REVIEW ARTICLE

# Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome

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ADAMTS13

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Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome is an acute illness with abnormalities in multiple organ systems. Patients typically present with thrombotic microangiopathy, thrombocytopenia, and microangiopathic hemolytic anemia without another apparent cause. Additional features include fever, neurologic, and renal abnormalities depending on the site of microangiopathic damage. Potential causes include congenital deficiencies, Shiga-Toxin producing bacteria, numerous drugs, factors related to malignancy, allogeneic hematopoietic cell transplant, cardiovascular surgery, and pregnancy. A medical emergency, appropriate treatment needs to be initiated promptly or the disease can be fatal. Plasma exchange is the initial treatment of choice, but plasma infusion can be used until plasma exchange is available. Adjunctive treatment with glucocorticoids may be used in certain scenarios. If left untreated, the syndrome typically progressively worsens. Affected individuals experience irreversible renal failure, progressive neurological deterioration, cardiac ischemia, and death. With a prompt recognition of the disease and treatment initiation, patients have a better prognosis and mortality rate.

## INTRODUCTION

Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome (TTP-HUS) is an acute illness with abnormalities in multiple organ systems. Patients typically present with thrombotic microangiopathy, thrombocytopenia, and microangiopathic hemolytic anemia without another apparent cause. Additional features include fever, neurologic, and renal abnormalities depending on the site of microangiopathic damage. Potential causes include congenital deficiencies, Shiga-Toxin producing bacteria, numerous drugs, factors related to malignancy, allogenic hematopoietic cell transplant, cardiovascular surgery, and pregnancy. A medical emergency, appropriate treatment needs to be initiated promptly or the disease can be fatal. Plasma exchange is the initial treatment of choice, but plasma infusion can be used until plasma exchange is available. Adjunctive treatment with glucocorticoids may be used in certain scenarios. If left untreated, the syndrome typically progressively worsens. Affected individuals experience irreversible renal failure, progressive neurological deterioration, cardiac ischemia, and death. With the prompt recognition of the disease and treatment initiation, patients have a better prognosis and mortality rate.[1]

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## CASE:

In August of 2013, a 62-year-old female presented to the hospital emergency department complaining of abdominal pain, nausea, vomiting, diarrhea, and generalized weakness after returning from a trip to the Dominican Republic. Four days after she returned to the United States, she began having non-bloody diarrhea that lasted for three days. The day after diarrhea stopped, she began vomiting up anything she ate or drank, appeared increasingly weak, and felt lightheaded/dizzy. Her vomiting was associated with subjective chills which resolved with each episode of emesis. She denied using any tap water while there and stated that they only used bottled water for drinking and cooking.

On physical examination in the emergency department, she was awake and alert, but appeared very weak and was non-verbal. Tenderness to palpation was noticed in the left lower quadrant of her abdomen. The remainder of her exam was within normal limits. Her labs were significant for a prothrombin time (PT) of 18.4, international normalized ratio (INR) 1.52, blood urea nitrogen (BUN) 20, Creatinine (CR) 2.0, Albumin 2.2, Calcium 6.2, white blood cell count (WBC) 13.53, Hemoglobin 8.4, Hematocrit 25.3, and a manual platelet count of 104. Cerebrospinal Fluid Cultures (CSF) were performed which showed clear colorless fluid with no growth on the gram stain. The CSF glucose was 107, and the CSF protein was 207.9. A CT of the abdomen and pelvis without contrast was ordered which showed colonic diverticula without definitive diverticulitis.

The patient was admitted to the general medical floor, and placed on Ciprofloxacin and Metronidazole for a diagnosis of Diverticulitis.

The following day, labs revealed an increased BUN at 32 and a Creatinine of 3. That evening she had a seizure and was moved to the ICU. Emergent labs drawn at that time showed a BUN of 41, Cr of 4.7, and lactate of 5.9. The following day she had three witnessed tonic-clinic seizures lasting approximately 2-3 minutes each followed by a post-ictal state. An electroencephalogram (EEG) showed a deep focal structural malfunction. Labs drawn the same day showed her BUN/Cr had increased to 44 and 5.7 respectively, and Hemodialysis treatments were started. A hematology consult was placed on hospital day four. After reviewing the patient's medical record and hospital course up to that point, a workup for TTP-HUS was done.

An ADAMTS-13 level was ordered, and found to be abnormal at 63. A blood smear was done and reviewed showing red cell fragments indicating microangiopathic hemolytic anemia and thrombocytopenia. With all these clinical and laboratory findings the diagnosis of TTP-HUS was made. The patient was emergently transferred to a neighboring institution with the ability to perform plasma exchange. Due to the prompt recognition of this patients symptoms, she was able to receive plasma exchange to treat her illness and save her life. While she was left with residual evidence of chronic renal failure, the remainder of her symptoms completely resolved.

TABLE 1:

Laboratory values seen in our patient versus the standard values

| LAB TEST | ILLUSTRATIVE CASE PATIENT | NORMAL VALUE |
|---|---|---|
| White Blood Cell Count | 13.53 | 5.2-12.4 |
| Hemoglobin | 8.4 | 12-16 |
| Hematocrit | 25.3 | F 37-47<br>M 40-54 |
| Blood Urea Nitrogen | 20 | 10-25 mg/dl |
| Creatinine | 2.0 | F 0.5-1.1 mg/dl<br>M 0.7-1.3 mg/dl |
| Albumin | 2.2 | 3.2-4.8 g/L |
| Calcium | 6.2 | 8.6-10 mL/dl |
| Prothrombin Time | 18.4 | 9-11/7 sec |
| International Normalized Ratio | 1.52 | 0.9-1.2 |
| Manual Platelet Count | 104 | 130-400,000 |

## METHODS:

A Google scholar search was completed with the keywords Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome. A total of 7,230 articles were found. This was reduced by only including those articles published since 2010 that specifically covered the topic of TTP-HUS as a whole and not the individual syndromes. A final list of 13 articles were included.

Thrombotic Thrombocytopenic Purpura (- Hemolytic Uremic Syndrome is a multisystem disease defined by a pentad of thrombocytopenia, microangiopathic hemolytic anemia, neurologic defects, renal disease, and fever. Currently only thrombocytopenia and microangiopathic hemolytic anemia are the diagnostic criteria used to make the diagnosis when no other apparent alternate etiology is found. The majority of patients typically present with no identifiable precipitating factor for this illness. As a result, one should have this diagnosis at the top of their differential in the appropriate clinical context with patients presenting with microangiopathic hemolytic anemia and thrombocytopenia with no obvious explanation. It is best to begin treatment if suspicion is high for the illness to avoid a delay that could potentially be very harmful to the patient.[2]

## CLINICAL PRESENTATION:

Thrombotic Thrombocytopenic Purpura is a clinical syndrome that can present to clinicians in a wide variety of settings. The particular case that I referenced presented in a hospital emergency room, but patients with this condition can show up in a primary care office as well if their symptoms are not severe. Thus, if a patient presents with any number of these clinical symptoms one should have this diagnosis in their differential.

TABLE 2:

Etiologies of TTP/HUS

| INFECTION | **Hemorrhagic Colitis due to E.Coli O157:H7,O104:H4 Human Immunodeficiency Virus** |
|---|---|
| Immunosuppressant's | Cyclosporine |
| Autoimmune Disorders | Systemic Lupus Erythematosus |
| Chemotherapeutics | Mitomycin, Cisplatin, Gemcitabine |
| Malignancy | |
| Drugs | Ticlopidine, Clopidogrel, Gemcitabine 3 |
| Pregnancy | Pregnancy and Postpartum Period |
| Idiopathic | |

The clinical symptoms a patient presents with cover a wide range of body systems. Acute hemolytic anemia can lead to fatigue, dyspnea on exertion, skin pallor, and scleral icterus. Thrombocytopenia can lead to thrombocytopenia purpura, epistaxis, bruising, bleeding in the gastrointestinal tract, hematuria, petechiae, and mucosal bleeding depending on the severity. Microvascular ischemia may appear as neurologic, renal, cardiovascular, and gastrointestinal issues, as well as visual disturbances. These in particular are concerning for widespread platelet microaggregate formation, and thus require urgent evaluation and therapy initiation.[4]

From a laboratory standpoint, severe anemia and thrombocytopenia are characteristic of this illness. An elevated reticulocyte count and elevated indirect bilirubin in the absence of serum haptoglobin indicate ongoing intravascular hemolysis. Serum lactate dehydrogenase is often elevated indicating red blood cell destruction and ongoing tissue ischemia. One may also see fragmented red blood cells on peripheral blood smear. This disorder is however not a result of an issue with coagulation or thrombin activation thus the activated partial thromboplastin time (APTT), the thrombin time (PT), and the fibrinogen concentration will all be normal. [4]

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### TABLE 4:

Required diagnostic criteria for TTP/HUS[5]

| THROMBOCYTOPENIA | PLATELET COUNT OFTEN LOWER THAN 20 X 10^9/L |
|---|---|
| Microangiopathic Hemolytic Anemia | Fragmented red blood cells on peripheral blood smear, Reticulocytosis, Decreased haptoglobins, Negative direct coombs test, Increased indirect bilirubin level |
| Fever | >37.5C |
| Neurologic Abnormalities | Transient Focal Abnormalities, Seizures, Stroke, Coma, Headaches, Mental Status Changes |
| Kidney Abnormalities | Renal Insufficiency – any serum creatinine value greater than or equal to 1.5 mg/dL<br><br>Acute Renal Failure – increase in serum creatinine of greater than or equal to 0.5 mg/dL/d for 2 consecutive days or a serum creatinine greater than or equal to 4.0 mg/dL with dialysis |

### TABLE 3:

Presenting clinical characteristics of TTP/HUS[5]

| CHARACTERISTICS | TYPICAL |
|---|---|
| Age | 49 +/- 20 |
| Sex | Female 68% |
| Ethnicity | African-Americans highest rate |
| Neurologic Symptoms | >50% - confusion, headache, paresis, aphasia, dysarthria, visual problems, seizure, stroke, coma |
| Fever | >37.5 Degrees C/99.5 degrees F |
| Hemoglobin | 9.0 +/- 2.1 |
| Platelet Count | Thrombocytopenia - 49,000 +/- 57,000<br>signs: epistaxis, bruising, petechiae, GI bleeding, hematuria, etc. |
| Serum Creatinine | Serum creatinine 3.2 +/- 2.6, proteinuria, microhematuria |
| Comorbid Conditions | Cancer, HIV, Organ Transplant, Sepsis, Hep C, etc. |
| Gastrointestinal Tract | Abdominal pain, nausea, vomiting, diarrhea |
| Cardiac | Chest pain, heart failure, hypotension |
| Jaundice | Typically resulting from microangiopathic hemolytic anemia |
| Other | Weakness, fever, cough, dyspnea |

## DIFFERENTIAL DIAGNOSIS:

There are several clinical conditions that can present very similar to TTP-HUS. These include disseminated malignancy, systemic vasculitis, sepsis, and eclampsia/preeclampsia. In acutely ill patients with symptoms of TTP-HUS such as fever, thrombocytopenia, and multiorgan dysfunction, sepsis with disseminated intravascular coagulation (DIC) must be ruled out. Those with preeclampsia or eclampsia along with seizures, thrombocytopenia, and microangiopathic hemolytic anemia typically have milder hematologic manifestations than those with TTP. One can check a plasma antithrombin III level for assistance in these cases as it will be reduced in those with TTP & normal in patients with pure preeclampsia/eclampsia. Autoimmune hemolytic anemia and immune thrombocytopenic purpura, collectively known as Evans Syndrome, can present like TTP-HUS. However, these patients will have a positive direct Coombs test, a lack of red blood cell fragmentation, and absence of other organ involvement.[4]

## TREATMENT OPTIONS:

Considered a medical emergency, appropriate treatment needs to be initiated promptly or the disease can be fatal. Plasma exchange is the initial treatment of choice, but plasma infusion can be used temporarily until plasma exchange is available. Adjunctive treatment with glucocorticoids can be instituted in certain clinical scenarios as well.

This syndrome constitutes a medical emergency that can prove fatal if treatment is not initiated promptly Plasma exchange is the treatment of choice, as most patients with this form of the disease have decreased ADAMTS13 activity due to an inhibitory antibody. However, the level of ADAMTS13 activity is not required to make the diagnosis, and treatment should be initiated if the presenting clinical signs and symptoms suggest it.[6] The overall goal of treatment is the complete recovery of body function and return to the pre-illness quality of life. The initial primary goal once treatment has begun is the achievement of a normal platelet count. Plasma exchange removes the inhibitory antibody and supplies replacement ADAMTS13 from the donor plasma. Plasma exchange reverses the microvascular thrombus formation and subsequent symptoms characteristic of TTP-HUS. It should be initiated even if the diagnosis is a possibility but not confirmed. The dangers of rapid deterioration from the illness outweigh the risk of initiating plasma exchange. [7] If the diagnosis is eventually excluded, plasma exchange may be discontinued. There are a few exceptions to using plasma exchange. These include HUS in children, those who have had cancer chemotherapy or hematopoietic cell transplantation, and those with pneumococcal infection. [8]

Large volumes of plasma are needed for exchange treatment. Approximately 115 units per treatment course are required in a 60kg individual. Typical products that are used include Fresh Frozen Plasma, Cryoprecipitate-Poor Plasma, and Virally Inactivated Plasma. This procedure is initially performed daily until the patient's platelet count has normalized and hemolysis largely ceased. This is evident by a return of the serum lactate dehydrogenase concentration returning to normal or near-normal levels. Typically, 7-16 daily exchanges are required to endure remission, but this number has ranged from 3-145 treatments in some patients. Once plasma exchange has been instituted, a clinician must decide whether or not corticosteroids are appropriate for their patient. [9]

Those with a severe ADAMTS13 deficiency are the best candidates for this therapy as corticosteroids suppress the autoantibodies inhibiting ADAMTS13 activity. Individuals, where the cause of TTP-HUS is unclear, should also be treated with steroids. Steroids are contraindicated in those who are unlikely to have a severe ADAMTS13 deficiency (patients with severe renal failure), have a history and clinical features suggesting drug-associated TTP, or an *E. Coli* 0157:H7 infection. Clinical criteria are sufficient to use when deciding whether or not initiating steroids is appropriate for your patient.[10]

Once a normal platelet count has been achieved and maintained for 30 days after stopping plasma exchange therapy, the patient is considered to be in clinical remission.[2] Most often the neurologic symptoms and LDH improve in the first 1-3 days of treatment, followed by the platelet count several treatments later. Improvement in renal function is unpredictable, and many patients have a residual impairment and possibly persistent hypertension. In some cases, twice daily plasma exchange is used for patients with refractory or recurrent illness. After stopping plasma exchange, patients need to have complete blood counts and lactate dehydrogenase (LDH) levels monitored frequently. If levels remain stable, monitoring frequency can be decreased. Exacerbations of a continuing episode of illness occur within thirty days of stopping plasma exchange treatment.

Relapses typically occur within the first year but have been seen as late as ten years following discontinuation of treatment. At a minimum, relapse has been defined as a recurrence of the illness after at least 30 days of no treatment and no evidence of the disease. [11] With severe adamst13 deficiency risk of relapse is approximately

TABLE 5:

Key treatments for TTP/HUS

| KEY TREATMENTS | |
|---|---|
| Plasma Exchange Therapy | Standard first course of treatment for all individuals diagnosed with the illness |
| Steroids | Indicated for use in those with ADAMTS13 deficiency & in cases of relapse |
| Rituximab | Indicated for those with an exacerbation (recurrent thrombocytopenia) & in cases of relapse |

40%.[2] All patients should have a platelet count checked immediately when any acute symptoms occur as any could indicate recurrent illness. While relapse is the main concern, many patients are left with a significantly abnormal health-related quality of life. They may suffer from fatigue, neurocognitive issues, deficits of attention, decreased processing speed and memory problems. If left untreated, thrombocytopenia purpura-hemolytic uremic syndrome typically progressively worsens. Affected individuals experience irreversible renal failure, progressive neurological deterioration, cardiac ischemia, and death. With the prompt recognition of the disease and treatment initiation, patients have a much better prognosis and mortality rate. [8]

## ANALYSIS/DISCUSSION

In reviewing some of the most recent literature on this illness, it appears increasingly rare for a patient to present with all the features of TTP-HUS. Fifty years ago, the majority of patients had the classic pentad (thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, renal abnormalities, and fever). Fast forward to 2009, and a review article published in Kidney International. This article made the following statement, "TTP is the diagnostic term used for adults, with or without neurologic or renal abnormalities...HUS is the term used for children who have renal failure..." [12] In 2012, a publication by the American Society of Hematology stated that, "patients may present with only microangiopathic hemolytic anemia and thrombocytopenia, neurologic and renal abnormalities are often not present, fever rarely occurs; the complete "pentad" of these clinical features almost never occurs in current practice." [4] While it has been noted that the morbidity and mortality rate of this disease has vastly improved since the introduction of plasma exchange therapy, it appears we have changed our perspective on how we name this illness based on the age of presentation. This shows just how rare our case is in medicine today.

Our patient initially presented with signs and symptoms of gastrointestinal illness and was given the presumptive diagnosis of diverticulitis. Over the next twenty-four hours, her renal function dramatically worsened, and she began having seizures. It was not until hematology was brought onto the case that TTP-HUS was considered as a diagnosis. Additional tests including a blood smear and ADAMTS-13 level were ordered and thus lead us to the diagnosis of this patient's ailment. Fifty years ago patients walked in the door like they stepped out of the pages of a hematology textbook with the complete pentad of symptoms making the diagnosis simple. Now in present-day medicine, this is a rare occurrence, and we as clinicians must be diligent to consider this in our differential diagnosis even if a patient only presents with one symptom from the textbook pentad.

## SUMMARY/TAKE HOME MESSAGE:

Patients with TTP-HUS benefit from the prompt recognition of their condition, and quick transfer to a facility where plasma exchange can be completed. If left untreated, TTP-HUS typically progressively worsens. Affected individuals experience irreversible renal failure, progressive neurologic deterioration, cardiac ischemia, and death. Due to its rare occurrence, many clinicians do not recognize this syndrome until irreversible damage has been done. A workup for this is warranted in any case that displays these symptoms whether it is just one or all five. The patient's life was saved by the quick recognition of her clinical presentation by an experienced hematologist/oncologist. With the prompt recognition of the disease and treatment initiation, patients have a much better prognosis and mortality rate. This clinical manuscript will ideally help clinicians better recognize this syndrome, and provide patients with the prompt treatment they need. [13]

### AUTHOR DISCLOSURES

No relevant financial affiliations.

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