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An unlikely case although it exists

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CLINICAL PRESENTATION

We present a case of 41-year-old man, native of Angola, accountant, who frequently visits Portugal. He has a family and personal history positive for homozygotic sickle cell anemia with 2-3 crises/year during infancy and a relatively controlled disease during adulthood with exception of ocular thrombosis and ischemic cerebrovascular disease necessitating anti-platelet and vasodilation therapy.

Chronic kidney disease was documented in 2016 with a serum creatinine of 1.9 mg/dL with unknown proteinuria plus some respiratory infections (viral, fungal and bacterial) associated with trips within Africa in the last couple of years.

He was asymptomatic until summer of 2017, when he was hospitalized for a difficult-to-control anemia, requiring multiple blood transfusions. He denied hematuria. Further studies revealed a positive Coombs (starting prednisolone) and the gastro-intestinal tract endoscopy reported an erosive bulbitis and an inflammatory polyp.

In March 2018, he went to the Emergency Department with anemia (Hb 6.5g/dL) and a respiratory infection, already medically treated with Cefixime. After administration of blood transfusion, the patient discharged himself from hospital. Four days later, he returned to the department due to exacerbation of symptoms. The follow-up tests showed severe anemia (Hb 4.7 g/dL); hemolysis (total bilirubin 3.16 mg/dL; LHD 875 U/L) with a positive Coombs; acute on chronic renal disease (serum Cr 3.66 mg/dL, urinary proteins 300 mg/dL and erythrocytes 1/mcL); hypoxia (SpO2 92% with O2 1.5 L/min); mixed respiratory and metabolic acidosis and a bilateral infiltrate in lung X-ray.

At this time, his ambulatory medication was prednisolone 7.5 mg/day, folic acid; lysine acetilsalicilate; calcitriol; esomeprazole; allopurinol; furosemide; ursodeoxycholic acid; cinnarizine.

During hospitalization in the nephrology department, the patient was treated with amoxicillin-clavulanate and azithromycin for respiratory infection, which improved. He initiated prednisolone 1mg/Kg/day and blood transfusions were avoided regarding allo and auto-immunization, after discussion with Hematology. Due to deterioration of renal function (SCr 5.17 mg/dL; ureia 222 mg/dL; K 6.7 mEq/L) with fluid overload, the patient initiated hemodialysis. After revision with Hematology it was decided to wean prednisolone, be cautious with blood transfusions (target Hb: 5-7g/dL), and start erythropoiesis stimulating agents and hydroxyurea.

During his stay on the ward, the patient's clinical situation worsened with an acute chest syndrome/new respiratory infection, although he recovered with medical treatment with piperacillin/tazobactam, blood transfusion and oxygen.

Work-up while patient was admitted showed: chromatography measurements of hemoglobin – after transfusions (HbS 55%, HbF 3.5%); kidney US doppler with normal-sized kidneys and increased resistance index, chest tomography revealing cardiomegaly and oedematous/inflammatory changes in lung parenchyma. The remaining exams such as serologic tests (CMV, VDRL, hepatitis, HIV); serum immunofixation test; ANA; DNA Parvovirus B19, urine and blood cultures; respiratory virus and upper endoscopic study were negative or without relevant findings.

The patient underwent a renal biopsy (Figures 1, 2, 3, 4, 5) which resulted in a retroperitoneal hematoma of significant dimensions.

After optimization of the possible clinical parameters, the patient remained hemodialysis-dependent.

QUESTIONS

1. **What are the light microscopy findings? According to the clinical and histological picture, what is the diagnosis?**
   Data not shown: Immunofluorescence revealed glomerular IgM and C3 segmentary; electronic microscopy presented dense, granular particles within proximal tubules' cytoplasm.
2. **What are the main features of this disease and what are the pathologic mechanisms leading to the renal disease/injury mentioned?**
3. **Which are the renal manifestations that we expect to occur in this disease?**
4. **Is renal transplantation an option in these patients? What are the main challenges?**

Figure 1

Periodic Acid Schiff (PAS) stain (200x)

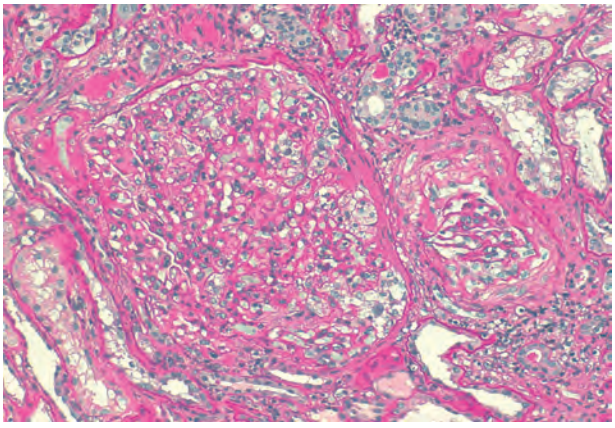


Figure 2

Silver stain (400x)

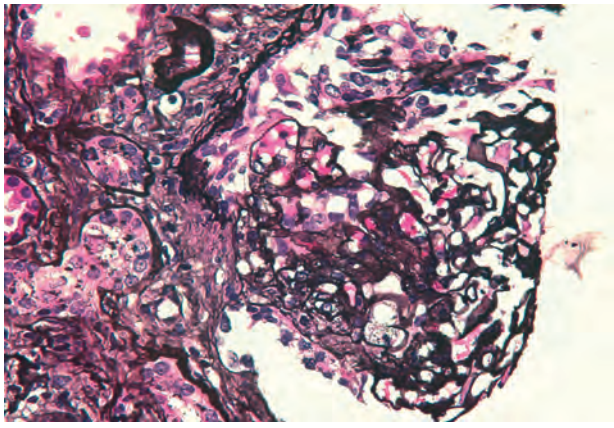
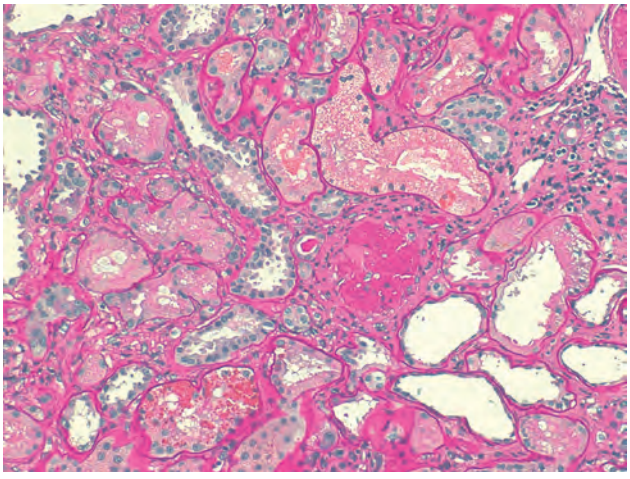


Figure 3

PAS stain (200x and 400x)



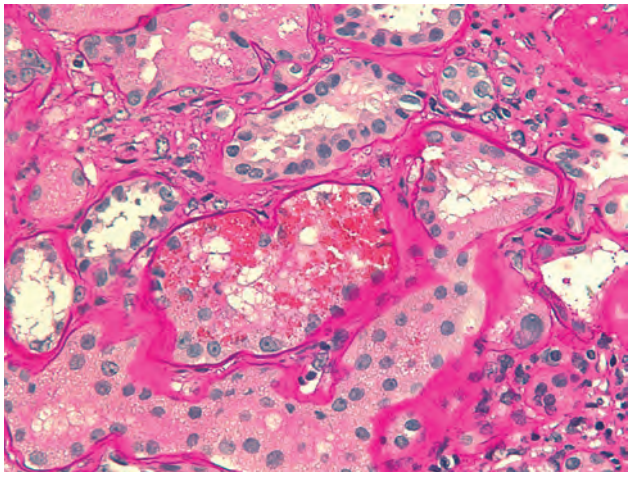


Figure 4

Perls stain (200x)

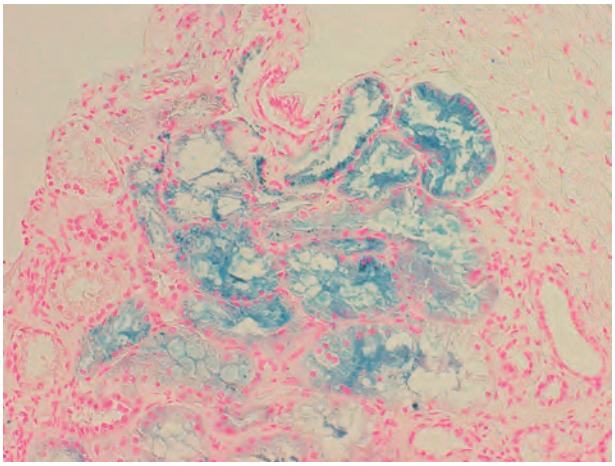
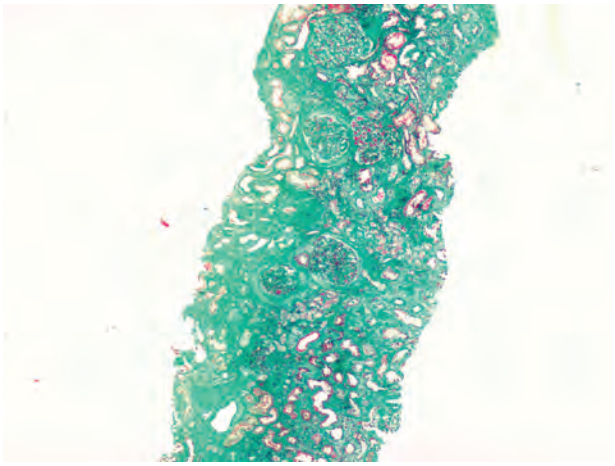


Figure 5

Trichrome stain (x40)



ANSWERS

1. What are the light microscopy findings? According to the clinical and histological picture, what is the diagnosis?

Figure 1: Periodic Acid Schiff (PAS) stain (200x) shows glomerulomegaly with podocyte hypertrophy, mild mesangial expansion, capillary novel adhesion to Bowman's capsule and Bowman's capsule thickening.

Figure 2: Silver stain (400x) shows a segmentary sclerotic lesion with podocyte hypertrophy and brown deposits in proximal tubules.

Figure 3: PAS stain (200x and 400x) showing proximal tubules with intracytoplasmic brown granules.

Figure 4: Perls stain (200x) confirms hemosiderin accumulation in renal tubules.

Figure 5: Trichrome stain (x40) representing the extensive fibrosis and tubular atrophy.

The previous images show features of a focal and segmental glomerular sclerosis (FSGS). Although there are no pathognomonic lesions that define sickle cell nephropathy (SCN), FSGS is the most common pattern.

In this specific case, after a thorough clinical investigation and exclusion of secondary causes and considering the clinical and histological information with inclusively hemosiderin deposits proven in Perls staining and corroborated by electronic microscopy, we conclude to be in the presence of SCN.

2. What are the main features of this disease and what are the pathologic mechanisms leading to the renal disease/injury mentioned?

Sickle cell anemia (SCA), the most common form of sickle cell disease (SCD) group, is a hereditary hematologic disease resulting from homozygosity for the sickle hemoglobin (HbS) gene by substitution of valine for glutamic acid at its sixth amino acid in the β-globin gene.[1]

SCD is an increasing health problem worldwide. It is estimated that every year approximately 300,000 infants are born with it. The majority of these births occur in Nigeria, Democratic Republic of the Congo, and India.[2]

When deoxygenated, HbS polymerizes, damaging the erythrocyte and resulting in hemolytic anemia and vasoocclusive events which lead to endothelial dysfunction, functional nitric oxide deficiency, inflammation, oxidative stress and reperfusion injury, hypercoagulability, increased neutrophil adhesiveness and platelet activation. It presents as a multisystemic disorder, responsible for many clinical manifestations such as acute chest syndrome, acute ischemic stroke, splenic sequestration, avascular necrosis of bones, leg ulcerations, hepatopathy and renal disease.[2]

CKD is present in 11.6% of patients with SCD, with median age of onset 37 years, and is a major cause of death in this specific population.[3] Renal involvement may have different renal histological patterns, with FSGS the vast majority and a membranoproliferative glomerulonephritis or thrombotic microangiopathy the least frequent.[4]

SCN reflects the underlying vasculopathy with altered hemodynamics, a perfusion paradox due to cortical hyperperfusion and medullary hypoperfusion and, more than that, a stress-induced vasoconstrictive response.[4] Medullary hypoperfusion results from a hypoxic, acidotic and hyperosmolar environment promoting polymerization of HbS and consequently vascular stasis which induces ischemia and potentially infarction or ischemia-reperfusion phenomena with inevitable oxidative stress, inflammatory and fibrotic mediators. Subsequent ischemia in the renal papillae may occur.[3,5] Cortical hyperperfusion is still not completely understood but it seems to be not only an increased cardiac output driven by anemia and increased plasma volume but also reflects the activity prostaglandins-induced vasodilation which are increased in SCD probably due to medullary ischemia.[3,4,6,7]

CKD progresses due to many processes in the vascular, glomerular, tubular and interstitial compartments in the kidney taking place in SCA.

The hemodynamic glomerular injury that results from the increased glomerular filtration rate (GFR) and the glomerular plasma flow rate leads to damage to the glomerular endothelium, the podocyte and the glomerular filtration barrier, thereby causing proteinuria and progressive injury to the tubulointerstitial compartment. Those damaged podocytes may form focal adhesions to the parietal epithelium, which cause FSGS.[4,7] Glomerular enlargement with podocyte hypertrophy tends to increase with age in patients with SCD, with glomerular congestion starting to appear in children over the age of 2 years.[3]

The free plasma HbS resulting from hemolysis (the one not haptoglobin-bound) passes through the glomerular filtration barrier, leading to haemoglobinuria with subsequent tubular incorporation of HbS followed by intracellular break-down of HbS and heme. In that way, iron accumulates in renal tubules. More than that, HbS has a pro-oxidant effect and unregulated proinflammatory and fibrogenic genes, with hemoglobinuria associated with CKD progression.[4]

Vasoocclusive episodes induce endothelial injury with release of proinflammatory and profibrotic cytokines; also cortical and medullar hypoxia and damage of tubular epithelium occurs.[4]

In SCD there is a hyperfunction of the proximal tubules due to an increased GFR predisposing to tubulointerstitial injury as well.[3,4]

In conclusion, the medullary ischemia exacerbated in SCD leads to prostaglandin-induced vasodilation with subsequent renal hyperperfusion. This medullary ischaemia is responsible for the distal nephron dysfunction inducing hyper functioning of proximal tubules as a compensatory mechanism.[4]

3. Which are the renal manifestations that we expect to occur in this disease?

Regarding renal manifestations, SCD can present with hyperfiltration, hypertrophy and hyposthenuria, as early as infancy. Microalbuminuria is observed in childhood and macroalbuminuria in early to middle adulthood. Hematuria and AKI may occur at any age.[4] Naturally as the SCN progress with CKD development, the GFR tends to decrease and eventually results in end-stage renal disease (ESRD) with a rapid decline in GFR when it drops below 40 mL/min/1.73m2.[3-5] On the other hand, we should remember that GFR can significantly overestimate renal function due to increased secretion of creatinine.[7]

When in hemodialysis, SCD-ESRD patients carries a poor survival prognosis with a mortality rate 2.8 times higher than that of non SCD-ESRD patients on hemodialysis.[3,4,8]

Hematuria is one of the most common manifestations in SCD, typically unilateral in the left kidney due to higher pressure in the longer left renal vein. Hematuria can present as microscopic or macroscopic and the majority is asymptomatic although some patients may experience back pain or abdominal pain. Hematuria results from papillary necrosis, renal infarction, vessel rupture and in rare cases from renal medullary carcinoma usually in sickle cell trait.[4]

Proteinuria is an early sign of SCN; it is age dependent and a predictor of SCN progression. It occurs in up to 27% in the first thirty years, and up to 68% in older SCA patients, occasionally reaching nephrotic range.[3,4,5] Inhibitors of the renin angiotensin system are used to reduce proteinuria, even when blood pressure is normal, in order to delay the progression of CKD.[4]

Hyposthenuria is an almost universal and early manifestation among SCD patients due to red blood cells sickling which diminishes blood flow into the medulla with loss of concentration gradient leading to impaired sodium reabsorption in the medullary collecting ducts. This urinary concentration defect, with a dehydration risk mainly in children, may become irreversible due to medullary fibrosis and permanent destruction of renal collecting ducts.[4,7]

Incomplete distal renal tubular acidosis (RTA) and hyperkaliemia may develop due to impairment of juxtamedullary nephrons responsible for bicarbonate reabsorption. Urinary acidification defect is present in approximately 38% of adults with SCD. [4]

Though acute kidney injury (AKI) is less frequent than CKD, many factors such as sepsis, heart failure and profound hypovolemia may precipitate an AKI.[4]

4. Is renal transplantation an option in these patients? What are the main challenges?

In the last century (1992-1997) SCD-ESRD patients were less prone to be placed on transplant waiting list/receive a renal transplant than non SCD-ESRD. Even in the USA, from 1988 to 2011, patients with SCD represented only 0.003% of the overall black/African-American kidney transplant population, obviously denoting a limited experience.[8] Nevertheless SCD should not be considered a contraindication for transplantation.[9]

Despite the implied challenges and possible complications associated with kidney transplantation in SCD-ESRD patients, some authors believe that it remains the preferred renal replacement therapy.[3,7] In SCD-ESRD, transplantation is able to improve the survival outcome when compared with chronic dialysis with a projected 10-year survival of 56%, compared to only 14%.[3]

There are various challenges associated with kidney transplant in this patient population which is prone to various organ dysfunctions such as hematologic, cardiovascular, pulmonary, and immunologic complications.

The surgery itself may present some challenges, as general anaesthesia may worsen the hypoxic state and promote dehydration due to fluid loss/deprivation, exposing those patients to increased risk of sickle cell crises and AKI. Also in addition, anemia correction with blood transfusion, pre/into and post-transplantation contains such risks as alloimmunization and/or vasoocclusive events, with the last also a notable risk when we see improvement of erythropoiesis after transplantation. The risk of infection is also high, regarding auto or iatrogenic splenectomy with significant immunodeficiency characteristic of SCD patients, which is exacerbated with immunosuppressive transplantation therapy.[9]

According to Huang E. *et al.*, although the post renal transplantation survival still benefits non-SCD over the SCD patients with ESRD, patient survival over 6 years has substantially increased in the SCD post-transplantation populations since the last century and is now comparable with black recipients with diabetes as a cause of ESRD.[8]

Beyond that, in this specific case, this patient has also a documented auto and alloimmunization requiring extra attention in donor/organ selection, with this yet another challenge. Remember that sickle cell patients are exposed to multiple blood transfusions, increasing their risk of alloimmunization.

Disclosure of potential conflicts of interest: none declared

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