ml/min per 1.73 m(^2))</td>
<td>454 ± 21</td>
<td>514 ± 59</td>
<td>837 ± 34(^b)</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>filtration fraction (%)</td>
<td>22 ± 1</td>
<td>19 ± 1(^b)</td>
<td>15 ± 1(^b)</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>urinary concentrating ability (mosmol/kg H(_2)O)</td>
<td>994 ± 54</td>
<td>593 ± 35(^b)</td>
<td>447 ± 10(^b)</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1055 ± 24</td>
<td>745 ± 33(^b)</td>
<td>493 ± 16(^b)</td>
<td>11</td>
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<td></td>
<td>79 ± 4</td>
<td>74 ± 6</td>
<td>60 ± 5(^b)</td>
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<tr>
<td></td>
<td>136 ± 14</td>
<td>127 ± 7</td>
<td></td>
<td>13</td>
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<tr>
<td></td>
<td>153 ± 41</td>
<td>114 ± 14(^b)</td>
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<td>14</td>
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<td></td>
<td>88 ± 2</td>
<td>88 ± 2</td>
<td>93 ± 1(^b)</td>
<td>10</td>
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<tr>
<td></td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>15</td>
<td></td>
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<tr>
<td><strong>Pathologic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>disruption of medullary architecture</td>
<td>Present</td>
<td>Present</td>
<td>1–3, 7, 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>papillary necrosis</td>
<td>Present</td>
<td>Present</td>
<td>1–3, 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>glomerular disease and nephrotic syndrome</td>
<td>Absent</td>
<td>Present</td>
<td>1, 3, 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>renal insufficiency</td>
<td>Absent</td>
<td>Present</td>
<td>1, 3, 4</td>
<td></td>
<td></td>
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</tbody>
</table>

\(^a\) PAH, para-aminohippurate; \(\mu\)eq, microequivalent.

\(^b\) \(P < 0.05\) versus control; values are presented as mean ± SEM.

\(^c\) Net acid excretion after ammonium chloride load.

\(^d\) Maximum potassium excretion after potassium chloride load.

\(^e\) Urate clearance/creatinine clearance \(\times 100\).

Table 2. Common causes of renal papillary necrosis

<table>
<thead>
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<th>Cause</th>
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<tbody>
<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Analgesic abuse</td>
</tr>
<tr>
<td>Pyelonephritis</td>
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<tr>
<td>Urinary tract obstruction</td>
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<tr>
<td>Sickle hemoglobinopathy</td>
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<tr>
<td>Tuberculosis</td>
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Increase the pH, and increase the oxygen tension of the renal medulla. Hypotonic intravenous solutions are administered, along with a loop diuretic (such as furosemide), which will reduce medullary tonicity and maintain a high rate of urine output. The use of a loop diuretic may also reduce oxygen consumption and increase medullary oxygen tension. Urinary alkalization may be achieved by giving 8 to 12 g of sodium bicarbonate daily (26). Addition of acetazolamide will further alkalize the urine (25). Patients are generally kept at bed rest to avoid dislodging of blood clots.

If these measures are unsuccessful in halting the bleeding, epsilon aminocaproic acid (EACA) may be given intravenously or orally. This is an inhibitor of urokinase, the urinary enzyme that activates plasminogen. Thus, EACA prevents formation of excess plasmin responsible for fibrinolysis. The recommended dose of EACA is 3 to 4 g three to four times daily, which will usually result in the clearing of the urine within a few days (27). Common side effects include nausea, vomiting, and diarrhea, along with the rare complication of causing clot formation within the urinary excretory system.

The administration of oral urea has also been found to be effective in the treatment of persistent sickle trait hematuria (28). Oral urea is given at a dose of 160 g daily in four divided doses. This will generally increase the blood urea nitrogen to greater than 80 mg/dl by day 3, and the hematuria resolves. Urea has been demonstrated to decrease the viscosity and gelation of deoxygenated sickle hemoglobin, and has been found to prevent or reverse sickling. The osmotic diuretic effect of urea may also lower medullary osmolality.

If bleeding remains uncontrolled, arteriography with local embolization of the involved kidney region may be used. In rare instances, nephrectomy may be required.

**Papillary Necrosis.** The treatment of renal papillary necrosis in patients with sickle cell trait does not differ from that of other causes of renal papillary necrosis.

Table 3. Medical management of hematuria in sickle cell disorders\(^a\)

<table>
<thead>
<tr>
<th>Management</th>
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<tr>
<td>Maintain high urine flow rate</td>
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<tr>
<td>hypotonic fluid intake (4 L/1.73 m(^2) per d) either po or iv</td>
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<tr>
<td>furosemide 40 mg po BID</td>
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<tr>
<td>Urinary alkalization</td>
</tr>
<tr>
<td>NaHCO(_3) 2 to 3 g QID</td>
</tr>
<tr>
<td>± acetazolamide 250 mg QID</td>
</tr>
<tr>
<td>If bleeding persists after 72 h:</td>
</tr>
<tr>
<td>urea 40 g QID or EACA 3 to 4 g QID</td>
</tr>
</tbody>
</table>

\(^a\) po, by mouth; iv, intravenously; BID, twice daily; QID, four times daily; EACA, epsilon aminocaproic acid.
of other causes of papillary necrosis (22). Aggressive antibiotic therapy for treatment of infection and early relief of obstruction due to sloughed papilla is essential. Other factors that may contribute to the development of papillary necrosis, such as nonsteroidal anti-inflammatory drugs, should be avoided. Use of nonionic contrast agents for radiographic studies may be less likely to cause sickling of RBC than ionic contrast.

The outcome of papillary necrosis in sickle cell trait is generally good. Papillae seem to be affected one at a time. Serial follow-up intravenous pyelograms of a case of sickle-cell trait with hematuria revealed initially unilateral, then bilateral, evidence of partial papillary necrosis (29). Despite bilateral lesions involving one or two papillae in each kidney, there is sufficient uninvolved kidney tissue (the average is eight pyramids per kidney) to maintain normal renal function. The impairment of concentrating ability that occurs in sickle cell anemia may protect against further injury due to sickling. Due to sloughed papilla is essential. Other factors that may contribute to the development of papillary necrosis, such as nonsteroidal anti-inflammatory drugs, should be avoided. Use of nonionic contrast agents for radiographic studies may be less likely to cause sickling of RBC than ionic contrast.

The impairment of concentrating ability that occurs in sickle cell anemia due to sloughed papilla is essential. Other factors that may contribute to the development of papillary necrosis, such as nonsteroidal anti-inflammatory drugs, should be avoided. Use of nonionic contrast agents for radiographic studies may be less likely to cause sickling of RBC than ionic contrast.

In summary, we have presented a case of papillary necrosis due to sickle cell trait that presented as gross hematuria. Sickle cell trait should be included in the differential diagnosis of any patient who presents with unexplained hematuria.

References
State University of New York at Buffalo Nephrology Training Program

The Nephrology Training Program at the State University of New York at Buffalo is focused at two of the major teaching hospitals affiliated with the Medical School: the Erie County Medical Center and the Veterans Administration Medical Center, but uses other hospitals as necessary to enhance teaching and research. Our large faculty, with varied interests and backgrounds, affords fellows the opportunity to be exposed to a variety of approaches to nephrologic problems. Trainees develop competence in all aspects of clinical nephrology in compliance with the special requirements for training programs in nephrology. These include structured and focused training, comprehensive instruction, and active participation in various dialysis modalities, renal transplantation, and continuous renal replacement therapy. The nephrology fellows are also trained in procedures such as percutaneous renal biopsy and dialysis catheter insertions. Experience in the care of end-stage renal disease (ESRD) patients is offered through direct involvement of the fellows in the ESRD team approach to management of both hospitalized and nonhospitalized ESRD and transplant patients. The opportunity for both clinical and basic research is available and encouraged for the fellows. The program prepares the nephrology trainees for clinical practice of nephrology, subspecialty board examination, and academic medicine or research. The length of the program is 2 yr with the possibility for extension, if desired, to continue research training. During this 2-yr period, fellows are able to organize a work system that will be conducive to an efficient and productive experience for inpatient care delivery, training, and education. Constant growth in education is accomplished through journal clubs, teaching responsibilities, research experience, and attendance and participation in regional and national nephrology scientific meetings.