Is There a Shared Pathophysiology for Thrombotic Thrombocytopenic Purpura and Hemolytic-Uremic Syndrome?

Karl Desch* and David Motto†

Department of Pediatrics, University of Michigan, Life Sciences Institute, Ann Arbor, Michigan; and †Departments of Internal Medicine and Pediatrics, University of Iowa, Iowa City, Iowa

ABSTRACT

Thrombotic microangiopathy is characterized by microvascular thrombosis coupled with thrombocytopenia, hemolytic anemia, and red blood cell fragmentation. Familiar to nephrologists and hematologists alike, classically associated with thrombotic microangiopathy are the hemolytic-uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP), the histories and presentations of which are closely intertwined. Not surprising, these two disorders are considered by many to be manifestations of the same disease process, whereas others consider HUS and TTP to be distinct clinical and pathologic entities. Herein are reviewed HUS and TTP along with recent progress shedding new light on possible shared pathophysiological mechanisms for these two intriguing disorders.


Since its first description in 1925, thrombocytopenic purpura (TTP) has been considered to be a systemic hematologic disease. TTP typically presents abruptly with fever, thrombocytopenia, microangiopathic hemolytic anemia, and varying degrees of neurologic and renal dysfunction, although the clinical picture can be variable. These findings occur secondary to the widespread deposition of platelet-rich thrombi in the microvasculature of various organs, most notably the heart, brain, and kidneys. Historically referred to as “hyaline thrombi,” these lesions are thought to underlie the thrombocytopenic purpura (TMA) findings of thrombocytopenia (secondary to platelet consumption) and microangiopathic hemolytic anemia (resulting from abnormally high levels of shear stress in the microcirculation). Although some degree of renal impairment with proteinuria and/or hematuria is common, hypertension and acute renal failure that requires dialysis are rare in TTP. In a manner not soon forgotten, TTP can progress rapidly with a shock-like clinical picture to coma and death, with untreated mortality >90%. However, even with modern intensive care including plasma exchange (the current standard of care), mortality in recent series is still reported in the 10 to 20% range.

Initially described in 1955 as a syndrome comprising renal failure, hemolytic anemia, and thrombocytopenia, hemolytic-uremic syndrome (HUS) is often considered to be a renal disease with systemic complications. Widespread deposition of microthrombi throughout the kidneys is thought to cause thrombocytopenia and microangiopathic hemolytic anemia in a manner analogous to TTP, although renal damage typically is more severe in HUS and systemic thrombosis may not be as widespread. Nonetheless, neurologic findings are common and, when present, greatly complicate the distinction from TTP.

Although both disorders share a strong clinical and historical relationship, much recent investigation into HUS and TTP has followed independent and seemingly unrelated directions. TTP research has focused on regulation of the blood coagulation protein von Willebrand factor (VWF), whereas much HUS effort has been concentrated on understanding the mechanisms of injury to the renal endothelium.

Considerable recent evidence demonstrates TTP to be a disorder of VWF regulation. VWF synthesized by endothelial cells either is constitutively secreted in the form of low molecular weight multimers or is stored in specialized granules termed Weibel-Palade bodies. In response to vascular injury, stored VWF is released as ultralarge multimers (UL-VWF). However, some UL-VWF remains associated with the endothelial...
surface, providing binding sites for platelets and possibly other blood components such as leukocytes. The presence of UL-VWF may lead to spontaneous platelet aggregation in the circulation or on the endothelial surface if not processed by the metalloprotease ADAMTS13. Lack of UL-VWF cleavage by ADAMTS13 is thought to be the primary defect underlying TTP pathogenesis. Deficiency of ADAMTS13 can be genetic (the rare Upshaw-Schulman syndrome) or more common, acquired, resulting from autoimmune production of inhibitory anti-ADAMTS13 antibodies.

In contrast to TTP, for which efforts have focused on VWF and ADAMTS13, much of the latest work in HUS has been directed toward understanding mechanisms of damage to the renal endothelium. In the case of diarrhea-associated HUS (D+HUS), renal endothelial damage is mediated (at least in large part) by the bacterial agent Shigatoxin (Stx), which is actually a family of toxins elaborated by certain strains of Shigella dysenteriae (in North America principally shiga-toxigenic E. coli [STEC] strain O157:H7). STEC infection localizes to the gastrointestinal mucosa and is followed by release of Stx and its subsequent translocation through the epithelium and into the circulation. Likely bound to neutrophils, Stx then circulates throughout the body but may preferentially localize to the kidney as a result of the high concentration of its receptor, globotriaosylceramide, on the renal endothelium. After receptor-mediated endocytosis, Stx inactivates the 285 ribosomal RNA, shutting down protein synthesis and leading either to cellular necrosis or to apoptosis.

Although the subsequent events are less well understood, it is becoming clear that the mechanisms by which Stx induces the thrombotic state of HUS involve more than the direct toxic effects described. For example, Stx induces expression of proinflammatory genes in endothelial cells and leukocytes, upregulates expression of adhesion molecules, and can directly activate platelets. In addition, after STEC infection, pro-thrombotic coagulation abnormalities that precede clinical evidence of renal damage can be detected. The end result of these and, undoubtedly, other mechanisms is a shift in the hemostatic balance of the renal circulation toward thrombosis and TMA and the subsequent development of renal injury and clinical HUS.

Although approximately 90% of HUS cases result from infection with STEC, much insight into the pathogenesis of HUS has been gained from investigations into diarrhea-negative, or “atypical,” HUS (aHUS), which accounts for approximately 5% of HUS cases. Insight into the pathogenesis of this disorder stemmed from observations that occasional patients demonstrated severely reduced serum levels of complement factor C3, suggesting systemic complement activation. It is now known that approximately 50% of patients with aHUS carry a heterozygous mutation in one of four genes encoding complement factor H, complement factor I, complement factor B, or membrane co-factor protein. These proteins function to control complement activation on cellular surfaces and therefore to limit complement-mediated damage to host tissues. Thus, a decrease in their activity results in the loss of ability to suppress complement activation throughout the body. However, for reasons that are only partially understood, the glomerular endothelium is especially sensitive to loss of complement regulation, and microvascular damage in aHUS principally is restricted to the renal circulation.

Similar to Stx-mediated endothelial damage and the development of TMA, the mechanisms following complement activation that lead to TMA and aHUS are not yet well understood and are the subject of considerable research effort. However, complement activation on the glomerular endothelium likely recruits inflammatory cells, resulting in endothelial injury, platelet aggregation, and activation of the coagulation cascade and the subsequent development of TMA and clinical aHUS.

Most relevant to the distinction of TTP from HUS are cases of aHUS, because D+HUS is predominantly a disease of childhood (or sporadic STEC outbreaks), and patients typically exhibit diarrhea before the onset of renal failure. It is interesting that recent evidence demonstrates that neither deficiency of ADAMTS13 nor deficiency of complement regulation is sufficient for the development of TTP or aHUS, respectively. In each case, disease pathogenesis is thought to involve additional unknown genetic modifying factors and/or environmental triggers. Not surprising, a similar wide range of potential precipitating factors has been reported for both TTP and HUS, including but not limited to infections, pregnancy, malignancy, collagen vascular disease, and various medications.

In addition to similar precipitating factors, several new and intriguing findings indicate that HUS and TTP may also share more of a common mechanistic link than suggested by the independent and seemingly unrelated research directions discussed thus far. Although it has become clear that ADAMTS13 deficiency and UL-VWF play a major role in TTP pathogenesis, their role in HUS was more uncertain. Recently, however, it was demonstrated that nanomolar concentrations of Stx stimulated the release of stored UL-VWF from cultured human endothelial cells and impaired its cleavage by ADAMTS13, revealing additional possible mechanisms of action for Stx in HUS. Subsequently, this finding was extended in vivo, when it was demonstrated that Stx is able to induce a TTP-like syndrome in ADAMTS13-deficient mice, suggesting a role for this toxin (and perhaps other sources of endothelial injury) as potential triggers for TTP.

If Stx can function to stimulate TTP pathogenesis in the setting of ADAMTS13 deficiency, then what about other HUS-related sources of endothelial injury, such as complement dysregulation? It is interesting that a recent report of two sisters with familial ADAMTS13 deficiency and TTP may shed some light on this matter. One of the two siblings experienced a clinical course typical of familial TTP with primarily neurologic disease and re-
mains in relatively good health with plasma therapy. However, the other sibling demonstrated a much more severe course, with progressive renal deterioration and severe neurologic findings that culminated in her death from a cerebrovascular event at age 55. In addition to ADAMTS13 deficiency, this patient was found to have a heterozygous mutation in the complement factor H gene, which, interestingly, did not cause clinical disease in four other siblings. Thus, ADAMTS13 deficiency and complement dysregulation may have combined to produce a more serious phenotype than expected from either alone.

Although requiring additional human and animal studies for confirmation, these new findings provide more support for the intriguing possibility that similar factors may trigger both TTP and HUS and that these two disorders may share some degree of overlapping pathophysiology (Figure 1). It is interesting to speculate that factors affecting ADAMTS13 and VWF activity may function to potentiate the endothelial injury seen in HUS and, conversely, that endothelial injury triggered by factors typically associated with HUS may be prerequisites for the TMA that is thought to result from ADAMTS13 and VWF dysfunction. At a minimum, it seems prudent to extend better the current TTP investigation to include mechanisms of endothelial injury and likewise to expand HUS research to reconsider ADAMTS13 and VWF as potential mediators of endothelial injury leading to TMA. It is likely that future research into these potential common mechanisms of disease will eventually explain the shared clinical findings of TTP and HUS with which we are struggling today.

DISCLOSURES
None.

REFERENCES
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