Thrombotic Thrombocytopenic Purpura

Another cause of thrombocytopenia resulting from platelet activation and clearance is TTP. In patients with congenital or familial TTP, mutations in the vWF-cleaving protease, ADAMTS-13 (*a*disintegrin *a*nd *m*etalloproteinase with *t*hrombospondin type 1 motif, member 13), abrogate its activity. Patients with acquired TTP usually have an antibody that blocks the normal function of vWF-cleaving protease to less than 10% of normal. Ultralarge vWF multimers released by EC normally anchor to EC through P-selectin and form long strings that adhere and aggregate platelets in the microcirculation. ADAMTS-13 downregulates the size of these multimers by docking to the A1/A3 vWF domains and cleaving within the A2 site. Deficient cleaving protease function in TTP leads to an increase in the larger, highest-molecular-weight vWF multimers, which are most effective in anchoring and activating platelets. These, in turn, cause increased platelet adhesion and clearance *without* activating the coagulation cascade. Therefore, both the prothrombin time (PT) and the PTT are normal in TTP, unlike in DIC.

TTP after chemotherapy (mitomycin C) or in association with pregnancy, stem cell transplantation, lupus, or HIV infection appears to have a similar pathogenic mechanism of thrombosis. Thrombocytopenia (often severe) is accompanied by microangiopathy with schistocytes on smear and increased serum lactate dehydrogenase. Microvascular occlusions in multiple organs cause symptoms, especially in the kidney and brain. The classic pentad (fever, thrombocytopenia, microangiopathic hemolysis, neurologic symptoms, and renal insufficiency) is present in fewer than 25% of patients with TTP. The diagnosis is typically made based on the clinical assessment of thrombocytopenia and microangiopathic hemolytic anemia; assays for ADAMTS-13 activity and inhibitor do not have a rapid turnaround time in most laboratories.

Treatment of familial TTP is based on replenishment of cleaving protease activity with plasma transfusion; acquired TTP additionally requires removal of the antibody. The latter is accomplished by plasma exchange, whereby patient plasma is removed (plasmapheresis) and replaced with fresh-frozen plasma, which often had been made "cryo-poor" to reduce ultralarge vWF multimers in transfused plasma. Steroids and antiplatelet drugs (e.g., aspirin, dipyridamole) are often administered simultaneously, but any added benefit to plasma exchange remains unclear. Platelet transfusions are relatively contraindicated in TTP because of the risk of thrombosis, and they should not be given for thrombocytopenia in the absence of significant bleeding. When plasma exchange fails to remit acquired TTP or when early relapse occurs, immunosuppressive therapy with anti-CD20 may be successful. The mortality rate associated with severe TTP (defined as undetectable ADAMTS-13 activity) is still significant, almost 10% at 18 months after therapy with plasma exchange. Replacement of ADAMTS-13, which is present in fresh-frozen plasma and in cryoprecipitate, is a potential treatment.

The *hemolytic-uremic syndrome* (HUS) is part of the TTP spectrum of disease and also is associated with microvascular platelet thrombi. However, the hemolytic anemia and renal failure of HUS are not usually accompanied by neurologic impairment, and HUS usually does not produce the same degree of thrombocytopenia or microangiopathy as TTP. Moreover, fewer than 3% of HUS cases are associated with decreased vWF-cleaving protease activity. Unlike TTP, HUS is primarily diagnosed in children (and less commonly in adults) who have hemorrhagic colitis caused by Shiga-like, toxin-producing bacteria, especially the *Escherichia coli* O157:H7 serotype. Atypical HUS (i.e., without diarrhea or Shiga-like toxin) is rarely associated with other bacterial infections or with complement dysregulation due to mutations or polymorphisms in factors H, I, and B. These mutations increase platelet activation through complement (C3) deposition on the platelet surface. Atypical HUS cases are those that are clinically consistent with HUS but are not associated with toxin-producing bacteria. Some HUS cases, particularly atypical forms, may respond to plasmapheresis with plasma exchange along with maintenance hemodialysis until renal function recovers. Data increasingly suggest that anti-C5a complement therapy can help prevent the complement-mediated damage associated with this disease.

CLINICAL EVALUATION OF THROMBOSIS

The approach to patients with thromboembolism is defined by the clinical history, results of laboratory studies, and even physical findings. Events that trigger VTE disease include immobilization, orthopedic and other surgical procedures, use of oral contraceptives, and pregnancy. VTE that is recurrent (thrombophilia) may manifest at an early age or at unusual thrombotic sites (e.g., cerebral vessels) and may be accompanied by a family history of VTE suggesting an inherited disorder. Acquired VTE risk may be associated with systemic disorders such as hemolysis (e.g., PNH, autoimmune hemolytic anemia), collagen vascular disorders (e.g., lupus), or various malignant diseases (e.g., adenocarcinoma). In contrast, arterial thromboembolic disease is more commonly superimposed on ruptured atherosclerotic plaque (e.g., coronary artery disease) or on atheroembolic disorders (e.g., ischemic stroke, peripheral arterial disease). Arterial vascular disease is mainly associated with metabolic risk factors including hypertension, hypercholesterolemia, and diabetes. The clinical approach to thrombotic disease is tailored to the location of the disease (arterial versus venous and the specific vascular bed) and whether there are abnormalities of the vascular endothelium, platelets, or soluble coagulation factors that predispose the patient to thromboembolic risk.

Laboratory Diagnostics

Recurrent VTE is a strong indication for laboratory testing for causes of thrombophilia, especially in patients younger than 50 years of age, in those with unexplained VTE, and in those with a family history of VTE. Any risk factors that may predispose these individuals to recurrence must be defined, as well as any inherited disorders that may necessitate family counseling or avoidance of additional environmental risks. The current work-up for VTE thrombophilia includes the following: (1) APC resistance, (2) genotyping for prothrombin G20210A, (3) lupus anticoagulant assay and anticardiolipin and anti–β_2-glycoprotein I antibody serologies, (4) functional AT and protein C levels, and (5) free protein S (Table 52-4). Genotyping for the FVL mutation can substitute for APC resistance and also determines whether the