Table 14-10 Thrombotic Microangiopathies: Causes and Associations

Thrombotic Thrombocytopenic Purpura
Deficiency of ADAMTS13
Inherited Acquired (autoantibodies)
Hemolytic Uremic Syndrome
Typical: *Escherichia coli* strain 0157:H7 infection
Endothelial damage by Shiga-like toxin
Atypical: alternative complement pathway inhibitor deficiencies
(complement factor H, membrane cofactor protein (CD46), or factor I) Inherited Acquired (autoantibodies)
Miscellaneous associations
Drugs (cyclosporine, chemotherapeutic agents) Radiation, bone marrow transplantation Other infections (HIV, pneumococcal sepsis) Conditions associated with autoimmunity (systemic lupus erythematosus, HIV infection, lymphoid neoplasms)

HIV, Human immunodeficiency virus.

Although certain features of the various thrombotic microangiopathies overlap, the triggers for the pathogenic platelet activation are distinctive and provide a more satisfying and clinically relevant way of thinking about these disorders; these are summarized in Table 14-10. **TTP is usually associated with a deficiency in a plasma enzyme called *ADAMTS13***, also designated "vWF metalloprotease." ADAMTS13 normally degrades very high-molecular-weight multimers of von Willebrand factor (vWF). In its absence, these multimers accumulate in plasma and tend to promote platelet activation and aggregation. Superimposition of endothelial cell injury (caused by some other condition) may further promote the formation of platelet microaggregates, thus initiating or exacerbating clinically evident TTP.

The deficiency of ADAMTS13 can be inherited or acquired. In the acquired form, an autoantibody that inhibits the metalloprotease activity of ADAMTS13 is present. Less commonly, patients inherit an inactivating mutation in *ADAMTS13*. In those with hereditary ADAMTS13 deficiency, the onset is often delayed until adolescence and the symptoms are episodic. Thus, factors other than ADAMTS13 (e.g., some superimposed vascular injury or prothrombotic state) must be involved in triggering full-blown TTP.

TTP is an important diagnosis to consider in any patient presenting with thrombocytopenia and microangiopathic hemolytic anemia, because delays in diagnosis can be fatal. With plasma exchange, which removes autoantibodies and provides functional ADAMTS13, TTP (which once was uniformly fatal) can be treated successfully in more than 80% of patients.

In contrast, HUS is associated with normal levels of ADAMTS13 and is initiated by several other distinct defects. "Typical" HUS is strongly associated with infectious gastroenteritis caused by *Escherichia coli* strain O157:H7, which elaborates a Shiga-like toxin. This toxin is absorbed from the inflamed gastrointestinal mucosa into the circulation, where it alters endothelial cell function in some manner that results in platelet activation and aggregation. Children and older adults are at highest risk. Those affected present with bloody diarrhea, and a few days later HUS makes its appearance. With appropriate supportive care complete recovery is possible, but irreversible renal damage and death can occur in more severe cases.

"Atypical" HUS is often associated with defects in complement factor H, membrane cofactor protein (CD46), or factor I, three proteins that normally act to prevent excessive activation of the alternative complement pathway. Deficiencies of these proteins can be caused by inherited defects or acquired inhibitory autoantibodies and are associated with a remitting, relapsing course. Unlike TTP, the basis for the platelet activation in typical and atypical HUS is unclear. Therapeutic antibodies that inhibit the activation of the complement factor C5 are effective in preventing thrombosis in patients with inherited deficiencies of complement regulatory proteins, proving that excessive complement activation underlies the pathogenesis of this form of HUS. Similarly, immunosuppression can be beneficial to patients with inhibitory antibodies against complement regulatory factors. Typical HUS is treated supportively. Patients who survive the acute insult usually recover, but some have permanent renal damage and eventually require dialysis or renal transplantation. The impact of HUS and TTP on the kidneys is discussed further in Chapter 20.

Thrombotic microangiopathies resembling HUS can also be seen following exposures to other agents that damage endothelial cells (e.g., certain drugs and radiation therapy). The prognosis in these settings is guarded, because the HUS is often complicated by chronic, life-threatening conditions.

Bleeding Disorders Related to Defective Platelet Functions

Qualitative defects of platelet function can be inherited or acquired. Several inherited disorders characterized by abnormal platelet function and normal platelet count have been described. A brief discussion of these rare diseases is warranted because they provide excellent models for investigating the molecular mechanisms of platelet function.

Inherited disorders of platelet function can be classified into three pathogenically distinct groups: (1) defects of adhesion, (2) defects of aggregation, and (3) disorders of platelet secretion (release reaction).

- *Bernard-Soulier syndrome* illustrates the consequences of defective adhesion of platelets to subendothelial matrix. Bernard-Soulier syndrome is caused by an inherited deficiency of the platelet membrane glycoprotein complex Ib-IX. This glycoprotein is a receptor for vWF and is essential for normal platelet adhesion to the subendothelial extracellular matrix (Chapter 4). Affected patients have a variable, often severe, bleeding tendency.
- Bleeding due to *defective platelet aggregation* is exemplified by *Glanzmann thrombasthenia,* which is also transmitted as an autosomal recessive trait. Thrombasthenic platelets fail to aggregate in response to adenosine diphosphate (ADP), collagen, epinephrine, or thrombin because of deficiency or dysfunction of glycoprotein IIb-IIIa, an integrin that participates in "bridge formation" between platelets by binding fibrinogen. The associated bleeding tendency is often severe.