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CASE REPORT

An improbable and unusual case of thrombotic thrombocytopenia purpura

Jaymon Patel, MD*, Preeti Patel, MD and Zohair Ahmed, MD

Department of Internal Medicine, OSF Saint Francis Medical Center, University of Illinois Peoria, Peoria, IL, USA

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening medical emergency which may be difficult to recognize given the wide spectrum in which it presents. A delay in treatment may be catastrophic as untreated cases of TTP have a mortality rate exceeding 90%. Given the high fatality rate of untreated TTP and its range of presenting symptoms, we present our unusual case of TTP in a post-splenectomy patient with early treatment and positive outcome. This case describes a 54-year-old female who presented with hematuria and gingival bleeding, followed by the development of a bilateral lower extremity petechial rash. Her past medical history was significant for multiple episodes of TTP, the last of which resulted in a splenectomy and a 20-year history of remission thereafter. On exam, she was alert, well appearing, and neurologically intact. Her only significant finding was a bilateral lower extremity petechial rash. Laboratory studies revealed mild anemia and thrombocytopenia, an elevated lactate dehydrogenase, and a decreased haptoglobin. Peripheral smear showed poikilocytosis, helmet cells, and schistocytes. Corticosteroid therapy was promptly initiated, her platelets were monitored closely, and she underwent urgent therapeutic plasma exchange. Due to the risk of significant morbidity and mortality that may result from delayed treatment of TTP as well as the significant variations of presentation, TTP requires a consistently high index of suspicion. Our patient suffered multiple relapses of TTP within a 30-year span, underwent splenectomy in early adulthood, and presented with atypical symptoms during her most recent relapse illustrating how persistent TTP can be as well as how unusually it may present. Providers should be aware of the vast spectrum of presentation and remember that TTP may recur following splenectomy despite prolonged remission.

Keywords: *thrombotic thrombocytopenic purpura*; *relapse*; *refractory*; *splenectomy*; *hematuria*; *gingival bleeding*

*Correspondence to: Jaymon Patel, Department of Internal Medicine, OSF Saint Francis Medical Center, University of Illinois Peoria, 530 NE Glen Oak Ave, Peoria, IL 61637, USA, Email: Jaymon.B.Patel@osfhealthcare.org

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Thrombotic thrombocytopenic purpura (TTP) is a life-threatening medical emergency that results in thrombocytopenia, microangiopathic hemolytic anemia, and may result in end-organ injury. It is the result of decreased activity of a protease called ADAMTS13, which is responsible for cleaving multimers of von Willebrand factor. The decreased ADAMTS13 activity results in large von Willebrand factor multimers that generate platelet adhesion and subsequent thrombosis (1). The thrombotic complications may result in kidney injury, myocardial infarction, pulmonary embolism, and cerebrovascular accident (2, 3).

TTP may be acquired, as a result of autoantibodies against the ADAMTS13 protease, or may be congenital, as a result of ADAMTS13 gene mutations. The incidence of TTP is approximately 3 cases per 1 million adults per year (4). The presentation of TTP is classically described as a pentad of fever, microangiopathic hemolytic anemia, neurological manifestations, thrombocytopenia, and renal failure. However, presenting with the pentad is rare, and the severity of each manifestation varies considerably (5). Presenting symptoms may include fever, fatigue, mucosal bleeding, petechiae, nausea, vomiting, and weakness to underscore a few. Griffin et al. published a report documenting initial presenting symptoms in 34 patients with TTP and found that neurological symptoms, although widely varied, were the most common overall (44%), while the most common single symptom was abdominal pain (23.5%). Interestingly, fewer than 10% of patients reported bleeding as a symptom (6).

Since the presenting symptoms and their severities can vary greatly, there is a substantial risk of delay in treatment. A delay in treatment may be catastrophic as TTP has a mortality rate exceeding 90% in the absence of appropriate

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treatment. Given the high fatality rate of untreated TTP and its unusual presenting symptoms, we present our unusual case of TTP in a post-splenectomy patient with early treatment and positive outcome.

Case

A 54-year-old female presented to the emergency department with complaints of gingival bleeding, hematuria, and bilateral lower extremity petechial rash that began 2 days prior to admission. Her symptoms started with gross hematuria for which she was evaluated at a prompt care and started on ciprofloxacin for a presumed urinary tract infection. The following day, she experienced gingival bleeding while brushing her teeth and a petechial rash on her lower extremities, prompting her to undergo further evaluation at the emergency department. Her past medical history was significant for idiopathic thrombocytopenic purpura diagnosed in 1995, TTP and acute cerebrovascular attack diagnosed in 1997, a relapse of TTP which resulted in a splenectomy in 1999, hyperthyroidism secondary to Grave's disease, and hyperlipidemia. Her family history was not significant. Her social history was negative for any alcohol use and she formerly smoked cigarettes.

On physical exam, she was afebrile and had normal vital signs with the exception of tachycardia with a heart rate of 103. She was alert, well appearing, and neurologically intact. She did not exhibit pallor or further evidence of gingival bleeding. Her lower extremities showed petechiae bilaterally. Initial laboratory studies were significant for mild anemia and thrombocytopenia with a hemoglobin 11.5 g/dL, hematocrit 34.4%, MCV 84.5 fL, and platelet count 17×10^3/mcL. Her white blood cell count was normal at 11.86×10^3/mcL. Her LDH was 1236 U/L, her haptoglobin was <8 mg/dL, and her reticulocyte count was 2.3%. Her peripheral smear showed poikilocytosis, helmet cells, and schistocytes. Her chemistry panel and liver enzymes were unremarkable with the exception of a total bilirubin of 2.4 mg/dL and a direct bilirubin of 0.7 mg/dL. Corticosteroid therapy was promptly initiated, and hematology and nephrology were consulted for presumed TTP. Direct and indirect Coombs testing was negative. An ADAMTS13 activity level was drawn and sent for evaluation. Due to her Grave's disease, thyroid peroxidase antibody and TSH were evaluated and found to be 180 IU/mL and <0.010 mIU/L, respectively. She was asymptomatic and requested outpatient follow-up with her endocrinologist for the initiation of hyperthyroidism treatment.

Without delay, she underwent temporary dialysis catheter placement and began therapeutic plasma exchange (TPE). Her platelet counts immediately improved following her first session of TPE, and she continued daily TPE with corticosteroid therapy until her platelet count was maintained greater than 150×10^3/mcL (Fig. 1). Her ADAMTS13 activity level resulted on day 4 after the admission and was decreased at 13%. Her ADAMTS13 inhibitor was found to be positive. In total, she received 5 days of TPE and corticosteroid therapy before ceasing TPE and initiating a 6-week oral steroid taper. Her platelet count at the time of discharge was 338×10^3/mcL. An ADAMTS13 activity was repeated 1 week after her initial draw, which resulted as 43% activity, and again 1 month later, with a value of 56% activity (Fig. 2).

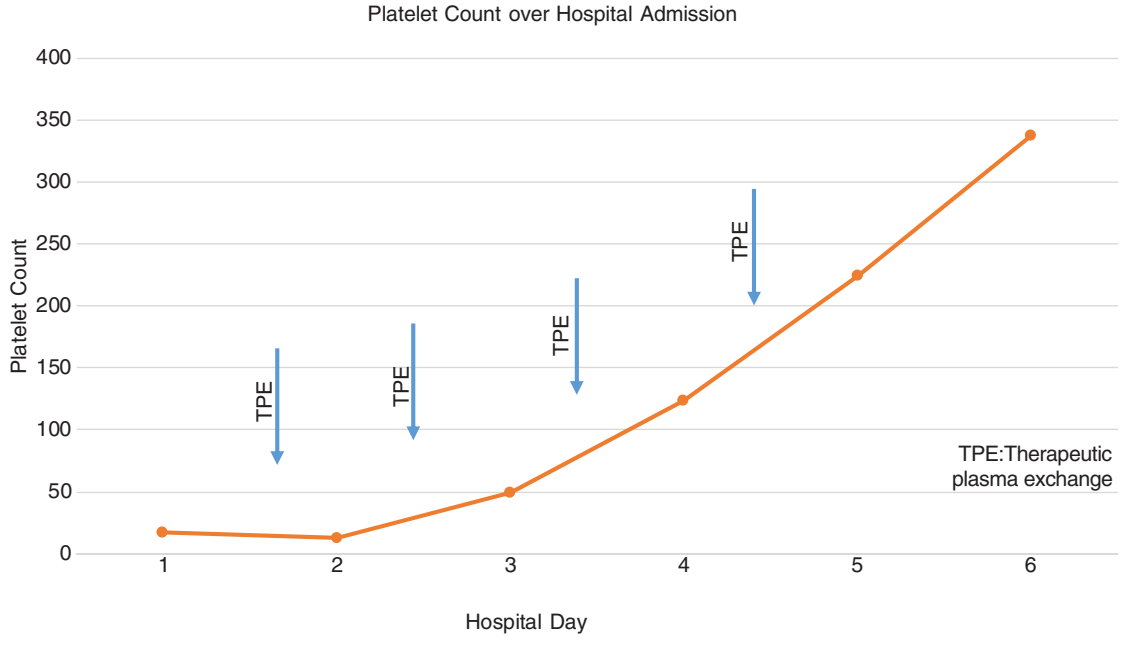

Fig. 1. Response of platelet count to therapeutic plasma exchange.

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Discussion

TTP is presumptively diagnosed by clinical and diagnostic evaluations with the presence of microangiopathic hemolytic anemia, thrombocytopenia, elevated LDH, and bilirubin with negative Coombs testing. The diagnosis is definitive with the presence of decreased ADAMTS13 activity, with levels less than 10%. In the cases reviewed by Griffin et al., the differential diagnosis considered in patients with TTP prior to the diagnosis of TTP included meningitis, urosepsis, immune thrombocytopenia, stroke, systemic lupus erythematosus, gastroenteritis, arthritis, and stroke to name a few (6).

Owing to its high fatality rate, treatment is initiated with a presumptive diagnosis of TTP, prior to obtaining the results from more confirmative testing such as the ADAMTS13 levels. Prior to the 1980s, before the era of therapeutic plasma exchange for treatment of TTP, fatality rates were greater than 90% (7, 8). Treatment consists of prompt and daily therapeutic plasma exchange and glucocorticoid administration, which may be oral or intravenous depending on the patient's neurological status. Platelet counts should be monitored daily since the count reflects disease response to therapy. Once the platelet count is maintained above 150,000/μL for 2 days, therapeutic plasma exchange can be discontinued while continuing steroid therapy. As the platelet count plateaus, a steroid taper can be initiated while continuing platelet-count monitoring.

If patients have a recurrence of TTP within 1 month, they have refractory disease and will need to undergo retreatment with plasma exchange, glucocorticoids, and may additionally be treated with rituximab. If the patient remains recurrence free for 1 month, they are in remission. If the recurrence occurs after 1 month, they have relapsing TTP and must also repeat therapy as mentioned for refractory disease and may also require the use of rituximab or splenectomy. Rituximab, a monoclonal antibody against CD20, has been shown to be effective in treating refractory disease in acquired TPP 9–11. Relapses may occur in approximately 40% of patients (12). One study found that the relapse rate was approximately 36% within a 30-month follow-up period and approximately 76% of those occurred within the first 24 months (13).

In patients with relapsing or refractory disease, splenectomy remains a viable, but not curative, treatment option. In a case series by Dubois and Gray, patients who underwent splenectomy for relapsing TTP fared better than those who underwent splenectomy for refractory disease. They noted the aggregate complication rate to be 6% versus 10%, and mortality rate to be 1.2% versus 5% in the relapsing TTP group that underwent splenectomy versus the refractory group. Furthermore, they found the post-splenectomy relapse rate for TTP was approximately 17% (14).

Due to the risk of significant morbidity and mortality that may result from delayed treatment of TTP as well as the significant variations of presentation, TTP requires a consistently high index of suspicion. Additionally, once a patient has been diagnosed with TTP, the rate of relapse is 40%, which may be decreased to approximately 17% after splenectomy. Our patient suffered multiple relapses within a 30-year span, underwent splenectomy in early adulthood, and presented with atypical symptoms during her most recent relapse illustrating how persistent TTP can be as well as how unusually it may present. TTP should be considered as part of the differential for any

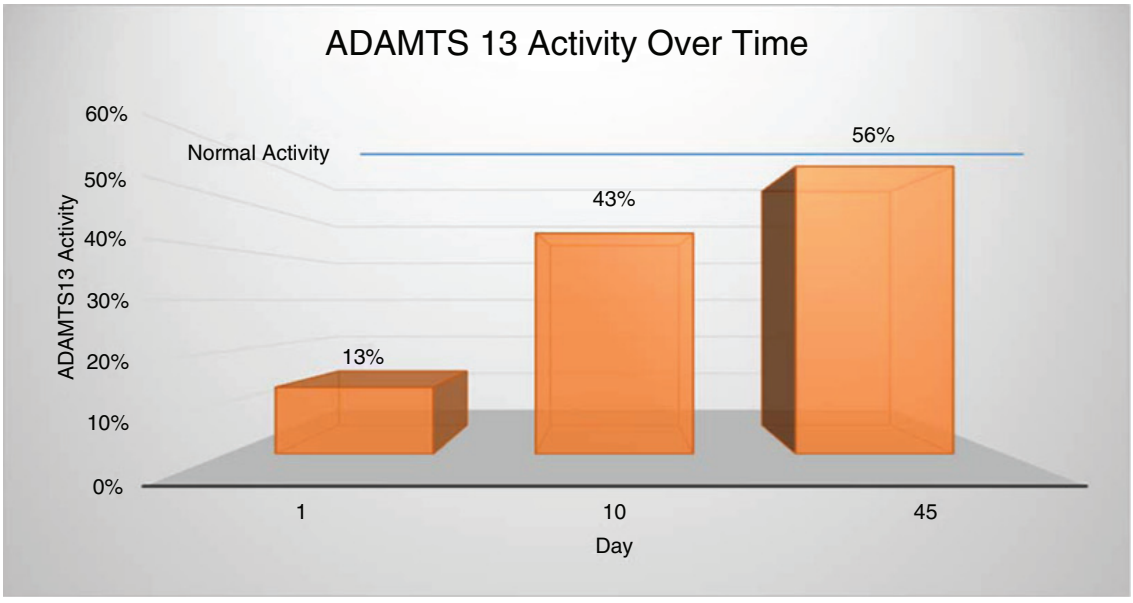

Fig. 2. ADAMTS13 activity from initial encounter to 45 days after discharge.

patient presenting with anemia and thrombocytopenia, regardless of lack of other symptoms as they may often be absent. Additionally, we recommend that patients who have experienced TTP receive education on relapsing and refractory disease, as well as typical and atypical symptoms that may indicate a recurrence. Lastly, we recommend educating patients to inform their provider of their history of TTP early in their diagnostic process should there be concern for a recurrence.

Author contributions

JP and PP reviewed the literature, drafted the manuscript, and approved the final version of the article to be published. ZA reviewed the literature, made critical revisions related to the content of the article, and approved the final version of the article to be published.

Conflict of interest and funding

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Disclaimer

The views expressed in the submitted article are our own and not an official position of the institution.

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