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Untying the Knot of Thrombotic Thrombocytopenic Purpura and Atypical Hemolytic Uremic Syndrome

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ABSTRACT

Patients presenting with microangiopathic hemolysis and thrombocytopenia are often given the diagnosis of thrombotic thrombocytopenic purpura and treated with plasma exchange until the acute episode is over. Recent findings have shown that acquired thrombotic thrombocytopenic purpura is a chronic autoimmune disease with inhibitory antibodies of a disintegrin and metalloprotease with thrombospondin repeat, member 13 and are at risk of relapses that may be preventable. Furthermore, many of the patients given the diagnosis of thrombotic thrombocytopenic purpura really have atypical hemolytic uremic syndrome due to defective complement regulation that can be more effectively treated to prevent death and end-stage renal failure with eculizumab, a humanized monoclonal antibody of complement C5. These advances indicate that an accurate differential diagnosis of microangiopathic hemolysis is essential for optimal patient management.

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KEYWORDS: ADAMTS13; Atypical hemolytic uremic syndrome; Complement regulation; Microangiopathic hemolytic anemia; Thrombotic thrombocytopenic purpura

First recognized in the 1970s as a disorder distinct from thrombotic thrombocytopenic purpura and the typical shiga toxin–associated hemolytic uremic syndrome, atypical hemolytic uremic syndrome refers to the constellation of acute renal failure, thrombocytopenia, and microangiopathic hemolysis without antecedent shiga toxin induced hemorrhagic diarrhea. Subsequent studies show that atypical hemolytic uremic syndrome also occurs sporadically and affects adults. The severity of renal failure is variable, ranging from severe, irreversible renal failure to mild reversible azotemia.

Because of its overlap with thrombotic thrombocytopenic purpura in the features of microangiopathic hemolytic anemia and thrombocytopenia, atypical hemolytic uremic syndrome has often been considered merely a variant of thrombotic thrombocytopenic purpura. Consequently, the diagnosis of atypical hemolytic uremic syndrome is unrecognized or viewed as a form of thrombotic thrombocytopenic purpura, and treated as such with plasma exchange. Without a pathogenetic basis, the original view of thrombotic thrombocytopenic purpura and atypical hemolytic uremic syndrome as 2 distinct disorders fell to disfavor and has been held only by a minority of physicians.

Advances in the last 15 years have shown that thrombotic thrombocytopenic purpura and atypical hemolytic uremic syndrome not only differ in pathogenesis but also require different management. The similarity between the 2 disorders in causing thrombocytopenia and microangiopathic hemolysis is an epiphenomenon of microvascular thrombosis. With eculizumab newly approved for the treatment of atypical hemolytic uremic syndrome, it is more critical than ever to distinguish the disease from thrombotic thrombocytopenic purpura.

PATHOGENESIS OF MICROANGIOPATHIC HEMOLYSIS

Fragmentation of the red blood cells occurs in 2 types of clinical conditions that share the common feature of abnor-

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mal intravascular shear stress: vascular devices, such as prosthetic heart valves, ventricular assist devices and extracorporeal oxygenators; and microvascular stenosis (**Figure 1**). In the absence of vascular devices, fragmentation of the red blood cells signifies stenosis in the arterioles and capillaries.

At least 5 different types of arteriolar stenosis are observed to be associated pathologically with microangiopathic hemolysis (**Table 1**): (1) von Willebrand factor–platelet thrombosis, as typically observed in patients with thrombotic thrombocytopenic purpura (**Figure 2A-D**); (2) platelet-fibrin thrombosis, as exemplified in patients with disseminated intravascular coagulopathy; (3) tumor cell invasion of the microvasculature in patients with metastatic neoplasm; (4) microvascular vasculitis complicating autoimmune disorders such as systemic lupus erythematosus or certain infections such as Rocky Mountain spotted fever; and (5) thrombotic microangiopathy, as observed in patients with shiga toxin–associated hemolytic uremic syndrome or atypical hemolytic uremic syndrome (**Figure 2E-H**).

CLINICAL SIGNIFICANCE

- Thrombotic thrombocytopenic purpura and atypical hemolytic uremic syndrome are major disorders causing microangiopathic hemolysis in patients without vascular devices or other diseases.
- Severe ADAMTS13 deficiency defines the diagnosis of thrombotic thrombocytopenic purpura, which is treated with plasma exchange or infusion and rituximab.
- Advanced renal failure, hypertension, or abnormal vascular permeability favor atypical hemolytic uremic syndrome due to complement dysregulation, which is treated with eculizumab.

In thrombotic microangiopathy, endothelial changes such as endothelial cell swelling or disruption, accompanied with intimal expansion and cellular proliferation, are prominent. With or without thrombosis, these changes may cause microvascular stenosis or occlusion. In addition, abnormal vascular permeability may cause interstitial edema of the brain and other organs, as well as fluid accumulation in cavitary spaces, contributing to organ dysfunction in patients with thrombotic microangiopathy. In contrast, in thrombotic thrombocytopenic purpura, organ dysfunction results primarily from ischemia; the endothelium and vessel wall structures are intact, and no abnormal permeability or inflammatory cell infiltration is evident.

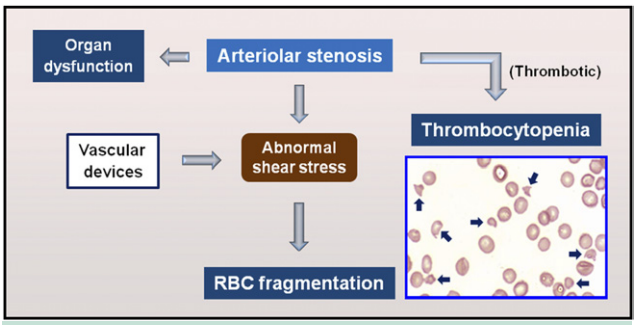

Figure 1 Pathogenesis of microangiopathic hemolytic anemia. Abnormally high levels of shear stress, created by vascular devices (eg, left ventricular assist device, extracorporeal membrane oxygenator, or prosthetic heart valves) or arteriolar stenosis, may lead to fragmentation of the red blood cells. In the absence of vascular devices, microangiopathic hemolysis signifies arteriolar stenosis, which is accompanied by thrombocytopenia if the stenosis is due to thrombosis. RBC = red blood cell.

It has been a common practice to equate the clinical constellation of thrombocytopenia and microangiopathic hemolysis with thrombotic microangiopathy (TMA); and the syndrome of thrombocytopenia, microangiopathic hemolysis and renal failure with thrombotic thrombocytopenic purpura (TTP) or thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS). Either practice obscures the important difference among the various causes of microangiopathic hemolysis.

Two types of molecular mechanisms have been identified to cause idiopathic microangiopathic hemolysis:[1-6] ● Defective regulation of von Willebrand factor activity due to deficiency in a disintegrin and metalloprotease with thrombospondin repeat, member 13 (ADAMTS13), causing von Willebrand factor–platelet aggregation in thrombotic thrombocytopenic purpura; and ● Defective regulation of the complement system due to mutations or autoantibodies of complement activators or regulators, causing thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome.

Whereas ADAMTS13 deficiency is the only known cause of von Willebrand factor–platelet thrombosis in thrombotic thrombocytopenic purpura, thrombotic microangiopathy is not specific for defective complement regulation because it may result from other causes of endothelial injury.

VON WILLEBRAND FACTOR, ADAMTS13, AND THROMBOTIC THROMBOCYTOPENIC PURPURA

von Willebrand factor is a glycoprotein secreted from endothelial cells as a large polymeric form but exists in normal plasma as a series of multimers with progressively smaller sizes. The primary function of von Willebrand factor is to support platelet adhesion at sites of microvascular injury, where it binds to type VI collagen and other components of the exposed vessel wall, becoming rapidly unfolded and activated by the high levels of shear stress at the blood-vessel wall boundary, thereby providing the substrate to support platelet adhesion and aggregation. Thanks to its responsiveness to shear stress, von Willebrand