



Case report

Renal papillary necrosis in a patient with sickle cell disease

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Introduction

Renal manifestations in sickle cell disease (SCD) occur in one-third of adolescents and young adults.¹ These manifestations occur because the kidney is sensitive to hypoxia-induced vaso-occlusion resulting from the adhesion of sickled red blood cells to the endothelium.^{2,3} The renal medulla is characterized by acidosis, hypertension, and hypoxia. These factors promote the polymerization and sickling of hemoglobin (Hb) S, which makes this area of the kidney susceptible to changes in the supply of oxygen.³

Proteinuria associated with anemia increases the risk of renal insufficiency mainly among the elderly with SCD.⁴ These chronic complications and the imminent risk of a severe acute vaso-occlusive event should be emphasized to clinicians and pediatricians who treat SCD patients in emergency rooms, which justifies the need to review the clinical findings of renal involvement enabling diagnosis, monitoring, and early treatment.

This article reports a clinical case of a patient with SCD with a possible diagnosis of renal papillary necrosis and renal insufficiency that required dialysis.

Case report

We report on a case of a 30-year-old married mulatto male, who was born and raised in São Paulo and is self-employed.

He presented to the emergency room with dyspnea and reddish-colored urine that had contained clots for three days prior to his clinic visit. He had a cough with yellow sputum, and occasional episodes of bilateral chest pain. For five days, he had also experienced diffuse body pain, similar to previous painful crises, but which evolved to continuous right flank pain associated with three episodes of gross hematuria. He reported taking 2 mg/night of clonazepam, dipyrone, and 5 mg/day of folic acid at home. No fever, headache, dysuria, or edema of the lower limbs was present.

The patient had previously been diagnosed with SCD and referred to the Hematology Clinic of the Hospital das Clínicas of the Medical School, Universidade de São Paulo (FMUSP) for monitoring. The patient brought with him his records from the other service however, the patient had not been seen for three years, and his most recent exams (12/29/2005) showed preserved renal function (urea: 17 mg/dL and creatinine: 0.65 mg/dL). The patient reported having undergone a

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Table 1 – Routine laboratory tests.

Parameter	Results
Urea (mg/dL)	141
Creatinine (mg/dL)	4.66
Sodium (mEq/L)	130
Potassium (mEq/L)	3.7
Hemoglobin (g/dL)	7.2
Hematocrit (%)	20.4
Leukocytes ($\times 10^9/L$)	27.26
Band cells ($\times 10^9/L$)	0.6
Neutrophils ($\times 10^9/L$)	19.0
Eosinophils ($\times 10^9/L$)	0.3
Lymphocytes ($\times 10^9/L$)	4.9
Monocytes ($\times 10^9/L$)	1.6
Platelets ($\times 10^9/L$)	337.0
C-reactive protein (mg/dL)	145
Ionized calcium (mmol/L)	4.6
Phosphorus (mg/dL)	5.7
Direct bilirubin (mg/dL)	0.8
Indirect bilirubin (mg/dL)	0.95
Urinalysis	
pH	6.0
Density	1010
Protein (g/L)	1.0
Urobilinogen (mg/dL)	0.2
Leukocytes (cells/field)	100
Red blood cells (cells/field)	100
Alkaline phosphatase (U/L)	236
Gamma-GT (U/L)	349
Aspartate aminotransferase (U/L)	45
Alanine aminotransferase (U/L)	25
Lactate dehydrogenase (U/L)	1344
No dysmorphic red blood cells were found.	

splenectomy five years previous to admission; this information could not be confirmed because it is assumed that at an adult age, the occurrence of significant hyposplenism may have occurred.

The patient smoked, consumed alcohol (2–3 beers/day), and was a daily drug user (marijuana plus inhaled and intravenous cocaine), but reported being abstinent for three days.

In the physical examination the patient presented with general overall discoloration of the skin (2+/4+) and icterus (2+/4+); he was also acyanotic and eupneic. He was afebrile with a blood pressure of 200/110 mmHg and a heart rate of 96 beats per minute. On lung auscultation, vesicular breath sounds were found throughout the chest, as were crepitant rales in the left pulmonary base; the respiratory rate was 18 breaths per minute. Upon auscultation of the cardiocirculatory system, normophonic rhythmic sounds were found with two normal sounds and a 1+/6+ systolic panfocal murmur. The abdomen was flat with a splenectomy scar, and pain was induced upon right flank palpation; the abdomen was also flaccid, negative on abdominal decompression test, and negative for Giordano's sign. An examination of the lower limbs showed good peripheral perfusion and no edema or signs of deep venous thrombosis.

Upon arrival at the emergency room (6/18/2010), a chest X-ray and routine laboratory tests were performed (Table 1).

Hypertensive emergency and uremic syndrome were identified in association with severe low back pain and

a possible concomitant infection. The indication of treatment included emergency treatment for hypertension with sodium nitroprusside, antibiotics (ceftriaxone 1g IV b.i.d. and clarithromycin 250 mg IV b.i.d.) for possible urinary and tracheal-bronchial infections, and emergency hemodialysis.

A Doppler ultrasound (US) of the renal arteries revealed right renal hydronephrosis with the right kidney measuring 12 cm, a hyperechoic right kidney without obstruction and no thrombi in the renal arteries and veins. Moreover, US showed a hyperechoic left kidney measuring 10 cm, without hydronephrosis. An abdomen and pelvic computed tomography (CT) revealed mild/moderate right pyelocalyceal dilatation and proximal ureteral ectasia with hyperattenuating material in the middle third (clot). Hydronephrosis was not identified in the left kidney. A presumptive diagnosis was made of renal infarction and renal papillary necrosis complicated by SCD. After the patient's blood pressure was stabilized and antibiotic treatment was completed, he continued to receive chronic dialysis as an outpatient.

Discussion

Fortunately, renal changes that occur in patients with SCD are less severe, usually have a slower onset, and are less progressive than the renal changes that this patient experienced. Three years previously, the patient had preserved renal function, and therefore, it is suggested that an acute condition occurred at the time of admission, remembering that the time from loss of renal function to dialysis levels is very short in chronic infarctions. In addition, the kidney imaging at admission indicated no contracted kidney (secondary to fibrosis), as occurs in chronic infarctions. In this case, the clinical picture was one of a sudden onset of renal papillary necrosis, which led to severe renal failure that required dialysis.

The presence of a normal contralateral kidney associated with an obstructed kidney after papillary necrosis is an uncommon finding in cases of severe renal insufficiency that requires dialysis. Possible papillary necrosis of the left kidney was not evident on imaging. In addition, the presence of a contracted kidney, as occurs in chronic renal infarctions, was not observed. Notably, these renal changes are the result of the sickling of red blood cells and vaso-occlusive events. The adherence of erythrocytes to the vascular endothelium is likely the primary mechanism by which molecular alterations that occur in red blood cells affect tissues.^{5,6}

The urinary and pulmonary tract infections also contributed to the patient's admission to hospital. Among the conditions that are commonly seen in these patients are cardiopulmonary complications (especially congestive heart failure and acute chest syndrome), renal insufficiency, and strokes; infections may precede or be concomitant with these complications, as was observed in this patient.^{5,6}

In patients with SCD, certain functional and structural changes in the kidney can be observed. These affect the entire nephron, from the glomerulus to the renal papilla. Due to a high consumption of oxygen during cellular metabolism, the kidney is highly affected in the setting of vaso-occlusive crises, which are characteristic of SCD. The environment surrounding the renal medulla is characterized by acidosis, hypertonicity,

and hypoxia, and these factors contribute to the sickle cell crisis that is responsible for the occlusion of the renal vessels.³ The most important consequence of these crises is damage to the renal tubules; this causes atrophy or dilation of the tubules, the presence of protein cylinders, and iron deposition along with degeneration of the tubule epithelium.^{1,7}

Regarding the patient's complaint of hematuria, we note that this is a common clinical manifestation. Bleeding occurs due to the polymerization of red blood cells within the renal medulla. In 80% of cases, bleeding occurs in just one kidney. Treatment for hematuria is conservative and includes bed rest, maintenance of a high urine flow rate, urine alkalinization, and (if necessary) blood transfusions.¹ Most episodes are limited but can occur due to micro infarctions in the renal pyramids, which may be associated with renal papillary necrosis.^{3,7}

Upon admission to the emergency room, the following clinical picture was observed: a hypertensive emergency associated with renal failure, which previously did not exist. Renal insufficiency due to nephropathy is observed in 4-21% of adult SCD patients. Renal insufficiency is one of the most serious complications of this disease and contributes to the early mortality of patients. Disease duration, severity of anemia, and genetic features are risk factors that influence the development of renal insufficiency.⁸

This patient experienced a long interval during which his disease was not regularly monitored, and because it is viewed as a chronic disease, the patient's serious drug addiction problems were detrimental to the clinical and laboratory parameters of renal impairment prior to hospitalization. Several markers have been studied as early indicators of renal impairment, including the estimated glomerular filtration rate (eGFR), microalbuminuria, and proteinuria. Microalbuminuria, an early marker of kidney damage, may be directly related to age, and is inversely related to hemoglobin levels.⁸

Nephrotic syndrome would indicate a chronic evolution of focal segmental glomerulosclerosis. However, no clinical report revealed nephrotic syndrome prior to the admission of this patient to the hospital. In addition, clinical symptoms of acute vaso-occlusive events, such as those that occur in papillary necrosis, were observed. Therefore, imaging exams were important to confirm this finding.

Renal papillary necrosis is characterized by pyelocalyceal and ureteral occlusions, which are due to clots and necrotic papillae, and may have various causes including diabetes, analgesics, and SCD. The main cause of papillary necrosis in SCD is related to the environment of the renal medulla, which is hypertonic, hypoxic, and favors the sickling of red blood cells.⁵ If the ischemic process is due to a temporary spasm and normal circulation is restored, the tissues that are affected would be able to recover. However, if the ischemia continues and perfusion is not restored, these factors lead to coagulative necrosis and tubular fibrosis, which are irreversible processes.⁹

A CT scan shows ischemic changes with greater accuracy than US. In helical CT, changes that lead to renal papillary necrosis may be observed at the beginning of the corticomedullary phase, but these can be better described using urography. In urography, changes are presented as poorly

marginated areas of enhancement, which are reduced at the point of the medullary pyramid.¹⁰

In this case, no regular outpatient follow-up was conducted, which hampered the possibility of early intervention with respect to the renal manifestations or any attempts to prevent the vascular event in question. Measures to prevent such renal lesions include angiotensin converting enzyme inhibitors and hydroxyurea, which are believed to provide the greatest benefits in the control of sickle cell nephropathy. The early identification of risk factors for renal involvement may allow the physician to provide appropriate treatment to the patient.^{5,7,8}

Studies indicate that lactate dehydrogenase (LDH) may be used as an early marker for identifying the risk of kidney failure in SCD patients. The serum LDH levels are used as a measure of intravascular hemolysis, which is a major pathological mechanism of cardiovascular complications as well as pulmonary, gastrointestinal, and renal manifestations of SCD patients.^{8,10} Exacerbated hemolysis is associated with early mortality in patients with this disease.⁸

Regarding the clinical evolution of his disease, this patient received hypertensive emergency treatment, including intravenous sodium nitroprusside and dialysis for blood volume and metabolic control. He was then discharged and continued to receive outpatient dialysis. The evolution of this disease will undoubtedly increase the morbidity of SCD patients and it is correlated with an increased mortality rate.

Conclusions

It is extremely important to recognize sickling mechanisms and how they affect renal disorders. It is also necessary to understand that renal changes occur over the years in SCD patients, and when accompanied by clinical symptoms such as hematuria, microalbuminuria, and proteinuria, it signals the necessity of improved patient care. Prompt care will prevent more serious and permanent injuries such as renal papillary necrosis and consequent renal insufficiency that requires dialysis and can further impair the quality of life and increase the mortality of SCD patients.

Conflicts of interest

The authors declare no conflicts of interest.

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