Challenge Cases

Petechiae, Altered Mental Status, Fever and IV Drug Abuse

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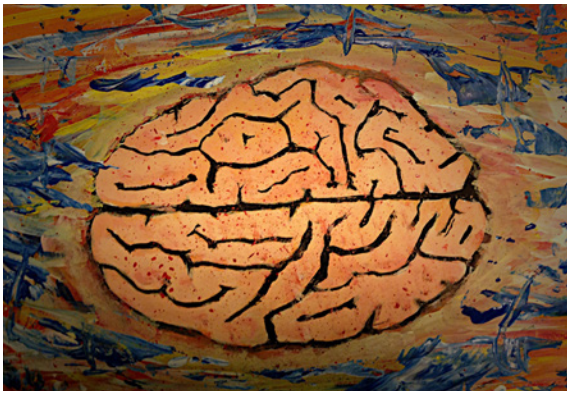
Mary Wittler, MD[1]



Artwork by Will McKay

The patient is a 28-year-old Caucasian male with a past medical history of intravenous (IV) drug abuse, methicillin-sensitive *Staphylococcus aureus* (MSSA) endocarditis status post mechanical mitral valve replacement, end-stage renal disease (ESRD) secondary to septicemia on peritoneal dialysis, asplenia, and hypertension. He presents with fever, nausea and vomiting of 2 days duration. He reports subjective fever and chills at home in addition to non-bloody, non-bilious vomiting and non-bloody diarrhea. He denies shortness of breath, headache, dizziness, and mental status changes. Medications include warfarin for his mechanical heart valve, and recent IV drug abuse, which upon further questioning includes IV oxymorphone abuse 2 days ago. He also has not been compliant with his peritoneal dialysis for the last 2 days. He denies recent travel, tick exposure, or known sick contacts.

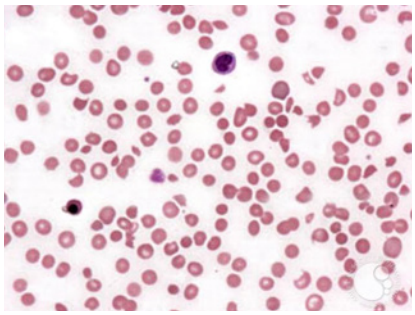
On exam, the patient has a fever of 103.8° F., is tachycardic (105 beats per minute), diaphoretic, and somewhat lethargic (arousable to voice) on interview. Auscultation of his chest reveals an III/VI systolic murmur at the left lower sternal border and a II/VI diastolic murmur. He exhibits generalized tenderness of his abdomen without rigidity or rebound. He has petechiae on his face, palate, neck, and chest which appeared in last 24 hours. Blood and peritoneal fluid cultures are obtained. The patient had a hemoglobin value of 9.7 g/dl (normal range 14 – 18 g/dl), a platelet count of 71,000 (normal range 160,000 – 360,000), lactic acid of 1.8 mmol/l (normal range 0.5 – 2.2 mmol/l), lactate dehydrogenase level of 261 U/L (normal range 90 – 271 U/L), haptoglobin of 46 mg/dl (30 – 200 mg/dl), reticulocyte count of 1.3 % (0.5 – 2.5%) and total bilirubin of 0.7 mg/dl (0.1 – 0.2 mg/dl). Because of the patient's septic presentation, he is empirically started on IV antibiotics, including vancomycin and piperacillin-tazobactam. Due to lethargy, fever, and petechial rash, ceftriaxone is added for coverage of meningococcemia in an asplenic patient.

The differential upon admission included endocarditis, thrombotic thrombocytopenic purpura (TTP), thrombotic microangiopathy (due to IV oxymorphone), meningococcemia, and sepsis (due to infected peritoneal fluid).

Q1: What Do You Do Next?

Based upon this clinical concern for TTP, which peripheral smear (right) would fit best with this patient's diagnosis?

A.



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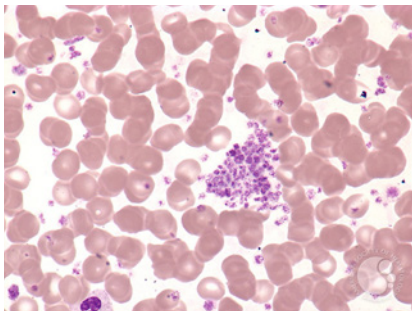

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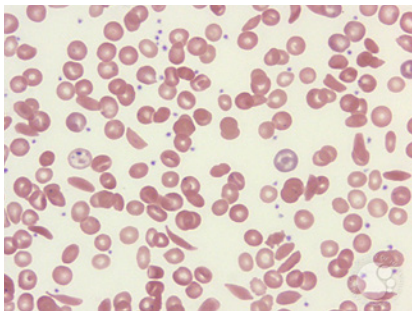
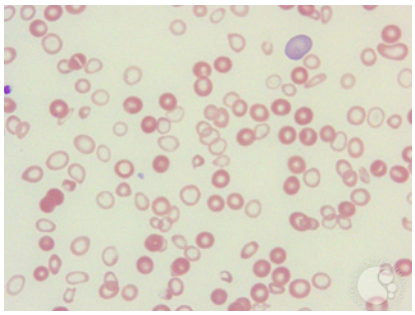


D.



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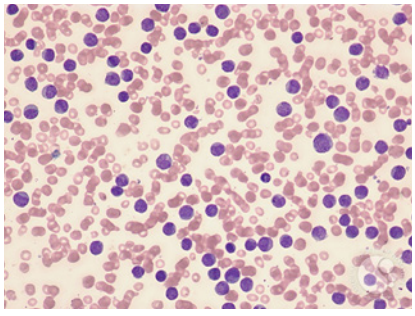

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Q2: Which two clinical features of TTP must a patient have in order to consider a diagnosis of TTP?

A. Microangiopathic hemolytic anemia and renal dysfunction

B. Microangiopathic hemolytic anemia and fevers

C. Microangiopathic hemolytic anemia and altered mental status

D. Microangiopathic hemolytic anemia and thrombocytopenia

E. Thrombocytopenia and renal dysfunction

Correct answer for Q1: A (Schistocytes)

Thrombotic thrombocytopenic purpura (TTP) is classically thought of as being associated with a pentad of different features, but not all five of these characteristics are necessary for the diagnosis.

Correct answer for Q2: D

While the patient was ultimately diagnosed with recurrent endocarditis based on blood cultures and echocardiographic findings of vegetations, microangiopathic hemolytic anemia due to oxymorphone was also strongly considered. We asked experts in toxicology and hematology to comment on how IV abuse of oxymorphone hydrochloride extended-release tablets (Opana ER®) could cause symptoms that mimic TTP.

Discussion

Leslie Ellis (Hematologist):

Despite the pentad of features associated with TTP (fevers, altered mental status, renal dysfunction, microangiopathic hemolytic anemia [MAHA], and thrombocytopenia), only two are technically required for the diagnosis to be considered – the abnormalities in the blood counts.[1,2] Laboratory evidence of hemolytic anemia should be present, specifically low hemoglobin due to increased red blood cell destruction, reticulocytosis due to increased red blood cell production, elevated lactic dehydrogenase levels due to increased cell turnover, and decreased haptoglobin due to its filtration out of the circulation by the liver as it binds to free hemoglobin. Sometimes increased bilirubin is also seen due to breakdown of the protoporphyrin rings that contain the heme moieties by macrophages (although this will be more elevated in examples of extravascular hemolysis). Microangiopathic hemolytic anemia is characterized by the presence of schistocytes, red cell fragments that develop as the red blood cells try to pass through fibrin clots in the microvasculature, which have a classic helmet shape.

Other disorders can be associated with microangiopathic hemolytic anemia, many of which are relevant to this patient. Sepsis is often associated with disseminated intravascular coagulation, which can also cause MAHA and thrombocytopenia. Mechanical heart valves can also cause hemolytic anemia with evidence of schistocytes, through extracorpuscular intravascular hemolysis due to shearing of the red blood cells as they pass through the foreign valve. However, this in and of itself would not explain the fevers and altered mental status.

Once TTP is suspected based upon MAHA and thrombocytopenia, the diagnosis is typically confirmed by performing an assay of ADAMTS13 activity. ADAMTS13 is a metalloproteinase enzyme that is endogenously produced to cleave von Willebrand factor (vWF), which is made in ultralarge multimers and must be cleaved into multimers of smaller molecular weights to prevent inappropriate clot formation through binding of vWF to platelets. Most adult cases of TTP are due to the development of acquired autoantibodies to ADAMTS13. These markedly decrease levels of the enzyme, and therefore increase the amounts of vWF multimers, which leads to TTP[2]. Current diagnostic criteria at our institution, where ADAMTS13 activity is assessed internally, define an activity level of less than 5% as consistent with TTP as classically described. These cases of TTP typically respond to plasma exchange, which both removes autoantibodies, and increases the recipient's ADAMTS13 levels via the donor's plasma[3].

Mary Wittler (Toxicologist):

In 2012, the Tennessee Department of Health received reports of a TTP like-illness associated with IV abuse of oxymorphone hydrochloride extended-release tablets (Opana ER®). Further investigation by the Centers for Disease Control and Prevention (CDC) and increased awareness by clinicians has further defined this uncommonly reported illness. The current extent of disease is unknown. Opana ER® is a crush-resistant formulation containing polyethylene oxide (PEO), an inactive ingredient used to prevent crushing and extraction.[5] Unfortunately, drug abusers can circumvent the formulation, producing a solution for injection. The illness has only been reported after intravenous or subcutaneous injection, but its etiology is unknown. Other drugs containing PEO have not been associated with this illness. Solvents used to dissolve and extract the drug or an added adulterant might be responsible. Quinine, used infrequently as an adulterant, has previously been associated with TTP. Additionally, hepatitis C, HIV, and systemic infections are associated with drug abuse and acquired TTP; the presence of these illnesses in this patient population is a confounder.

In contrast to classic TTP, cases of MAHA associated with IV abuse of Opana ER® typically have higher platelet counts, and normal or mildly decreased ADAMTS13 activity.[6] The original case definition used in the CDC's investigation was the presence of microangiopathic hemolytic anemia, thrombocytopenia with platelets < 50,000/μL, report of injecting Opana ER®, and no other known etiology. For the 15 patients meeting the case definition, platelets ranged from 9,000 - 49,000/μL and ADAMTS13 activity ranged from 42 – 131%.[4] In a second case series of 18 TTP like-illnesses associated with injection of Opana ER®, platelets ranged from 9,000–128,000/cm^3 and ADAMTS13 activity ranged from 12–79%.[7] The CDC recommends screening patients presenting with a TTP-like illness of unknown etiology for drug abuse. Of note, the typically used immunoassay urine drug screen for opiates will not usually detect oxymorphone.

Leslie Ellis (Hematologist):

It is well documented that a subset of cases of TTP-like illnesses are drug-induced[8]. Except for ticlopidine—associated TTP, none of these drug-associated cases was associated with ADAMTS13 activity levels close to the threshold of less than 5%, and none responded to plasma exchange. Based upon these findings in the literature, and our experience with cases of IV Opana ER®-associated MAHA, plasma exchange would not be recommended and treatment should include supportive care measures only.[9, 10]

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Sources of Funding: There was no funding for this project.

Conflicts of Interest: The authors have no conflicts of interest to report.

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11. **Answer Choice A:** This image was originally published in ASH Image Bank. John Lazarchick. Thrombotic Thrombocytopenic Purpura - 1. ASH Image Bank. 2001; 00001344. ©the American Society of Hematology.

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