

# Atypical Hemolytic Uremic Syndrome: When the Environment and Mutations Affect Organ Systems. A Case Report with Review of Literature

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Atypical hemolytic uremic syndrome (aHUS) is a rare thrombotic microangiopathy (TMA) with a genetic predisposition. Like other TMAs, it presents clinically with thrombocytopenia and microangiopathic hemolytic anemia, which is accompanied by disruption of at least one organ system. In general, it is important to distinguish aHUS from other TMAs because of the different prognosis and treatment options. We present a case of a 42-year-old female who presented with abdominal pain, nausea and vomiting. She had hemolytic anemia, thrombocytopenia and acute kidney injury suggestive of TMA. She was started on hemodialysis and plasma exchange and had an extensive workup including ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), which was normal, and complement factor mutations, which showed a complement factor H-related protein mutation. The diagnosis of aHUS was confirmed; plasma exchange was stopped; and she was started on eculizumab, which she tolerated well. However, she was diagnosed with end-stage renal disease and will need long-term renal replacement therapy.

**Key words:** Microangiopathy, hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, ADAMS 13, eculizumab.

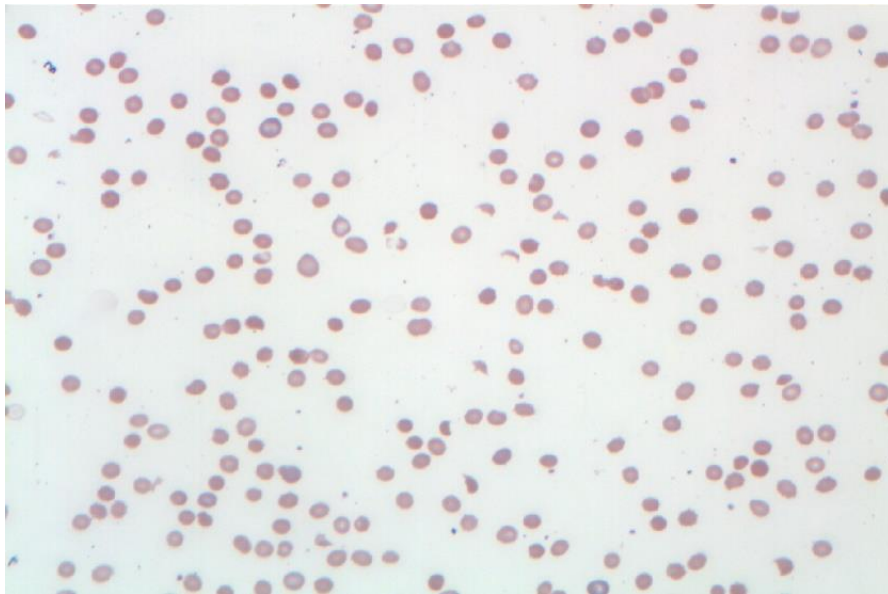
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## Introduction

Thrombotic microangiopathies (TMAs) are a group of disorders characterized by a tendency to develop endothelial cell damage and vascular thrombi resulting in thrombocytopenia and hemolysis (1). Additionally, they are accompanied by disruption of at least 1 organ system (2,3). Atypical hemolytic uremic syndrome (aHUS) is a chronic genetic disorder associated with defective complement control (3-6). Even though a mutation or a genetic predisposition is present at birth, the presentation of aHUS can occur at any age. Environmental events that hyper-activate the alternative complement pathway may be required to cause the overt signs and symptoms (4,7,8). It is important to distinguish aHUS from other TMAs, especially thrombotic thrombocytopenic purpura (TTP), as the treatment and prognosis differ remarkably (8,9). Patients with aHUS are less likely to respond to plasma exchange, and the outcome is poor in those patients treated with plasma exchange alone (2,9). Eculizumab is a recombinant, humanized, monoclonal antibody that binds human C5 and has been described in the treatment of aHUS (9,10).

## Case presentation

A 42-year-old female with a past medical history of benign essential hypertension and depression presented to our institution with lower abdominal pain, nausea, and vomiting. She recalled eating at a fast-food restaurant two weeks prior to the onset of symptoms. Her initial laboratory workup was as follows: white cell count 5,800/cmm (normal 4,000-11,000/cmm), hemoglobin 5.8 g/dL (normal 12-16 g/dL), platelet count 73,000/cmm (normal 150,000-450,000), reticulocyte count 6.2 % (normal 0.5-1.5%), sodium 124 mmol/L (normal 136-144 mmol/L), chloride 88 mmol/L (normal 95-105 mmol/L), potassium 6.1 mmol/L (normal 3.6-5.1 mmol/L), bicarbonate 7 mmol/L (normal 20-24 mmol/L), blood urea nitrogen (BUN) 98 mg/dL (normal 8-14 mg/dL), creatinine 15.12 mg/dL (normal 0.9-1.2 mg/dL), international normalized ratio (INR) 1, lactate dehydrogenase (LDH) 1265 units/L (normal 30-200 units/L), haptoglobin <10 mg/dl (41-165 mg/dl) and lipase 140 units/L (normal 13-60 units/L). Her blood film is shown in Figure 1. Given her acute kidney injury and electrolyte abnormalities, she was started on fluid hydration, and two units of packed red blood cells (PRBCs) were transfused. She was admitted to the intensive care unit for close observation.



**Figure 1.** The peripheral blood smear on presentation showed evidence of microangiopathic hemolytic anemia with multiple schistocytes.

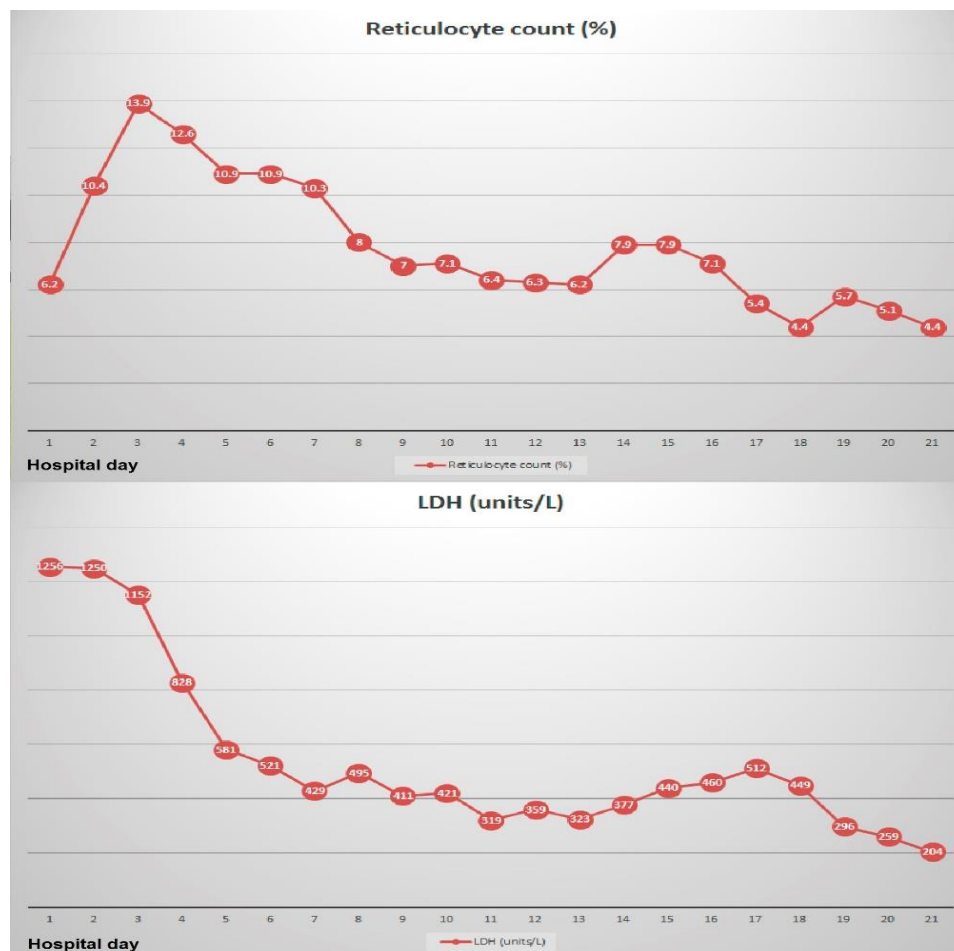
The nephrology team suspected nonsteroidal anti-inflammatory drug-induced nephropathy or HUS. The patient's urine eosinophil test was negative. On day 3 of the patient's hospitalization, the nephrology team recommended the insertion of a dialysis catheter to start hemodialysis (HD) due to uremia, anuria and electrolyte abnormalities. They also recommended performing renal biopsy in case the patient did not improve with HD.

The hematology team thought it was most likely HUS; however, TTP could not be excluded at that time. The patient was started on plasma exchange with daily follow-up on platelet count, hemoglobin, reticulocyte count, lactate dehydrogenase (LDH), haptoglobin, and bilirubin. The

goal of plasma exchange was set to keep the platelet count > 150,000/cmm and the LDH < 300 units/L.

The Shiga toxin test was negative. A renal biopsy was performed on day 6 of the hospitalization and showed both an acute and subacute thrombotic microangiopathy with 60% interstitial fibrosis and tubular atrophy. Eventually, the ADAMTS-13 test (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) showed 76% activity, which excluded primary TTP. At this point, the hematology team suspected aHUS. The plan was to continue plasma exchange until the diagnosis of aHUS could be confirmed.

C3 complement level and complement factor H mutation were ordered. The C3 level was near normal, but it was also inconclusive because mutations occur in only approximately 50% of cases. Once the patient's hemolytic parameters started to improve and stabilize (Figure 2), she was discharged on hospital day 21, and the plan was to continue with HD and plasma exchange three times weekly as an outpatient.



**Figure 2.** The trend of the patient's LDH and reticulocyte count during the hospital stay. Notably, the patient was discharged on day 21 of hospitalization.

The patient's complement factor H mutation testing came back after 6 weeks. The results showed complement factor H-related protein (CFHRs) mutations of unknown significance. Plasma exchange was stopped, and the patient was started on eculizumab. She received the meningococcal conjugate vaccine and ciprofloxacin prophylaxis prior to initiation. She is currently being followed in the hematology clinic and is tolerating the eculizumab treatment well. Her kidney function did not completely improve, and she was diagnosed with end-stage renal disease (ESRD). The patient continues to need HD and may need an arteriovenous fistula in the future.

## Discussion

TMA syndromes are a group of very diverse diseases that share common clinical and pathologic features. These diseases are characterized by a tendency to develop endothelial cell damage and vascular thrombi (1). Clinically, they present with thrombocytopenia, microangiopathic hemolytic anemia and at least one organ system disruption (1-3). Characteristic laboratorial findings include: evidence of intravascular hemolysis with low hemoglobin, high reticulocyte count, low haptoglobin, an elevated LDH, schistocytes on a peripheral blood smear and a negative direct Coombs assay. TMAs may be primary or secondary. The primary TMAs can be hereditary or acquired. The primary hereditary form involves hereditary mutations in the ADAMTS-13, mutations in complement genes (CFH, CFI, CFB, C3, CD46, and other complement genes); mutations in MMACHC (which cause metabolism-mediated TMA); and mutations in the DGKE, PLG and THBD genes (which cause coagulation-mediated TMA). The acquired primary TMA syndromes include autoimmune ADAMTS-13 deficiency (TTP), Shiga toxin-mediated TMA, drug-mediated TMA and complement-mediated TMA. TMAs can be secondary to a manifestation of systemic diseases such as systemic infection, disseminated intravascular coagulation (DIC), malignant hypertension, preeclampsia/eclampsia, HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, and catastrophic anti-phospholipid syndrome (3).

Most HUSs are triggered by a Shiga-like toxin-producing *Escherichia coli*. aHUS is less common. It is a genetic disorder associated with a defective complement control, mainly in the alternative pathway (3-6). Recent data show that 50% of aHUS cases are associated with mutations in genes that encode complement regulatory proteins (5,6).

The presentation of aHUS can occur at any age. This is usually the result of interaction of the genetic mutations that presents at birth with other environmental events that hyper-activate the complement pathway (4,7,8).

It is important to distinguish aHUS from TTP (8,9). This can be done based on ADAMTS-13 activity. TTP is associated with less than 5% activity because of the presence of an anti-ADAMTS-13 inhibitor, usually an IgG autoantibody (2,8,9). Normally, ADAMTS-13 activity is 67% to 100%. The autoantibodies to ADAMTS-13 are usually absent, but, low titers can be found in approximately 4% of the healthy population (7). Shiga toxin and ADAMTS-13 activity are important in the evaluation of any TMA, especially the one that is accompanied by diarrhea (7,8).

Usually, the response to plasma exchange is different between TTP and aHUS (8,9). TTP responds very well to plasma exchange. Its mortality declines from more than 90% to less than 10% with plasma exchange, but the outcome is poor in aHUS patients treated with plasma exchange alone (2). Consequently, plasma exchange should be started as soon as possible for any

new patient presenting TMA, even before the results of the specific laboratory tests come back. The response to plasma exchange in addition to other laboratory tests can be used to distinguish among main different types of TMAs (2).

Eculizumab is a recombinant, humanized, monoclonal immunoglobulin G antibody that is used in the treatment of aHUS (9,10). Eculizumab inhibit the formation of the membrane attack complex by binding human complement 5 and inhibiting the activation of terminal complement components (9).

The prognosis in aHUS is not that favorable (11). Up to 25% may die during the acute phase in the absence of appropriate management (11). Approximately, 50% of aHUS patients may progress to ESRD within a year and recurrence occurs in 60-100% of patients even after kidney transplantation (12).

## Notes

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