CLINICAL VIGNETTE

When Therapeutic Plasma Exchange is Not Enough

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Introduction

Thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy caused by reduced activity of ADAMTS13, the von Willebrand factor-cleaving protease. TTP can either be an inherited or acquired disorder. The acquired form is due to autoantibody mediated inactivation of ADAMTS13, which leads to platelet consumption in von Willebrand factor–platelet aggregates, leading to microvascular thrombosis. This results in thrombocytopenia, hemolytic anemia, and tissue ischemia, which can progress to multiorgan dysfunction. In many cases, the central nervous system is affected and patients can present with confusion, encephalopathy, coma or seizures.[1,2] Patients often present with gastrointestinal complaints most commonly abdominal pain, nausea, vomiting and diarrhea.[3-7] Cardiac and renal involvement can also be seen.[2] The complete pentad of TTP which includes: microangiopathic hemolytic anemia (MAHA), thrombocytopenia, fever, acute kidney injury, and severe neurologic findings is rarely seen in clinical practice. This was more common before widespread use of therapeutic plasma exchange (TPE) because the majority of patients with TTP developed progressive thrombotic microangiopathy and died from untreated disease.[8] TTP is a medical emergency that is almost always fatal if appropriate treatment is not initiated promptly.

However, not all patients with TTP are critically ill. In some patients, the diagnosis of TTP may not be considered until the complete blood count (CBC) reveals severe thrombocytopenia because they present with common symptoms including weakness, dizziness, abdominal pain, easy bruising, nausea or vomiting.[2,9] Given the spectrum of disease activity, it is important to identify severe TTP early due to high risk for rapid clinical deterioration and mortality. Severe TTP is defined by multiorgan involvement due to complications from ischemia induced by von Willebrand factor–platelet aggregates, leading to microvascular thrombosis. Multiorgan involvement is demonstrated by the presence of neurologic dysfunction (altered mental status, seizure or cerebrovascular accidents), acute kidney injury (elevated creatinine), cardiac injury (troponin elevation) and evidence of hemorrhage such as ecchymosis.[3-7] Another characteristic of severe TTP is clinical deterioration despite timely implementation of TPE, steroids and rituximab, which were the only treatment options prior to the approval of caplacizumab in 2019. Caplacizumab is a humanized, bivalent, variable-domain-only immunoglobulin fragment that targets the A1 domain of von Willebrand factor, preventing interaction with the platelet glycoprotein Ib-IX-V receptor and therefore preventing the ensuing microvascular thrombosis.[10] The phase 3 HERCULES trial (double-blind, randomized, parallel group, multicenter placebo-controlled trial) found patients with TTP who were treated with caplacizumab had faster normalization of their platelet count (2.69 days [CI 95%, 1.89 to 2.83] vs. 2.88 days [95% CI, 2.68 to 3.56], P=0.01) and a lower rate of recurrence of TTP during the trial compared to placebo (12% vs. 38%, P<0.001).[10] The trial treatment period also demonstrated improvement in a component of the composite outcome of TTP-related death, recurrence of TTP, or a major thromboembolic event occurred in 9 patients (12%) in the caplacizumab group and in 36 patients (49%) in the placebo group. This difference represented a 74% lower incidence with caplacizumab than with placebo (P<0.001).[10] We present a case of severe TTP requiring caplacizumab, in which the patient made a remarkable clinical recovery.

Case Presentation

A 66-year-old male with no significant past medical history was brought in to the emergency room by his roommate for one day of abdominal pain. He was initially mildly confused, however, quickly became encephalopathic within a few hours, to the point where he could no longer speak or follow commands. Collateral history was obtained from his roommate and was notable for one day of abdominal pain without any associated nausea, vomiting, or diarrhea. The patient had not mentioned to his roommate consumption of any new foods, recent travel, nor had he started any new medications or used any illicit drugs. He had no chronic medical conditions and did not take any medications. His mental status prior to presenting to the emergency room was normal. He was also independent in all ADL's and still employed as a construction worker. On physical exam, the patient was awake, alert but agitated, nonverbal, moving his limbs spontaneously, unable to follow commands with Glasgow Coma Scale of 12. He had multiple areas of ecchymosis over the right flank and abdomen along with a scaly plaque over his left tibia. The remainder of his exam was benign.

His labs on admission were notable for hemoglobin of 7.2 g/dl, platelets 7 K/cumm, reticulocyte percent of 9.7%, haptoglobin <15 mg/dL, folate 16.2 ng/ml, vitamin B12 of 248 pg/ml, LDH 1,129 U/L, total bilirubin 2.7 mg/dl, and direct bilirubin of 0.4 mg/dL. His PT/INR were 14.3 sec/1.13 and peripheral smear of the patient's blood demonstrated metamyelocytes, schistocytes, polychromasia and RBC fragments (Figures 1-3).

His labs were also notable for a Cr of 1.41 mg/dL, and urinalysis demonstrating moderate blood and RBC of 6-10. His urine toxicology screen was negative, and his ethanol level was <5mg/dl. Troponin was elevated at 1.110 ng/ml without any EKG abnormalities. CT of his abdomen and pelvis was negative for any acute process, but did demonstrate diffuse bone demineralization, chronic compression fractures of T12 and L1, and hepatomegaly (no measurement reported).

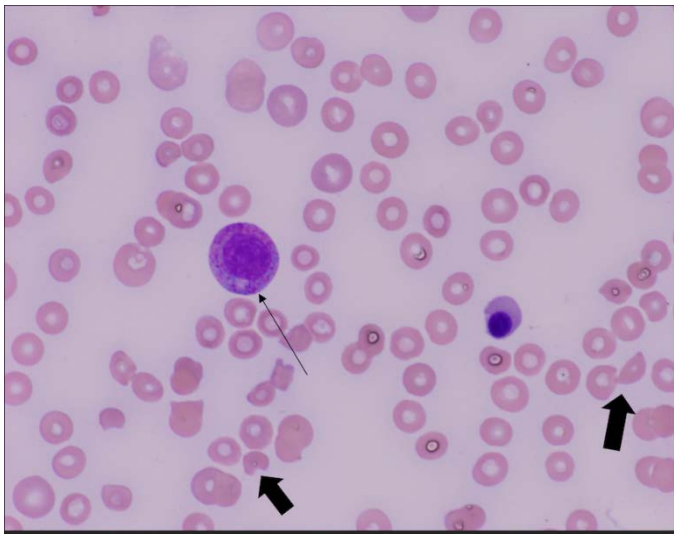

Figure 1 – Metamyelocytes (thin black arrow) and Schistocytes (block arrows)

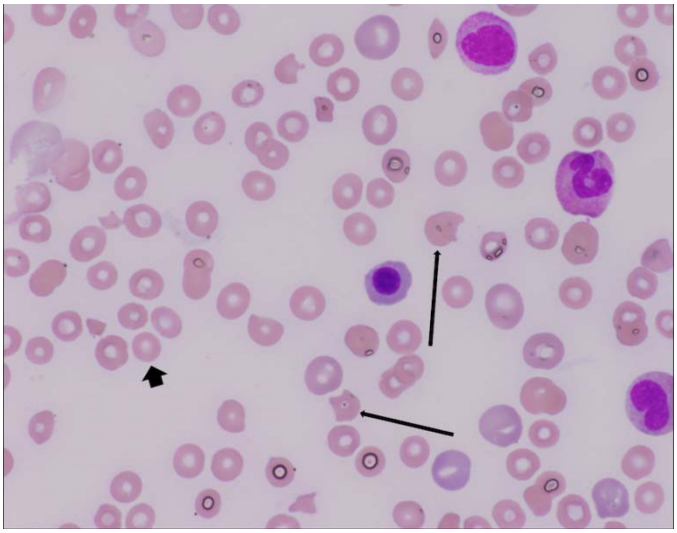

Figure 2 – Polychromasia (block arrow head) and RBC fragments (long arrow)

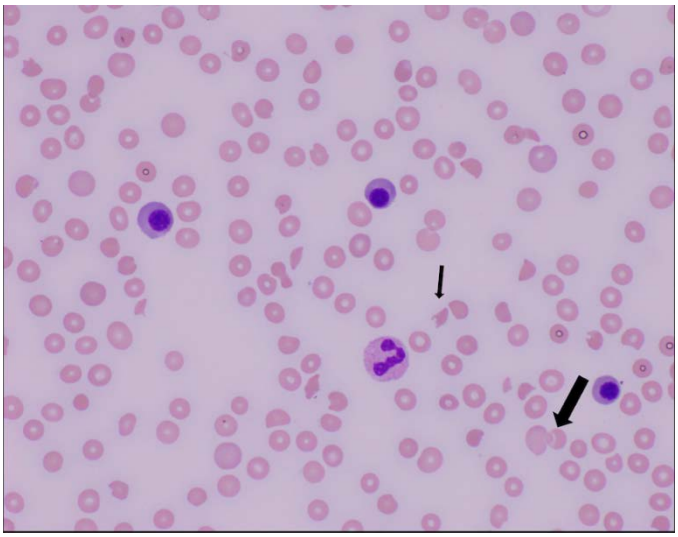

Figure 3 – Schistocytes (small black arrow) and RBC fragments (thick black arrows)

Hospital Course

Neurology was consulted on admission due to concern for cerebrovascular accident as the patient was acutely altered on presentation. CT of his head was unremarkable and EEG was consistent with diffuse cortical neuronal dysfunction. On the second day of admission, he suddenly developed a left gaze preference with bilateral flexion of elbows concerning for acute seizure, and underwent MRI brain, His MRI was notable for multiple areas of restricted diffusion in the left globulus pallidus, putamen, and caudate nucleus as well as a tiny punctate focus in the left parietal cortex consistent with an ischemic injury. This was thought to be likely secondary to his underlying MAHA. The patient did not have any neurologic deficits from his left subcortical infarction and right cortical parietal infarction.

This patient presented with a severe hematologic emergency causing neurologic dysfunction, MAHA, thrombocytopenia, acute kidney injury, and cardiac dysfunction. TTP was suspected given the patient had a negative direct antiglobulin test and the patient's peripheral smear demonstrated RBC fragments with schistocytes. TTP was highest on the differential because the patient's abnormal PLASMIC score of 6, which is an algorithm developed to estimate the probability of ADAMTS13 activity of less than <10 percent.[11] Given the high clinical suspicion, TPE, solumedrol, and rituximab were promptly initiated. On the patient's second day of admission, he had a seizure and MRI demonstrated acute cerebral vascular accident in the territory of the MCA. Given the rapid progression of this patient's neurologic symptoms and his lack of response to solumedrol, rituximab and TPE (his platelets continued to be low at 7-8 K/cumm), caplacizumab was initiated. The approval process for caplacizumab was lengthy, as it was the first time it had been requested for use at Olive-View Medical Center. On day 5 of admission, the patient was given his first dose of caplacizumab. Prior his first dose of caplacizumab, his labs were notable for platelets of 6 K/cumm, LDH of

464 U/L, haptoglobin mg/dL still undetectable, reticulocyte was 2.3%, total bilirubin was 3.7 mg/dL, creatinine of 1.34 mg/dL. After 11 days of once daily dosing of 11mg of intramuscular caplacizumab, daily solumedrol, weekly rituximab and daily TPE, the patient's hemolysis labs and creatinine had improved. Given the normalization of his platelets, TPE and caplacizumab were discontinued and the solumedrol dose was decreased. However, 2 days after discontinuing TPE and caplacizumab, the patient had an acute decline of his platelets from 180 to 11 concerning for rapid recurrence of TTP. TPE, 11mg of once daily caplacizumab were re-initiated, solumedrol and rituximab were continued. With this regimen, his platelets slowly normalized after about 20 days and his mental status returned to baseline without any neurologic sequalae from his left sided MCA stroke. The diagnosis of TTP was confirmed with an undetectable level of ADAMTS13 of <0.03. Evaluation for alternative causes of TTP was negative. He was discharged after a 6-week hospitalization on a prednisone taper and caplacizumab for an additional 21 days to complete 60 days per the HERCULES trial.

Discussion

Since the full pentad of TTP symptoms is present in less than 10% of cases, early diagnosis requires a high index of suspicion which is why the PLASMIC score is clinically useful.[2] An emergent peripheral smear should be performed in any patient who presents with new or unexplained thrombocytopenia and hemolytic anemia to examine for schistocytes, indicative of microscopic hemolytic anemia. The decision to initiate TPE can be challenging because it is a clinical decision and ADAMTS13 activity levels are not immediately available. TPE should not be delayed as it can be lifesaving. Recurrence of TTP is common and aggressive alternative treatments for patients who present with high-risk features including severe neurologic dysfunction with caplacizumab is warranted to avoid morbidity and mortality.

In our patient, the recognition of severe TTP and addition of caplacizumab was critical for his recovery as he initially had no response to the standard regimen of TPE, steroids and rituximab. With the addition of caplacizumab, he was able to make a full neurological recovery from his stroke, is back at this baseline functional status, and has returned to work in construction. His only current therapy is an outpatient Prednisone taper. This case highlights the importance of recognizing TTP early and utilizing caplacizumab in severe cases, with the potential for remarkable treatment response such as in our patient.

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