Atypical Hemolytic Uremic Syndrome

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KEYWORDS

• Atypical hemolytic uremic syndrome • Thrombotic microangiopathies
• Complement activation • Eculizumab

KEY POINTS

- Atypical hemolytic uremic syndrome is a rare form of thrombotic microangiopathy resulting from chronic uncontrolled activation of the alternative pathway of complement.
- Untreated, it carries a high degree of morbidity and mortality.
- Atypical hemolytic uremic syndrome is associated with nonimmune hemolytic anemia, thrombocytopenia, and renal involvement; it is distinguished from thrombotic thrombocytopenic purpura and Shigatoxin-positive *Escherichia coli* hemolytic uremic syndrome.
- Atypical hemolytic uremic syndrome is a systemic microangiopathy with extrarenal manifestations that involve the heart, brain, lungs, gastrointestinal tract, pancreas, and skin.
- Acquired and genetic abnormalities in the complement regulatory system can be demonstrated in up to 70% of patients with atypical hemolytic uremic syndrome.

INTRODUCTION

The term thrombotic microangiopathy (TMA) refers to a spectrum of disorders characterized by widespread thrombosis of the arterioles and capillaries of the microvasculature affecting multiple organs including the kidneys, brain, heart, lungs, and gastrointestinal tract.[1] The pathologic features are vascular damage manifested by arteriolar occlusion with endothelial cell detachment, widening of the subendothelial space, and the presence of intraluminal fibrin and platelet thrombi (**Fig. 1**).[2] Hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) comprise the primary TMA syndromes, but with different pathophysiology (**Fig. 2**). TMA is also associated with a number of miscellaneous conditions (see **Fig. 2**). The pathophysiology of

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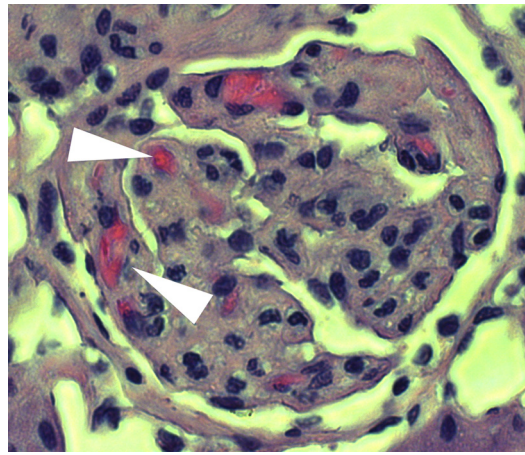

Fig. 1. Thrombotic microangiopathy evident on a renal biopsy from a patient with atypical hemolytic uremic syndrome (aHUS). Note the fibrin thrombi and red blood cell fragments present in the capillary loops (*white arrowheads*). (Hematoxylin and eosin stain, 40× magnification.)

TMA associated with these conditions is less well-understood. HUS is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure. In children, approximately 85% to 90% of cases of HUS are caused by Shigatoxin-positive *Escherichia coli* enteric infection (STEC-HUS).[3] The remaining cases, so-called atypical HUS, are due to genetic or acquired defects of the alternative pathway of

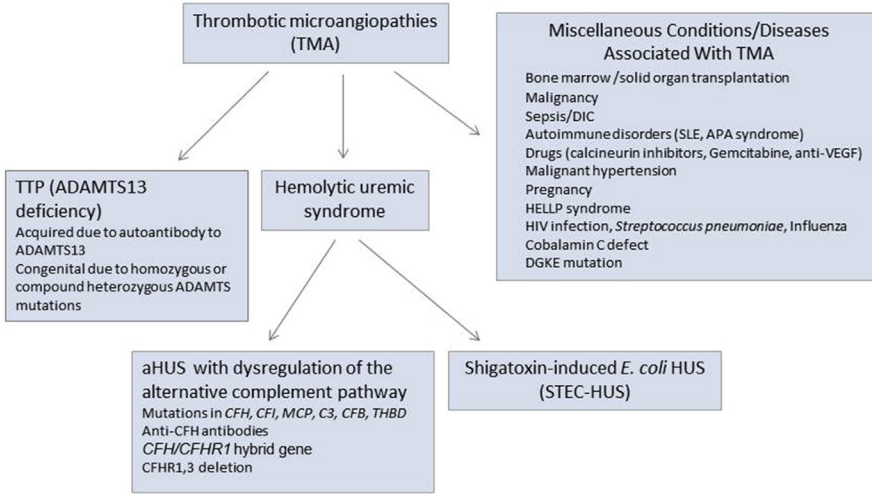

Fig. 2. Classification of the thrombotic microangiopathies based on etiology. ADAMTS13, A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; APA, antiphospholipid antibody syndrome; CFB, complement Factor B; CFH, complement Factor H; CFI, complement Factor I; DGKE, diacylglycerol kinase ε; DIC, disseminated intravascular coagulation; HELLP syndrome, hemolysis, elevated liver enzymes and low platelet count syndrome; HIV, human immunodeficiency virus; HUS, hemolytic uremic syndrome; MCP, Membrane Cofactor Protein (CD46); SLE, systemic lupus erythematosus; STEC, Shiga toxin-producing *Escherichia coli*; THBD, thrombomodulin gene; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura; VEGF, vascular endothelial growth factor.