Thrombotic Thrombocytopenic Purpura: Successful Treatment Unlocks Etiologic Secrets*

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The cause of platelet agglutination in thrombotic thrombocytopenic purpura has been an enigma. Current evidence indicates that the interaction of platelets with a platelet-aggregating factor or unusually large multimers of factor VIII:von Willebrand factor, or both, may cause the abnormal platelet agglutination. Recent success in the treatment of thrombotic thrombocytopenic purpura with intravenous infusion of immunoglobulin suggests that the abnormal platelet agglutination in thrombotic thrombocytopenic purpura may reflect a deficiency of immunoglobulins that normally inhibit platelet-aggregating factors or large multimers of factor VIII:von Willebrand factor.

In 1924, Moschcowitz initially described a fulminating febrile illness in a 16-year-old girl characterized by the diffuse deposition of hyaline thrombi in terminal arterioles. In this original description of thrombotic thrombocytopenic purpura (TTP), Moschcowitz reported pallor, petechiae, fever, and slight paralysis. Laboratory studies revealed anemia and proteinuria. Nucleated erythrocytes were present in the peripheral blood smear; no schistocytes were described. No platelet count was obtained. At autopsy, hyaline thrombi were seen in "every section of heart muscle"; occasional thrombi were present in the spleen, liver, and kidneys. Moschcowitz stated, incorrectly, that the hyaline thrombi resulted from the agglutination of erythrocytes. He concluded that a toxin with pronounced hemolytic and agglutinating properties was the cause of the diffuse thrombotic process.

TTP is a very rare disease. Petitt calculated an incidence of about one case per million population in Olmsted and Fillmore counties in his review of the Mayo Clinic experience for a 30-year period (1950 through 1979). The peak incidence is in the fourth decade of life, and 60% of cases occur in women.

MANIFESTATIONS
The characteristic clinical pentad of TTP consists of thrombocytopenic purpura, microangiopathic hemolytic anemia, varying neurologic symptoms or signs, renal disease, and fever.

Clinically, the thrombocytopenia, which is attributable to diffuse platelet agglutination, may produce various bleeding complications such as petechiae, purpura, epistaxis, and cerebral and retinal hemorrhages. Neurologic manifestations include headache, confusion, aphasia, transient paresis, ataxia, sensory disturbances, and coma. Hematuria, proteinuria, and renal insufficiency (occasionally, acute renal failure)
are the renal abnormalities. The cause of the moderate increases in body temperature is unknown. Anemia is frequently severe, the hemoglobin concentration being less than 5.5 g/dl in 30% of the patients.\(^5\)

Consistent with this nonimmune intravascular hemolytic process, the peripheral blood smear demonstrates schistocytes without spherocytes. The indirect bilirubin, lactate dehydrogenase, reticulocyte count, and plasma hemoglobin values are increased, and hemosiderin is present in the urine. Additionally, haptoglobin is decreased or absent, and the direct Coombs test is negative. Thrombocytopenia is pronounced; platelet counts seldom exceed 20,000/mm\(^3\). Marrow megakaryocytes are normal or increased. Although fibrinogen may be consumed inadvertently during the process of diffuse platelet agglutination, mild disseminated intravascular coagulation is uncommon. Other clinical manifestations may include cardiac dysfunction, hepatosplenomegaly, and pancreatitis.

**DIAGNOSIS**

The diagnosis of TTP is suggested by the aforementioned clinical pentad; no specific diagnostic test exists. The presence of hyaline thrombi in biopsy specimens of skin, subcutaneous tissue, muscle, bone marrow, gingiva, or lymph nodes lends support to the diagnosis. These microvascular occlusions are evidence of the diffuse platelet agglutination that characterizes TTP. The differential diagnosis of TTP includes the hemolytic uremic syndrome, disseminated intravascular coagulation, autoimmune hemolytic anemia, immune thrombocytopenic purpura, Evans’ syndrome, immune-mediated microangiopathy (such as systemic lupus erythematosus), subacute bacterial endocarditis, nonbacterial thrombotic endocarditis, meningococcemia, disseminated carcinomatosis, malignant hypertension, eclampsia, and the HELLP (hemolysis with elevated liver enzymes and low platelet count) preeclamptic syndrome.\(^6\) The hemolytic-uremic syndrome may occur in adults; although similar to TTP clinically, the platelet agglutination is primarily limited to the kidney. The local absence of fibrinolytic activity in thrombosed vascular lesions distinguishes TTP from other disseminated intravascular coagulopathies.\(^7\)

**ETIOLOGY AND PATHOGENESIS**

The cause of TTP is unknown. Associations have been observed with pregnancy, toxins, drugs, and various immunologic disorders. Some investigators have suggested that any episode characterized by tissue necrosis (such as an injury, infection, or surgical procedure) may precipitate TTP.\(^8\) Specific etiologic considerations have included the following: nonspecific tissue factors,\(^8\) cytotoxic immunoglobulins,\(^9\) primary vasculopathy,\(^5\) localized loss of fibrinolytic activity,\(^7\) prostacyclin deficiency,\(^10\) “exhausted” platelets,\(^11\) platelet-aggregating activity,\(^12\) lack of immunoglobulin inhibitors of platelet-aggregating activity,\(^13\) presence of unusually large multimers of factor VIII:von Willebrand factor (VIII:vWF), and lack of immunoglobulin inhibitors of the large multimers of VIII:vWF.\(^8\)

Although investigators agree that the intravascular hyaline thrombi are composed primarily of platelet aggregates, the sequence of events leading to this platelet agglutination remains controversial. Whether endothelial vascular damage initiates or results from the platelet agglutination is unclear. In support of a primary vasculopathy, subintimal “prethrombotic” hyaline deposits containing immunoglobulin have been observed in areas devoid of intraluminal thrombi. An immunoglobulin cytotoxic for cultured endothelial cells was isolated from the serum of three patients with TTP.\(^9\) An alternative suggestion is that the vascular endothelial cell proliferation noted in TTP is simply reendothelialization caused by previous local platelet agglutination.\(^5\)

Endothelial damage may be responsible for the localized absence of fibrinolysis that distinguishes TTP from other disseminated intravascular coagulopathies; however, because platelets contain large quantities of inhibitors of both plasminogen activator and plasmin, the platelet-rich thrombi that characterize TTP are resistant to fibrinolysis.\(^7\)

Other speculations about the cause of TTP include prostacyclin deficiency and “exhausted”
platelets. Prostacyclin is a naturally occurring inhibitor of platelet aggregation and is synthesized by the vascular endothelium. A deficiency of this mediator has been demonstrated by several investigators, and infusion of prostacyclin has reversed platelet aggregation in vivo. Kitchens described "exhausted" platelets in a young woman with TTP, who had prolongation of the bleeding time and bruising just before thrombocytopenic relapse.

The most cogent explanations reflect increasing understanding of the interactions of the platelet-aggregating activity described by Lian and associates, unusually large multimers of VIII: vWF, and the lack of inhibitors of these substances.

In 1977, Bukowski and colleagues demonstrated that most patients with TTP respond to plasma exchange. This finding suggested that the disease could be controlled by removal of a "toxic" substance that caused platelets to aggregate. Previous and subsequent successful treatment with plasma infusion alone led Lian and co-workers and Aster to suggest that TTP resulted from a deficiency of a normal plasma component. Purification of the protein (or proteins) of the platelet-aggregating activity is currently in progress. Murphy and associates recently suggested that a calcium-dependent cysteine protease is responsible for the platelet-aggregating activity in TTP.

Plasma from patients with TTP will induce agglutination of both washed platelets from normal donors and platelets from patients with TTP in remission. The platelet-aggregating activity of plasma from patients with TTP diminishes as a function of time during incubation with normal plasma at 37°C. Platelet-aggregating activity is heterogeneous. Lian and colleagues demonstrated that the plasma from a 3-year-old boy obtained during his second episode of TTP inhibited the platelet agglutination induced by plasma obtained during his first episode of TTP. An inhibitor of this platelet-aggregating activity has been found in plasma from patients with TTP. It is an immunoglobulin, and the activity resides in the Fab fragment. Infusion of immunoglobulin has been shown to halt platelet agglutination both in vitro and in vivo. In acute TTP, perhaps an initial insult (such as pregnancy, drugs, infection, or tissue necrosis) triggers production of a platelet-agglutinating factor that causes, or is associated with, a subtle defect or deficiency in the humoral immune response during the disease state only.

Lian and Savaraj demonstrated that platelet agglutination induced in vitro did not necessitate the production of thromboxane A\textsubscript{2}, promote release of platelet granule contents, or alter metabolism of platelets or flux of calcium or magnesium ions.

vWF is synthesized by megakaryocytes and vascular endothelium. It is present in platelet α granules and is stored in the Weibel-Palade bodies. In plasma, it circulates as multimers of 4 to 60 subunits (molecular weights 1 to 21 x 10\textsuperscript{6}) in a flexible filament that interacts with fibrinogen and is necessary for platelet adhesion to injured subendothelium at the high shear rates of rapid blood flow. In vitro, ristocetin (a positively charged substance) induces attachment of the largest VIII: vWF multimeric forms present in normal plasma to platelets and promotes platelet agglutination.

In 1982, Moake and co-workers observed that the platelet agglutination in patients with TTP was similar to the platelet agglutination induced in vitro by large multimeric vWF components of VIII: vWF. They found unusually large VIII: vWF multimers in four patients with chronic relapsing TTP. The plasma levels of the multimers decreased during clinical relapses, a result that suggests binding to (and subsequent agglutination of) platelets. During clinical remissions, these same patients had abnormally high concentrations of these unusually large VIII: vWF multimers.

Moake and associates suggested that patients with chronic TTP lack the ability to cleave large VIII: vWF multimers. They speculated that certain initiating factors (for example, pregnancy, drugs, infection, or tissue necrosis) release cationic polyamines (an in vivo ristocetin), which then neutralize the negatively charged platelet membrane and thus allow large multimers of VIII: vWF to be adsorbed and promote
platelet agglutination. This sequence of events may result from a deficiency of or a defect in VIII:vWF depolymerase, which normally degrades these large multimers. The platelet agglutination induced by large multimers is inhibited by immunoglobulin (the activity is in the Fc fragment, in contrast to the Fab location of anti-platelet-agglutinating factor activity) by its binding to the platelet membrane Fc receptor.12 Transfusion of a normal spectrum of factor VIII:vWF has reversed the hematologic abnormalities in one patient with TTP in whom unusually large vWF multimers had previously been demonstrated.22

In 1984, Kelton and colleagues15 suggested that both the platelet-aggregating activity described by Lian and co-workers14 and the unusually large multimers of VIII:vWF described by Moake and associates8 were involved in the platelet agglutination that characterizes TTP. They described a method for the qualitative detection of platelet-agglutinating activity and noted that this activity was augmented by the addition of large VIII:vWF multimers.

The concentration of platelet-associated immunoglobulin is frequently increased in patients with TTP.12,23 The level of platelet-associated antibody has been correlated with disease activity.24 Perhaps immunoglobulins directed against platelet-agglutinating factor and large multimers of VIII:vWF are responsible for this increase.

Figure 1 depicts the current theory of the potential pathogenesis of TTP. TTP is a syndrome with diverse causes and probably different pathogenetic mechanisms. An excellent review of the diverse pathogenesis of TTP has recently been published by Lian.25 In addition, extensive material on thrombotic microangiopathy organized by Kwaan26 should be of interest to hematologists.

**TREATMENT**

The therapeutic effect of single agents in patients with TTP is difficult to determine because multiple treatment modalities are generally used concomitantly for this life-threatening disease. Treatment options include the following: corticosteroids, antiplatelet agents (such as dextran, sulfinpyrazone, aspirin, or dipyridamole), prostacyclin, infusion of plasma, plasma exchange, *Vinca* alkaloids, splenectomy, and infusion of immunoglobulin. Currently, initial therapy generally includes antiplatelet agents (aspirin and dipyridamole), corticosteroids, and either plasma exchange or infusion of fresh-frozen plasma.

Although in vitro data suggest that platelet inhibitors fail to prevent platelet aggregation,20 the survival rate of patients treated with antiplatelet agents (aspirin and dipyridamole) and concurrent plasma manipulation is improved.27 Perhaps the inhibition of platelet adhesion and of further platelet aggregation and release in vivo explains the beneficial effects of platelet inhibitors in patients with TTP.20 The ineffectiveness of platelet inhibitors (and the bleeding complications) noted by one group of investigators28 may have been due to suppression of the platelet-inhibiting effect of prostacyclin.29

Infusion of prostacyclin has reversed TTP in vivo but is associated with severe hypotension from its vasodilatory effects.10 One brief controlled trial demonstrated an increase in fatal cerebral hemorrhage with use of heparin.27

Although platelet transfusions occasionally have been given because of bleeding associated with severe thrombocytopenia, Harkness and co-workers30 described a young female patient with TTP who had rapid deterioration of the central nervous system (with autopsy evidence of extensive deposition of platelet aggregates within the small blood vessels of the brain) immediately after the transfusion of platelets. This outcome raises the possibility that platelet transfusion may fuel ongoing platelet agglutination. Moreover, Gordon and associates31 extended this observation by noting that, in addition to platelet transfusion, reaccumulation of the circulating platelet pool (as a result of reversal of the disease process) also may be associated with clinical deterioration. They suggested that antiplatelet therapy be delayed until platelet counts begin to increase steadily in response to initial treatment (plasmapheresis with fresh-frozen plasma and corticosteroids).
Infusion of fresh-frozen plasma has been the basis of successful treatment of TTP, perhaps by supplying the immunoglobulin inhibitors to platelet-agglutinating factor and VIII:vWF. Plasma exchange may be used if infusion of fresh-frozen plasma is inadequate or complicated by volume overload. The added efficacy of plasma exchange over infusion of fresh-frozen plasma in some patients may reflect the removal of large VIII:vWF multimers or platelet-aggregating activity.

Other treatment options include splenectomy, Vinca alkaloids, and infusion of immunoglobulin. The demonstrated effectiveness of infusion of immunoglobulin in halting platelet agglutination in patients with TTP makes such treatment an attractive option. In one recently reported case, TTP was treated successfully with infusion of high doses of immunoglobulin after the failure of plasmapheresis, exchange transfusion, splenectomy, antiplatelet agents, glucocorticoids, and vincristine.

CONCLUSION
TTP has changed from a disease once universally fatal to an illness that, when recognized, has a remission rate exceeding 90%. Increasing success in the treatment of TTP with the use of plasma and its components is unlocking etiologic secrets.

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REFERENCES


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