Thrombotic Thrombocytopenic Purpura and the Atypical Hemolytic Uremic Syndrome

An Update

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KEYWORDS

• Thrombotic thrombocytopenic purpura • Atypical hemolytic uremic syndrome
• Microangiopathic hemolysis • Shear stress • ADAMTS13 • Complement regulators

KEY POINTS

- Both thrombotic thrombocytopenic purpura (TTP) and atypical hemolytic uremic syndrome (aHUS) are chronic diseases that often present with thrombocytopenia and microangiopathic hemolysis (MAHA), yet they have entirely different pathology and pathogenesis and require different therapeutic approaches.
- Patients presenting with thrombocytopenia and MAHA are started on plasma exchange therapy for presumed TTP unless history and laboratory test results clearly indicate that patients have one of the disorders that do not require plasma therapy.
- Plasma exchange is continued for acquired TTP until clinical remission. The treatment may be switched to plasma infusion for hereditary TTP unless the patient has renal failure. Depending on its course, acquired TTP may require rituximab treatment to prevent relapses.
- Plasma exchange is switched to eculizumab for patients without severe ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13) deficiency and considered to have aHUS.
- Both TTP and aHUS are chronic diseases that require long-term monitoring and management.

A major challenge in the management of patients presenting with thrombocytopenia and microangiopathic hemolytic anemia (MAHA) is making a distinction between TTP and aHUS. The discovery of ADAMTS13 and its deficiency in TTP has provided a pathogenetic definition of TTP.[1] Nevertheless, some investigators continue to view aHUS as a subtype of TTP without severe ADAMTS13 deficiency.[2] Under such schemes, aHUS in adult patients is treated indiscriminately from TTP.

In reality, TTP and aHUS not only differ in pathology, pathogenesis, pathophysiology, and prognosis but also require different therapeutic management. The similarity

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Hematol Oncol Clin N Am 27 (2013) 565–584
http://dx.doi.org/10.1016/j.hoc.2013.02.006 **hemonc.theclinics.com**
0889-8588/13/$ – see front matter

between TTP and aHUS in causing thrombocytopenia and microangiopathic hemolysis is an epiphenomenon of microvascular stenosis resulting from entirely different mechanisms.

Fragmentation of the red blood cells occurs in 2 types of clinical conditions: vascular devices, such as prosthetic heart valves, ventricular assist devices, and extracorporeal oxygenator, and microvascular stenosis. These 2 conditions share a common feature of abnormal intravascular shear stress that is sufficient to cause fragmentation of the red blood cells (**Fig. 1**). In the absence of vascular devices, fragmentation of the red blood cells signifies stenosis in the arterioles and capillaries.

Pathologically at least 5 different types of arteriolar stenosis are observed (see **Fig. 1**): (1) von Willebrand factor (VWF) platelet thrombosis, typically observed in patients with TTP due to severe ADAMTS13 deficiency; (2) platelet fibrin thrombosis, as exemplified in patients with disseminated intravascular coagulopathy (DIC); (3) tumor cell invasion of the microvasculature in patients with metastatic neoplasm; (4) microvascular vasculitis complicating autoimmune or certain infectious disorders; and (5) thrombotic microangiopathy, as observed in patients with the typical shiga toxin–associated hemolytic uremic syndrome after certain *Escherichia coli* infection or aHUS due to defective regulation of the alternative complement pathway.

In thrombotic microangiopathy, endothelial changes are prominent. Endothelial cell swelling or disruption, accompanied by intimal expansion and cellular proliferation, may cause microvascular stenosis or occlusion with or without thrombosis. In addition, edema of the brain and other organs and fluid accumulation in cavitary spaces due to abnormal vascular permeability may contribute to organ dysfunction in patients with thrombotic microangiopathy. In TTP, tissue injury results from ischemia of microvascular thrombosis; the endothelium and vessel wall structures are intact and complications of abnormal vascular permeability do not occur.

The various types of microvascular stenosis, in particular types 1 to 4, are often incorrectly referred to as thrombotic microangiopathy without distinction. Furthermore, thrombocytopenia and microangiopathic hemolysis are often equated in practice with thrombotic microangiopathy, ignoring other types of pathology causing microvascular stenosis. Both practices obscure the important differences among the various types of pathology and contribute to the unfounded view of TTP and aHUS as one disease entity.

PATHOGENESIS AND PATHOPHYSIOLOGY OF TTP AND AHUS

The pathogenesis of TTP and aHUS are different. TTP results from severe ADAMTS13 deficiency due to genetic mutations or, more commonly, autoimmune inhibitors,[3] whereas aHUS results from defective regulation of the complement system. Although a recent report describes the activation of the complement system in TTP,[4] presumably by the ADAMTS13-inhibitor complexes, there is no evidence that complement dysregulation contributes to the development of TTP.

ADAMTS13 is a major determinant preventing VWF platelet aggregation in the normal circulation. Inflammation, infection, surgery, or pregnancy may decrease the plasma ADAMTS13 activity level by suppressing the biosynthesis of ADAMTS13 or possibly enhancing its inactivation.[5,6] Although inflammation or pregnancy-mediated decrease in ADAMTS13 per se is insufficient to induce microvascular thrombosis, it may lead to disease exacerbation in patients with preexisting TTP.

In the presence of severe ADAMTS13 deficiency, the propensity of VWF and platelet to form aggregates is affected by multiple other factors, including the platelet count,