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# Case Report of a Peculiar Presentation of Hereditary Complement-Mediated Thrombotic Microangiopathy

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**Abstract** Thrombotic microangiopathies (TMAs) are clinical conditions classified by a combination of low platelets causing microthrombi, which can ultimately lead to hemolytic anemia. The most common conditions include thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). In this case report, we focused on a rare subtype of HUS. A 25-year old female presented to our tertiary care facility from a community hospital with nausea, vomiting, and bloody diarrhea after consuming mussels. A presumptive diagnosis of TTP was given and unfortunately treatment efforts did not improve the patient's status. Investigative laboratory studies showed leukocytosis, thrombocytopenia, presence of schistocytes on peripheral smear, and no evidence of hemoglobinuria. The patient had negative Shiga toxin and E.coli 0157 and imaging showed diffuse colitis. Despite antibiotics, dialysis and plasmapheresis efforts, the patient's condition worsened and she developed severe sepsis and was then intubated. At that point, an atypical HUS genetic test result demonstrated a heterozygous missense variant, and she was emergently started on eculizumab and steroids which improved her condition. This case illustrates an atypical presentation for thrombotic microangiopathy, complicated by significant multiorgan dysfunction.

***Keywords:*** *Thrombotic microangiopathy, thrombotic thrombocytopenic purpura (TTP), atypical hemolytic uremic syndrome (aHUS), thrombocytopenia, anemia, microthrombi, Escherichia coli 0157:H7, complement, Eculizumab, plasmapheresis, pregnancy*

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## 1. Introduction

Thrombotic microangiopathies (TMAs) are clinical conditions classified by a combination of low platelets, decreased haptoglobin, and increased lactate dehydrogenase (LDH) levels [1]. With these conditions, there is a broad spectrum of presentations due to microthrombi formation within capillaries and arteries, leading to end-organ dysfunction [1]. The most common TMAs include thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). TTP occurs primarily in adults due to inherited lack of ADAMTS13, a proteolytic enzyme responsible for cleaving von Willebrand factor (vWF) [2]. HUS occurs mainly in children and is secondary to an infection, most commonly due to the Shiga toxin of Escherichia coli 0157:H7 [3]. Many factors contribute to TMA which include: medications (quinine, bevacizumab), auto-immune conditions (systemic lupus erythematosus (SLE), antiphospholipid syndrome, scleroderma), cancer, vasculitis, pregnancy, malignant hypertension, organ transplant, and other metabolic conditions [4].

We focused on a rare subtype of HUS not associated with infections or coexisting disease. The case of atypical hemolytic uremic syndrome (aHUS) is described as a dysregulation of the complement pathway, resulting in overactivation [3]. Most aHUS patients are found to have a genetic mutation in the complement system or an auto-antibody that interferes with the normal complement regulation pathway [4]. Whether hereditary or acquired, aHUS is challenging to diagnose. This is particularly true at the time of presentation as specific markers such as ADAMTS13 and Shiga toxin are not involved in the pathogenesis and are helpful only as exclusion criteria. Furthermore, aHUS may have diverse presentations, such as in the patient we wish to discuss.

## 2. Clinical Presentation

The presented patient is a 25-year old female who was transferred to our tertiary care facility from a community

hospital where she had presented with nausea, vomiting, and bloody diarrhea after eating mussels. A presumptive diagnosis of TTP and acute anuric renal failure (initial creatinine 0.7, rising to 5.2 in 48 hours) were cited as the reason to transfer for emergent hemodialysis and plasmapheresis. However, she did not respond to therapy, and the constellation of laboratory results suggested a more insidious condition. Subsequent labs were significant for leukocytosis (31,000 cells/dL), normocytic anemia (Coombs-negative), and thrombocytopenia (123,000 cells/dL), transaminitis (AST 220, ALT 208, Alk Phos 44), and the aforementioned renal failure. A diagnosis of TTP was abandoned due to poor response to plasmapheresis and an ADAMTS13 activity of 45%. This led to a working diagnosis of Hemolytic Uremic Syndrome.

## 3. Case Investigation

Evaluation for HUS was not initially promising as stool antigens, notably Shiga toxin and E.coli 0157, were negative. Additionally, there were negligible schistocytes on peripheral smear, serum haptoglobin was elevated (134 mg/dL), LDH was elevated (3697u/L), and there was no evidence of hemoglobinuria. Imaging showed diffuse colitis, and the patient developed sepsis. Disseminated intravascular coagulation (DIC) was considered as the patient had markedly elevated D-dimer and INR, with a precipitous decrease in platelet count. Therefore, she was started on antibiotics.

The patient's condition worsened, resulting in acute systolic heart failure with large bilateral pleural effusions. Mentation continued to decline despite dialysis and plasmapheresis. Ultimately, she began having tonic-clonic seizures refractory to antiepileptic therapy, as well as acute respiratory distress and she was subsequently intubated.

At that time, an atypical HUS genetic test result demonstrated a heterozygous missense variant (c.3628C>T) in the complement factor H (CFH) gene - a finding previously reported in multiple individuals with complement-mediated TMA. The patient was emergently started on Eculizumab and steroids. Renal biopsy was consistent with thrombotic microangiopathy. After the third dose of Eculizumab, the patient's altered mental status resolved, and she started producing urine.

## 4. Discussion

This case illustrates an atypical presentation for thrombotic microangiopathy, complicated by significant multiorgan dysfunction. Prompt recognition of this syndrome was challenging. The initial working diagnosis was TTP, but this was quickly abandoned due to lack of response to plasmapheresis and an ADAMTS13 activity of 45%. After a renal biopsy and testing for the CFH gene, she was diagnosed with aHUS and given the appropriate treatment, Eculizumab, and steroids, which improved her presentation.

### 4.1. Epidemiology of Atypical HUS

Atypical HUS is rare and, like HUS, it occurs more frequently in children less than five years of age (Noris 2009; Yan). The incidence in those under 20 years in Europe ranged between 0.23 and 1.9 per million annually (Yan). About 5- 10% of HUS cases are classified as aHUS and aHUS has a poor prognosis, with progression to end-stage renal disease in about 50% and death in about 25% of patients (Noris 2005; Kaplan; Yan; NORD). In childhood, the incidence of aHUS is similar in males and females. However, in adulthood the incidence of aHUS is higher in females than males, possibly because pregnancy is a triggering event. (NORD)

### 4.2. Pathogenesis and Pathophysiology of Atypical HUS

As previously mentioned, aHUS is mainly caused by a dysregulation of the complement pathway, resulting in overactivation [3]. Most aHUS patients are found to have a genetic mutation in the complement system or an autoantibody that interferes with the normal complement regulation pathway [4]. Although gene mutations are implicated in the pathogenesis of aHUS, the development of disease is multifactorial as a trigger such as viral infection, pregnancy, certain medications, etc is required for aHUS to occur [11].

The complement dysregulation in aHUS results in complement deposition on endothelial cells, thickening of arterioles and capillaries, and platelet accumulation on cell surfaces which induce a pro-thrombotic state. The microthrombi formed in the vessels consume platelets and shear red blood cells resulting in thrombocytopenia and hemolytic anemia. While aHUS affects multiple organ systems, microthrombi in the renal vessels is thought to cause the renal impairment seen in aHUS. [11,12]

### 4.3. Diagnosis and Differential Diagnosis of Atypical HUS

Patients with Shiga toxin HUS as well as those with aHUS usually present with i) microangiopathic hemolytic anemia (MAHA) characterized by low hemoglobin, elevated serum lactate dehydrogenase (LDH) level, low serum haptoglobin level, and the presence of schistocytes on a peripheral blood smear, ii) thrombocytopenia and, iii) acute kidney injury (AKI). (10) However, the diagnosis of Shiga toxin HUS is typically based on a history of prodromal diarrhea and confirmed by positive serological tests or microbiological cultures for Shiga toxin-producing *E. coli.* Atypical HUS and idiopathic thrombotic thrombocytopenic purpura (TTP) are considered in the absence of diarrhea, bloody stool or Shiga toxin-producing *E. coli* tests. [10,11]

Since idiopathic TTP, characterized by low ADAMTS-13 activity, can mimic HUS, and the assay takes several days to complete, a blood specimen should be drawn and sent for ADAMTS-13 activity testing when HUS is suspected [10,11]. Normal ADAMTS-13 in the absence of Shiga toxin HUS raised the clinical suspicion for aHUS. Commercially available genetic testing for gene mutations can confirm the presence of aHUS. However, aHUS may still be present in the absence of a specific mutation, as up to 40% of patients may lack them [10]. Additionally, the presence of hypocomplementemia raises concerns for aHUS; however, deficiencies of C3 and C4 are only

present in about 27-44% and 0-7% of aHUS, respectively. [10] The results of the investigations may not be available immediately, and initiation of treatment should not be delayed once there is strong clinical suspicion [10,11].

## 4.4. Treatment

Fresh frozen plasma infusion and plasma exchange (plasmapheresis) is initially used to treat aHUS. In this process, blood from an affected patient is removed, and plasma is separated from the blood cells. Fresh plasma from a donor is used to replace the removed plasma, and the blood is transfused back to the patient. This works to remove autoantibodies from the blood. Plasma exchange is effective for some individuals, and many relapse without long-term maintenance therapy. [5]

Eculizumab, a humanized anti-C5 monoclonal that blocks excessive complement activation in aHUS patients, was approved by the U.S Food and Drug Administration (FDA) in 2011. Eculizumab is now the first-line therapy in both children and adults with aHUS. As was the case in our patient, Eculizumab has been shown to reduce hemolysis and thrombocytopenia and reverse acute kidney injury in aHUS patients. [5,10,11] However, the underlying defect in aHUS patients with diacylglycerol kinase epsilon (DGKE) genes does not involve complement proteins, and the effectiveness of Eculizumab in this sub-group of patients has not been established. In new patients with suspected aHUS, initial treatment with plasma exchange is reasonable while awaiting ADAMTS-13 activity level results. For patients who do not respond to plasma exchange, Ezulizumab may be started while waiting for a confirmation of aHUS [10].

Patients who fail treatment may benefit from renal transplantation. [5,10,11] However, renal transplant in patients with aHUS is controversial because about half of aHUS patients who received renal transplant had a reoccurrence of disease in the transplanted kidney, and graft failure historically occurred in 80 to 90% of those with recurrent disease [5,7]. However, Eculizumab has been reported to prevent and treat the recurrence of post-transplant aHUS effectively. [5]

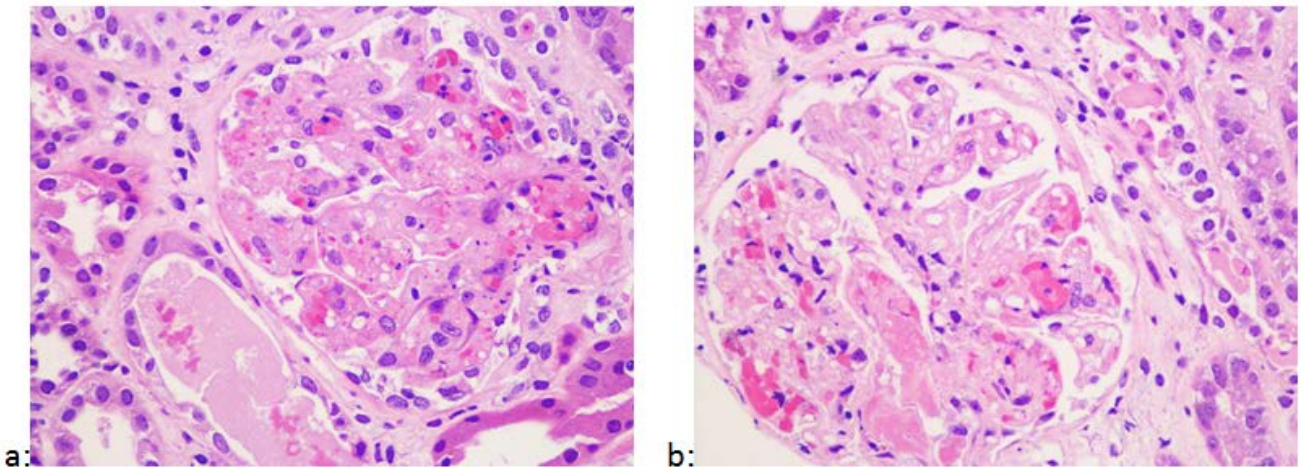


**Figure 1.** Renal biopsy: Fibrin in Afferent Arteriole

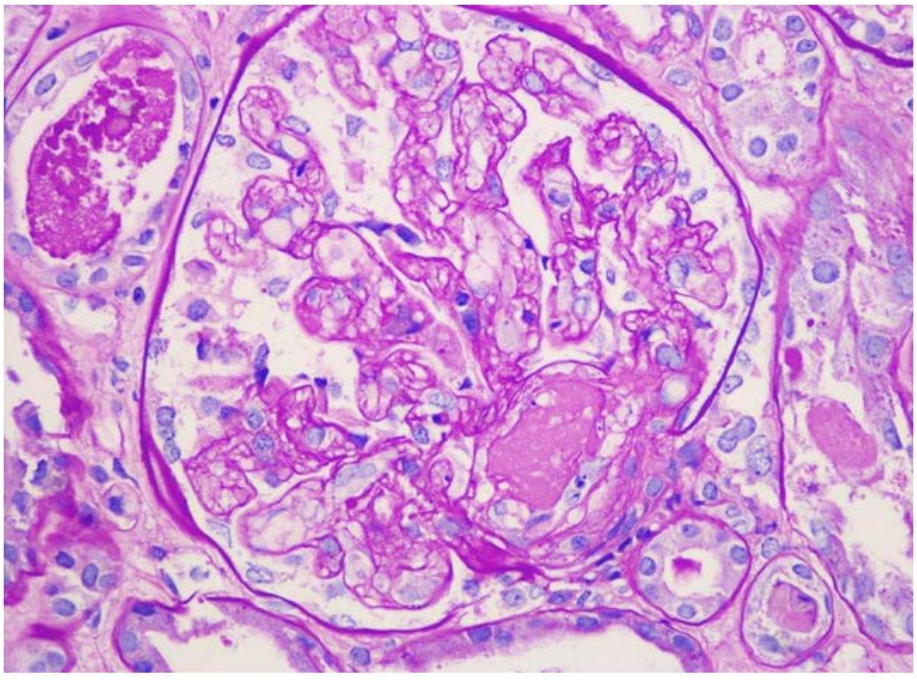

**Figure 2.** Early Crescent Formation

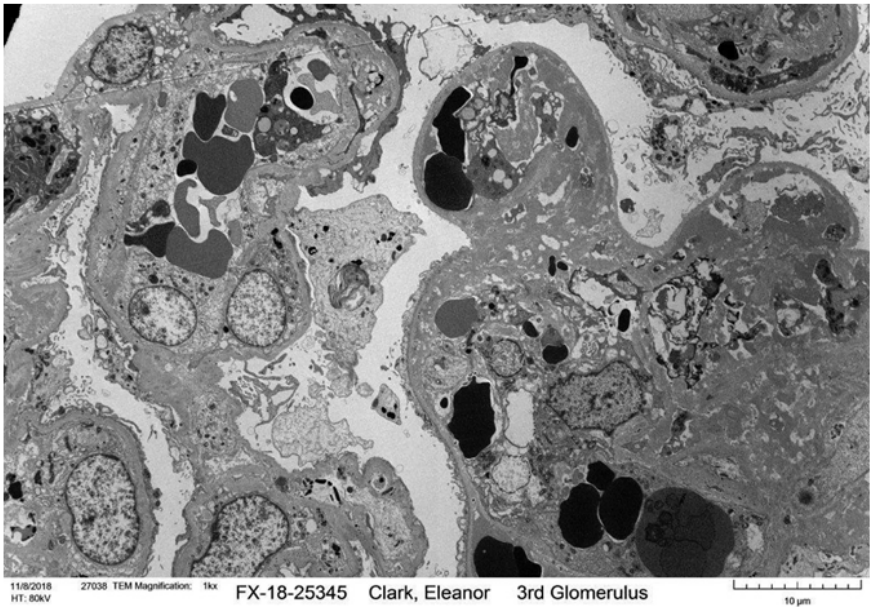


**Figure 3.** Renal Biopsy: Electron Microscopy with Ischemic Necrosis of Glomeruli

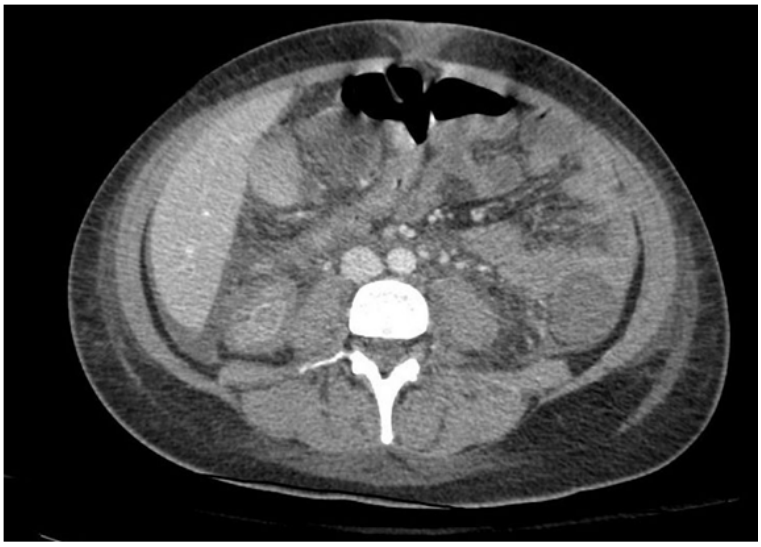

**Figure 4.** C.T. Abdomen/Pelvis with IV contrast showing colonic wall thickening indicative of colitis

## 5. Conclusion

Diagnosis of aHUS can be quite challenging. Diagnosis of aHUS involves ruling out the two most common mimics, HUS and TTP. Additionally, morbidity and mortality associated with untreated aHUS are high, and treatment should commence once there is strong clinical suspicion. Currently, treatment with Eculizumab has shown promise in most cases of aHUS. In more severe cases, affected individuals might be purely dependent on dialysis or they may require a kidney transplant [6]. In conclusion, we report a rare case of atypical HUS with non-specific findings initially thought to be TTP.

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