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Fatal Fatigue: Thrombotic Thrombocytopenic Purpura

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Cover Page Footnote

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CASE

A 75 year old Caucasian female presented to the family medicine clinic with complaints of increasing fatigue over the course of one month. This occurred in spite of quality sleep each night. Associated symptoms included intermittent, non-radiating epigastric pain for one and a half months; decreased appetite with a five pound weight loss over two months; easy bruising; and bilateral upper extremity tremors for two days. Depression screening was negative. Medical history included mixed hyperlipidemia with declined statin therapy, osteopenia treated with 250mg calcium citrate PO BID, seborrheic keratosis, and urinary urge incontinence. All preventative care was up to date, including negative mammogram and colonoscopy within three months of her appointment. On exam, the patient had normal vital signs and did not appear in acute distress. Scattered ecchymoses were noted to the posterior left forearm and right hip, as well as a fine tremor in the bilateral upper extremities with +5/5 muscle strength. No cardiovascular, pulmonary, gastrointestinal, or other neurologic abnormalities were found. Lab workup was ordered for fatigue and epigastric symptoms. Gastroesophageal reflux disorder precautions were provided. Additional workup such as a CT abdomen/pelvis and sleep study were considered for further evaluation should lab results be unremarkable.

Within an hour of leaving the clinic, the patient began experiencing stroke-like symptoms and was brought to the Emergency Department. Retrospectively, labs drawn during her clinic visit showed markedly low platelets at 16K/mcL; elevated ferritin, bilirubin, and BUN levels; normal folate, TSH, T4, T3, electrolyte, and iron levels; and decreased vitamin B12, RBC, Hgb, Hct, and eGFR levels. During evaluation at the Emergency Department, the patient was hypertensive, and her platelet level had further dropped to 12 K/mcL. Stroke workup was negative. EKG showed normal sinus rhythm with sinus tachycardia. The patient was airlifted to a higher level facility. CT head without contrast and CT perfusion studies showed findings consistent with mild chronic microangiopathic ischemic change. EEG showed a region of localized dysfunction in the left hemisphere. Platelets dropped further to 6 K/mcL. Peripheral blood smear showed 3-4 schistocytes per HPF. The PLASMIC score was applied and found to be 7, indicating a high probability of Thrombotic Thrombocytopenic Purpura (TTP). Dialysis catheter was placed to initiate plasma exchange and possible steroid course, but the patient decompensated into respiratory and vascular failure, with a STEMI apparent on EKG. Attempts at resuscitative measures produced no response;

the patient was pronounced dead at 10:07pm. Had the patient survived to obtain treatment for her condition, she would have received therapeutic plasma exchange every 72 hours, 1mg/kg prednisone daily, and possibly rituximab at discharge to prevent relapse.

DISCUSSION

Thrombotic Thrombocytopenic Purpura (TTP) is a rare, life-threatening hematologic condition caused by severe deficiency of the ADAMTS13 protease.[1] This protease normally cleaves vonWillebrand factor (vFW).[1] TTP is either acquired due to the formation of an autoantibody against ADAMTS13 protease**,** called immune TTP (iTTP), or inherited due to genetic mutations in the ADAMTS13 protease, in which case it is termed Upshaw-Schulman syndrome.[1,2] Immune TTP is more common than the inherited form, occurring in over 95% of cases.[1,3] iTTP affects approximately ten per one million adults per year, with approximately one new case per one million adults per year.[1] Ninety percent of cases occur in adulthood, with a peak incidence in the fourth decade.[1,4] Women are affected two and a half times more than men.[1] Other risk factors include black ethnicity, obesity, pregnancy, infection, O blood group, and HLA-DRB1*11 and DQB1*03 alleles.[1,2,4] Figure 1 illustrates the downstream effects of the ADAMTS13 protease dysfunction. When vFW is unable to be cleaved, large, hyperadhesive vWF multimers circulate in the bloodstream.[1] These multimers form platelet-rich microthrombi which occlude small arterioles in various areas of the body.[1]

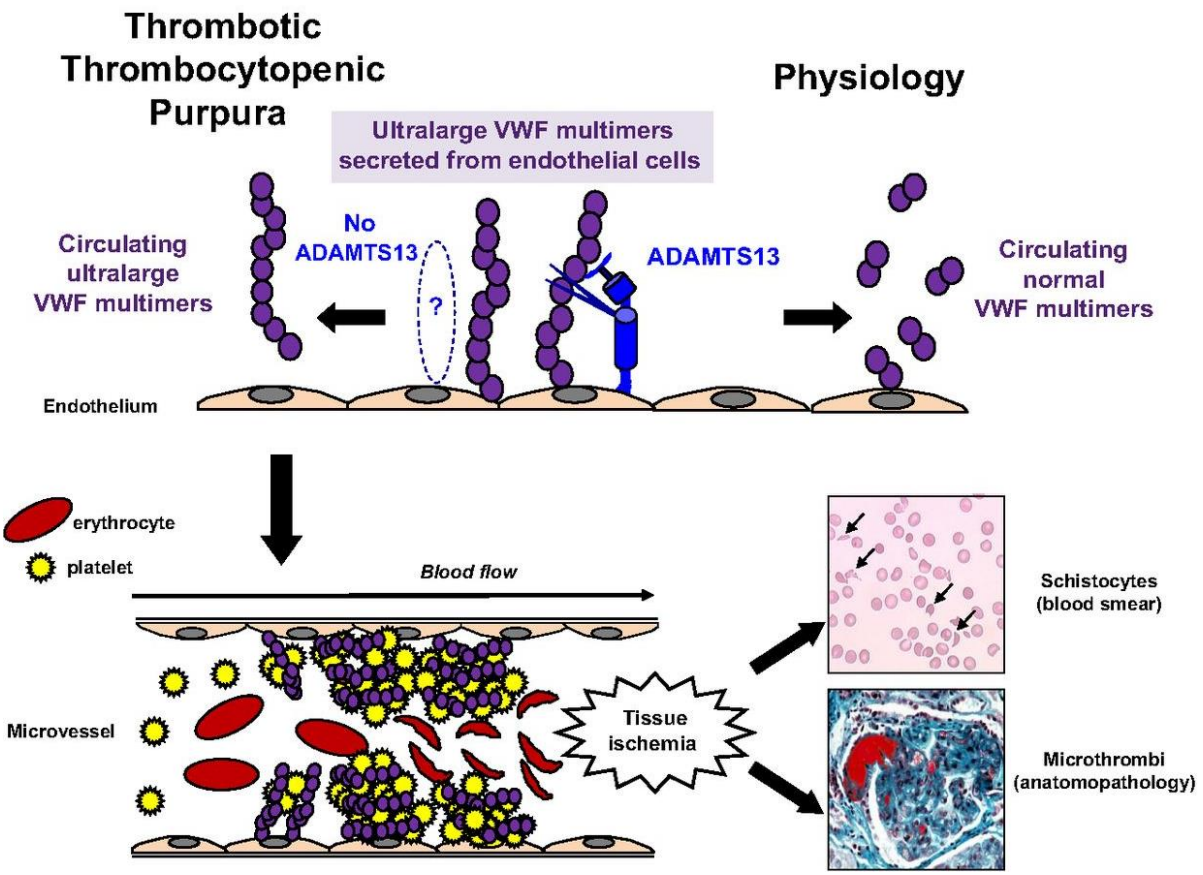

Figure 1[1]

Patients with iTTP may appear anywhere on the spectrum from normal to critically ill.[3] They may display different symptoms corresponding to thrombocytopenia, ischemia, and/or infarction in various body systems.[1,3] While there is a classic pentad of symptoms (microangiopathic hemolytic anemia, thrombocytopenia, neurologic impairment, fever, and renal dysfunction), less than ten percent of patients present with all five.[4] Patients sixty years old or greater may have more atypical presentations, such as reporting earlier in the course of iTTP with more neurologic and renal involvement and less severe thrombocytopenia.[4] Figure 2 depicts common presenting complaints and percentages of case study patients with iTTP who experienced those symptoms.

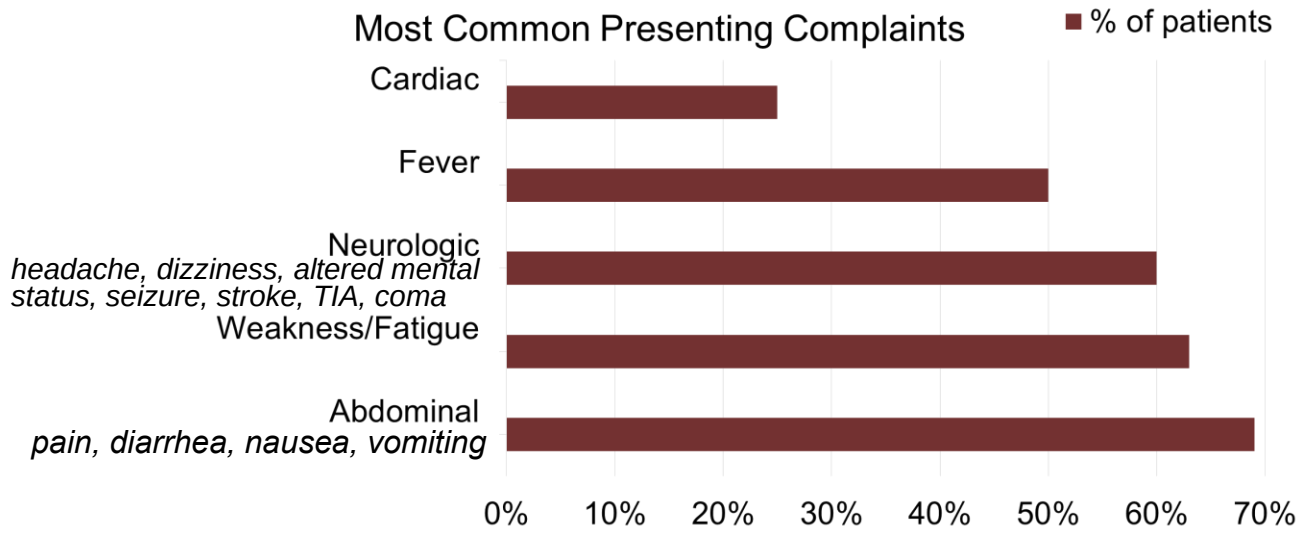

Figure 2[1,3,5]

When iTTP is suspected, the following tests should be included in the patient workup: CBC, reticulocyte count, peripheral blood smear, BUN and creatinine, serum LDH, direct and total bilirubin, serum haptoglobin, PT/PTT/INR, fibrinogen, D-dimer, direct antiglobulin Coombs test, HIV screening, and ADAMTS13 activity and inhibitor testing.[1,3] A diagnosis of iTTP is strongly supported if ADAMTS13 activity is <10%.[1] Provided the patient meets the prerequisite of schistocytes on peripheral blood smear, the PLASMIC score as illustrated in Table 1 may be applied to determine the patient's likelihood of having severely decreased ADAMTS13 activity.[4,5] The PLASMIC score may be less sensitive for patients ≥60 years old.[4] Sole use of ADAMTS13 activity for diagnosis or determination of therapy is not recommended, and treatment should not be delayed waiting for results.[3,5] Further testing such as EKG, troponin levels, and imaging studies can be conducted based on each patient's symptoms.[1,3] Of note, most patients have normal findings on imaging, although it is possible to see changes such as infarction.[4] Tissue biopsy does not provide any specific findings to distinguish iTTP from other primary thrombotic microangiopathies (TMAs), and generally reveals platelet-rich and fibrin-poor thrombi.[3] However, a normal or mild reduction in kidney function does help distinguish iTTP from other primary TMAs.

Parameter		**PLASMIC score**
Platelet count <30,000 μL		+1
Serum creatinine level <2.0 mg/dL		+1
Markers of hemolysis (need 1 of the following)	Indirect bilirubin >2mg/dL	+1
	Undetectable haptoglobin	
	Reticulocyte count >2.5%	
No active cancer in previous 1 year		+1
No history of solid organ or stem cell transplant		+1
International normalized ratio (INR) <1.5		+1
Mean corpuscular volume (MCV) <90 fL		+1
Likelihood of severe ADAMTS13 deficiency (<10%) ***Severe deficiency is specific for and considered a hallmark of TTP***		**Score= 0-4: 0-4%** (Low risk) **Score= 5: 9-24%** (Intermediate risk) **Score= 6-7: 62-82%** (High risk)

Table 1[1,4,5]

Thrombotic thrombocytopenic purpura has a high morbidity and up to 90% mortality rate if not promptly recognized and treated.[3] Rapid initiation of treatment for those with PLASMIC scores of 5 or more without an alternate explanation for their condition is imperative to decreasing morbidity and mortality.[4,5] Treatment includes daily therapeutic plasma exchange (TPE), which usually entails a 1.5x plasma volume exchange for the first few treatments, with a decrease to 1.0x plasma volume exchange thereafter until an improvement in clinical status.[1,3] If not contraindicated for the patient, 1.5mg/kg/day of methylprednisolone for 3 weeks may be included.[1] Caplacizumab, which blocks interactions between platelets and vWF, can be used as an adjunct.[3] In severe cases, treatment may expand to include TPE twice daily, salvage splenectomy, or use of cyclophosphamide, vincristine, or cyclosporine A pulses.[1] Future treatments may include N-acetylcysteine, bortezomib, and recombinant ADAMTS13.[1] In fact, recombinant ADAMTS13 was approved for inherited TTP in 2013.[3]

If treatment is swift and appropriate, first episode survival rates of 80-90% are expected.[1] A patient whose platelet counts are above $150x10^9/\mu L$ for two consecutive days, with normal or normalizing LDH and clinical recovery is considered to have a complete treatment response.[1] Following the discontinuation of TPE, a patient may experience an exacerbation of iTTP if the episode occurs within the first thirty days, or a relapse if it occurs after thirty days.[1] Of those successfully treated, 40% of patients with iTTP experience one or more relapses.[1] These are most common in the first year after the initial diagnosis, and can be treated with rituximab $375mg/m^2$ weekly/4 weeks, a monoclonal anti-CD20 antibody, in addition to TPE and methylprednisolone.[3,6] Relapses are uncommon four years after response to treatment, but have been reported up to nine years after.[3,6] Patients with TTP should have long-term follow up, with clinicians monitoring ADAMTS13 activity, assessing for the development of other autoimmune diseases, and treating any deficits incurred during the episode.[1] Patients are especially prone to neurocognitive deficits and cardiovascular events following an acute episode.[3] If the patient's ADAMTS13 activity decreases to less than 10 IU/dL, preemptive therapy should be initiated to prevent relapse.[3] Preemptive use of rituximab has been found to decrease relapse of TTP in 85% of patients with a favorable benefit-risk profile.[7] This medication depletes autoantibody production, normalizes ADAMTS13 activity, and changes ADAMTS13 conformation from open to closed.[7]

CONCLUSION

Thrombotic thrombocytopenic purpura (TTP) is an uncommon disorder, especially for this patient due to her age, which made other diagnoses more likely. An additional challenge to the diagnosis included her inconsistent primary care visits over the years. TTP most frequently affects those in their fourth decade of life, but is a very important diagnosis to consider for patients of all ages with neurologic or gastrointestinal complaints, easy bruising, and fatigue. A clinician must have a high index of suspicion to diagnose and treat this life-threatening disease to decrease morbidity and mortality. Completion of appropriate lab work-up, and, given the presence of schistocytes on peripheral blood smear, application of the PLASMIC score can aid in prompt diagnosis and treatment. The current mainstay of treatment for an acute episode is therapeutic plasma exchange, methylprednisolone given no contraindications, and the discretional addition of rituximab. Severe cases require further treatment options. Patients should be closely monitored by clinicians for

evidence of relapse, other autoimmune diseases, or health issues including neurological and cardiovascular conditions as a result of their acute episode.

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