Thrombotic Microangiopathy in a 59-year-old Woman

TIMOTHY J. BOARDMAN, MD; WILLIAM BINDER, MD, MA, FACEP

From the Case Records of the Alpert Medical School of Brown University Residency in Emergency Medicine

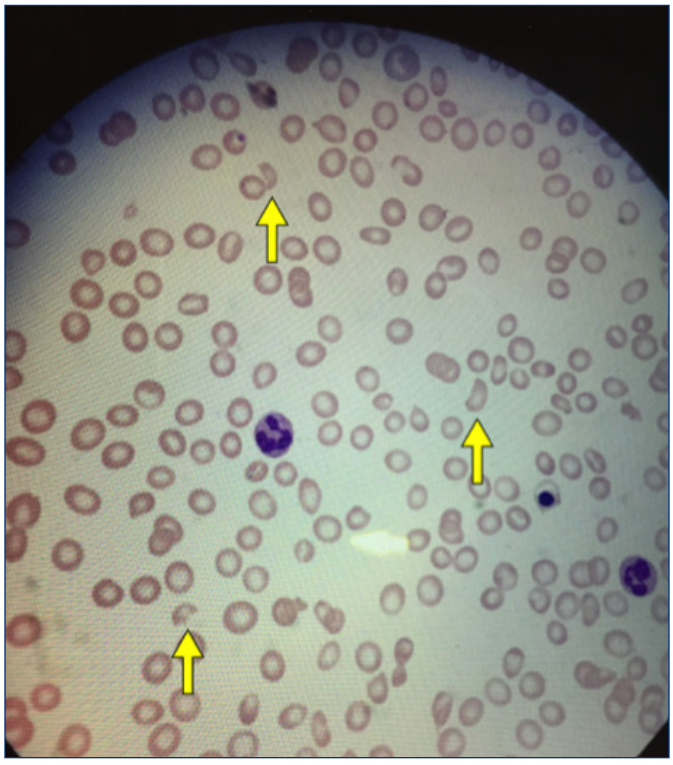
DR. TIMOTHY BOARDMAN: Today's patient is a 59-year-old woman who presents to the Emergency Department with 3 days of decreased oral intake, fatigue, generalized weakness, and dizziness. She reports 2 days of fevers and confusion, but denies vomiting, diarrhea, chest pain or shortness of breath. The patient is accompanied by her daughter, who assists with the history and reports that the patient normally ambulates without assistance, but today was unable to walk due to weakness.

The daughter reported that her mother had developed a facial droop 19 days prior to presentation and had been prescribed prednisone at a local hospital in New York for Bell's palsy. Four days later she traveled to Rhode Island and was brought to the hospital by her daughter due to headache, dizziness, and persistent right-sided facial nerve palsy. Additional investigation revealed that the patient was from Liberia, but had been living in New York for 12 years. While she had no recent international travel, she had visited family in Liberia within the past year. It was unknown as to whether she had taken malaria prophylaxis. She resides in an urban setting and had no known tick exposures. On this visit the patient had a normal complete blood count (CBC) and metabolic panel. An MRI of the brain was performed and the patient was found to have enhancement of the right 7th nerve and valacyclovir and gabapentin were added to her regimen. HSV titers were positive for IgG, suggesting a remote exposure, and Lyme studies were negative. The patient was admitted for 48 hours and while her headache improved, her dizziness worsened. She completed the valacyclovir and prednisone, but continued the gabapentin, and now presents 14 days after her initial hospitalization in Rhode Island with the above stated complaints.

DR. BRUCE BECKER: The travel history is important to consider. Malaria is endemic in Liberia, and it remains the leading cause of morbidity and mortality in the West African nation.[1] However, *Plasmodium falciparum* is the primary malarial species noted in Liberia (almost 100% of cases) and incubation is usually 7–30 days after inoculation, making this diagnosis unlikely.[2] The length of time since the patient's travel rules out most viral hemorrhagic diseases including yellow fever, as well as most rickettsioses, leptospirosis, typhoid, and many other travel-related diseases. On the other hand, the patient's symptoms began almost 3 weeks ago with the facial droop and only in the past several days did she become weak and confused. Her symptoms could be related to a more proximal disorder. The differential diagnosis for a peripheral 7th nerve palsy is quite broad, and taken in conjunction with her weakness and confusion includes HSV, HIV, Zika virus, EBV, and non-infectious disorders including neoplasms.[3] Did the physical and laboratory exam provide any other clues?

DR. BOARDMAN: The patient's vitals were remarkable for a fever of 38.1°C and a heart rate of 130 bpm. She had a blood pressure of 118/77 mm Hg, a respiratory rate of 30 and her oxygen saturation was 96% on room air. The patient

Figure 1. Patient's blood smear demonstrating thrombocytopenia with the paucity of platelets as well as abnormal red blood cell morphology in the form of schistocytes (arrows).



had normal pupils, pale conjunctiva, and no nystagmus was appreciated. The cardiovascular exam was remarkable for tachycardia. Her abdomen was soft and without hepatosplenomegaly and she had no blood in her stool. Neurologic exam revealed a right-sided facial droop with sparing of the forehead and flattening of the right nasolabial fold and she was unable to fully close the right eye. The other cranial nerves were normal. The patient had normal strength and reflexes. She was lethargic, but arousable to voice and oriented to person.

Laboratory testing revealed a mildly elevated white blood cell count at $11.8x10^9$, a hemoglobin of 7.7 g/dL, hematocrit of 23.6%, a platelet count of 31,000, and an MCV of 81.1 fL. A repeat platelet count several hours later was 19,000. A cell differential demonstrated 1+ nucleated RBC's and 1+ schistocytes (see **Figure 1**). A coagulation panel and cardiac enzymes were normal. The patient's metabolic panel showed an elevated creatinine at 1.35 mg/dL, a transaminitis with AST of 72 IU/L and ALT of 116 IU/L, an elevated alkaline phosphatase of 205 IU/L, and a bilirubinemia with direct bilirubin of 0.5 mg/dL and total bilirubin of 2.2 mg/dL. Lipase, ammonia levels, a urinalysis, and a toxicology screen were unremarkable. A thick and thin smear was negative for parasites. EBV and HIV studies were negative. A chest x-ray was clear.

DR. BECKER: To summarize, we have a patient originally from Liberia, who presented with 19 days of a right-sided facial droop, followed by 2–3 days of fever, weakness, dizziness, and confusion. She was pale and tachycardic. She had normal labs about 14 days prior to this admission but today she had a mild transaminitis and mild renal insufficiency. Additionally, her CBC revealed thrombocytopenia and an abnormal smear demonstrating schistocytes. Malaria is unlikely given the negative parasite smear and a travel history incongruent with plasmodium falciparum infection. Was a lumbar puncture considered? In an immunocompetent individual, the triad of mental status changes, neck stiffness, and fever occur in less than 50% of patients with bacterial meningitis.[4]

DR. BOARDMAN: Prior to consideration of a lumbar puncture, a CT scan of the brain was performed and was negative. However, an alternative diagnosis was entertained and a lumbar puncture was deferred. In addition, while evidence is poor, current standards suggest that a lumbar puncture should not be performed in patients with platelets <40,000.[5]

DR. THOMAS GERMANO: While initially I was leaning toward an infectious etiology or perhaps an autoimmune disorder such as SLE, I am intrigued by the patient's hematologic parameters – she was anemic and had 1+ schistocytes on laboratory exam. Anemia can be due to blood loss, insufficient red cell production, or destruction of red blood cells. In this case, the patient did not have evidence of blood loss. While failure of red cell production is possible due to EBV, parvovirus, or hepatitis, evidence of schistocytes is suggestive of extrinsic red cell destruction due to a microangiopathic hemolytic anemia (MAHA).

Fragmentation of the red cells occurs due to a number of infectious disorders including rickettsial diseases, HIV, and malaria. It can also be due to diverse disorders such as thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), eclampsia, HELLP syndrome, malignant hypertension, scleroderma renal crisis, and drug induced thrombotic microangiopathy (DITMA), as well as mechanical destruction from intravascular devices such as prosthetic cardiac valves and shunts.[6]

DR. BOARDMAN: Hemolysis labs were obtained and the patient was noted to have an elevated lactate dehydrogenase of 1,855 IU/L, low haptoglobin less than 8 mg/dL, an elevated free plasma hemoglobin B of 35.9 mg/dL, elevated fibrinogen of 247 mg/dL, and an elevated D-dimer of 6,219 ng/mL. A direct antiglobulin test (direct Coombs test) was negative, and the patient had a normal complement level. This additional data suggested hemolysis, but it was not consistent with disseminated intravascular coagulation (DIC).

DR. WILLIAM BINDER: Of the non-infectious causes of MAHA noted, the patient does exhibit several features of TTP – she has a low-grade fever, neurologic changes and confusion, thrombocytopenia, and anemia. Was this diagnosis considered?

DR. BOARDMAN: TTP was our leading diagnosis. TTP is a disorder marked by a congenital deficiency of, or acquired autoimmune response against, the ADAMTS13 enzyme, a metalloproteinase that normally cleaves Von Willebrand factor (VWF) into smaller multimers. In patients with decreased ADAMTS13 activity, the accumulation of uncleaved large VWF molecules leads to platelet aggregation and the formation of large microthrombi in blood vessel lumens.[7] With the generation of these large microthrombi, a consumptive thrombocytopenia occurs. Importantly, the microthrombi shear passing red blood cells and result in intravascular hemolysis and the formation of schistocytes.

From a clinical standpoint, symptoms of TTP are driven by the microvascular thrombi and include fatigue, dyspnea, petechiae, gastrointestinal distress, and easy bruising or bleeding.[8,9] Neurologic involvement can be present in about 50% of cases of TTP and symptoms can range from transient focal abnormalities to stroke and coma. Facial palsies have been reported.[10,11] Neurologic imaging is frequently normal and symptoms are often reversible upon effective treatment.[12,13] The pentad of TTP – MAHA, fever, thrombocytopenia, neurological abnormalities, and renal injury – is infrequently noted and several studies have demonstrated

that the presence of all 5 symptoms occur in less than 10% of cases.[14] Acute renal failure is unusual in TTP, although if present, does not exclude the diagnosis.[14]

DR. ELIZABETH SUTTON: How common is TTP? How is the diagnosis made?

DR. BOARDMAN: TTP is a rare hematologic disorder, with an annual incidence of approximately 1–3 case per million people.[12,14,15] About 90% of cases occur in adults with a median age of 41 years, and there is an increased prevalence in female and black populations.[16]

The diagnosis of TTP in the emergency department is based on the patient's clinical and laboratory characteristics. Laboratory testing for ADAMTS13 activity is a critical adjunct but often is not immediately available. Therefore, treatment for TTP must be initiated when there is a high clinical suspicion and should not be withheld while the confirmatory testing is being performed.

DR. SELIM SUNER: Recently, the PLASMIC score has been developed to help guide the clinical diagnosis of TTP. What was the patient's PLASMIC score?

DR. BOARDMAN: The PLASMIC score is a seven-component clinical prediction tool that stratifies patients according to the risk of having a decreased ADAMTS13 activity level (≤10%), thereby confirming the diagnosis of TTP.[17] At many institutions there is a lengthy turnaround time for ADAMTS13 testing and this makes it unsuitable for real-time decision making. The PLASMIC score helps to stratify patients into low-, intermediate-, and high-risk categories using readily available history and laboratory results. Like all clinical decision tools, the PLASMIC score can only be used in the patient population for which it was designed. In the original study, the PLASMIC score was validated on patients who were 18 years or older, had thrombocytopenia (<150x10^9 platelets/L), and who had evidence of MAHA. The PLASMIC score awards one point for each of the following criteria: Platelets <30x10^9 /L; evidence of hemolysis; no active cancer; no history of solid-organ or stem-cell transplant; MCV <90fL; INR <1.5; creatinine <2.0 mg/dL. A score of 0–4 were considered low-risk, 5 was intermediate-risk, and 6–7 were high-risk. These risk categories were created based on internal and external validation data, which compared the PLASMIC score against ADAMTS13 testing. Using the data in the case, our patient had a PLASMIC score of 6 (7 after repeat CBC), which would put her in the high-risk category.[18]

DR. RACHAEL WIGHTMAN: What is the most effective treatment for TTP and how was this patient managed?

DR. BOARDMAN: Prior to the 1980s, mortality from TTP was approximately 90%. With the advent of plasma exchange (PEX), which is now standard treatment, mortality has decreased to approximately 10%.[14] A patient should undergo daily PEX sessions until end-organ damage and hemolysis resolves, or confirmatory testing returns as negative for TTP. TTP is considered successfully treated after the patient displays a platelet count greater than 150x10^9/L for two consecutive days. If there is no response to treatment within 30 days, or if labs do not normalize in 60 days, then the disease is considered refractory. If symptoms return within 30 days of successful treatment, this is considered an exacerbation of the patient's current TTP episode and if symptoms return greater than 30 days after successful treatment, this is considered a relapse of disease. Unfortunately, despite appropriate therapy, about 40% of those with TTP experience one or more relapses.[14]

Glucocorticoids are routinely administered to patients with an intermediate or high-risk presentation and PLASMIC score. Rituximab, a humanized anti-CD20 monoclonal antibody, has been studied and used in the treatment of TTP, particularly in cases of refractory or recurrent disease. Several studies have shown shorter hospitalizations and have found that patients have had fewer relapses when rituximab is used in conjunction with PEX. Alternatively, caplacizumab, an anti-von Willebrand Factor monoclonal antibody, can be used in patients with high-risk presentations and in patients with low ADAMTS13 levels.[14,19,20]

Our patient did receive treatment for TTP upon transfer to the MICU from the emergency department. She received methylprednisolone and after placement of a central line, she received PEX. The following morning, however, her ADAMTS13 activity level resulted and was > 70%, and von Willebrand factor inhibitor level was found to be < 5%. PEX was discontinued.

DR. BINDER: Given the schistocytes and abnormal hematologic studies, are there other possible causes of the patient's MAHA?

DR. BOARDMAN: It would be unusual, although not impossible, to find normal ADAMTS13 activity in patients with TTP, and 3 cases have been described within the Oklahoma TTP-HUS registry.[12] The anti-ADAMTS13 antibody may not tightly bind to its epitope and can be eluted from ADAMTS13 during the incubation phase of the assay, leading to a falsely negative (i.e. normal ADAMTS13 activity) result.[21, 22] Alternatively, drug-induced TMA (DITMA) is a well-recognized, although infrequent event, and there are sporadic reports of valacyclovir causing a thrombotic microangiopathy.[23,24] DITMA is either immune-mediated or toxicity-mediated and is usually associated with significant kidney injury, however. Of the primary TMA syndromes, TTP is distinctive in that it rarely causes notable acute kidney injury.[25]

DR. NAOMI GEORGE: What was the patient's outcome?

DR. BOARDMAN: The patient was admitted to the MICU from the ED and underwent plasma exchange and did well. Her mental status improved within about 24 hours and she was transferred to the medical service on hospital day 3 and discharged on hospital day 6. The patient's thrombocytopenia and anemia slowly improved as well, and her platelets were >150,000 approximately 10 days after discharge. Her fatigue, Bell's palsy, and laboratory abnormalities had completely resolved at follow-up 3 months after her initial admission.

FINAL DIAGNOSIS: Thrombotic Thrombocytopenic Purpura or Drug-Induced Thrombotic Microangiopathy.

Acknowledgments

The authors would like to acknowledge Dr. James George for his suggestions and insights with this manuscript.

References

1. https://www.usaid.gov/liberia/fact-sheets/president's-malaria-initiative-liberia.
2. Scaggs Huang FA, Schlaudecker E. Fever in the Returning Traveler. Infectious Disease Clinics of North America. 2018; 32: 163–168.
3. Reich S. Bell's Palsy. Continuum: Lifelong Learning in Neurology. 2017; 23: 447 -466.
4. Chavez-Bueno S, McCracken GH Jr. Bacterial Meningitis in Children. Pediatric Clinics of North America. 2005; 52: 795–210.
5. Ning S, Kerbel B, Callum J, Lin Y. Safety of Lumbar Punctures in Patients with Thrombocytopenia. Vox Sang. 2016; 110: 393-400.
6. Phillips J, Henderson AC. Hemolytic Anemia: Evaluation and Differential Diagnosis. *American Family Physician*. 2018; 98: 354-361.
7. Zander CB, Cao W, Zheng XL. ADAMTS13 and von Willebrand factor interactions. *Curr Opin Hematol.* 2015;22:452-459.
8. Brain MC, Dacie JV, Hourihane DO. Microangiopathic haemolytic anaemia: the possible role of vascular lesions in pathogenesis. *Br J Haematol.* 1962;8:358-374.
9. Griffin D, Al-Nouri ZL, Muthurajah D, et al. First symptoms in patients with thrombotic thrombocytopenic purpura: what are they and when do they occur? *Transfusion.* 2013;53:235-237.
10. Aksay E, Kiyan S, Ersel M, Hudaverdi O. Thrombotic thrombocytopenic purpura mimicking acute ischemic stroke. *Emerg Med J*. 2006; 23: e51.
11. Badugu P. Idowu M. Atypical Thrombotic Thrombocytopenic Purpura Presenting as Stroke. *Case Reports in Hematology*. 2019; Jan 14; 2019: 7425320.doi:10.1155/2019/7425320.
12. George JN. The remarkable diversity of thrombotic thrombocytopenic purpura: a perspective. *Blood Adv.* 2018; 2: 1510-1516.
13. Page EE, Kremer Hovinga JA, Terrell DR, Vesely SK, George JN. Thrombotic thrombocytopenic purpura: diagnostic criteria, clinical features, and long-term outcomes from 1995 through 2015. *Blood Adv.* 2017;1:590-600.
14. Joly BS, Coppo P, Veyradier A. Thrombotic thrombocytopenic purpura. *Blood*. 2017; 129: 2836 -2846.
15. Mariotte E, Azoulay E, Galicier L, et al. French Reference Center for Thrombotic Microangiopathies. Epidemiology and pathophysiology of adulthood-onset thromboic microangiopathy with severe ADAMTS13 deficiency (thrombotic thrombocytopenic purpura): a cross-sectional analysis of the French national registry for thrombotic microangiopathy. *Lancet Haematol*. 2016; 3: e237-e245.
16. Terrell DR, Vesely SK, Kremer Hovinga JA, Lammle B, George JN. Different disparities of gender and race among the thrombotic thrombocytopenic purpura and hemolytic-uremic syndromes. *Am J Hematol.* 2010;85:844-847.
17. Bendabudi PK, Li A, Hamdan A, Fry MA, et al. Derivation and Prospective Validation of a Predictive Score for the Rapid Diagnosis of Thrombotic Thrombocytopenic Purpura: The Plasmic Score. *Blood*. 2014; 124: 231.
18. Bendapudi PK, et al. Derivation and external validation of the PLASMIC score for rapid assessment of adults with thrombotic microangiopathies: a cohort study. *The Lancet. Haematology.* 2017; 4(4): e157-64.
19. Jasti S, Coyle T, Gentile T, Rosales L, Poiesz B. Rituximab as an adjunct to plasma exchange in TTP: a report of 12 cases and review of literature. *J Clin Apher*. 2008;23(5):151-156.
20. Scully M, McDonald V, Cavenagh J, Hunt B, Longair I, Cohen H, Machin S. A phase 2 study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura. *Blood*.2011;118(7):1746-1753.
21. Personal Communication, Dr. James George, April 28, 2019.
22. Froehlich-Zahnd R, George JN, Vesely SK, Terrel DR, et al. Evidence for a role of anti-ADAMTS13 autoantibodies despite normal ADAMTS13 activity in recurrent thrombotic thrombocytopenia purpura. *Haemotologica*. 2012; 97: 297-303.
23. Bell WR, Chulay JD, Feinberg JE. Manifestations resembling thrombotic microangiopathy in patients with advanced human immunodeficiency virus (HIV) disease in a cytomegalovirus prophylaxis trial (ACTG 204). *Medicine*. 1997; 76: 369-380.
24. Rivaud E, Massiani MA, Vincent F, Azoulay E, Couderc LJ. Valacyclovir hydrochloride therapy and thrombotic thrombocytopenic purpura in a HIV-infected patient. *Archives of Internal Medicine*. 2000; 160: 1705–1706.
25. George JN, Nester CM. Syndromes of Thrombotic Microangiopathy. *NEJM*. 2014; 371: 654-666.

Authors

Timothy J. Boardman, MD, PGY 3, Resident, Brown University Department of Emergency Medicine.

William Binder, MD, MA, FACEP, Associate Professor of Emergency Medicine, Alpert Medical School of Brown University.

Correspondence

William_Binder@brown.edu