Refractory acquired thrombotic thrombocytopenic purpura in a patient with sickle cell trait successfully treated with caplacizumab

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ABSTRACT

Methods: We report a case of a 20-year-old Nigerian male who presented with acquired thrombotic thrombocytopenic purpura (aTTP) and sickle cell trait. The coexistence of published cases of TTP and sickle cell hemoglobinopathies is rare.

Results: Despite the initial treatment with plasma exchange and glucocorticoids, our patient relapsed and also required caplacizumab which resulted in successful remission.

Discussion: We conclude by reviewing the cases of TTP in patients with sickle cell hemoglobinopathies and review how vaso-occlusive crises with multiorgan injury can mimic TTP.

Conclusion: Ours is the first published case of aTTP with confirmed ADAMTS13 autoantibodies in a patient with a sickle cell hemoglobinopathy and contributes to the literature on the successful use of caplacizumab in clinical practice.

KEYWORDS

Caplacizumab; TTP; sickle cell; acquired thrombotic thrombocytopenic purpura; plasma exchange; vaso-occlusive crisis; ADAMTS13; hemoglobinopathy

Introduction

Acquired thrombotic thrombocytopenic purpura (aTTP) is a thrombotic microangiopathy (TMA), resulting from an acquired inhibitory autoantibody against a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13), resulting in severe functional impairment (generally <10% activity). ADAMTS13 is a protease that cleaves von Willebrand factor (vWF) multimers secreted from vascular endothelial cells [1]. In patients with TTP, uncleaved vWF multimers promote the formation of platelet-rich thrombi in the microvasculature leading to thrombocytopenia, microangiopathic hemolytic anemia (MAHA), and organ ischemia [1]. The annual incidence of aTTP is about 2 cases per one million adults [2]. The median age of diagnosis is in the fourth decade of life with a female to male ratio of 2:3:1 [2]. Beyond female gender, other risk factors include black race, pregnancy, systemic lupus erythematosus, and certain human leukocyte antigen subtypes [2,3].

Sickle cell disease is caused by a point mutation in the beta globin gene which renders the resultant hemoglobin tetramer poorly soluble when deoxygenized (hemoglobin S). Whereas sickle cell disease is due to homozygous mutations of beta globin, sickle cell trait is a heterozygous condition with one mutant and one wild-type allele [4]. Symptoms of sickle cell trait are relatively benign; however, patients are at increased risk for pulmonary embolism and exertional rhabdomyolysis [4,5]. Additionally, renal medullary carcinoma is almost exclusively seen in patients with sickle cell trait [6].

Here we report a case of a young male with biochemically confirmed refractory aTTP and sickle cell trait which was successfully treated with caplacizumab.

Case

A 20-year-old Nigerian male presented to hospital for progressive fatigue and confusion. He had a two-day history of abdominal pain, melena, and emesis. He had been seen in the emergency department one month prior for headaches; however, these were felt to be benign and he was discharged. He presented with an initial temperature of 36.7°C, a heart rate of 120 bpm, blood pressure of 131/65 mmHg, respiratory rate of 30 bpm, and oxygen saturation of 97% on room air. His initial Glasgow Coma Score (GCS) was 14/15; however, upon re-assessment this declined to 11/15. A computed tomography (CT) scan of his head showed no acute intracranial abnormalities.

Initial labs revealed a hemoglobin of 48 g/L, a mean corpuscular volume (MCV) of 90.4 fl, hematocrit of 14.0%, white blood cell count of $24.3 \times 10^3$/mm$^3$, and platelets of $34 \times 10^3$/mm$^3$. Peripheral blood smear showed polychromasia, microspherocytes and schistocytes. Sodium was 141 mmol/L, potassium 3.9 mmol/L, chloride 104 mmol/L, bicarbonate 18 mmol/L, urea 17.7 mmol/L and creatinine 260 umol/L. Liver
biochemistry revealed ALT of 126 U/L, total bilirubin 99 mmol/L, and direct bilirubin 19 mmol/L. LDH was 3721 U/L. Direct antiglobulin test and G6PD screen were both negative. The D-dimer was >10,000 ng/mL. INR, APTT, and fibrinogen were normal. Serum ferritin was 5325 µg/L; transferrin saturation was 92% and serum iron was 56 umol/L. Troponin was 2700 µg/L. Venous blood gas pH was 7.25 and lactate was 8.5 mmol/L. A hemoglobinopathy study revealed a Hb S/total Hb ratio of 39.1% – diagnostic of sickle cell trait (HbAS). Other pertinent investigations included negative blood cultures, negative HIV serology, and negative malaria testing. Anti-nuclear antibody (ANA) testing was negative. Normal levels of complement C3, C4, and vitamin B12 level were detected. A genetic testing panel, including ADAMTS13, C3, cluster of differentiation 46 (CD46), complement factor B (CFB), complement factor H (CFH), complement factor H-related protein 5 (CFHR5), complement factor I (CFI), diacylglycerol kinase epsilon (DGKE), and thrombomodulin (THBD), was reported as negative.

The history and initial investigations were consistent with a diagnosis of TTP; therefore, emergent plasma exchange (PEX) was arranged upon admission. Platelet count was 9 × 10^3/mL on post admission day one, 10 × 10^3/mL on day two and a clear rise was seen by day three. Methylprednisolone 1 g intravenously was given daily for five days, followed by oral prednisone 1 mg/kg daily thereafter. He received plasma exchange for 6 days, his neurologic status and platelet count normalized, and subsequently was transferred to the ward. There are differing opinions as to whether PEX should be tapered or abruptly discontinued once platelet count and LDH normalize. The 2019 guidelines on the use of therapeutic apheresis note that although prospective data for the tapering strategy are lacking, it may be used. As a result of inconclusive evidence of benefit and the risks associated with persistence of the central venous catheter and greater exposure to PEX, we elected not to pursue a tapering strategy [7].

Five days later, PEX had to be re-initiated due to an exacerbation noted by rising LDH and falling platelets. This exacerbation upon discontinuation of PEX meets the criteria for refractory disease and many experts agree that rituximab should be considered in this setting. Our patient did not receive rituximab. Due to the severity of the initial clinical presentation with neurologic impairment, significant myocardial injury, and multiorgan involvement, rapid control of microvascular thrombosis was sought at the time of exacerbation. Furthermore, a reduced length of stay was prioritized in light of the COVID-19 pandemic with consideration of hospital resource utilization. As a result, caplacizumab was chosen for therapy with 10 mg given intravenously once, followed by 10 mg subcutaneously daily for 30 days.

Initial ADAMTS13 activity from a sample drawn on admission was 10% with an inhibitor detected with Bethesda titer of 6.9 (reference value <0.4). Repeat ADAMTS13 testing a few days after discharge was 100%. The patient was discharged on day 18, with no signs of recurrence at 2-month follow-up and ADAMTS13 activity levels >70% on weekly measurements for four weeks.

**Discussion**

We describe here the case of a 20-year-old male with sickle cell trait presenting with severe aTTP. Despite the immunosuppressive therapy with glucocorticoids and PEX, he had refractory disease leading to the

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**Table 1. Summary of previously identified cases of TTP and sickle cell disease or sickle cell trait.**

| Literature reference | Age (gender) | Diagnosis | Method of diagnosis | Outcome |
|----------------------|--------------|-----------|---------------------|---------|
| Bolanos-Meade J et al., 1999 [9] | 44yo (M) | TTP + HbSS | Clinical presentation and response to plasma exchange | Relapse, death 2 months post diagnosis |
| Chinowsky MS, 1994 [10] | 22yo (F) | TTP + HbSC | Clinical presentation and response to plasma exchange | Unknown |
| Majiga V et al., 2010 [11] | 3yo (M) | TTP + HbSC | Clinical presentation and response to plasma exchange | Well at 3-year follow-up |
| Geigel EJ et al., 1997 [12] | 23yo (M) | TTP + HbSS | Clinical presentation and response to plasma exchange | Unknown |
| Lee H et al., 2003 [13] | 24yo (M) | TTP + HbSC | Clinical presentation and response to plasma exchange | Discharged with no known TTP recurrence |
| Chatinala JS et al., 2006 [14] | 48yo (M) | TTP + HbSS | Clinical presentation and response to plasma exchange | Discharged with no known TTP recurrence |
| Vlachaki E et al., 2014 [15] | 30yo (M) | TTP + HbS/beta plus thalassemia | Clinical presentation and response to plasma exchange | Death post admission day 12 due to multiorgan failure |
| Chehal A et al., 2002 [16] | 40yo (M) | TTP + HbS/beta plus thalassemia | Clinical presentation and response to plasma exchange | Discharged with no known TTP recurrence |
| Gajegmi AJ et al., 2015 [17] | 48yo (F) | TTP + HbS/beta plus thalassemia | Clinical presentation and response to plasma exchange | Death 3 months after recovery from TTP due to Pneumocystis jirovecii |
| Prichard JG et al., 1988 [18] | 37yo (M) | TTP + HbAS | Clinical presentation and response to plasma exchange | Discharged with no known TTP recurrence |

HbSS – sickle cell disease; HbSC – sickle cell-hemoglobin C disease; HbS/beta plus thalassemia – sickle beta plus thalassemia; HbAS – sickle cell trait.
addition of caplacizumab which resulted in sustained remission at 2-month follow-up.

Caplacizumab is an antibody against the A1 domain of von-Willebrand factor, which prevents its interaction with the platelet glycoprotein Ib-X-V receptor [8]. This protects against the microvascular thrombosis seen in TTP. Caplacizumab has been shown to improve time to normalization of the platelet count, recurrence of TTP, number of days of plasma exchange, and length of stay in both the ICU and hospital [8].

The co-existence of published cases of TTP and sickle cell disease or sickle cell trait is very rare (Table 1). In our literature review there have been six reported cases of patients with sickle cell disease or sickle cell hemoglobin C disease also presenting with TTP [9–14]. There have also been three cases of TTP diagnosed in a patient with sickle cell thalassemia [15–17]. However, there has only been one reported case of TTP in a patient with sickle cell trait [18]. It should be noted that these diagnoses of TTP were made clinically and based on the response to plasma exchange (PEX) rather than the measured ADAMTS13 deficiency. We chose to omit cases that had a documented normal ADAMTS13 level, as these likely represent other etiologies of thrombotic microangiopathy.

TTP can present similarly to a sickle cell crisis complicated by vaso-occlusion and multiorgan injury. A sickle cell vaso-occlusive crisis is commonly associated with pain in the back, legs, knees, arms, chest, or abdomen, often presenting bilaterally and with similar patterns in recurrent episodes [19]. In contrast, initial symptoms of TTP may include fatigue, dyspnea, petechiae, weakness, abdominal pain, or nausea and vomiting and is less likely to present with bony pain [20]. Treatment of multiorgan injury in the setting of a sickle cell vaso-occlusive crisis is incompletely understood. Small studies have supported the use of red blood cell transfusion for acute multiorgan injury; however, the optimal type (simple or exchange) and duration of transfusion are unknown [21]. TTP, however, requires immediate initiation of PEX to reduce morbidity and mortality, with adjunctive therapies such as glucocorticoids, rituximab and caplacizumab.

A limitation of previously reported cases of TTP in patients with sickle cell disease or trait is that many were diagnosed clinically without confirmatory testing of ADAMTS13 activity. This allows for the possibility that some of these cases were not true TTP, but rather sickle cell vaso-occlusive crises with MAHA, thrombocytopenia, and multiorgan injury. ADAMTS13 levels can also be influenced by confounders such as hyperbilirubinemia, severe hemolysis, and hyperlipidemia [22,23]. Our case includes confirmation of the diagnosis of aTTP in a patient with sickle cell trait and contributes to the literature on the successful use of caplacizumab in clinical practice.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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