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Case Report: A Case of TTP in the ED

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Abstract:

We report a case of a 54-year-old female who presented with mild shortness of breath, lower chest discomfort, fatigue, and weakness ongoing for several days and was diagnosed with thrombotic thrombocytopenic purpura (TTP). TTP is characterized by microangiopathic hemolytic anemia and thrombocytopenia due to either an inherited or immune-mediated reduction in von Willebrand Factor (VWF) cleaving protease ADAMTS13.
Patients presenting with non-specific symptoms is becoming increasingly common and initial bias could be to attribute symptoms to viral syndrome or upper respiratory tract infection. However, the differential for non-specific complaints is extensive and thorough review of labs and re-evaluations of patients is important for discovering other potentially medically emergent causes of symptoms including TTP.

Case Presentation:

A 54-year-old female presented to the emergency department (ED) with complaints of mild shortness of breath with associated cough, lower chest discomfort, fatigue, and weakness. She had been evaluated by her primary care physician three days prior with the onset of HER symptoms and was diagnosed with a upper respiratory tract infection and was given supportive care. The patient tested negative for influenza and covid at the time. She presented three days following the onset of symptoms with no additional complaints denying fever, chills, nausea, vomiting, arthralgias, rash, hemoptysis, hematemesis, hematochezia or hematuria.
She was alert and oriented to time, place and person with her usual baseline mental status according to her adult son who presented with her. Her medical history was significant for Still's Disease which had been in remission for several years. She was not taking any medications. The patient noted that she had recently returned from a vacation in Paris and had contracted shingles soon thereafter. The symptoms resolved and the patient denied experiencing associated rash or hyperesthesia on presentation. She otherwise denied history of cancer or surgeries including transplants.

The patient's vitals on presentation were as follows: heart rate 83 beats per minute, respiratory rate of 18 breaths per minute, blood pressure 130/82 mmHg, and temperature of 98.1°F. Physical examination was largely unremarkable as lungs were clear to auscultation without wheezing, rales or rhonchi and without dullness to percussion. No murmurs were appreciated on auscultation of the heart. Petechial rashes were noted on the bilateral breasts on physical examination.

EKG returned with normal sinus rhythm with a rate of 72 BPM, PR 172 ms, QRS 90 ms, QTc 359 ms and normal axis and no ST segment changes. Labs that were initially obtained included CBC and BMP with troponin, COVID-19, and Influenza A/B added given her complaints of chest pain with dyspnea. However, while the labs were pending she had an acute episode of altered mental status with neurologic evaluation which was significant for orientation to self only, mild facial asymmetry, mild aphasia and dysarthria thereby giving her a National Institutes of Health Stroke Scale (NIHSS) of 4. A stroke alert was called within 10 minutes of symptom onset and head computed tomography (CT) as well computed tomography angiography (CTA) imaging was obtained which did not show acute abnormalities including intraparenchymal hemorrhage or large vessel occlusion.

The patient returned to baseline mental status and had resolution of neurologic deficits (NIHSS 0) before the decision to begin thrombolytic therapy was made. Laboratory results showed a hemoglobin of 8.0 g/dL (baseline 12.0 g/dL) with a MCV of 82.7 fL and the platelet count of 10 B/L. The peripheral blood smear was significant for schistocytes along with multiple other abnormal cells. Renal function is at baseline from results 5 years prior with a BUN of 25 mg/dL, creatinine of 1.12 mg/dL, and eGFR of 58. A LDH and INR was subsequently ordered which returned with a value of 1,262 IU/L and 1.15, respectively. The Patient had a troponin of 94 ng/L and once again tested negative for Influenza A and B and COVID-19. Given these new findings, CT scans of the chest, abdomen and pelvis were also obtained which did not show acute abnormalities including hemorrhage.

(References available on request)

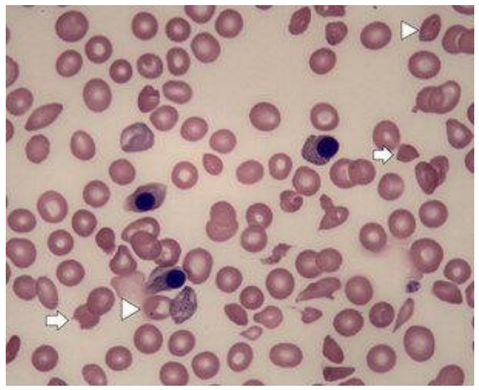

Figure 1: Typical smear of TTP with schistocytes (arrows) and lack of platelets. Howell-Jolly bodies (arrowheads) are also noted.

Case Presentation (Continued):

The PLASMIC score (Platelet count; Combined hemoLysis; absence of Active cancer; absence of Stem-cell or solid-organ transplant; MCV; INR; Creatinine) was found to be 6 placing the patient in the high-risk group for TTP with a 72% risk of severe ADAMSTS13 deficiency. Hematology was consulted who analyzed the blood smears and given shared concerns of TTP, the patient was subsequently admitted to the ICU with recommendations for plasmapheresis and further management. The dialysis catheter procedure was cancelled in the ICU as the patient had sudden onset back pain, had another episode of altered mental status and soon after went into ventricular fibrillation arrest. Unfortunately, the patient did not survive despite advanced cardiac life support (ACLS) measures and it is believed that the patient had an acute dissection of the aorta as there was new onset widened mediastinum on chest X-ray in the ICU.

Discussion:

The patient presented with nonspecific complaints including shortness of breath with cough and bilateral lower chest pain with an acute and transient episode of neurologic deficits during ED course. She was found to have TTP.

Incidence of TTP:
TTP is a rare and often fatal condition with an incidence of TTP of approximately 1 in 1,000,000 in children and 3 in 1,000,000 in adults. [1] Mortality rate estimated to be 10-20%. [2] The autoimmune etiology is apparent in the increased occurrence of other autoimmune conditions with analysis of the Oklahoma TTP Registry (1995-2019) significant for 14 of the 69 children with TTP having an additional autoimmune disorder. [3] Clinical presentation varies widely but relates to the underlying disease process of immune mediated response against ADAMTS13. In line with other autoimmune conditions, TTP appears to be more common in females and immune TTP is very rare in children under 9 years of age. [3]

Pathophysiology:
The pathophysiology of TTP, hereditary or acquired, is thought to be due to reduced activity of ADAMTS13. ADAMTS13 is a plasma protease that functions to cleave large fragments of von Willebrand Factor (VWF) which otherwise remains as extremely long molecules the made up of many multimers known as ultralarge VWF (ULVWF). [4] Cleavage of VWF by ADAMTS13 into smaller fragments prevents accumulation of ULVWF, particularly in areas of high shear stress such as capillaries and arterioles. Absence of ADAMTS13 protease activity results in attachment of platelets to the large fragments of VWF and promotes microvascular thrombosis. Roughly 95% of cases of TTP are immune mediated and due to inhibitory autoantibodies against ADAMTS13.[5]

Discussion (Continued):

Presentation of Thrombotic Thrombocytopenic Purpura:
TTP is commonly taught in medical school using a mnemonic that lists fever, anemia, thrombocytopenia, renal dysfunction, and neurologic symptoms in succession. Of note however is that TTP is unique among primary thrombotic microangiopathy syndromes for rarely causing severe acute kidney injury. [6] Clinical presentation can be widely variable and nuanced as presentation is tied to the underlying pathophysiology of ADAMTS13 deficiency with MAHA and thrombocytopenia as a result in a previously healthy individual. As such, symptoms can be gradual or sudden in onset, with minimal symptoms or with patients presenting critically ill. [7] Weakness, gastrointestinal symptoms, purpura and transient focal neurologic abnormalities are common, however, one third of patients present without neurologic abnormalities. [6] When neurologic abnormalities are present symptoms may mimic stroke [8] and may prompt imaging to rule-out ischemic or hemorrhagic causes of neurologic findings. A third to half of patients with TTP have recurrence of symptoms over a period of months to years. [5]
TTP is a clinical diagnosis [5] and diagnosis in the clinical setting is made using the PLASMIC Score. The PLASMIC Score predicts the pretest probability of TTP by taking into account seven parameters: platelet count, hemolysis (reticulocyte count >2.5, undetectable haptoglobin, indirect bilirubin >2 mg/dL), no active cancer, no solid organ or stem cell transplant, MCV < 90 fL, INR < 1.5, Creatinine < 2.0 mg/dL. Schistocytes are a pre-requisite for use of the PLASMIC Score. One point is given for each of the features and a higher cumulative score indicates a greater likelihood of TTP with ≥6 indicating high probability of TTP, 5 points intermediate probability, 0-4 points indicating low probability of TTP. [9,10,11]

Laboratory studies:
As mentioned, schistocytes indicating hemolysis is a prerequisite for the diagnosis of TTP. Final diagnosis of TTP is made using ADAMTS13 assay with severe ADAMTS13 deficiency (<10 percent activity) confirming the diagnosis of TTP. Other laboratory studies are CBC with platelet count, peripheral blood smear, serum chemistry, serum lactate dehydrogenase (LDH), serum bilirubin level, serum haptoglobin level, coagulation testing (pT, aPTT, fibrinogen, D-dimer), direct antiglobulin test.

Imaging:
Neuroimaging studies in the setting of TTP may be done in the context of focal neurologic deficits. Lesions seen on brain CT or MRI can include reversible cerebral lesions with MRI features of posterior reversible leukoencephalopathy syndrome (PRES), infarcts or hematomas. [12] Retrospective analysis of 47 patients with acute TTP and neuroradiologic studies found that 10 patients (25%) of those that had head CT had acute changes seen on imaging with PRES being the most common with 48% of those patients with acute changes showing evidence of PRES. Large infarctions or hemorrhages were infrequent. [13]

Management:
The PLASMIC score was developed to identify patients most likely to have a thrombotic microangiopathy due to immune TTP and therefore benefit from plasma exchange [9,14,15] and treatment is initiated based on a presumptive diagnosis if patients have a PLASMIC Score of 5-7 (intermediate-high risk) until ADAMTS13 assay is available. Plasma exchange is used all patients thought to have TTP as TTP typically progresses from to neurologic deterioration to cardiac ischemia, renal failure and death. [16] In addition to plasma exchange, glucocorticoids either prednisone or methylprednisone are indicated in patients high PLASMIC Scores. Other potential therapies that should be made in conjunction with other specialists are Rituximab and Caplacizumab.

Conclusions:

Thrombotic thrombocytopenic purpura is a hematologic emergency with a high mortality rate, especially without recognition and treatment. This was a case of a 54-year-old female who presented with TTP who presented with nonspecific complaints. The case highlights that patients with TTP may initially present well-appearing clinically but with an underlying severely acute disease process evidenced by her rapid decompensation while in the ICU.