# Thrombotic Microangiopathy

## Focus on Atypical Hemolytic Uremic Syndrome

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**KEYWORDS**

• Thrombotic microangiopathy • Atypical hemolytic uremic syndrome
• Hemolytic uremic syndrome • Thrombotic thrombocytopenic purpura

**KEY POINTS**

- Thrombotic microangiopathies (TMA) are a diverse group of diseases with distinct as well as overlapping pathophysiologic mechanisms.
- TMA is a multifactorial disease, and depends on the relative strengths of constitutional predisposition and external triggers.
- Atypical hemolytic uremic syndrome is characterized by dysregulated activity of the alternative pathway of complement for which blockade at C5 is an effective therapy.
- Owing to heterogeneity in pathophysiology, therapy for TMA must be individualized. An individual patient may exhibit multiple mechanisms of disease.

### CASE PRESENTATION

A 31-year-old female presented at 20.2 weeks gestation with fever, dyspnea, acute kidney injury (creatinine, 1.9 mg/dL), dusky painful fingertips, red cell fragmentation, and a platelet count of 7000 cells/mm$^3$. On the second hospital day, she delivered a nonviable fetus. Continuous venovenous hemodialysis was initiated, and laboratory studies were notable for mildly prolonged coagulation times, hypofibrinogenemia, and D-dimer greater than 30 mg/L. A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) activity was 41% (normal, 70%–155%) and complement C3 and C4 were normal. Despite improving with supportive care, she developed seizures on hospital day 10. The C3 was now low at 70 mg/dL (normal, 79–152), and therapeutic plasma exchange (TPE) was initiated. Over the next

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2 weeks, she received daily TPE with recovery of both platelets and renal function, and ADAMTS13 activity normalized. After discontinuation of TPE, however, platelets and renal function worsened, and ADAMTS13 activity fell to 19%. TPE was reinitiated, and rituximab was administered. Renal biopsy obtained 48 days after her presentation revealed focal cortical infarction, congested glomeruli with loss of capillary endothelial cells, mesangiolysis with embedded erythrocyte fragments, and intimal edema with endothelial activation in an interlobular artery. Immunofluorescence was notable for segmental granular mesangial immunoglobulin (Ig)A (sparse 1–2+), IgM (1+), C3 (1+), kappa (1–2+), and lambda (sparse trace – 1+). Segmental capillary wall staining for C3 (1–3+) was present, and electron microscopy revealed subendothelial widening, capillary loop collapse, and endothelial cell swelling with no electron dense deposits. Platelets and renal function normalized after 29 plasma exchanges. Relevant serologic testing for antinuclear antibodies, antiphospholipid antibody syndrome, and human immunodeficiency virus was negative. Nine months after her presentation, genetic testing identified a heterozygous pathogenic mutation in thrombomodulin (*THBD*; c.1456G>T; p.Asp486Tyr), and a previously unreported heterozygous mutation in complement factor H related protein-5 (*CFHR5*; c.1357C>G; p.Pro453Ala) of unknown significance, consistent with a diagnosis of atypical hemolytic uremic syndrome. Two years later she remains in remission with serum creatinine 0.7 mg/dL (estimated glomerular filtration rate, >60 mL/min/1.73 $m^2$), normal urine protein excretion, and normal hematologic parameters.

## CLASSIFICATION OF THROMBOTIC MICROANGIOPATHY

This case demonstrates the complexity of thrombotic microangiopathy (TMA) syndromes and the challenges clinicians face in arriving at a diagnosis and delivering targeted therapy. TMAs are clinical syndromes defined acutely by the presence of fragmented red cells, anemia, thrombocytopenia (<150,000 cells/$mm^3$), and microvascular thrombi, with end-organ dysfunction attributed to small vessel occlusion.[1] Chronic, smoldering TMA, particularly renal limited, may not exhibit significant anemia and thrombocytopenia.[2,3] Clinically, TMA is most commonly represented by thrombotic thrombocytopenic purpura (TTP), enteric infection-associated hemolytic uremic syndrome (HUS), complement-mediated atypical HUS (aHUS), and disseminated intravascular coagulation. Many clinical syndromes, however, are characterized by 1 or more of these features, including this patient in whom disseminated intravascular coagulation secondary to fetal demise was initially considered.

Moschcowitz' 1924 report of a 16-year-old with TTP was followed decades later by Gasser's description of HUS in a group of children following diarrheal illness.[4,5] The link between enteric infection by *Escherichia coli* and HUS was established in the 1980s, and molecular diagnostics have firmly established the role of complement dysregulation in the pathogenesis of aHUS.[6–9] Classification rubrics, however, are challenging, given the large number of conditions associated with TMA, the inconsistent use of terminology, and the recognition of overlapping features in these diseases. Many would agree that TTP is characterized by deficiency of ADAMTS13 (activity classically < 5%–10% in TTP), HUS by the presence of Shiga or Shiga-like toxin producing enteric infection (STEC-HUS), and aHUS by complement-mediated disease with the frequent identification of complement-related mutations. Nonetheless, the list of TMA-associated conditions is long (**Box 1**).

Histologically, TMA may be indistinguishable among the different etiologies, with biopsy findings of endothelial injury and thrombus formation, and in the kidney, both intravascular and intraglomerular fibrin thrombi.[10,11] In the acute phase of aHUS, vessels