

A case report of diffuse renal cortical necrosis in sickle cell trait

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Case Report

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Abstract

Background:

Sickle cell disorders are the most common hereditary hematological disorders; they are characterized by a genetic mutation at the β -globin locus, the heterozygous inheritance leads to sickle cell trait (SCT), a largely benign phenotype with mild clinical manifestations, if any. Unlike sickle cell disease (SCD), clinical presentations for SCT patients are rarely attributed to their underlying hematological status. Different types of renal manifestations have been identified in SCT. Renal cortical necrosis (RCN) is a rare and severe form of kidney injury that has not been associated in the literature with SCT. We report a case of diffuse RCN with stage 3 of acute kidney injury in a patient with SCT with no apparent trigger and partial recovery.

Case presentation:

A 41-year-old non-smoker male, with a background of SCT and no other medical history presented with acute abdominal pain and an initial serum creatinine of 530 $\mu\text{mol/L}$. His toxicology, viral, and immunological screen were negative with a normal renal ultrasound scan. His urea was 14 mmol/L, hemoglobin of 12 g/dL, normal platelet levels and no schistocytes. His urine protein to creatinine ratio was 1040 mg/g. Lactate dehydrogenase (LDH) and total bilirubin were elevated at 2606 U/L and 31 $\mu\text{mol/L}$, respectively. His kidney biopsy showed diffuse renal cortical necrosis. The patient received conservative therapy and had partial recovery of renal function; his creatinine improved to 176 $\mu\text{mol/L}$ six months later with an eGFR of 42 ml/min/1.73m².

Conclusions:

SCT has long been considered a benign condition. However, recent evidence suggests that, although uncommon, vaso-occlusive manifestations can occur, especially in the context of stressors such as dehydration or physical exhaustion. This is the first described case of diffuse RCN in SCT, highlighting the need for vigilance in managing SCT and its potential severe clinical manifestations.

Background

Sickle cell disorders are a group of autosomal recessive genetic disorders in which the individual carries the sickle cell variant at the β -globin locus, [1] The homozygous inheritance of the sickle mutation leads to sickle cell disease (SCD), where clinical sickling of red blood cells takes place with subsequent vaso-occlusion and end-organ damage. SCD is associated with a substantial burden of mortality and morbidity.[2] On the other hand, the heterozygous inheritance leads to sickle cell trait (SCT), a much milder condition which has been long considered a benign disorder, [3] with low rates of renal complications.

Diffuse renal cortical necrosis (RCN) is a severe ischemic destruction of all elements of the kidney's cortex. It usually occurs as a result of substantial compromise of the renal arterial perfusion [4]. It is a rare cause of acute kidney injury (AKI), accounting for 2% of all cases of AKI in adults [5, 6] and more than 50% of cases are caused by obstetric emergencies [7]. Patients with RCN typically present with hematuria, pain, and anuria [5]. RCN can be diagnostically challenging in the absence of classical risk factors, and treatment is largely supportive with limited chances of renal recovery, as over 40% are dialysis dependent by 6 months [8]

There is growing evidence of morbidity associated with SCT, including a number of renal manifestations, [9]. However, we describe the first case of diffuse RCN on background of SCT which presented with stage 3 AKI and was followed by partial recovery of renal function. This case report highlights the importance of recognizing RCN as a potential complication of SCT.

Case Presentation

A 41-year-old non-smoker male with a background of SCT presented with acute severe non-radiating lower abdominal pain that was associated with nausea and vomiting. There was no history of diarrhea, jaundice, urinary symptoms, use of nonsteroidal anti-inflammatory medications, or exposure to iodinated contrast studies.

On examination, the patient was visibly in pain with a blood pressure measuring 159/94mmHg on the right arm and 149/91mmHg on the left. He was tachycardic with a heart rate of 112 bpm, afebrile with a temperature of 36.8°C and a 100% oxygen saturation. His abdominal examination was notable for lower abdominal tenderness but was soft with normal bowel sounds.

At the time of presentation, laboratory investigations revealed a serum creatinine of 530 µmol/L with an estimated glomerular filtration rate (eGFR) of 11 ml/min/1.73m², urea of 14 mmol/L, hemoglobin of 12 g/dL, normal platelet levels and no schistocytes. The electrolyte panel, blood glucose, and HbA1c were all normal. The urine exam showed + albumin, + glucose, ++ leukocyte esterase, - nitrate, 25-50 white blood cells (WBCs), and 10-25 red blood cells (RBCs), with a negative urine culture. His urine protein to creatinine ratio was 1040 mg/g. Lactate dehydrogenase (LDH) and total bilirubin were elevated at 2,606 U/L and 31 µmol/L, respectively.

His autoimmune profiles, including ANA, Anti DNA, Anti-SM, ANCA, and Anti-GBM antibodies, were all negative with normal complement levels. Serologic tests for hepatitis B, C, and human immunodeficiency virus (HIV) were negative. His toxicology screen was also negative. A hemoglobin electrophoresis showed a Hemoglobin S level of 31%, consistent with his known SCT status. Abdominal imaging in the form of kidney ultrasound was normal in size, position and echogenicity. However, a non-contrast computed tomography (CT) scan showed both kidneys had mild atrophy, more severe on the left kidney, but without patchy or wedge-shaped lesions or surrounding fat stranding.

Management was prioritized with the commencement of steroids pending the initial serological work-up and an urgent kidney biopsy was performed without requiring kidney replacement therapy. The biopsy consisted of 2 cores of renal cortex with diffuse extensive coagulative necrosis where the tubules and glomeruli are lined by pale ghost cells and pyknotic nuclei. There was marked, interstitial inflammatory infiltrate composed predominantly of ghost of neutrophils. On immunofluorescence, frozen sections of the renal core tissue stained with fluorescein isothiocyanate (FITC), IgG, IgA, IgM, C3, Fibrinogen & C1q showed no deposits for any of the proteins **(Figure 1-2)**. This was consistent with diffuse renal cortical necrosis. The patient's steroids were held and was managed conservatively. He had partial recovery of his kidney function with a creatinine level of 176 $\mu\text{mol/L}$ and eGFR of 42 ml/min/1.73m^2 six months later **(Figure 3)**. The patient had persistent proteinuria and was started on Perindopril 5mg and Empagliflozin 25mg daily.

Discussion and conclusions

We report a case of diffuse RCN with partial renal recovery in a patient with SCT, an unexpected complication for a condition which is classically associated with mild clinical manifestations, if any, and no end organ damage [3]. This highlights the importance of recognizing and managing RCN as a possible complication in SCT.

Sickle cell disorder is considered one of the most common hereditary hematologic diseases [9, 10], with prevalence in some African countries as high as 40% and 2% for SCT and SCD, respectively [11, 12]. SCD is associated with occlusion of the microvasculature and subsequent ischemia and injury due to the polymerization of sickle hemoglobin S (HbS), promoted by decreased local oxygen tension, acidosis, and hyperosmolarity. Furthermore, the abnormal membrane of the sickle erythrocytes leads to high adhesion to the endothelium, further promoting sickling and vaso-occlusion.[13] Although patients with SCT rarely show clinical manifestations due to their low levels of HbS, there has been a growing literature in recent years on the clinical implications of SCT, this may manifest in different ways in the kidneys, such as hematuria [14], chronic kidney disease, proteinuria [15], hyposthenuria [16, 17], renal medullary carcinoma [18] and renal papillary necrosis (RPN) [19].

The pathophysiology of the ischemic injury and infarction appears to be similar to SCD [20], the medulla has been the main target in the kidney due to the polymerization-promoting environment with the hypoxemia, hypertonicity, acidosis, and hyperthermia of the arterial blood passing through the long vasa recta of the renal medulla. [21] However, renal cortical necrosis has not been reported before.

In addition, there have been several reports of severe sickle cell-related complications affecting other organs in patients with SCT, such as cerebral infarction, avascular necrosis, pulmonary embolisms, and splenic infarcts[22–25]. In many occasions, the complications happens in the context of demanding physical stress or decreased oxygen tension pressure such in high altitudes or after plane trips [25, 26]. Interestingly, a previous case of patchy RCN was reported in SCT, however, it was in the context of a newly transplanted kidney and the necrosis was attributed to the basiliximab-cyclosporine interaction. [27]

Diffuse RCN is a rare phenomenon and renal recovery is uncommon [4]. In the non-obstetric population, a number of causes for RCN have been identified such as septicemia, hemolytic uremic syndrome (HUS), snake bite, renal allograft rejection, gastroenteritis, and pancreatitis [7], in a 22 years' experience from Eastern India, Prakash J and colleagues reported almost 72% of the non-obstetric cases of RCN were caused by HUS[28]

Although the exact pathogenesis of RCN is not well-understood, endothelial injury precipitated by vasospasm or exposure to toxins appears to play a crucial initiating event in the process of RCN. [29, 30] The role of endothelium-derived vasoactive substances particularly endothelin-1 have also been suggested in the pathogenesis of the ischemic insult as renal vasculature appears to be 10 times more sensitive to this effect compared to all other vascular organ [31]

In addition, intravascular thrombosis has also been implicated in the process, [32] with the compromised renal arterial perfusion being the final step which results in the ischemic necrosis of the cortex. [4] The higher sensitivity of vasculature in pregnancy to vasoconstrictors likely contributes to RCN being primarily an obstetric phenomenon. [29, 30]

Although the pathophysiology of SCT-related nephropathy is multifactorial, endothelial dysfunction, vaso-occlusion and compromised blood flow play an integral part in the injury process. [33], these among others are likely to be common steps between both SCT and RCN. In our case, the diagnosis was confirmed with the kidney biopsy; also, the findings of elevated LDH and bilirubin, along with the acute clinical presentation of abdominal pain, are likely to represent a vaso-occlusive phenomenon, although a clear precipitant has not been identified. In addition, there was no evidence of alternative causes for RCN with no elements of sepsis, inflammation, disseminated intravascular coagulation or exposure to snake bites. The normal level of platelets, hemoglobin and lack of schistocytes made the spectrum of thrombotic microangiopathy unlikely. Renal angiography to investigate the renal macro-vasculature was not done as the exposure to contrast was not feasible due to the severe AKI.

This case highlights the importance of vigilance for renal vaso-occlusive complications of SCT as having a high suspicion will likely bring more cases into the physicians' attention. To our knowledge, this is the first report of RCN in SCT confirmed via a kidney biopsy.

Abbreviations

AKI
Acute kidney injury
eGFR
Estimated glomerular filtration rate
HbS
Sickle hemoglobin S
HIV
Human immunodeficiency virus

HUS
Hemolytic uremic syndrome
LDH
Lactate dehydrogenase
RBCs
Red blood cells
RCN
Renal cortical necrosis
SCD
Sickle cell disease
SCT
Sickle cell trait
WBCs
White blood cells

Declarations

a. Ethics approval and consent to participate

No ethics approval was required as this a case report. Written and verbal consent was obtained from the patient.

b. Consent for publication

Written informed consent was obtained from the participant for the publication of the identity revealing information / images.

c. Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

d. Competing interests

The authors declare that they have no competing interests.

e. Funding

None

f. Author's contributions

AA, EA, ZA, MMA did the literature review. BA, HA, JA, MA completed the case study. SA reviewed the pathology slides. OA contributed to the clinical management and manuscript preparation. All authors

read and approved the manuscript.

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Figures

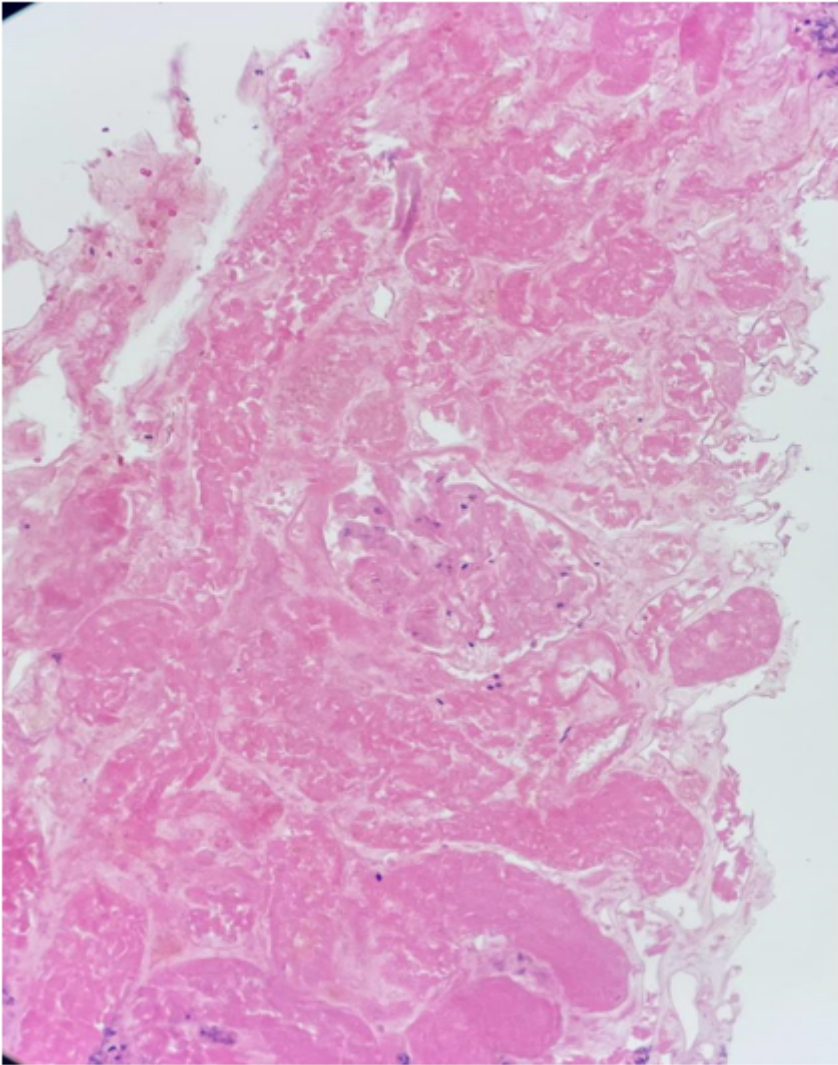


Figure 1

H&E Stain showing diffuse coagulative necrotic areas containing ghost outlines of glomeruli and tubules with loss of cellular details.

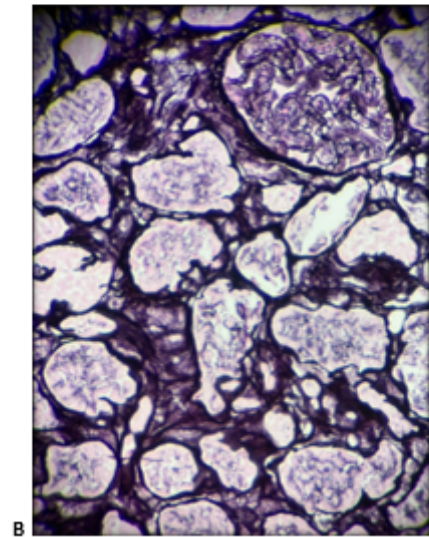
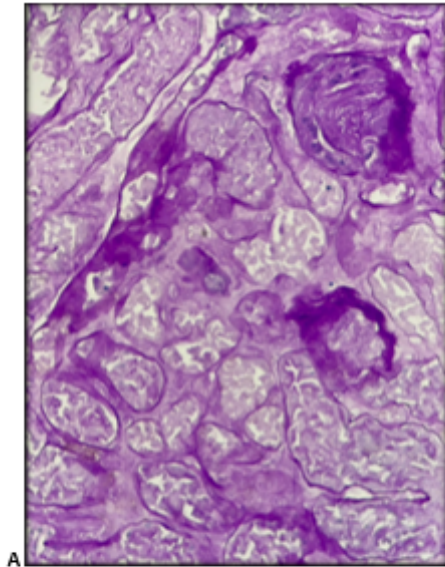


Figure 2

A – PAS stain, B - silver stain

Visible tubular and glomerular basement membrane without viable nuclei

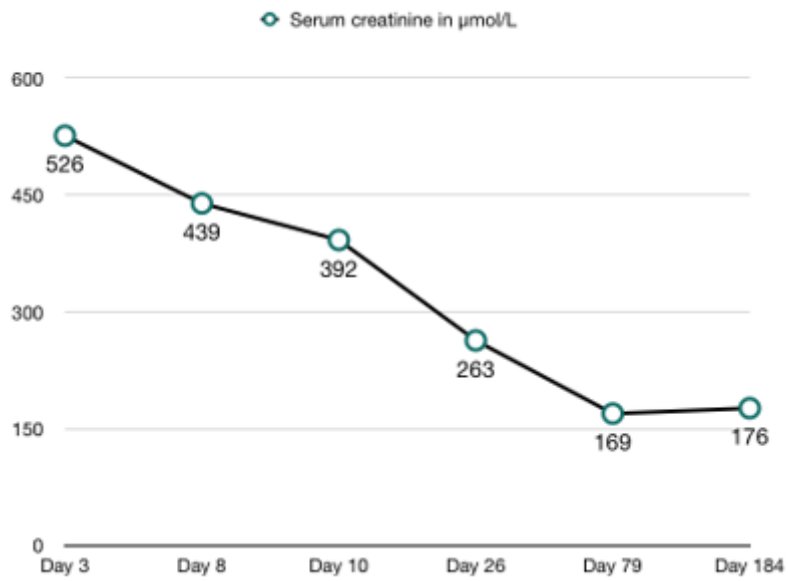


Figure 3

Trend of kidney function from presentation over time.