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Genitourinary manifestations of sickle cell disease

ABSTRACT

Sickle cell disease is a common genetic disorder characterized by sickling of red blood cells under conditions of reduced oxygen tension. In turn, sickling leads to intravascular hemolysis and vaso-occlusive events with subsequent tissue ischemia-reperfusion injury affecting multiple organs, including the genitourinary system. Our review of the genitourinary manifestations of sickle cell disease focuses on sickle cell nephropathy, priapism, and other genitourinary complications such as papillary necrosis and renal medullary carcinoma.

KEY POINTS

Microalbuminuria as seen in diabetic nephropathy is the earliest manifestation of sickle cell nephropathy, and the prevalence increases as these patients get older and live longer.

Ischemic priapism is a medical emergency. Treatment with aspiration and phenylephrine injections should begin immediately and should not await treatment measures for sickle cell disease.

In patients with sickle cell trait and sickle cell disease, chronic hypoxia and subsequent sickling of erythrocytes in the renal medulla can lead to papillary hypertrophy and papillary necrosis.

SICKLE CELL DISEASE IS a common genetic disorder in the United States that disproportionately affects people of African ancestry. The characteristic sickling of red blood cells under conditions of reduced oxygen tension leads to intravascular hemolysis and vaso-occlusive events, which in turn cause tissue ischemia-reperfusion injury affecting multiple organs, including the genitourinary system.¹⁻³

In this paper, we review the genitourinary effects of sickle cell disease, focusing on sickle cell nephropathy, priapism, and renal medullary carcinoma.

THE WIDE-RANGING EFFECTS OF SICKLE CELL DISEASE

In the United States, sickle cell disease affects 1 of every 500 blacks and 1 of every 36,000 Hispanics.¹ The term describes hemoglobinopathies associated with sickling of red blood cells.

Sickling of red blood cells results from a single base-pair change in the beta-globin gene from glutamic acid to valine at position 6, causing abnormal hemoglobin (hemoglobin S), which polymerizes under conditions of reduced oxygen tension and alters the biconcave disk shape into a rigid, irregular, unstable cell. The sickle-shaped cells are prone to intravascular hemolysis,² causing intermittent vaso-occlusive events that result in tissue ischemia-reperfusion injury. Genitourinary problems include impaired ability to concentrate urine, hematuria, renal medullary carcinoma, and increased frequency of urinary tract infection.

SICKLE CELL NEPHROPATHY

The kidney is one of the most frequently affected organs in sickle cell disease. Renal

The "Addressing Disparities in Healthcare" series promotes culturally competent, personalized care by offering practical approaches to complex health issues affecting racial and ethnic minorities.

doi:10.3949/ccjm.82a.14029

Signs of kidney involvement may appear in early childhood

manifestations begin to appear in early childhood, with impaired medullary concentrating ability and ischemic damage to the tubular cells caused by sickling within the vasa recta renalis precipitated by the acidic, hypoxic, and hypertonic environment in the renal medulla.

As in early diabetic nephropathy, renal blood flow is enhanced and the glomerular filtration rate (GFR) is increased. Increased cardiac output as a result of anemia, localized release of prostaglandins, and a hypoxia-induced increase in nitric oxide synthesis all play a role in the increase in GFR.^{4,5}

Oxidative stress, an increase in markers of inflammation, and local activation of the renin-angiotensin system contribute to renal damage in sickle cell disease.⁵⁻⁷ The resulting hyperfiltration injury leads to microalbuminuria, which occurs in 20% to 40% of children with sickle cell anemia^{8,9} and in as many as 60% of adults.

The glomerular lesions associated with sickle cell disease vary from glomerulopathy in the early stages to secondary focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, and glomerular thrombotic microangiopathy.¹⁰

Clinical presentations and workup

Clinical presentations are not limited to glomerular disease but include hyperchloremic metabolic acidosis and hyperkalemia resulting from defects in potassium secretion and renal acidification.

Hyperphosphatemia—a result of increased reabsorption of phosphorus, increased secretion of uric acid, and increased creatinine clearance—is seen in patients with sickle cell disease.^{11,12} About 10% of patients can develop an acute kidney injury as a result of volume depletion, rhabdomyolysis, renal vein thrombosis, papillary necrosis, and urinary tract obstruction secondary to blood clots.^{11,13}

Up to 30% of adult patients with sickle cell disease develop chronic kidney disease. Predictors include severe anemia, hypertension, proteinuria, nephrotic syndrome, and microscopic hematuria.¹⁴ From 4% to 12% of patients go on to develop end-stage renal disease, but with a 1-year mortality rate three times higher than in patients without sickle cell disease.¹⁵

In general, patients with sickle cell anemia have blood pressures below those of age- and sex-matched individuals, but elevated blood pressure and low GFR are not uncommon in affected children. In a cohort of 48 children ages 3 to 18, 8.3% had an estimated GFR less than 90 mL/min/1.73 m², and 16.7% had elevated blood pressure (prehypertension and hypertension).¹⁶

In patients with sickle cell disease, evaluation of proteinuria, hematuria, hypertension, and renal failure should take into consideration the unique renal physiologic and pathologic processes involved. Recent evidence^{17,18} suggests that the Chronic Kidney Disease Epidemiology Collaboration equation provides a better estimate of GFR than the Modification of Diet in Renal Disease and Cockcroft-Gault equations, although all three creatinine-based methods overestimate GFR in patients with sickle cell disease when compared with GFR measured with technetium-99m-labeled diethylenetriamine penta-acetic acid renal scanning.

Treatment options

Treatment of sickle cell nephropathy includes adequate fluid intake (given the loss of concentrating ability), adequate blood pressure control, use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) in patients who have microalbuminuria or proteinuria (or both),^{9,11,19} and hydroxyurea. Treatment with enalapril has been shown to decrease proteinuria in patients with sickle cell nephropathy.⁹ In a cohort of children with sickle cell disease, four of nine patients treated with an ACE inhibitor developed hyperkalemia, leading to discontinuation of the drug in three patients.⁹

ACE inhibitors and ARBs must be used cautiously in these patients because they have defects in potassium secretion. Hydroxyurea has also been shown to decrease hyperfiltration and microalbuminuria in recent studies,^{20,21} and this could protect against the development of overt nephropathy.

Higher mortality rates have been reported in patients with sickle cell disease who developed end-stage renal disease than in patients with end-stage renal disease without sickle cell disease. Sickle cell disease also increases the risk of pulmonary hypertension and the vaso-occlusive

complication known as acute chest syndrome, contributing to increased mortality rates. Of note, in a study that looked at the association between mortality rates and pre-end-stage care of renal disease using data from the Centers for Medicare and Medicaid Services, patients with sickle cell disease who had had predialysis nephrology care had lower mortality rates.¹⁵

Treatments for end-stage renal disease are also effective in patients with sickle cell disease and include hemodialysis, peritoneal dialysis, and renal transplantation. Data from the Organ Procurement and Transplantation Network and the United Network for Organ Sharing show that from 2000 to 2011, African American kidney recipients with sickle cell disease had better survival rates than patients who had undergone transplantation from 1988 to 1999, although rates of long-term survival and graft survival were lower than in transplant recipients with other diagnoses.²²

It is important to note that complications as a result of vaso-occlusive events and thrombosis can lead to graft loss; therefore, sickle cell crisis after transplantation requires careful management.

Take-home messages

- Loss of urine-concentrating ability and hyperfiltration are the earliest pathologic changes in sickle cell disease.
- Microalbuminuria as seen in diabetic nephropathy is the earliest manifestation of sickle cell nephropathy, and the prevalence increases as these patients get older and live longer.
- ACE inhibitors or ARBs should be used with caution, given the heightened risk of hyperkalemia in sickle cell disease.
- Recent results with hydroxyurea in decreasing hyperfiltration and microalbuminuria are encouraging.
- Early referral for predialysis nephrologic care is needed in sickle cell patients with chronic kidney disease.

■ PRIAPISM IN SICKLE CELL DISEASE

Priapism was formerly defined as a full, painful erection lasting more than 4 hours and unrelated to sexual stimulation or orgasm. But priapism is now recognized as two separate disorders—ischemic (veno-occlusive,

low-flow) priapism and nonischemic (arterial, high-flow) priapism. The new definition includes both disorders: ie, a full or partial erection lasting more than 4 hours and unrelated to sexual stimulation or orgasm.

Ischemic priapism

Hematologic disorders are major contributors to ischemic priapism and include sickle cell disease, multiple myeloma, fat emboli (hyperalimentation),²³ glucose-6-phosphate dehydrogenase deficiency, and hemoglobin Olmsted variant.²⁴

Ischemic priapism is often seen in sickle cell disease and is considered an emergency. It is characterized by an abnormally rigid erection not involving the glans penis. Entrapment of blood in the corpora cavernosa leads to hypoxia, hypercarbia, and acidosis, which in turn leads to a painful compartment syndrome that, if untreated, results in smooth muscle necrosis and subsequent fibrosis. The results are a smaller penis and erectile dysfunction that is unresponsive to any treatment other than implantation of a penile prosthesis. However, scarring of the corpora cavernosa can make this procedure exceedingly difficult, requiring advanced techniques such as corporeal excavation.²⁵

Men with a subtype of ischemic priapism called “stuttering” priapism²⁶ suffer recurrent prolonged erections during sleep. The patient awakens with a painful erection that usually subsides, but sometimes only after several hours. Patients with this disorder suffer from sleep deprivation. Stuttering priapism may lead to full-blown ischemic priapism that does not resolve without intervention.

Nonischemic priapism

In nonischemic priapism, the corpora are engorged but not rigid. The condition results from unregulated arterial inflow and thus is not painful and does not result in damage to the corporeal smooth muscle.

Most cases of nonischemic priapism follow blunt perineal trauma or trauma associated with needle insertion into the corpora. This form of priapism is not associated with sickle cell disease. Because tissue damage does not occur, nonischemic or arterial priapism is not considered an emergency.

Treatments for end-stage renal disease are also effective in patients with sickle cell disease and include hemodialysis, peritoneal dialysis, and transplantation

Treatment guidelines

Differentiating ischemic from nonischemic priapism is usually straightforward, based on the history, physical examination, corporeal blood gases, and duplex ultrasonography.²⁷

Ischemic priapism is an emergency. After needle aspiration of blood from the corpora cavernosa, phenylephrine is diluted with normal saline to a concentration of 100 to 500 µg/mL and is injected in 1-mL amounts repeatedly at 3- to 5-minute intervals until the erection subsides or until a 1-hour time limit is reached. Blood pressure and pulse are monitored during these injections. If aspiration and phenylephrine irrigation fail, surgical shunting is performed.²⁷

Measures to treat sickle cell disease (hydration, oxygen, exchange transfusions) may be employed simultaneously but should never delay aspiration and phenylephrine injections.²⁵

As nonischemic priapism is not considered an emergency, management begins with observation. Patients eventually become dissatisfied with their constant partial erection, and they then present for treatment. Most cases resolve after selective catheterization of the internal pudendal artery and embolization of the fistula with absorbable material. If this fails, surgical exploration with ligation of the vessels leading to the fistula is indicated.

Prevalence in sickle cell trait vs sickle cell disease

Ischemic priapism is uncommon in men with sickle cell trait, but prevalence rates in men with sickle cell disease are as high as 42%.²⁸ In a study of 130 men with sickle cell disease, 35% had a history of prolonged ischemic priapism, 72% had a history of stuttering priapism, and 75% of men with stuttering priapism had their first episode before age 20.²⁹

Rates of erectile dysfunction increase with the duration of ischemic episodes and range from 20% to 90%.^{28,30} In childhood, sickle cell disease accounts for 63% of the cases of ischemic priapism, and in adults it accounts for 23% of cases.³¹

Take-home messages

- Sickle cell disease accounts for two-thirds of cases of ischemic priapism in children, and one-fourth of adult cases.
- Ischemic priapism is a medical emergency.

- Treatment with aspiration and phenylephrine injections should begin immediately and should not await treatment measures for sickle cell disease (hydration, oxygen, exchange transfusions).

OTHER UROLOGIC COMPLICATIONS OF SICKLE CELL DISEASE

Other urologic complications of sickle cell trait and sickle cell disease include microscopic hematuria, gross hematuria, and renal colic. A formal evaluation of any patient with persistent microscopic hematuria or gross hematuria should consist of urinalysis, computed tomography, and cystoscopy. This approach assesses the upper and lower genitourinary system for treatable causes. Renal ultrasonography can be used instead of computed tomography but tends to provide less information.

Special considerations

In patients with sickle cell trait and sickle cell disease, chronic hypoxia and subsequent sickling of erythrocytes in the renal medulla can lead to papillary hypertrophy and papillary necrosis. In papillary hypertrophy, friable blood vessels can rupture, resulting in microscopic and gross hematuria. In papillary necrosis, the papilla can slough off and become lodged in the ureter.

Nevertheless, hematuria and renal colic in patients with sickle cell disease or trait are most often attributable to common causes such as infection and stones. A finding of hydronephrosis in the absence of a stone, however, suggests obstruction due to a clot or a sloughed papilla. Ureteroscopy, fulguration, and ureteral stent placement can stop the bleeding and alleviate obstruction in these cases.

Renal medullary carcinoma

Another important reason to order imaging in patients with sickle cell disease or trait who present with urologic symptoms is to rule out renal medullary carcinoma, a rare but aggressive cancer that arises from the collecting duct epithelium. This cancer is twice as likely to occur in males than in females; it has been reported in patients ranging in age from 10 to 40, with a median age at presentation of 26.³²

When patients present with symptomatic renal medullary cancer, in most cases the cancer has already metastasized.

Early referral for predialysis nephrologic care is needed in sickle cell patients with chronic kidney disease

On computed tomography, the tumor tends to occupy a central location in the kidney and appears to infiltrate and replace adjacent kidney tissue. Retroperitoneal lymphadenopathy and metastasis are common.

Treatment typically entails radical nephrectomy, chemotherapy, and in some cir-

cumstances, radiotherapy. Case reports have shown promising tumor responses to carboplatin and paclitaxel regimens.^{33,34} Also, a low threshold for imaging in patients with sickle cell disease and trait may increase the odds of early detection of this aggressive cancer.

REFERENCES

1. Centers for Disease Control and Prevention (CDC). Sickle cell disease (SCD). Data and statistics. www.cdc.gov/ncbddd/sicklecell/data.html. Accessed August 18, 2015.
2. Paulin L, Itano HA, Singer SJ, Wells IC. Sickle cell anemia, a molecular disease. *Science* 1949; 110:543–548.
3. Powars DR, Chan LS, Hiti A, Ramicone E, Johnson C. Outcome of sickle cell anemia: a 4-decade observational study of 1056 patients. *Medicine (Baltimore)* 2005; 84:363–376.
4. Haymann JP, Stankovic K, Levy P, et al. Glomerular hyperfiltration in adult sickle cell anemia: a frequent hemolysis associated feature. *Clin J Am Soc Nephrol* 2010; 5:756–761.
5. da Silva GB Jr, Libório AB, Daher Ede F. New insights on pathophysiology, clinical manifestations, diagnosis, and treatment of sickle cell nephropathy. *Ann Hematol* 2011; 90:1371–1379.
6. Emokpae MA, Uadia PO, Gadzama AA. Correlation of oxidative stress and inflammatory markers with the severity of sickle cell nephropathy. *Ann Afr Med* 2010; 9:141–146.
7. Chirico EN, Pialoux V. Role of oxidative stress in the pathogenesis of sickle cell disease. *IUBMB Life* 2012; 64:72–80.
8. Datta V, Ayengar JR, Karpate S, Chaturvedi P. Microalbuminuria as a predictor of early glomerular injury in children with sickle cell disease. *Indian J Pediatr* 2003; 70:307–309.
9. Falk RJ, Scheinman J, Phillips G, Orringer E, Johnson A, Jennette JC. Prevalence and pathologic features of sickle cell nephropathy and response to inhibition of angiotensin-converting enzyme. *N Engl J Med* 1992; 326:910–915.
10. Maigne G, Ferlicot S, Galacteros F, et al. Glomerular lesions in patients with sickle cell disease. *Medicine (Baltimore)* 2010; 89:18–27.
11. Sharpe CC, Thein SL. Sickle cell nephropathy—a practical approach. *Br J Haematol* 2011; 155:287–297.
12. Battle D, Itsarayongyuen K, Arruda JA, Kurtzman NA. Hyperkalemic hyperchloremic metabolic acidosis in sickle cell hemoglobinopathies. *Am J Med* 1982; 72:188–192.
13. Sklar AH, Perez JC, Harp RJ, Caruana RJ. Acute renal failure in sickle cell anemia. *Int J Artif Organs* 1990; 13:347–351.
14. Powars DR, Elliott-Mills DD, Chan L, et al. Chronic renal failure in sickle cell disease: risk factors, clinical course, and mortality. *Ann Intern Med* 1991; 115:614–620.
15. McClellan AC, Luthi JC, Lynch JR, et al. High one year mortality in adults with sickle cell disease and end-stage renal disease. *Br J Haematol* 2012; 159:360–367.
16. Bodas P, Huang A, O Riordan MA, Sedor JR, Dell KM. The prevalence of hypertension and abnormal kidney function in children with sickle cell disease—a cross sectional review. *BMC Nephrol* 2013; 14:237.
17. Asnani MR, Lynch O, Reid ME. Determining glomerular filtration rate in homozygous sickle cell disease: utility of serum creatinine based estimating equations. *PLoS One* 2013; 8:e69922.
18. Arlet JB, Ribeil JA, Chatellier G, et al. Determination of the best method to estimate glomerular filtration rate from serum creatinine in adult patients with sickle cell disease: a prospective observational cohort study. *BMC Nephrol* 2012; 13:83.
19. McKie KT, Hanevold CD, Hernandez C, Waller JL, Ortiz L, McKie KM. Prevalence, prevention, and treatment of microalbuminuria and proteinuria in children with sickle cell disease. *J Pediatr Hematol Oncol* 2007; 29:140–144.
20. Laurin LP, Nachman PH, Desai PC, Ataga KI, Derebail VK. Hydroxyurea is associated with lower prevalence of albuminuria in adults with sickle cell disease. *Nephrol Dial Transplant* 2014; 29:1211–1218.
21. Aygun B, Mortier NA, Smeltzer MP, Shulkin BL, Hankins JS, Ware RE. Hydroxyurea treatment decreases glomerular hyperfiltration in children with sickle cell anemia. *Am J Hematol* 2013; 88:116–119.
22. Huang E, Parke C, Mehrnia A, et al. Improved survival among sickle cell kidney transplant recipients in the recent era. *Nephrol Dial Transplant* 2013; 28:1039–1046.
23. Klein EA, Montague DK, Steiger E. Priapism associated with the use of intravenous fat emulsion: case reports and postulated pathogenesis. *J Urol* May 1985; 133:857–859.
24. Thuret I, Bardakdjian J, Badens C, et al. Priapism following splenectomy in an unstable hemoglobin: hemoglobin Olmsted beta 141 (H19) Leu→Arg. *Am J Hematol* 1996; 51:133–136.
25. Montague DK, Angermeier KW. Corporeal excavation: new technique for penile prosthesis implantation in men with severe corporeal fibrosis. *Urology* 2006; 67:1072–1075.
26. Levey HR, Kutlu O, Bivalacqua TJ. Medical management of ischemic stuttering priapism: a contemporary review of the literature. *Asian J Androl* 2012; 14:156–163.
27. Montague DK, Jarow J, Broderick GA, et al; Members of the Erectile Dysfunction Guideline Update Panel; American Urological Association. American Urological Association guideline on the management of priapism. *J Urol* 2003; 170:1318–1324.
28. Emond AM, Holman R, Hayes RJ, Serjeant GR. Priapism and impotence in homozygous sickle cell disease. *Arch Intern Med* 1980; 140:1434–1437.
29. Adeyoku AB, Olujohungbe AB, Morris J, et al. Priapism in sickle-cell disease: incidence, risk factors and complications—an international multicentre study. *BJU Int* 2002; 90:898–902.
30. Pryor J, Akkus E, Alter G, et al. Priapism. *J Sex Med* 2004; 1:116–120.
31. Nelson JH, 3rd, Winter CC. Priapism: evolution of management in 48 patients in a 22-year series. *J Urol* 1977; 117:455–458.
32. Liu Q, Galli S, Srinivasan R, Linehan WM, Tsokos M, Merino MJ. Renal medullary carcinoma: molecular, immunohistochemistry, and morphologic correlation. *Am J Surg Pathol* 2013; 37:368–374.
33. Gangireddy VG, Liles GB, Sostre GD, Coleman T. Response of metastatic renal medullary carcinoma to carboplatin and Paclitaxel chemotherapy. *Clin Genitourin Cancer* 2012; 10:134–139.
34. Walsh AM, Fiveash JB, Reddy AT, Friedman GK. Response to radiation in renal medullary carcinoma. *Rare Tumors* 2011; 3:e32.

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