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CASE REPORT

Coagulopathy and functional hyposplenism during an episode of thrombotic thrombocytopenic purpura in a HgbS/β^+-thalassemia patient

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Key Clinical Message

We report a case of TTP in a sickle cell/β+-thalassemia heterozygote with non-specific complaints and a evidence of hemolysis, initially attributed to sickle crisis. Included in this case is a discussion of the development of functional hyposplenism, a rarely reported complication, limitation of ADAMTS-13 in diagnosis, and the use of platelet transfusion.

Keywords

Hyposplenism, sickle cell disease, thrombotic thrombocytopenic purpura, β^+-thalassemia.

Background

Thrombotic thrombocytopenic purpura (TTP) is a systemic disease characterized primarily by microangiopathic hemolytic anemia and thrombocytopenia; the classic pentad that includes fever, neurologic complications, and renal failure is variably seen today due to early recognition and prompt initiation of total plasma exchange (TPE) [1]. The pathogenesis is attributed to antibody-mediated inhibition of a metalloprotease, ADAMTS13 (A disintegrin and metalloprotease with thrombospondin-1-like domains); inhibition of this enzyme prevents cleavage of von Willebrand factor (VWF), leading to accumulation of ultra-large von Willebrand Factor (ULVWF) multimers and disseminated thrombus formation [1]. TPE is warranted when this condition is suspected and is usually continued until thrombocytopenia and hemolysis have resolved [1]. This case report describes an episode of TTP that presented in a patient with HgbS/β^+-thalassemia heterozygosity. As has been reported in similar cases [2–4], the TTP episode developed after initial presentation of the painful vaso-occlusive crises typical of sickle cell disease (SCD) and delayed treatment with TPE, a modality that raises survival in this condition to 80% [5, 6].

Case Presentation

This patient is a 48-year-old African American female, with a past history of HgbS/β+-thalassemia heterozygosity, hypertension, and cholelithiasis who reported 24 h of back pain, shortness of breath, bilateral lower extremity pain, and marked fatigue. She was a well-established patient having presented multiple times with painful vaso-occlusive crises. Initially, she was alert with no focal neurologic symptoms. Blood work demonstrated WBCs at 10.5 k/μL, hemoglobin 10.2 g/dL, and initial platelet count of 180 k/μL. Evidence of hemolysis included nucleated RBCs at 121 per 100 WBCs, reticulocyte count 6.6% (absolute count 268 k/μL), elevated LDH at 3556 U/L and bilirubin 1.3 mg/dL. Additional relevant laboratories included BUN of 14 mg/dL and creatinine 1.15 mg/dL that improved to 0.79 following hydration. Coagulation studies and fibrinogen levels were within normal limits and D-dimer was elevated at 5250 μg/L. Chest X-ray and initial lower extremity venous Doppler ultrasound were unrevealing. Review of the peripheral smear demonstrated schistocytosis, some sickled RBCs, and marked increase of nucleated red blood cells that was uncharacteristic for this patient. No platelet clumps were seen. Over the course of 15 h, the platelet count, however, did drop to 35 k/μL; a heparin-induced thrombocytopenia antibody assay was negative. Blood and urine cultures also proved to be negative.

Despite conservative intervention, which had treated her numerous vaso-occlusive crises successfully in the past, creatinine increased from 0.79 mg/dL to 1.0 mg/dL with development of altered mental status over the following 72 h; neurologic exam at the time was without focal deficits. Transfusion of pRBCs for anemia of 6.9 g/dL and IV hypotonic saline were started along with empiric vancomycin plus cefepime for developing fever at 102.8°F. LDH acutely rose in addition to the decline in hemoglobin and platelet counts; a repeat peripheral smear at this time showed features of worsening microangiopathic hemolytic anemia with an increase in schistocytes out of proportion to sickled cells, along with several nucleated RBCs per high powered field, and, notably, Howell–Jolly bodies (see Figure 1). (A later review of 20 high powered fields from a smear performed 8 months prior to presentation, when the patient was in a noncrisis state, did not disclose any Howell–Jolly bodies, a potentially typical finding in sickle cell patients [7]). With the suspicion of TTP aroused, immediate transfusion of four units of fresh frozen plasma (FFP) and infusion methylprednisolone was initiated in anticipation of plasma exchange. TPE was performed at bedside using COBE® Spectra Apheresis System through central venous access. Hundred percent total blood volume (calculated to be 4.4 L in this patient) was replaced using FFP. An ADAMTS-13 assay was sent at this time and disclosed a mild decrease in activity at 61% (normal >66%). After the second-treatment course of daily TPE, the patient's mental status improved dramatically, LDH declined to 2386 U/L and creatinine improved to 0.8 mg/dL.

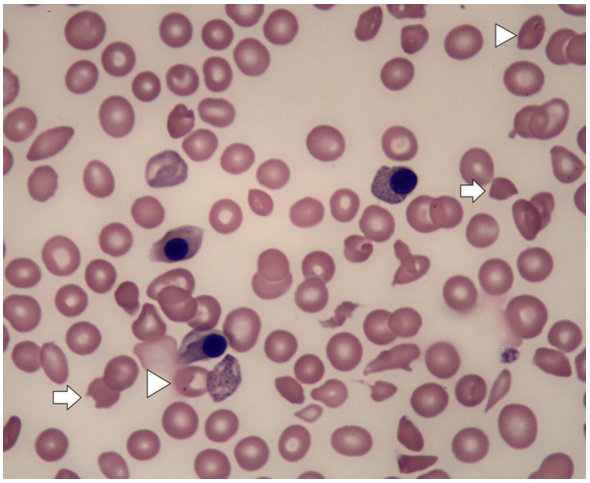

Figure 1. Peripheral smear in acute TTP crisis. Note the presence of schistocytes (arrows), classic markers of microangiopathic hemolysis, along with the almost complete absence of platelets. Also note the presence of Howell-Jolly bodies (arrowheads).

The patient laboratory values continued to improve with TPE. However, on the hospital day #8, the patient developed discomfort in the left calf along with edema. Venous Doppler ultrasound showed a left popliteal deep venous thrombosis (DVT). Simultaneous platelet count was 26 k/μL. Despite the stigma attached to platelet transfusion during a TTP episode [8], the risk of fatality from pulmonary embolus was considered greater and transfusion of one pool of platelets was administered in order to place a retrievable IVC filter. Hemostasis after IVC filter placement was excellent and the patient suffered no neurological sequelae following transfusion. Daily TPE was continued and weekly rituximab therapy at 375 mg/m^2 was commenced concurrently with steroids, because of the benefit of these therapies on the risk of relapse [5] on hospital day #16.

By hospital day #21, laboratories were significant for LDH 187 U/L, platelets 130 k/μL, and creatinine 0.98 mg/dL with a decline in reticulocyte count to near baseline at 4.4% and a marked decrease in nucleated RBC per 100 WBCs from 121 to 1. After 18 treatments of TPE, the patient abruptly developed tachycardia, hypotension to 110/90, and tachypnea. There was suspicion for early sepsis syndrome and empiric antibiotic

therapy was again initiated. Platelets transiently fell (thought to be due to septic thrombocytopenia as LDH remained stable) with some evidence of acute kidney injury; however, the patient rapidly improved. The patient was discharged after 24 days of hospitalization to home with close follow-up at the outpatient office 3 days after discharge. The patient was without complaints and had resumed normal activity. Laboratory data showed Hgb 9.4 g/dL, platelet count 111 k/μL, and resolving hemolysis with LDH 233 U/L, haptoglobin detectable at 68 mg/dL, and reticulocyte count at 4.7% (absolute count 162 k/μL). Creatinine returned to baseline. The patient continued weekly rituximab therapy for 4 weeks total and finished a steroid taper. This patient unfortunately succumbed to *Pneumocystis jiroveci* pneumonia 3 months following her TTP episode by which point she had not experienced any relapses. The cause of her *Pneumocystis* was attributed to immunosuppression by prolonged steroid course. The patient was not placed on prophylactic Bactrim and had no known immunodeficiency (an HIV antibody assay checked during the initial hospitalization was negative).

Discussion

We present here an acute case of TTP in a heterozygote HgbS/β^+-thalassemia patient complicated by DVT and functional hyposplenism. Other case reports have described both patients presenting during a sickle cell crisis with subsequent development of TTP [2–4], and, even more diagnostically challenging, episodes of TTP masquerading as a pain crisis [9–11]. Chehal et al. and Geigel et al. reported cases of multiorgan failure and subsequent remission upon initiation of plasma exchange therapy in patients with similar genetic background [12, 13]. A retrospective report from a medical center in Bahrain described the course and complications of 10 patients with SCD who presented with thrombotic microangiopathy [14]. Our case is significant as TTP occurred in a HgbS/thalassemia heterozygote, an association reported only rarely in the literature [12, 14]. Marked improvement with TPE certainly points toward the diagnosis of TTP [1]. Her smear demonstrated evidence in favor of fragmentation hemolysis over vaso-occlusive disease, with schistocytes far surpassing the amount of sickled cells seen on microscopy. Prichard et al. [11] have proposed that the minimal amount of sickling seen on microscopy may be the result of low oxygen conditions in the thrombosed microcirculation rather than the primary pathology.

Evidence suggests that the chronic hemolytic anemia of SCD contributes to the inhibition of ADAMTS13. It is interesting to note that ADAMTS13 activity is inhibited by free hemoglobin in vitro [15]. The authors demonstrated that the binding of hemoglobin to both VWF and ADAMTS13 was concentration dependent and through immunoprecipitation studies determined that ADAMTS13-mediated cleavage was prevented due to the binding of hemoglobin to VWF itself. Furthermore, specimens from 10 sickle cell patients compared to normal controls demonstrated an inverse relationship between free hemoglobin levels and ADAMTS13 activity [15]. In another study, sickle cell patients were shown to have comparable levels of ADAMTS13 to healthy controls, but lower ADAMTS13/VWF Ag ratios, with an even further reduction to acute painful crisis [16]. The authors of this study presented several explanations for the observed differences including enzyme consumption and inactivation due to elevated cytokines and circulating proteins involved in the coagulation cascade. They noted no difference in intrinsic ADAMTS13 activity [16], consistent with the finding mentioned above. The authors also mentioned the possibility of a relationship with TTP pathophysiology in light of their findings. It is possible then to hypothesize that the microangiopathic thrombosis seen in our patient can be attributed to secondary causes (sickle cell and β-thalassemia) without apparent deficiency in ADAMTS13.

With these considerations in mind, it is interesting to note that our patient demonstrated mild reductions in ADAMTS13 activity. Vesely et al. examined patients in the Oklahoma TTP Registry and found that 94 (or 66%) of their 142 patient cohort had "normal" (or >25% of ADAMTS13 activity); 17 of these 94 clinically diagnosed with TTP-HUS were diagnosed as having the idiopathic form while 34 were diagnosed with TTP-HUS secondary to a systemic disease (of which none were noted to have sickle cell disease or beta-thalassemia). They noted previous reports of severe ADAMTS13 deficiency in TTP ranged from 45 to 100%, although this is limited by confusion between the diagnosis of HUS and TTP [17]. In a retrospective analysis in 100 patients with TTP treated at Cleveland Clinic, with severe deficiency being defined as ADAMTS13 activity <5%, 21 of the 57 patients with enzymatic activity measured did not fit this severe criteria, in fact widely ranging from 8 to 56% [6]. For the most part, no significant differences were found in terms of both clinical and laboratory abnormalities between those patients with evidence of severe deficiency versus the remaining cohort. Exception was noted for renal impairment (with an inverse relationship noted with ADAMTS13 activity levels) and the need for hemodialysis as deficiency >5% was associated with these poorer outcomes [6]. The inconsistency between ADAMTS13 activity and the clinical diagnosis of TTP have been noted (reported in [18], and reviewed in [19]);

despite disagreement in recommendations regarding the diagnostic use of the enzyme, the emphasis to initiate plasma exchange therapy based on the clinical diagnosis of TTP regardless of pretreatment ADAMTS13 level is consistent [18, 19].

Our patient developed an acute DVT even after initiation of TPE. Both SCD and β-thalassemia predispose patients to hypercoagulable states. A sickle cell pain crisis, one of the hallmarks of the disease, is a vaso-occlusive event and both results in and predisposes to anoxic conditions, particularly in the bone marrow where ischemic release of pro-inflammatory cytokines activate pain fibers [20]. Ischemic events in multiple organs are generated by abnormalities in several key players of hemostasis, the mechanisms of which are reviewed in Ataga and Key [21]. Briefly, enhanced red cell adhesion to the endothelium and "sickling" of the red cells in the capillaries are responsible along with abnormal expression of phospholipids on the cellular membrane that may affect coagulation system activation. Dysregulation of the coagulation pathway, including decreased Protein C and Protein S and increased thrombin formation, are apparent in sickle cell patients compared to healthy controls and further complicated by a higher frequency of antiphospholipid antibodies. In terms of platelet adhesion, endothelial selectins, and adhesion molecules, including ICAM-1, are upregulated on circulating endothelial cells in sickle cell patients along with platelet-specific P-selectins and CD40L. Many of the above-mentioned changes are seen in noncrisis states and are accentuated during a pain crisis. This translates clinically with higher rates of thrombotic complications such as stroke and pulmonary embolism [21].

As reviewed in Cappellini et al. [22] coagulopathy can be seen among the different subtypes of β-thalassemia. β-thalassemia, a disorder normally associated with decreased β-chain production and anemia, may induce coagulation through a number of different mechanisms, including generation of reactive oxygen species due to iron uncoupling and a subsequent depletion of nitric oxide, decreased Protein C and Protein S expression, and enhanced endothelial adhesion [22]. In terms of this patient, this could compound the coagulopathy seen with SCD. The inheritance of β^{+}-*thalassemia* with *HgbS* may more closely mimic the SCD phenotype depending on the amount of β-chain expression [23].

This case is also significant in that we can report of the safety of platelet infusion for a surgical procedure. Because of the danger of untreated thrombosis and the inability to give heparin secondary to her thrombocytopenia, the best option was felt to be placement of an IVC filter. Transfusion during TTP has been associated with neurologic consequences [3, 11, 12]. Prichard et al. reported a decrease in mental status in their patient upon infusion of fresh frozen plasma during an acute TTP crisis; however, they did not expand on this issue in their discussion [11]. Likewise Lee et al. [3] reported a grand mal seizure occurring after infusion of 2 units of pRBCs; however, this patient's mental function was already compromised. Neurologic deterioration after RBC infusion was reported in a HgbS/thalassemia heterozygote as well [12]. A literature review in 2009 investigated the safety of platelet transfusion during a TTP episode [8]. This article quantified the adverse effects with data from the Oklahoma TTP-HUS Registry and found no significant difference between patients who received platelet transfusions and those who were treated with plasma exchange alone in terms of severe neurologic deficits (17/33 patients vs. 7/21; although most had occurred after platelet transfusion, the relationship is confounded by a wide time range between transfusion and onset of symptoms) or mortality (8/33 vs. 5/21; with 5/8 deaths in the transfusion group attributed to thrombosis vs. 4/5 patients in the control group). There was no correlation with number of platelet transfusions. Applicability of this report to the patient described here is limited as majority of patients (32/33 patients) received platelet transfusion before the initiation of plasma exchange therapy, although they did indicate that the safety of plasma transfusion after initiation of plasma exchange therapy had been suggested previously [8].

Surprisingly, our patient's smear demonstrated a functional hyposplenic state as evidenced by Howell–Jolly bodies. While both sickle cell and sickle cell/β^{+}-thalassemia patients may demonstrate Howell–Jolly bodies due to chronic infarction [7], such microscopic findings were not noted at baseline in this patient. To our knowledge, no other case reports have reported such transient findings during a TTP episode, but a literature search revealed the development of functional hyposplenism during the course of induced TTP in a baboon model [24]. The authors hypothesized that possible splenic infarction was occurring due to microvascular thrombosis that appeared as hyaline inclusions in splenic blood vessels [24]. In terms of splenic compromise and hypercoagulability, the OPTIMAL CARE study has associated thrombotic complications in thalassemia intermedia patients with prior splenectomy (relative risk 6.59) [25]. Follow-up analysis of data collected in the OPTIMAL CARE study, however, revealed a median 8 years between splenectomy and diagnosis of a thromboembolic event, suggesting long-term effects rather than an acute process responsible for this complication [26].

In conclusion, we have reviewed here a case of sickle cell/β^{+}-thalassemia patient developing TTP, with emphasis

on the hypercoagulable and splenic complications. We have also underscored the diagnostic challenges and benefits of platelet transfusions for treatment of thrombotic complications.

Consent

The following case was presented to the Abington Memorial Hospital Institutional Review Board for waiver of consent for publication. Family contacts could not be reached on multiple attempts *post mortem* to grant consent for the publication of this report.

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Conflict of Interests

The authors have no financial conflicts of interest to disclose.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1 Laboratory studies during treatment course.