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Case Report

Atypical Presentation of Thrombotic Thrombocytopenic Purpura in a Patient with Elevated Troponin Level in an Emergency Room and Critical Care Unit Setting

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Abstract

The following case report follows a 56-year-old male who presented to the emergency room complaining of chest pain, sweating, headache, and nausea. Initially, the patient was given a working diagnosis of non-ST-elevation myocardial infarction. However, further observation, lab studies, and specialty consultations contributed to a final diagnosis of thrombotic thrombocytopenic purpura. This report discusses the atypical presentation of thrombotic thrombocytopenic purpura, its differential diagnosis, and the critical management thereof, in order to promptly recognize and treat this life-threatening condition. In particular, this report highlights the following: 1) an elevated troponin level is not always indicative of myocardial infarction; 2) the ADAMTS-13 test cannot be relied upon immediately as it takes time (days or longer) to receive this lab result; 3) TMA is an umbrella term including TTP, HUS, and DIC, and must be differentially diagnosed; and 4) a peripheral smear exposing the presence of schistocytes can be decisive in confirming the diagnosis of thrombotic thrombocytopenic purpura.

Keywords: *ADAMTS13; Thrombotic Microangiopathy; Plasmapheresis; Schistocytes; Thrombotic Thrombocytopenic Purpura; Troponin*

Abbreviations

AIHA: Autoimmune Hemolytic Anemia; Ddx: Differential Diagnosis; DIC: Disseminated Intravascular Coagulation; ER: Emergency Room; HUS: Hemolytic Uremic Syndrome; ICU: Intensive Care Unit; MAHA: Microangiopathic Hemolytic Anemia; NSTEMI: Non-ST-elevation Myocardial Infarction; TMA: Thrombotic Microangiopathy; TTP: Thrombotic Thrombocytopenic Purpura; ROS: Review of Systems; vWF: von Willebrand factor

Background

Accurate and prompt diagnosis of thrombotic microangiopathy (TMA) in an emergency room (ER) or intensive care unit (ICU) is challenging. TMA can involve multiple organ systems, and comorbid conditions can impede an accurate diagnosis [1]. The following case

report describes a patient, who upon arrival to the ER, reported severe chest pain associated with diaphoresis, headache, and nausea. The EKG showed a non-ST elevation; mild troponin elevation was noted. The patient was diagnosed initially with non-ST-elevation myocardial infarction (NSTEMI) and treated accordingly. Establishing a differential diagnosis between a microvascular occlusive disorder and acute coronary syndrome was crucial in reducing further clinical complications and preventing patient death.

Case Presentation

We report on a 56-year-old male who presented to the ER complaining of chest pain, nausea, and headache. On physical examination, the patient described his chest pain as 7/10 in intensity and radiating into his left shoulder, as well as experiencing diaphoresis. Also, the patient reported bleeding the gums upon brushing his teeth, with a duration of about one week. Several small petechiae were observed on the patient's lower extremities. Laboratory data included: platelet count 34, Hb 8.7. After considering the patient's presenting signs and symptoms and laboratory results, differential diagnosis (Ddx) included: acute coronary syndrome or an immunological reaction with concomitant platelet involvement provoking a coronary thrombosis. A peripheral blood smear was ordered, which revealed the presence schistocytes; thus, a final diagnosis of thrombotic microangiopathy (TMA), specifically thrombotic thrombocytopenic purpura (TTP) was determined. In this condition, platelets initially caused coronary thrombosis and intermittent coronary ischemia. ADAMTS13 is a sensitive and specific biomarker for the diagnosis of TTP; however, it takes several days or longer to obtain the results. Therefore, the patient received plasma exchanged empirically while the ADAMTS-13 test was undertaken at the laboratory. After the patient received plasmapheresis, his platelet count returned to normal levels.

Review of systems

Positive: SOB on exertion, general weakness, mild headache, gingival bleeding upon brushing teeth.

Negative: Chills, fatigue, fever, diarrhea, nausea, vomit, fever, cough, sputum, recent travel, sick contact, blood in the urine, blood in the stool.

Initial evaluation

The patient was seen in the ER initially. Patient was AAOx3, showed no hepatosplenomegaly, and presented skin petechiae on the lower extremities; platelets were 9000 from 157000 (previous visit).

- Renal function BUN/Cr: 32/2.12 (non-baseline)
- CBC: HB/Hc 8.1/23.9 from 15.3/45.7 (previous visit)
- T.Bilirubin: 1.8
- Peripheral smear: Schistocytosis
- Past medical history: Patient was diagnosed with GERD/gastritis.
- Additional surgical history: Patient denied having any surgeries.
- PSX: Negative
- Family history: Patient denied any family history of blood dyscrasias, cancer, CAD < 40 yrs old, diabetes, and heart disease.
- Social: Patient was a former smoker. He reported that he quit smoking 25 years ago. Also, the patient reported that he drinks a 12-pack (of beer) occasionally on weekends and denies recreational drugs use.
- Medications: Famotidine

Vital signs

- Pulse Ox: 98
- B/P: 136/74

- B/P Mean: 94
- Temp: 36.9
- Pulse: 75
- Respiration: 16
- O_2 Delivery: Room air
- General appearance: Alert, awake, oriented
- HEENT: Anicteric
- Neck: Full range of motion, non-tender, supple/no meningismus
- Cardiovascular: Regular rate and rhythm, normal heart sounds, normal S1/S2
- Respiratory: Aerating well, clear to auscultation
- Abdomen: Non-tender, normal bowel sounds, no mass/organomegaly
- Genitourinary: No bladder distention, no flank pain
- Extremities: Moves all, normal capillary refill
- Musculoskeletal: Full range of motion, normal inspection
- Neuro/CNS: Alert, oriented X 3, normal speech, CNII-XII intact
- Skin: Petechiae, lower extremity
- Lymphatics: Axilla normal, inguinal normal, neck normal, no lymphadenopathy
- Psychiatry: Normal affect.

Laboratory results

- Sodium (135 - 145 mmol/L): 139
- Potassium (3.5 - 5.2 mmol/L): 3.4 L
- Chloride (95 - 110 mmol/L): 106
- Carbon Dioxide (19 - 34 mmol/L): 24
- BUN (6 - 22 mg/dl): 32 H
- Creatinine (0.43 - 1.13 mg/dL): 2.12 H
- Est GFR (African Amer): 39
- Est GFR (Non-Af Amer): 32
- Glucose (70 - 110 mg/dL): 138 H
- Calcium (8.4 - 10.2 mg/dl): 8.3 L
- Total Bilirubin (0.1 - 1.2 mg/dL): 1.8 H
- AST (10 - 40 Units/L): 45 H
- ALT (10 - 60 Units/L): 45
- Total Alk Phosphatase (20 - 130 units/L): 79
- POC Troponin I (0.00 - 0.07 ng/mL): 0.19 H
- Troponin I (0.017 - 0.056 ng/mL): 0.362 H
- Total Protein (5.5 - 8.7 g/dL): 7.7
- Albumin (3.2 - 5.0 g/dL): 3.6.

Hematology

- WBC (3.6 - 11.0 10^3/uL): 8.1
- RBC (4.50 - 5.90 10^6/uL): 2.80L
- Hgb (13.0 - 18.0 g/dL): 8.1L
- Hct (40.0 - 52.0 %): 23.9L
- MCV (81.0 - 97.0 mc3): 85.6
- MCH (26.0 - 34.0 pg): 29.1
- MCHC (31.0 - 37.0 gm/dL): 34.0
- RDW (11.5 - 15.0%): 15.1 H
- Plt Count (150 - 400 10^3/uL): 9 *L
- MPV (7.4 - 10.4 fl): 8.5
- Total Counted: 100
- Neutrophils % (36.0 - 66.0%): 62.4
- Seg Neuts % (Manual) (36.0 - 66.0%): 69.0H
- Lymphocytes % (23.0 - 43.0%): 20.9L
- Lymphocytes % (Manual) (23.0 - 43.0%): 18.0L
- Monocytes % (0.0 - 10.0%): 12.5H
- Monocytes % (Manual) (0.0 - 10.0%): 9.0
- Eosinophils % (0.0 - 5.0%): 3.3
- Eosinophils % (Manual) (0.0 - 5.0%): 2.0
- Basophils % (0.0 - 1.0%): 0.9
- Basophils % (Manual) (0.0 - 1.0%): 2.0H
- Absolute Neutrophils (1.6 - 8.2 10^3/uL): 5.1
- Seg Neutrophils # (1.6 - 8.2 10^3/uL): 5.0
- Lymphocytes # (1.1 - 4.7 10^3/uL): 1.7
- Lymphocytes # (Manual) (1.1 - 4.7 10^3/uL): 1.3
- Monocytes # (0.0 - 1.1 10^3/uL): 1.0
- Monocytes # (Manual) (0.0 - 1.1 10^3/uL): 0.6
- Eosinophils # (0.0 - 0.5 10^3/uL): 0.3
- Eosinophils # (Manual) (0.0 - 0.5 10^3/uL): 0.1
- Basophils # (0.0 - 0.4 10^3/uL): 0.1
- Basophils # (Manual) (0.0 - 0.4 10^3/uL): 0.1
- Platelet Estimate (Adequate): DECREASED*
- Platelet Morphology: Normal
- Stomatocytes: 1+
- Schistocytes: 2+

Radiology data

- Chest AP Only: No acute infiltrate.
- CT Brain WO Contrast: No acute intracranial findings.
- US Abdomen: Unremarkable abdominal ultrasound.
- US Doppler Portal Vein: No evidence of portal hypertension.

Active hematological complications

1. Thrombocytopenia with anemia (hemolysis/schistocytes) and acute renal failure. Platelets were reduced at 9K from 157K eleven days prior. Ddx: TTP/HUS (typical vs. atypical), infection (Shiga, *E. coli*, HIV, CMV, *H. pylori*), sepsis, HIT, clonal disease (acute leukemia vs. lymphoma), microangiopathic hemolytic anemia (MAHA), hemophagocytosis syndrome.
2. Hemolytic anemia with schistocytes in the peripheral smear, likely secondary to MAHA from TTP/HUS or complement-mediated thrombotic microangiopathology vs. other hemolytic anemias: autoimmune hemolytic anemia (AIHA), Babesia, H. pylori, B12, drug-induced.
3. Chest Pain: Need to r/o ACS with high risk for platelet-related thrombosis in the possible presence of TTP/HUS.

Treatment plan

- Patient will need urgent plasmapheresis until LDH is normalized.
- Patient will likely be monitored in ICU for initial treatment.
- Nephrologist consulted to initiate urgent plasmapheresis until LDH is normalized.
- STAT Labs: LDH, ADAMTS-13, D-dimer; Fibrinogen, PTT/PT, Haptoglobin, Hepatitis panel, ACE, Beta-2, PNH serology, B12, Homocysteine, Shiga toxin, Stool cx, Campylobacter, CMV serology, Toxoplasmosis, HIV, Mono test, Complement, Leukemia panel, Coombs test.
- Monitor CBC, LDH, coagulation panel.

Discussion

Thrombotic Thrombocytopenic Purpura (TTP) can be identified by its characteristic of forming thrombus in the small blood vessels. It is characterized by blood clotting in all blood vessels throughout the entire body [2-5]. The clot impedes the flow of blood, limiting the distribution of oxygen. Ultimately, TTP results in complications in vital organs, such as the heart and brain. As more platelets are diverted to the clotting process of the thrombus, the number of platelets available to the body becomes critically diminished. Generally, in the case of an injury, the fewer platelets available the longer the time to clot. Peyvandi *et al.* (2016) reported that TTP was first identified in 1924 [6]. However, clinicians and researchers continue to investigate the condition due to its complexity in its diagnosis and treatment. It has been reported that 37,000 people in 10,000,000 have this disorder. Signs of TTP include purple-colored skin, high fever, fatigue, increased breathing rate (tachypnea), stroke, coma, and heart-related signs and symptoms [6]. Specific risk factors, particularly in an ICU setting, have been identified.

The primary cause of TTP is a failure of the ADAMTS13 enzyme involved in blood clotting [2]. The failure of the enzyme leads to hyperactive blood coagulation. Thus, there is a resultant formation of blood clots in the small blood vessels. The formation of blood clots in these vessels is termed, TTP. The clots can limit the free flow of oxygen-rich blood to other organs; hence, serious health problems can occur.

Inherited TTP is caused by a mutation of the ADAMTS13 gene, resulting in a corresponding enzyme failure. The cause of acquired TTP is distinct from inherited TTP. Acquired TTP is not caused by the failure of the ADAMTS13 gene; instead, it results from the body producing

antibodies that block the ADAMTS13 gene from its regular and intended activity.

To better understand the rate at which TTP occurs in clinical settings, particularly in the ICU, a prospective-retrospective study was performed in which 173 patients were admitted to the ICU [2]. The researchers investigated patients who were admitted to the hospital with TTP, or those who contracted the condition while admitted in the ICU. An evaluation of these patients was performed, based on medical histories and laboratory examinations, for five days. Other data gathered included a history of the current illness, drugs being taken, rationale for admission, diagnosis, duration in the ICU, and any comorbidities. A platelet count was performed on the first, third, and fifth day. Patients who stayed longer than five days in the ICU were noted. Some patients were excluded from the study, such as those patients under an extensive blood transfusion program, and any patient who was suspected of having other hemotologic disorders, or had undergone chemotherapy [2]. Data analysis via SPSS revealed that 65 patients out of the 173 patients had TTP, either at the time of admission or during their stay in the ICU. The incidence of TTP stood at 37.75%, with a platelet count of 0.35 and 1.49 lacs/µl. The researchers concluded that platelet count is a valid biomarker in determining the presence of TTP.

Similarly, Kuter *et al.* (2010) undertook a study to investigate the rate of occurrence, risk factors, and incidence of TTP in critically ill patients [7]. The researchers recorded the number of platelets in the bloodstream of the patients who had been admitted with TTP and those who had acquired TTP while in the ICU. The study included 20,696 patients who were classified into 14 distinct categories based on the level of severity. The classification conformed to ICD-9 and ICD-10 conventions. These ICD codes were used to identify comorbidities and illness. Excluded from the study were 79 patients due to a lack of complete patient data. Statistical analysis, through standard deviation, revealed a 13.3% and 7.8% prevalence and incidence, respectively, of TTP, linked to a mortality rate of 14.3% and 24.7%, respectively. An increased mortality rate was noted in patients diagnosed with cancer, digestive disorders, or respiratory conditions. Other factors, such as sex, age, duration hospitalized, platelet count, and liver cirrhosis, contributed significantly to the mortality rate. The research concluded that TTP varied considerably based on the presenting diagnosis at admission.

Diagnosis and differential diagnosis of TTP

Diagnosis of TTP involves medical history, physical examination, and laboratory tests. A hematologist may be consulted to diagnose or rule out TTP. The patient might have fever, palor, petechiae, and tachycardia, among other presentations [8]. However, these observations may not be present in an ICU patient. Diagnostic tests are vital to an accurate diagnosis, which include a platelet count, blood smear, blood count, and bilirubin test. As previously noted, TTP is characterized by fewer platelets; if there is less than the average number per unit volume, there is a high likelihood of TTP [9]. In a typical blood smear, a small amount of blood is drawn from the arm and placed on a slide for viewing under a microscope. A patient's blood will show TTP positive if the red blood cells are torn, broken, or ruptured, usually due to a lack of oxygen in the blood for adequate cell respiration. Also, many cells die due to a lack of nutrients as an energy source. When more blood cells die than is normal, the bilirubin level will increase resulting in a positive bilirubin test, which is indicative of TTP.

TTP is differentially diagnosed from hemolytic uremic syndrome (HUS) and disseminated intravascular coagulation (DIC) [10].

Hemolytic uremic syndrome (HUS)

HUS is linked with Escherichia coli, a Shiga that produces toxins [2]; in this case, generally known as typical HUS. A Shiga-toxin HUS, caused by Escherichia coli, mainly occurs in children below the age of five years. This cause is rare in adults. A Shiga-toxin HUS is associated with diarrhea. After 1-2 days, the diarrhea turns bloody [6]. After 5–7 days, patients are typically diagnosed with hemolytic anemia, and experience renal complications. Such patients may have reduced ADAMTS13 activity due to fewer ADAMTS13 antibodies.

In a research study of twenty-nine children, one child's condition was complicated by an ADAMTS13 deficiency. In another study of 322 adults in Oklahoma, 21 had bloody diarrhea, and some had E. coli; two children had severe ADAMTS13 deficiencies. In a German study conducted during a 2011 outbreak, 33% of the patients had an ADAMTS13 deficiency; E. coli triggered the infection [7]. The study results showed that an infection (E. coli) could lead to an autoimmune reaction against ADAMTS13 antibodies. As such, the Shiga toxin binds with

von Willebrand factor (vWF) domains, adversely affecting its proteolysis in ADAMTS13.

Atypical HUS is a preferred differential diagnosis when renal insufficiency is rampant, and is associated with activation of an alternative pathway. One of the mechanisms involved includes mutations in CFB and C3; another mechanism is faulty regulation caused by mutated CD46, CFI, and CFH [6]. Atypical HUS is rare and accounts for only five percent of all HUS cases.

Disseminated intravascular coagulation (DIC)

DIC involves blood clots blocking small blood vessels. Symptoms include chest pain and pain in the legs, among other symptoms. In DIC, platelets are diverted resulting in severe bleeding. DIC symptoms can resemble those of HUS [7]. Patients with DIC show high D-dimer and fibrinogen levels. DIC can be acute (which progresses rapidly) or chronic.

Treatment of TTP

TTP is typically treated using plasma therapy, steroids, or Rituximab and newer drugs [11]. According to Kuter *et al.* (2010), plasmapheresis remains the primary method to treat TTP [7]. Plasmapheresis is performed daily until symptoms, such as renal failure and abdominal pain, are reduced and platelet count returns to a normal level. Steroids are effective in decreasing inflammation and reducing the activity of the immune system; a higher than standard dose of steroids is recommended, particularly for patients who are new to treatment [8]. Rituximab is an antibody used in conjunction with plasma therapy; however, it is not without side effects, which in some cases can be fatal [11].

Newer drugs have been discovered. N-acetylcysteine (NAC) is one such drug that inhibits platelets from linking with vWF, which promotes clotting). Bortezomib prevents plasma cell depletion; thus, there may be no need to conduct plasma therapy. Caplacizumab is limited to acquired TTP. Caplacizumab is a nanobody that obstructs the interface between ultra-large vWF multimers and platelets [9]. It can be considered an alternative treatment in acquired TTP.

Conclusion

Patients with thrombotic thrombocytopenic purpura typically present with fever, thrombocytopenia, hemolytic anemia, renal dysfunction, and neurologic dysfunction; tachycardia and tachypnea may also be present. Thrombotic thrombocytopenic purpura, a microangiopathic hemolytic anemia, can be congenital or acquired—an absence or decrease of the enzyme ADAMTS13, respectively. Low levels of this enzyme result in the formation of microthrombi, which if left untreated, can result in end-organ ischemia and impairment. The central nervous system and kidneys are most often affected. Accurate and prompt diagnosis of thrombotic thrombocytopenic purpura in an urgent care setting is crucial; without timely and effective treatment, TTP has high mortality. Its diagnosis is challenging as its presentation involves multiple organ systems, and comorbid conditions can impede a timely and accurate diagnosis. Understanding more about the various presentations of TTP and challenges in its diagnosis, through case reports such as the one presented herein, can reduce patient suffering and ultimately save lives. In this case report, the following take-home points regarding TTP should be kept in mind when a patient presents to the ER or ICU:

- An elevated troponin levels is not always indicative of myocardial infarction.
- The ADAMTS-13 test cannot be relied upon immediately, as it takes time (days or longer) to receive this lab result
- TMA is an umbrella term including TTP, HUS, and DIC; each must be differentially diagnosed.
- A peripheral smear exposing the presence of schistocytes can be decisive in confirming the diagnosis of thrombotic thrombocytopenic purpura.

Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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