



TTP-like syndrome associated with hemoglobin SC disease treated successfully with plasma and red cell exchange

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ABSTRACT

Background: Sickle cell hemoglobinopathies are associated with end organ damage but very rarely present with a clinical and laboratory picture of microangiopathic hemolytic anemia (MAHA) and thrombocytopenia, characteristic of thrombotic microangiopathy (TMA).

Case presentation: We present a patient with HbSC disease who developed thrombotic microangiopathy, needing both RBC exchange transfusion and therapeutic plasma exchange (TPE) for complete clinical recovery.

Conclusion: Although literature showed therapeutic plasma exchange alone can abrogate a similar clinical scenario, we did an in-depth review which concluded that in most of the TMA cases secondary to sickle cell disease, treatment with both with plasma exchange and red cell exchange transfusion are necessary.

1. Background

Thrombotic microangiopathy represents a group of disorders characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia and ischemic organ dysfunction. Although TMA associated with sickle cell disease is a rare entity, there have been reported cases in literature [1–5]. Therapeutic plasma exchange (TPE) is usually reserved for management of primary causes of TMA like thrombotic thrombocytopenia purpura (TTP), either acquired or congenital. Here, we report a case of a patient with HbSC disease who presented to our hospital for first time with painful crisis complicated by acute clinical and laboratory decompensation consistent with the diagnosis of TMA which responded to TPE initially but needed RBC exchange for complete recovery.

2. Case presentation

45-year-old African American female with past medical history of hypertension, HbSC disease presented with severe lower back pain and lower extremity pain of one day duration, not alleviated with her regular analgesics. She never had RBC exchange transfusion in the past but was supported with blood transfusion once previously, many years ago. Her family history was significant for sickle cell disease in her brother. Her medications included folic acid and antihypertensives and was not

allergic to any medications. She was a non-smoker and drank alcohol occasionally.

On general examination, the patient was hemodynamically stable. She was alert, oriented and was in minimal distress. Cardiovascular, respiratory, abdominal and neurological exam were non-contributory. Laboratory values showed microcytic anemia with hemoglobin 10.8 mg/dL, hematocrit 30.7%, reticulocyte count 3.6%, WBC count $8.8 \times 10^9/L$, platelet count $250 \times 10^9/L$ and lactate dehydrogenase (LDH) 758 IU/L. Her renal function and liver function tests were within normal limits. Her HIV test was negative. The initial chest radiograph and electrocardiogram were unremarkable.

She was admitted to the medical unit and was treated with intravenous fluids and analgesics. She refused laboratory testing on day 2. On the morning of day 3, she was found to be confused prompting activation of the rapid response team. Her vitals showed BP 122/84 | Pulse 153 | Temp 37.4 °C (99.3°F) (Oral) | Resp 18. Compared to admission laboratory test values there were critical changes on day 3 as noted in Table 2. Computed tomography (CT) scan of the head was unremarkable, while the CT scan of the chest/abdomen/pelvis showed minimal right lung base atelectasis, hepatic steatosis, and cholelithiasis.

The patient was admitted to Intensive Care Unit and Hematology team was consulted. Blood smear review on day 3 (Fig. 1) showed sickle cells, schistocytes, target cells, thrombocytopenia, increased neutrophils with vacuolization and toxic granulations. Hence, in the setting

Abbreviations: ADMSTS13, A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; NF-Kb, nuclear factor kappa-light-chain-enhancer of activated B cells

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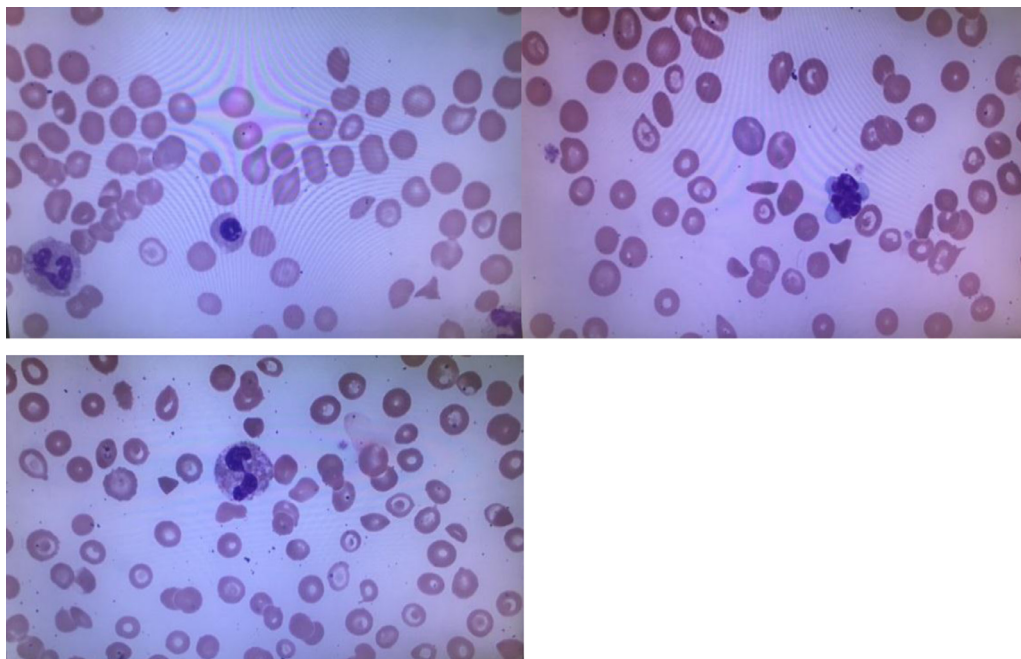


Fig. 1. Day 3 peripheral blood smear showing sickle cells and schistocytes (2–3 per HPF), target cells.

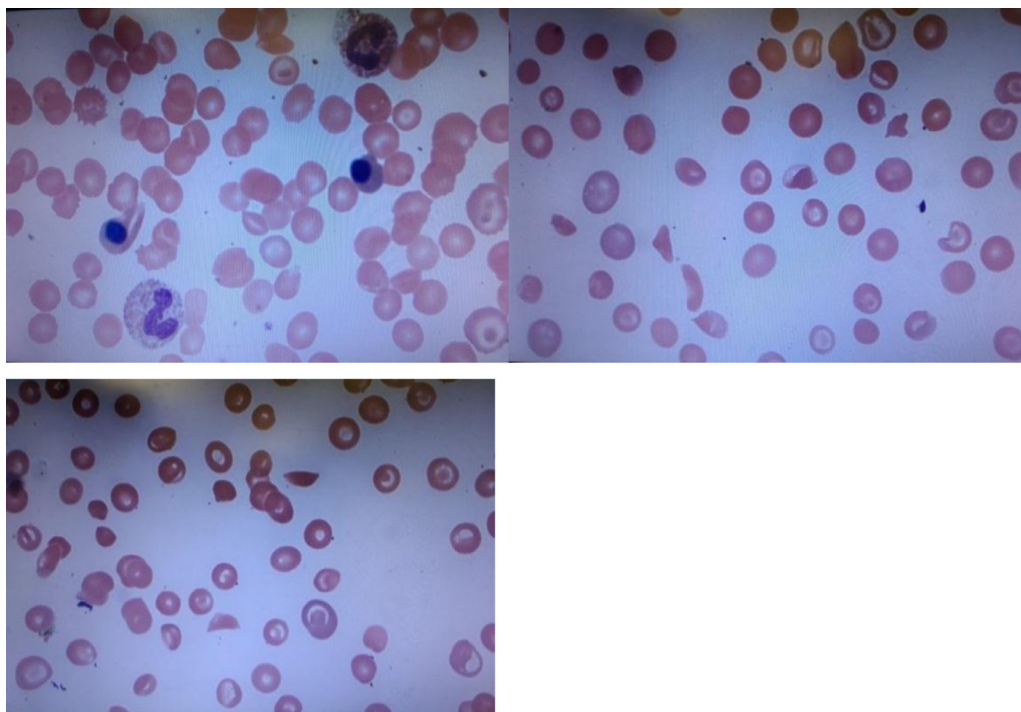


Fig. 2. Day 4 peripheral blood smear showing nucleated RBC, some sickle cells and 2–3 schistocytes per HPF.

of clinical presentation of altered mental status combined with laboratory evidence of microangiopathic hemolytic anemia (increased LDH, polychromasia, schistocytes) and new thrombocytopenia, suspicion of TTP was high in the differentials. Therapeutic plasma exchange (TPE) was performed after arranging for von Willebrand factor-cleaving protease (ADAMTS13) activity testing. On day 4, her mental status was still waxing and waning. She refused lumbar puncture and her laboratory values did not change significantly and was similar to that of day 3. Blood smear on day 4 demonstrated at least 2–3 schistocytes per high power field, few sickle cells, mature neutrophils with increased vacuolization and toxic granulations, many nucleated red cells and target

cells (Fig. 2). TPE was continued. Patient's mental status improved transiently but she became confused again. Magnetic resonance imaging (MRI) brain done on day 5, demonstrated new right corona radiata infarct.

Blood smear on day 5, demonstrated occasional schistocytes, few sickle cells, vacuolated and toxic granulated neutrophils, many nucleated red cells and target cells (Fig. 3). Given the new MRI findings and with no improvement in the laboratory values, a decision was made to perform a full RBC exchange transfusion. On day 6, the patient's confusion status started to improve clinically. Her laboratory parameters also started to show improvement, as noted in Table 2 except for

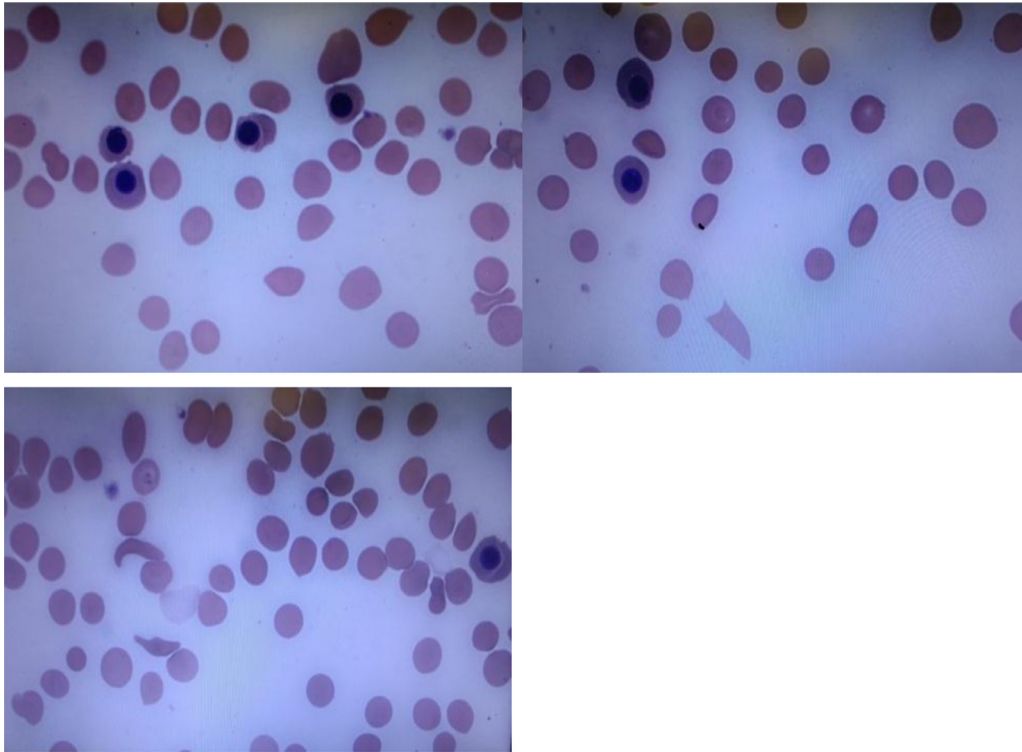


Fig. 3. Day 5 peripheral blood smear showing occasional schistocytes per high power field, some sickle cells and persistent nucleated RBC.

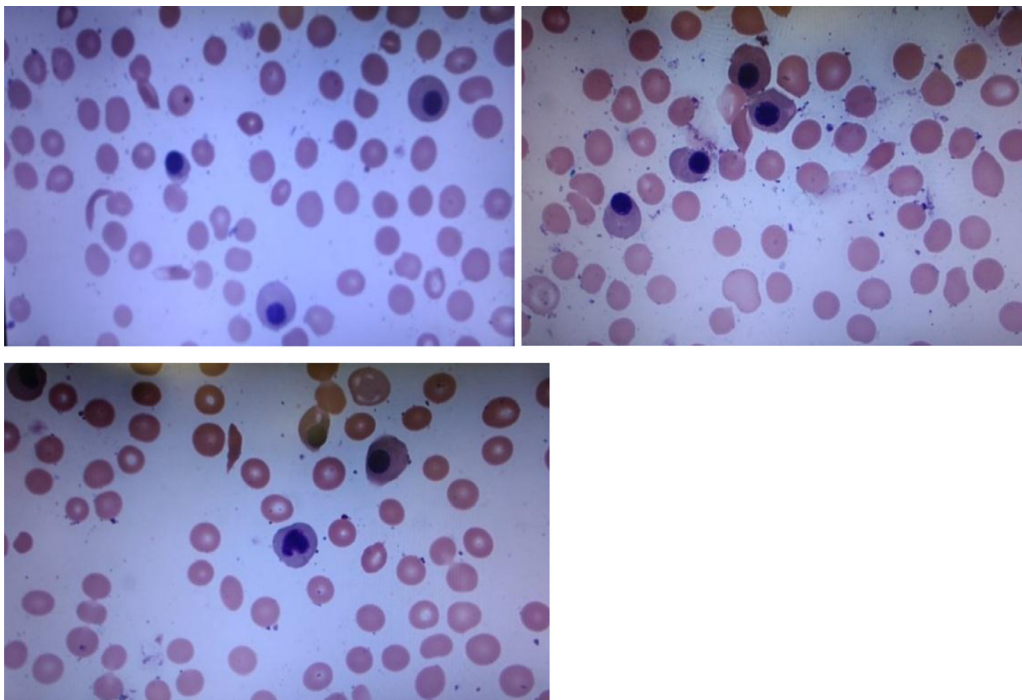


Fig. 4. Day 6 peripheral blood smear showing disappearance of schistocytes, some sickle cells and persistent nucleated RBC.

decrease in platelet count to $55 \times 10^9/L$. Day 6 blood smear demonstrated occasional schistocytes, few sickle cells, toxic granulated neutrophils and many nucleated red cells (Fig. 4). TPE was continued and one unit of packed red blood cells was transfused but no further red cell exchange was performed.

On Day 7, patient showed significant clinical improvement with complete resolution of her altered mental status. Her laboratory values were consistent with hemoglobin returning to baseline of 9.9 mg/dL,

platelets trending up to $67 \times 10^9/L$ and LDH trending down to 2685 IU/L (Figs. 5–7). Plasma exchange was stopped after a week.

Her ADAMTS13 activity levels was 99% from day 3 samples. Although LDH was trending up for uncertain reasons, patient was discharged from the hospital based on significant clinical improvement and arrangement was made for an outpatient appointment in hematology clinic. Follow up laboratory values in her hematologist office after one week showed hemoglobin 10.2 mg/dL, platelet count

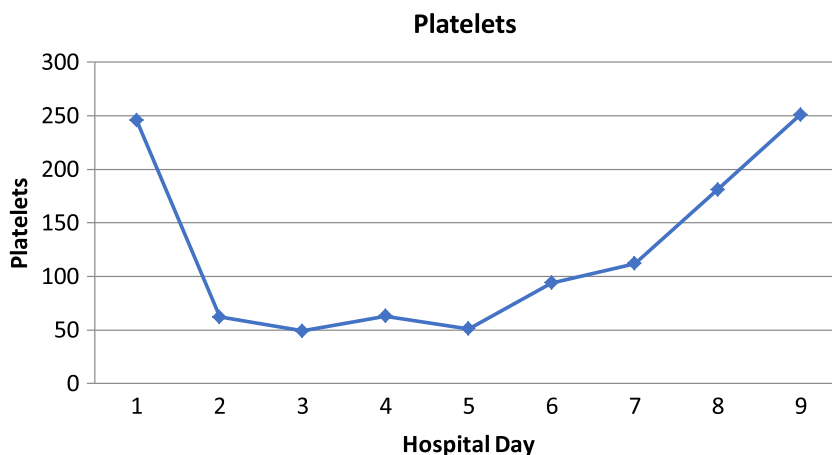


Fig. 5. Depicting platelet counts during hospital stay.

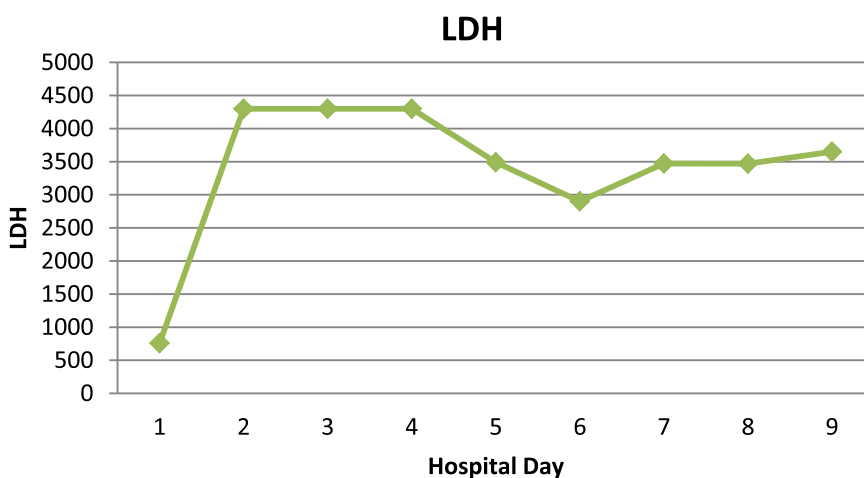


Fig. 6. Depicting LDH levels during hospital stay.

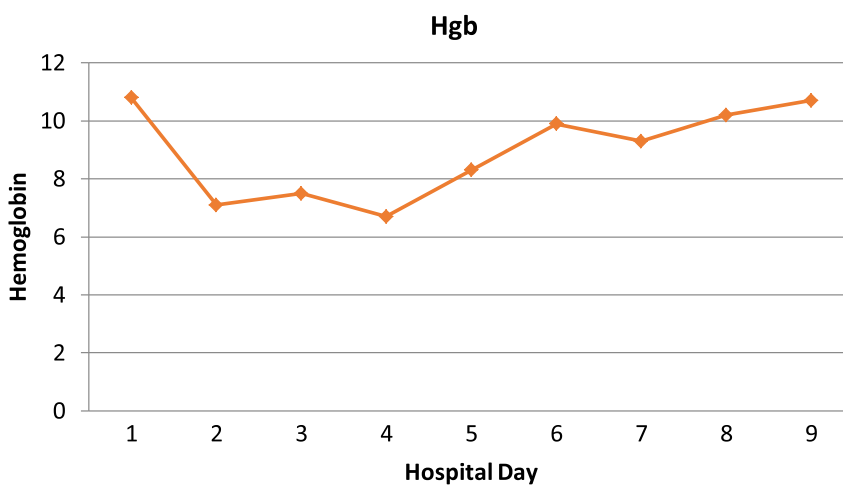


Fig. 7. Depicting hemoglobin levels during hospital stay.

181 × 10⁹/L and LDH 222 IU/L (normal was <250 IU/l).

3. Discussion

The incidence of HbSC disease in the US is 1 in 7386 newborns. HbSC disease is not usually associated with frequent vaso-occlusive crisis unlike HbSS disease. The incidence of sickle crisis in HbSC is around 23–36% as per few studies. These patients retain their splenic

activity into adulthood making them prone for sequestration crisis [6]. During splenic sequestration, the splenic sinuses become engorged leading to extravascular removal of platelets and erythrocytes. Though secondary thrombotic microangiopathy due to sickle cell disease is rare, schistocytes are sometimes seen in HbSC disease because of the splenic sequestration. Atypical folding of the RBC membrane, in addition to the presence of intracellular crystals, together deform HbSC red cells. The atypically folded red cells become microspherocytes and

misshapen cells containing compact hemoglobin with peculiar protuberances is sometimes confused with the fragmented cells of microangiopathic states [7]. The splenic sequestration syndrome usually presents as left upper quadrant pain, increasing splenomegaly, hemolytic anemia and thrombocytopenia. The absence of increasing splenomegaly and left upper quadrant pain makes it less likely for the diagnosis of splenic sequestration in our case [6].

The HbSC erythrocyte consists of equal parts of hemoglobin C (HbC) and hemoglobin S (HbS). It has been hypothesized that HbC depletes intracellular water in the erythrocyte through loss of cations by increasing the activity of potassium chloride cotransporter, non-selective P-sickle pathway calcium ion permeability, calcium-activated Gardos potassium channels to enhance polymerization of HbS resulting in a clinically significant disorder [8,9,33]. When compared to HbSS, HbSC disease has higher hemoglobin (Hb), lower mean corpuscular volume (MCV), higher white cell count, higher absolute neutrophil count, higher reticulocyte counts and poorly deformable dense erythrocytes. These differences likely increase whole blood viscosity, leading to compromised blood oxygen delivery to terminal arteries, thereby leading to higher incidence of sickle retinopathy, avascular necrosis, and renal involvement compared to HbSS patients [9,33]. Few studies have even reported incidence of retinopathy (56–70%), avascular necrosis (12–28%), renal involvement (8–13%) in HbSC disease [33]. Hydroxyurea is safe and effective in HbSC disease by helping in reducing blood viscosity, improving the rheological characteristics of SC erythrocytes, increasing vascular nitric oxide exposure, and enhancing blood flow [10–12].

Acute painful crisis occurred in around 33.8% in a series of 150 patients [13] which is similar to that of HbSS disease. Few studies have also described TTP-like syndromes in HbSC disease [4,14]. Acute clinical decompensation in our case along with laboratory features of thrombotic microangiopathy and thrombocytopenia prompted us towards plasma exchange therapy. Additional red cell exchange transfusion was commenced due to persistent sickling crisis with neurological deterioration. We believe that this combined therapy led to the complete recovery of clinical and laboratory picture of the patient.

Since the patient's renal functions improved with TPE, her clinical picture was not consistent with atypical hemolytic uremic syndrome. Pancreatitis induced TTP was also a differential in our case as our patient had high levels of lipase on day 6 of her admission. Although there are several reported cases of pancreatitis induced TTP, the timing of lipase elevation in our case provides more evidence for TMA causing pancreatic injury [15–17].

Detailed review of the literature cases with similar clinical picture is shown in Table 1. As per this study 13 out of the 17 cases needed combined modality therapy for full recovery. Four cases did not get the combined modality therapy. Among the four, one patient had erythrocyte apheresis prior to initiation of TPE which might have significantly contributed to the recovery of TMA picture [18]. The other patient in this group received multiple units of red cell transfusions prior to and after TPE which could have improved the clinical picture [19]. This patient also had severe renal failure needing hemodialysis, raising some concerns about the diagnosis. The third patient in this group, who had HbS/beta thalassemia did receive simple packed red blood cell transfusions prior to initiation of TPE in addition to multiple sessions of TPE and weekly rituximab. It is hard to ascertain which modality of treatment benefited this patient [20]. The last sickle cell patient in this group who had associated renal failure needed TPE and hemodialysis for recovery of his blood counts and renal function respectively. No clear details were available about simple red blood cell transfusion or exchange transfusion making it hard to comment on the role of TPE alone in the improvement of the patient [21]. Detailed analysis of literature as well as our personal experience favor combined modality therapy for these rare sickle cell patients presenting with thrombotic angiopathies.

TTP with associated features of microangiopathic hemolytic anemia

Table 1
Literatures reviewed the treatment modalities of either both RBC exchange and TPE or TPE alone in the cases of sickle anemia presented as TMA.

Case reports	Patient receiving plasma exchange alone	Patient receiving RBC and plasma exchange	Response to plasma exchange alone	Demographics
SCD patients (10) w/TMA (Ann Hem 2013) [17]	0	10	0	8 men/2 women, avg age 30.8 (range 18–51yo), 9 with HbSS, 1 with SC/B-thalassemia
SCD patient (1) w/TTP (Ann Hem 2003) [22]	1	0	1	24 yo man hemoglobin SC disease
SCD patient (1) w/TTP (Acta Anaesthesiol Scand 1997)	0	1	1	23 yo man
SCD patient (1) w/TTP (Hemoglobin 2002) [20]	0	1	1	40 yo man, sickle cell thalassemia
SCD patient (1) w/TTP (Blood 2006) [19]	1	0	1	48 yo man SS disease
SCD patient (1) w/TTP (Clinical and applied thrombosis/hemostasis 2010) [18]	1	0	1	16 yo woman, sickle cell SS
SCD patient (1) w/TTP (c53 critical care case reports 2010)	0	1	1	28 yo man hb SC
SCD patient (1) w/TTP (clinical case reports 2015) [21]	1	0	1	48 yo woman, hgbs/B thalassaemia
Total	4	13	17	

Table 2
Laboratory values during hospital stay.

Day	Hemoglobin (gm/dl)	Reticulocyte count (%)	LDH (IU/L)	Platelets (10 × 9/L)	Creatinine (mg/dL)
1	10.8	3.6	758	246	0.53
2	–	–	–	–	–
3	7.1	5.4	4300	62	1.89
4	7.5	5.7	4300	49	1.40
5	6.7	5.2	4300	63	0.90
6	8.3	1.9	3490	51	0.86
7	9.9	2.7	2900	94	0.70
8	9.3	3.8	3473	112	0.59
9	10.2	4.9	3470	181	0.55
10	10.7	11.0	3650	251	

(MAHA) and thrombocytopenia is easy to recognize in a healthy person. But in a patient with HbSC, presenting with sickle crisis and multiorgan failure, the clinical picture of more evolving thrombotic angiopathy may be masked due to constellation of other symptoms, which may lead to a delay in the diagnosis. Management of these patients is difficult due to rarity of cases and no clear consensus in management. It has been hypothesized that the endothelial injury caused by sickle cells releases the von Willebrand factor (VWF) multimers, which become coated with the hemoglobin released during the process of hemolysis, thereby preventing their degradation by ADAMST13 enzyme. This in turn leads to formation of small thrombi formation along with platelets and fibrin in the microvasculature [22]. Other mechanism significant in vaso-occlusive crisis in SCD patients, involve the monocytes, neutrophils, and platelets [23]. Monocytes release tumor necrosis factor alpha (TNF- α) and interleukin-1 beta, which activate the NF-KB pathway in endothelial cells leading to increased expression of ICAM1 (intercellular adhesion molecule) & VCAM1 (vascular cell adhesion molecule), causing mononuclear leukocytes to adhere to endothelial cells [24–26]. P & E selectins, located on endothelial cells, plays a significant role in the interaction between neutrophil and red cells, which in turn promotes vaso-occlusion. This is sustained by TNF- α , macrophage-1 antigen (MAC1) located on neutrophils, activated by E-selectin which promotes the adherence of neutrophils to RBC [27]. The activated platelets found in SCD patients promote the adhesion of sickle RBCs to vascular endothelium by secreting thrombospondin [28], which contributes to thrombosis and pulmonary hypertension. Platelet aggregation is also promoted by platelet interaction with monocytes and neutrophils [29,30]. Thrombotic angiopathies in sickle cell disease improves with TPE due to the removal of microthrombi, cytokines, inflammatory mediators as well as significantly decreases the interaction of different cell lineages involved in the pathogenesis of vaso-occlusion process. It is important to understand the role of RBC exchange in replacing sickle RBC with normal RBC thereby completely altering the dynamics of red cell interaction with leukocytes and endothelial cells [31,32].

4. Conclusions

Through this case report, we want to raise the awareness that thrombotic angiopathy can develop in sickle cell disease during acute crisis. When there is high suspicion, prompt decision has to be made to abort the vaso-occlusive crisis as early as possible, with combined modality therapy with plasma exchange and red cell exchange for effective treatment and full recovery.

Ethics approval and consent to participate

The case report study was approved by Brookdale University and Hospital Center Research and Clinical Projects Committee (RCPC/IRB).

Consent for publication

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of data and material

Data and supporting material were used from the patients' paper charts. Please contact authors for any additional information.

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

S.K. wrote the manuscript, reviewed the literature, and took care of the patient. I.R. took care of the patient, helped to review the literatures. P.R. helped to edit the manuscript and literature review. J.C.W. took care of the patients and mentored to formulate ideas and suggestions to write the manuscript. All authors read and approved the final manuscript.

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