

THROMBOTIC THROMBOCYTOPENIC PURPURA: A REVIEW OF THE DISEASE ENTITY, ITS CLINICAL AND LABORATORY FEATURES, AND MANAGEMENT STRATEGIES

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Case 1

The patient is a 47-year-old female with a history of coronary artery disease, hypertension, asthma, diabetes and obstructive sleep apnea who presented to an outside hospital with shortness of breath and lethargy. The patient was found to be in diabetic ketoacidosis, which was treated with an insulin drip. She also had a platelet count of $8 \times 10^9/L$ on initial laboratory studies. She was presumed to have immune thrombocytopenic purpura (ITP) and treated with five days of intravenous immunoglobulin (IVIG) without improvement. She was transferred to Thomas Jefferson University Hospital for further management.

Initial vital signs included a temperature of 100.1 degrees Fahrenheit, pulse of 101 beats per minute, respiratory rate of 20 breaths per minute, blood pressure of 107/45 mmHg and oxygen saturation of 100% on room air. On physical exam, she was lethargic and not oriented. She had pupils that were equally round and reactive to light; her extraocular muscles were intact. She had no lymphadenopathy. Her cardiac exam revealed a regular rate and rhythm with no murmurs. She had no crackles in her lung fields. Her abdomen was soft, non-tender, non-distended, with normal bowel sounds. Her extremities demonstrated purpuric lesions throughout, but were non-edematous. Laboratory studies showed a hemoglobin of 6.5 g/dl, white blood cell count of $13.3 \times 10^9/L$, and platelet count of $65 \times 10^9/L$. Her creatinine was 0.9 mg/dL.

As there was a concern for thrombotic thrombocytopenic purpura (TTP), a peripheral blood smear was evaluated and found to have schistocytes. There was also evidence for microangiopathic hemolytic anemia (MAHA) demonstrated by a lactate dehydrogenase (LDH) of 1451 IU/L (normal 100-200 IU/L) and a haptoglobin of 31 mg/dL (normal 16-200 mg/dL). Given the presence of a low grade fever, MAHA, thrombocytopenia, and mental status change, a diagnosis of TTP was presumed.

The patient required intubation for airway protection. An apheresis catheter was placed, and urgent plasmapheresis was started. Her course was complicated by transient low blood pressures which were treated with norepinephrine infusion for two days. Her course was complicated by a spontaneous retroperitoneal hematoma, which accounted for a further decrease in her hemoglobin and required transfusion of packed red blood cells. The patient was also treated for a multifocal pneumonia and clostridium difficile diarrhea. She also had acute renal failure which was thought to be acute tubular necrosis secondary to her transient hypotension rather than the TTP.

The patient received 3 weeks of daily plasmapheresis and high dose intravenous methylprednisolone and then oral prednisone, with monitoring of her LDH and haptoglobin. She

also received one dose of rituximab during her hospital stay. Her ADAMTS13 (an acronym for a disintegrin and metalloproteinase with thrombospondin-1-like domains) activity level was $< 5\%$ (normal more than 67%) and ADAMTS13 inhibitor level was > 8.0 Inhibitor Units (normal ≤ 0.4 Inhibitor Units). On discharge, her LDH was 218 IU/L, hemoglobin 10.4 g/dL, and platelet count $139 \times 10^9/L$.

Case 2

The patient is a 61-year-old female with a history of systemic lupus erythematosus, a transient ischemic attack, and human papilloma virus. Additionally, she had a prior episode of TTP six years ago that presented with symptoms of confusion and purpura. She was treated at that time with plasmapheresis. She presented to an outside hospital with confusion and numbness of the right neck that radiated down the right arm and leg. The patient could speak but could not respond appropriately to questions. She was transferred to Thomas Jefferson University Hospital for further management.

Initial vital signs included a temperature of 99.3 degrees Fahrenheit, pulse of 105 beats per min, respiration of 18 breaths per min, pulse oximetry 98% on room air, and blood pressure 159/85 mmHg. On physical exam, she was alert and oriented to person, place, and time. She had pupils that were equally round and reactive to light; her extraocular muscles were intact. She had no lymphadenopathy. Her cardiac exam had regular rate and rhythm with no murmurs. She had no crackles in her lung fields. Her abdomen was soft, non-tender, non-distended, with normal bowel sounds. Her extremities had no edema, but did have petechiae on the arms and legs. She had recovered sensation and strength of her right side. Laboratory studies showed a hemoglobin of 8 g/dl, white blood cell count of $11.7 \times 10^9/L$, and platelet count of $10 \times 10^9/L$. Her creatinine was 0.9 mg/dL.

A repeat peripheral blood smear confirmed the presence of schistocytes. Her LDH was 961 IU/L with a haptoglobin of less than 6 mg/dl, consistent with MAHA. The diagnosis of TTP was based on her history, as well as low grade fever, mental status change, thrombocytopenia, and hemolytic anemia.

Plasmapheresis was initiated emergently for a total of six daily sessions. She was also started on oral prednisone at 80mg daily, which was tapered after discharge. Her mental status and laboratory values improved with plasmapheresis. Her ADAMTS13 activity level was $< 5\%$ (normal more than 67%) and ADAMTS13 inhibitor level was < 0.4 Inhibitor Units (normal ≤ 0.4 Inhibitor Units). On the day of discharge, the patient's LDH was 174 IU/L, haptoglobin 264 mg/dl, hemoglobin 11.2 g/dL, and platelet count $508 \times 10^9/L$. One month after

discharge, ADAMTS13 activity level had risen to 34%, while the ADAMTS13 inhibitor level continued to be <0.4 Inhibitor Units. The hematologist consulted on this case believed that the patient had a congenital form of TTP demonstrated by an overlap syndrome with low activity levels in the absence of inhibitors.

Discussion

Thrombotic thrombocytopenic purpura (TTP) is a rare condition on the spectrum of disorders termed thrombotic microangiopathies (TMA). It is characterized by the presence of acquired microangiopathic hemolytic anemia (MAHA), thrombocytopenia, fluctuating neurological symptoms, renal dysfunction and fever.¹ TTP can be seen at any age though predominately it presents in the 4th decade of life. It is estimated that the annual incidence of TTP in the United States is 4 to 11 cases per a million individuals. Additionally, the incidence of TTP in women is greater than men by approximately 2 to 2.5 times, and black to non-blacks at approximately 3 to 5 times greater.² Though typical of TTP, the constellation of findings that constitute the classical pentad can also be seen in other TMAs. These include hemolytic uremic syndrome or MAHA associated with other causes including metastatic cancer, organ transplantation, and connective tissue diseases.³ Furthermore, not all features of the pentad need be present to diagnose TTP. Treatment initiation, particularly plasma exchange, can significantly decrease the mortality of the disorder and is often initiated prior to confirming the diagnosis. The purpose of this paper is to raise the index of suspicion for a diagnosis of TTP in cases of thrombocytopenia and to expedite prompt implementation of effective therapy.

Categories of TTP

TTP can be classified into subcategories, namely idiopathic TTP and familial TTP. Idiopathic TTP is the predominant form of TTP. It can be further subdivided into acute TTP (occurring without a known precipitant and once treated typically resolves within 4 weeks and without relapses), and relapsing TTP (wherein episodes of TTP respond to therapy with relapses occurring as early as 4 weeks after therapy). Familial TTP carries a poor prognosis and is usually transmitted via an autosomal recessive pattern of inheritance.¹

Pathophysiology

The hallmark feature of TTP is the presence of microvascular thrombi in arterioles and capillaries throughout the body. These microvascular thrombi consist of platelets with a small amount of fibrin surrounded by proliferative endothelial cells. This contrasts to the typical thrombi noted in HUS which are composed of mostly fibrin with few platelets. In addition, TTP thrombi are more disseminated than those of HUS, and

are found in the heart, pancreas, kidneys, adrenal glands and brain. Conversely, HUS thrombi typically affects the kidneys predominantly.⁴ Other organs including the lungs, skeletal muscles, liver and gastrointestinal tract may be affected by TTP thrombi albeit to a lesser extent and may contribute to the constellation of symptoms that an individual patient may express. The hemolytic anemia seen in TTP results from alterations in microcirculation, in addition to the passage of red blood cells through partially occluded vessels. The peripheral destruction of platelets and their aggregation into microthrombi, as well as disruption of circulating red blood cells, leads to the presence of schistocytes and the paucity of platelets characteristic of the blood smear in TTP.

Von Willebrand factor and ADAMTS13

Von Willebrand factor (vWF) is found in the platelet rich thrombi of TTP patients. It is a large, multimeric plasma glycoprotein that mediates platelet adhesion and subsequent thrombus formation at areas of vascular damage. It is synthesized in the endothelium and megakaryocytes and secreted into plasma as large multimers or “strings”. These multimers are subsequently cleaved by a metalloproteinase enzyme to prevent their entrance into or persistence in plasma. This metalloproteinase is called ADAMTS13. Once cleaved, the adhesion of platelets to monomers of vWF does not occur in the absence of vascular damage. In patients with a deficiency of ADAMTS13 or impaired activity of this enzyme, these large multimers of vWF are not cleaved. In this form, they may act as the nidus for platelet aggregation and subsequent thrombi formation. In patients with familial thrombotic thrombocytopenic purpura, unusually large multimers of vWF can be found in the plasma. Their plasma ADAMTS 13 activity is undetectable to barely detectable. For patients with idiopathic TTP, plasma levels of ADAMTS 13 are barely detectable during the episode but normalize following recovery.⁵

Remuzzi et al. showed that during the acute phase of TTP a complete deficiency of ADAMTS13 activity had a sensitivity of 92% and a specificity of 44%. For patients in remission, complete deficiency of ADAMTS13 activity had a sensitivity of 41% and a specificity of 82% for diagnosis of TTP. In patients with antibodies against ADAMTS13, the specificity of diagnosing TTP was 100%.⁷ Further studies have shown that survivors of an acute episode of acquired TTP with severely reduced levels of ADAMTS13 or with anti-ADAMTS13 antibodies during remission have an approximately three-fold greater likelihood of developing another episode of TTP than patients with higher protease activity and no antibody.⁶

Whether ADAMTS13 deficiency is the sole cause of TTP is uncertain. Studies evaluating the role of ADAMTS13 deficiency in the presence of multimeric vWF imply that other factors may play a role in the pathogenesis of TTP.⁷

Risk Factors

Apart from an inherited or acquired deficiency of ADAMTS13, other factors have been shown to be related to TTP exacerbations or acute episodes. These include pregnancy, HIV infection, and obesity.³ In addition, the use of several medications has been associated with TTP. These include antiplatelet agents (ticlopidine, clopidogrel), antineoplastic agents (mitomycin, cyclosporine and quinine), cocaine, as well as other drugs including antibiotics and statins.⁸

Clinical/Laboratory Manifestations

Of the classic pentad, hemolytic anemia, thrombocytopenia, and neurologic symptoms are most frequently identified and are found in 74% of patients. Conversely, fever and renal involvement are identified in 40% of patients.³ The multitude of organ systems involved leads to varied symptomatology.

Hematologic

Thrombocytopenia

Platelet counts on average can be $25 \times 10^9/L$, with approximately 55% of patients having a platelet count of less than $20 \times 10^9/L$. Peripheral platelet destruction or utilization can be the cause of thrombocytopenia.¹ Low platelets lead to the purpuric lesions, gingival bleeding, retinal hemorrhages, mucosal bleeding, and petechial hemorrhages.

Hemolytic anemia

Hemoglobin levels are usually greater than 10 g/dL, revealing a moderate anemia. Hemolytic anemia is suggested by a negative direct antiglobulin test (Coomb's test). Other findings of hemolytic anemia include increased reticulocytes, LDH, indirect bilirubinemia, and decreased or absent haptoglobin levels. In addition, schistocytes on the peripheral blood smear are characteristic in patients with TTP. Presence of schistocytes in the peripheral blood of TTP patients varies from 0% to 18% of red blood cells.³

Neurologic

Neurologic findings are the most common symptom and are identified in up to 75% of TTP cases. These can include confusion, headache, altered mental status, focal loss of motor or sensory functions, convulsions, stupor, and coma. Typically, neurological symptoms are transient and attributed to formation and dissolution of microthrombi in cerebral circulation. Because of their fleeting nature, the effects of TTP thrombi on cerebral circulation may be misdiagnosed as transient ischemic attacks.³

Renal failure

Renal involvement is a predominant feature in HUS, but found in variable degrees in TTP. Proteinuria and hematuria are the cardinal features.¹⁰ Elevations of creatinine and serum BUN are milder on average when compared to HUS cases. However, acute severe TTP cases may present with a higher degree of renal involvement compared to mild or relapsing cases. For these patients, markedly elevated serum BUN on admission may indicate a poor prognosis.¹¹

Other Manifestations

Fever, though a part of the pentad, is not frequently found in TTP episodes. High fevers should alert the clinician of a possible infectious etiology.⁸

Gastrointestinal. Microthrombotic lesions throughout the gastrointestinal tract can result in varying abdominal symptoms; abdominal pain is seen in 11 to 15% of patients. Pancreatitis is also seen as a result of TTP episodes.³

Treatment

The mortality of TTP surpassed 90% prior to the use of plasma therapy.¹⁷ A recent study from Johns Hopkins University revealed as high as a 91% survival benefit when prompt initiation of treatment could be achieved.¹² Additional findings in patients with severe TTP episodes showed that 83% of patients (20 of 24 patients with creatinine ranging from 1.4 to 10.8 mg/dl) had improvement of disease when treated with plasma exchange.¹³

Mainstay of Therapy

Plasma exchange (PE) is the main treatment modality for TTP. Several studies propose its superiority to other modalities including plasma infusion (PI).¹⁴ The theory behind the use of plasma exchange lies in the removal of auto-antibodies against the ADAMTS13 as well as the large vW multimers, while simultaneously supplying missing or deficient plasma constituents, such as the metalloproteinase ADAMTS13. PE should be instituted within 24 hours of presentation, particularly in severely affected patients. If PE is not available, patients should be bridged by PI (at least 25 ml/kg per day).¹⁵ Optimal dosing of plasma exchange is still unknown. Single volume PE, in which patients receive a plasma volume that is the same as their predicted plasma volume, can be initiated at presentation. More intensive exchange regimens can be used in cases of resistant TTP by either increasing PE volumes to 1.5 times the predicted patient's plasma volume or by performing twice daily PE of 1-1.5 plasma volumes. Daily PE should be continued until 2 days after remission; usually defined as normalization of neurological status, normal platelet count ($> 150 \times 10^9/L$), normal LDH values, and an increasing

hemoglobin.¹⁵ Adverse events associated with plasma exchange include systemic infections, allergies or anaphylactoid reactions, pneumothoraces, hemorrhages, catheter associated thrombi, hypoxemia, hypotension, and serum sickness.¹⁶

Ancillary Therapy

Glucocorticoid therapy has been shown to improve mild cases of TTP.¹⁴ Steroids are also used frequently during plasma exchange. Antiplatelet agents have shown no therapeutic advantage over plasma exchange. In addition, the use of antiplatelet agents may be associated with an increased bleeding risk; as a result, their use has largely fallen out of favor.^{14,15}

Though plasma exchange is still the preferred treatment modality for acute and relapsing cases of TTP, there exists a subgroup of patients with impaired response to this therapy. For such patients, other modalities may provide some benefit.

The use of vincristine in TTP predated that of plasma exchange. Recent studies indicate that its use may have therapeutic benefit in patients who are refractory to plasma exchange.¹⁹ Likewise, rituximab has also been shown to be helpful in patients who do not respond to plasma exchange therapy, particularly if a persistent inhibitor is noted.¹⁷ Splenectomy is also used in the management of TTP. Some studies report no therapeutic benefit during the acute episode.¹⁴ However, others have claimed that when performed in remission, splenectomy leads to a decrease in the recurrence rate of TTP in patients with a history of relapse.¹⁸

Summary

TTP is a rare condition, but one that carries a high mortality. Symptoms result from microthrombi affecting microcirculation and can be varied depending on the organs involved. The astute clinician must have a high index of suspicion for TTP in any patient presenting with hemolytic anemia and thrombocytopenia, particularly with concomitant fluctuating neurologic dysfunction. Not all characteristics of the classic pentad need to be present to raise suspicion or initiate therapy. The mainstay of therapy is plasma exchange, which may be used in conjunction with steroids. If plasma exchange is not readily available, plasma infusion can be initiated until plasma exchange is started. Other modalities that may provide therapeutic benefit in cases of relapsing TTP or in patients with slow or partial response to plasma exchange include vincristine and rituximab. Splenectomy done in remission may decrease recurrence in patients with relapsing TTP.

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