CME CREDIT

MARK A. CROWTHER, MD
Director, Division of Hematology, McMaster University, Hamilton, Ontario, Canada

JAMES N. GEORGE, MD
Hematology-Oncology Section, Department of Medicine, The University of Oklahoma Health Sciences Center, Oklahoma City

Thrombotic thrombocytopenic purpura: 2008 Update

ABSTRACT

Thrombotic thrombocytopenic purpura (TTP) is a spectrum of syndromes characterized by thrombocytopenia and microangiopathic hemolytic anemia, manifested by an elevated blood lactate dehydrogenase (LDH) concentration and red blood cell fragments. It classically occurs in patients with a hereditary or acquired lack of ADAMTS13, a metalloproteinase that cleaves large multimers of von Willebrand factor. Other TTP-like syndromes, including TTP associated with pregnancy, organ transplantation, and certain medications, likely have different underlying causes and may require different treatment. Unless TTP is recognized promptly and treated aggressively, most patients die of it.

KEY POINTS

Strokes and renal insufficiency are end-stage manifestations of TTP; the condition is usually diagnosed before they occur.

Classic TTP should be rapidly and aggressively treated with plasma exchange. Plasma infusion therapy plays a role for patients who cannot promptly receive plasma exchange or for patients with severe disease between episodes of plasma exchange.

Antiplatelet therapy may be appropriate along with plasma exchange for patients without severe thrombocytopenia.

If a renal transplant recipient develops systemic symptoms with TTP-like disease, one should consider modifying or withdrawing the immunosuppressive therapy, although this may result in loss of function and the need for transplant nephrectomy.

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) is one of the few hematologic emergencies. Untreated, most patients die, but prompt and appropriate treatment allows most patients not only to survive but to recover, frequently without long-term sequelae.

TTP is rare. The estimated annual incidence of all TTP syndromes is about 11 cases per million in the general population, and the incidence of severe ADAMTS13 deficiency (see discussion below) is about 2 per million. Therefore, even large medical centers typically see only one or two cases each year. The syndromes are much more common in women, and the incidence among blacks is nine times higher than the incidence among non-blacks. Nevertheless, despite the rarity of this disease, good evidence exists to help guide patient care, thanks to national registries and research organizations, such as the Canadian Apheresis Study Group and the Oklahoma TTP-Hemolytic Uremic Syndrome (HUS) Registry.

This article reviews the physiologic basis of TTP, how to recognize it, and how best to treat it. We also discuss other conditions that clinically resemble TTP but probably have different underlying causes.

A YOUNG WOMAN WITH ARM WEAKNESS

A 24-year-old black woman presents to a community hospital with weakness in her left arm, which began about 30 minutes previously. She has had progressive dyspnea over the last several weeks, but has otherwise been completely well and has had no medical problems in the past other than being obese.

Physical examination reveals weakness in her left arm as well as mild dysarthria, which

was not previously noted by the patient or her family. Her laboratory findings:

- White blood cell count 16.7 × 10^9/L (reference range 4.5–11.0)
- Platelet count 32 × 10^9/L (150–350)
- Hemoglobin concentration 6.5 g/dL (1.4–17.5)
- Peripheral blood smear: normal white cells, rare platelets, red cells normochromic with many fragments
- Lactate dehydrogenase (LDH) concentration 2,300 U/L (100–200).

In view of her symptoms and laboratory values, the physician suspects she may have TTP and refers her to McMaster University Medical Center in Hamilton, Ontario, Canada. Plasma exchange is started immediately; one plasma volume is removed and replaced with fresh frozen plasma. Nevertheless, the patient's condition deteriorates overnight, she becomes more confused and cannot protect her airway, her LDH concentration rises further, and her hemoglobin concentration falls. She is transferred to the intensive care unit. Her plasma exchange prescription is increased to 1.5 volumes twice daily (although little evidence exists that plasma exchange twice daily is more effective than once daily).

Devastating compromise and neurologic deficits are completely reversible in most cases

On the third day of her stay, she becomes completely paralyzed on the left side. In addition to her twice-daily plasma exchange procedures, a plasma infusion and corticosteroid therapy are initiated. Her platelet count stabilizes at about 20 × 10^9/L.

The patient next develops renal insufficiency and requires three acute hemodialysis treatments. (Plasma infusion frequently leads to volume overload in critically ill patients. Some intravascular volume can be removed with plasma exchange; however, significant volume overload with significant renal insufficiency can only be treated with renal replacement therapy.)

The patient undergoes 28 consecutive days of twice-daily plasma exchange and gradually improves, as measured by increasing platelet counts, a gradual fall in the LDH concentration, and stabilization of—and ultimately an increase in—the hemoglobin level. She is weaned off plasma infusions, and then plasma exchange is tapered to once a day and then to alternate days.

She is completely well at the time of discharge 4 weeks after her initial admission, with no residual deficits.

Comment. This case shows that even patients with apparently devastating compromise and neurologic deficits can completely recover with aggressive plasma exchange and other therapies. One child treated at the Hospital for Sick Children, affiliated with the University of Toronto, developed TTP and had 120 consecutive days of plasma exchange: she was unconscious and comatose for much of that time, but she ultimately recovered and is now completely well without residual neurologic deficits.

TTP MAY BE DUE TO ADAMTS13 DEFICIENCY

Twenty-five years ago, little was known about TTP except for its clinical manifestations. Now, it is known to be caused in some patients by an acquired deficiency of a circulating metalloproteinase. In very rare cases a hereditary deficiency of ADAMTS13 causes TTP. In addition, a number of conditions share clinical features with TTP but have other underlying causes.

In acquired TTP, an autoantibody forms against ADAMTS13, a zinc-containing metalloproteinase that is also known as von Willebrand factor-cleaving protease. Normally, von Willebrand factor circulates in plasma as multimers that allow platelets to adhere to vascular surfaces. When von Willebrand factor is initially released from endothelial cells, it exists as large multimers, which are more adhesive for platelets than normal. These large multimers are normally cleaved into smaller units by ADAMTS13. If ADAMTS13 is lacking, the very-high-molecular-weight von Willebrand factor multimers accumulate, causing platelet agglutination and the vascular occlusion that results in the manifestations of TTP.

In 1994, ADAMTS13, the gene of which is on the ninth chromosome, was shown to cleave von Willebrand factor under conditions of high shear stress. In 1996, a congenital homozygous deficiency of ADAMTS13 was found to be associated with platelet

microthrombi. Afterwards, some patients with TTP were shown to have low or undetectable levels of ADAMTS13, owing to immunoglobulin G antibodies directed against the enzyme.

TTP AND RELATED SYNDROMES

Clinically, TTP encompasses a number of different but related syndromes, some of which have different physiologic bases.

TTP

TTP is characterized by moderate to severe thrombocytopenia, red cell fragmentation, and elevated LDH levels (due to red cell destruction and also muscle and organ ischemia). The pentad of features classically associated with TTP in the era before effective treatment (thrombocytopenia, fever, renal failure, neurologic deficit, and microangiopathic hemolytic anemia) is rarely seen in countries with advanced medical care: renal insufficiency and neurologic events are end-stage manifestations, and the disease should be recognizable well before these manifestations occur. Otherwise unexplained thrombocytopenia, microangiopathic hemolytic anemia, and an elevated LDH should strongly suggest TTP. TTP is the appropriate designation for adults with these clinical features, even in the presence of renal failure. TTP is uncommon in children.

Most patients present with nonspecific constitutional symptoms, such as weakness, abdominal pain, nausea, and vomiting. Typically, the family physician orders a complete blood cell count and finds that the platelet count and hemoglobin are low. Red cell fragments are noted in the peripheral blood smear. Further testing reveals an elevated LDH concentration.

HUS

HUS was initially described 30 years after TTP in children with acute renal failure in addition to thrombocytopenia and microangiopathic hemolytic anemia. The term "HUS" is currently used primarily to describe the condition in children.

In children, two forms of HUS exist:

Diarrhea-associated HUS is associated with diarrhea that is commonly bloody, due to an enterotoxin produced by *Escherichia coli* O157:H7.

Endemic diarrhea-associated HUS is much more common than HUS associated with epidemics. Endemic cases are caused by *E coli* O157:H7 present in the environment. Other patients present with clinically apparent HUS but the causal bacterium cannot be detected. The kidney transplant program at our center often sees young patients with this disease who do not have *E coli* O157:H7 infection, and the pathogenesis is not understood. Epidemic cases are less common but the outbreaks are dramatic. About 10 years ago, *E coli* O157:H7 entered the water supply in the small city of Walkerton, Ontario, and many people developed the epidemic form of HUS over a period of several weeks. Most such patients spontaneously recovered without plasma exchange, although many were left with impaired renal function.

Atypical HUS. Less often, HUS in children is not associated with a prodrome of diarrhea and is referred to as "atypical" HUS. These children often have a more prolonged and complicated course and resemble adults with TTP.

Familial TTP-HUS

Familial TTP-HUS is very rare. It may present with hemolysis and thrombocytopenia in childhood or early adulthood. Many patients present with renal insufficiency, and only careful evaluation reveals hemolysis and thrombocytopenia. The disease typically manifests acutely: a patient may have an upper respiratory tract infection and subsequently develop an episode of TTP-HUS. Episodes tend to recur, and multiple family members may also be affected.

Plasma infusion is an effective treatment, and plasma exchange is usually not required. Since more patients are now surviving well into adulthood, some are being seen to develop antibodies to the ADAMTS13 in the infused plasma, analogous to patients with severe hemophilia developing inhibitors to factor VIII. The disease may progress despite treatment: we have been treating a young woman who has had a series of catastrophic complications

The classic TTP pentad is now rare: renal failure and neurologic events are end-stage features

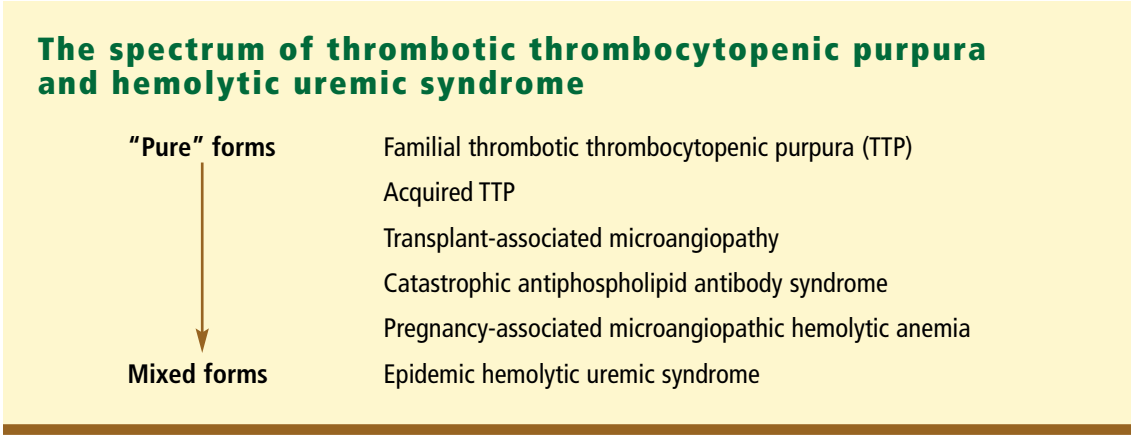

FIGURE 1

and now has chronic renal failure requiring hemodialysis (see discussion below).

Post-transplant microangiopathy

Post-transplant microangiopathy is most likely to develop after solid-organ or stem-cell allograft transplantation. Manifestations resemble those of TTP, but the mechanism is probably quite different. Multiple causes probably exist, depending on the setting.

Post-transplant microangiopathy does not respond to the usual therapies for TTP, although we treat it, like TTP, with corticosteroids, antiplatelet agents, and plasma exchange. Other centers do not use plasma exchange for these patients. Most patients have a poor prognosis, especially those with a transplant other than a kidney.

Low platelets and microangiopathic hemolytic anemia without another apparent cause are sufficient to diagnose TTP

A spectrum of related syndromes

A number of diseases clinically resemble TTP. Enhanced diagnostic capacity and better molecular biologic techniques are revealing that they often have very different underlying causes and that in some cases they require different treatment.

Traditionally, these diseases have been characterized as a spectrum of related syndromes (FIGURE 1). Familial TTP, caused by a hereditary deficiency of ADAMTS13, is probably at one end. The disease apparently most related to it is the "purest" form of acquired TTP and is caused by an acquired deficiency of the same enzyme. Further along the spectrum are other diseases that resemble TTP clinically but probably—at least in some cases—have very different mechanisms, including transplant-associated microangiopathy and catastrophic antiphospholipid antibody syndrome. Next is pregnancy-associated microangiopathic hemolytic anemia. Epidemic HUS is at the farthest end of the spectrum from familial TTP: it resembles TTP clinically but is caused by bacterial infection and requires different therapy.

TOWARD DIAGNOSTIC CRITERIA

Ruutu et al,[1] in a consensus conference, used rigorous methods to establish diagnostic criteria for microangiopathy associated with stem cell transplantation:

- More than 4% red blood cell fragments in the peripheral blood. A laboratory report that states that "few fragments" are present is not nearly as useful as one that estimates the quantity; eg, 1% fragments would have very different implications than 6% fragments.
- Thrombocytopenia—a platelet count of less than 50×10^9/L or more than a 50% reduction from previous counts
- Increased LDH concentration
- Reduced hemoglobin concentration or increased transfusion requirement
- Decrease in serum haptoglobin, which, like red blood cell fragments, is a marker of hemolysis rather than of reduced synthesis.

The ADAMTS13 level need not be assessed. Metalloproteinase deficiency need not be proved to diagnose TTP. Although our hospital is a TTP referral center, we do not routinely offer the test. Too often the test

results cause confusion: a patient can have a normal level of ADAMTS13 and still have TTP that responds to plasma exchange, and levels can be low in conditions other than TTP.

THE CHALLENGES OF TREATMENT

Plasma exchange is the primary treatment for TTP

Rock et al[2] performed a randomized trial in which 102 patients with TTP received either a 1.5-volume plasma exchange daily for 3 days and then 1-volume plasma exchanges as needed to control the disease or plasma infusion. Patients who received plasma exchange had a better initial response, a higher survival rate, and a lower rate of relapse than patients receiving plasma infusion. These findings established plasma exchange as the treatment of choice for TTP.

However, the trial had some inherent problems: patients who had plasma infusions tended to develop renal insufficiency and as a result did not receive as much plasma because they could not tolerate as much volume as those who had plasma exchange. Plasma exchange probably worked better because it could deliver more plasma over a fixed period of time, enabling patients to obtain more of the ADAMTS13 enzyme, rather than because it was an intrinsically better treatment. This interpretation is the basis for our occasional use of twice-daily plasma exchange in critically ill patients.

TTP is different from other autoimmune diseases such as idiopathic thrombocytopenia purpura, in which the primary treatments are immunosuppressive agents. Some evidence exists for treating TTP with immunosuppressive agents, but the primary treatment should be plasma exchange.

Plasma infusion is useful in some cases

Although small case series and our own experience provide evidence for the benefit of treating TTP with high-dose plasma infusions (25 mL/kg/day, or about 1.5 to 2.0 L/day for an average-sized adult), problems will likely arise with volume overload if the patient has any significant renal insufficiency. Dialysis or ultrafiltration may be used to treat volume overload; however, it is difficult to remove the large volumes of fluid required for high-volume plasma infusion.

Plasma infusion should be reserved for two situations:

- If plasma exchange cannot be promptly started
- For patients with very severe or refractory disease, between plasma exchange sessions.

Benefit of cryoprecipitate-poor plasma is uncertain

Fresh frozen plasma is believed to contain nearly physiologic levels of all of the plasma proteins. When plasma is cooled to around 4°C, a precipitate forms that contains a variety of substances, including the higher molecular weight multimers of von Willebrand factor. Because TTP involves excess large multimers, giving plasma in which the high molecular weight multimers have been removed should in theory be better. In many centers, such cryoprecipitate-poor plasma is routinely used to treat TTP.

However, evidence that cryoprecipitate-poor plasma is better is lacking. A large study in Canada evaluating this question was terminated because of a lack of patient accrual, a common fate of clinical trials of rare diseases. A randomized study in 17 patients failed to show an advantage of cryoprecipitate-poor plasma over regular plasma, but the study was too small to draw firm conclusions given large confidence intervals about the point estimate of the treatment effect.

High-dose plasma infusions often cause volume overload in patients with renal insufficiency

Cryoprecipitate-poor plasma is more expensive than regular plasma and is not as available. We do not routinely use it in our center to initially manage patients with TTP, but we do use it for patients who are refractory to standard treatment.

Scott et al[3] measured the concentration of ADAMTS13 in a variety of plasma products and found that there are significant amounts in cryoprecipitate. Although giving cryoprecipitate-poor plasma provides less of the high molecular weight multimers, which is desirable for patients with TTP, it also provides less ADAMTS13, which is not desirable.

Do antiplatelet agents have a role in acute TTP?

Most algorithms for managing acute TTP include the use of aspirin or dipyridamole (Persantine) or both, and there is some evidence in favor of this approach,[4] but whether antiplatelet therapy should be used for inpatients with severe thrombocytopenia remains controversial. In our practice, we usually provide antiplatelet therapy even for patients with severe thrombocytopenia because we believe TTP involves platelet-mediated hypercoagulability rather than increased bleeding risk.

Do corticosteroids have a role?

Corticosteroids were widely used to treat TTP even before the disease was discovered to be immune mediated. In our center we routinely use them.

Unfortunately, few data exist on the efficacy of steroid therapy for TTP. As a result, we can only make a weak recommendation for its use: using the American College of Chest Physicians rating system for the strength of clinical evidence, it would receive a 2C recommendation. This is the weakest possible recommendation, being based on widespread use but poor-quality data.

If the diagnosis is uncertain, the safest course is to treat with plasma exchange, then try to establish the diagnosis

Stopping vs tapering plasma exchange

Whether plasma exchange should be tapered or simply stopped is also controversial and not well studied. Nevertheless, a widespread clinical practice—once the platelet count returns to 200 × 10^9/L or higher and the patient looks and feels well—is to reduce the plasma exchange sessions to once every 3 days, then to once every 7 days, and then to once every 2 weeks.

In our practice, we taper plasma exchange in this fashion for a minimum of two treatments beyond what we think the patient really needs. As a result, we tend to treat about once every 2 weeks for weeks or even months after the acute illness.

Rituximab may help

Rituximab (Rituxan), a monoclonal antibody against mature B cells, is increasingly being used in treating TTP. Past and present treatments for TTP, including splenectomy, corticosteroids, and plasma exchange are immunomodulatory, so the use of rituximab may be justified. Case reports provided the rationale for a large, multicenter, randomized controlled trial, which is currently under way.[5]

CONDITIONS THAT ARE NOT TTP

Some conditions may be confused with TTP but are clearly something different:

Patients with isolated thrombocytopenia and normal blood smear findings and no coagulopathy most likely have idiopathic thrombocytopenia purpura or, in the correct clinical circumstance, heparin-induced thrombocytopenia.

A patient with an extremely low platelet count but no fragments or very few fragments with microangiopathic hemolytic anemia may have either drug-associated thrombocytopenia or disseminated intravascular coagulopathy, particularly if there is concomitant coagulopathy.

Many pregnancy-associated microangiopathies resemble TTP, and it may be difficult to differentiate them from TTP; if confusion as to the diagnosis exists, the patient should be treated with plasma exchange, as this therapy may be life-saving.

Many rheumatologic conditions are characterized by an acute illness with nonspecific findings, such as low-grade hemolysis and thrombocytopenia. For example, Wegener granulomatosis can present with evidence of hemolysis, thrombocytopenia, and renal impairment.

Systemic lupus erythematosus can also initially present with an "early-TTP"-like picture. Evidence of glomerulonephritis is not consistent with TTP, and urinary red cell casts makes the diagnosis of lupus more likely. Helmet cell fragments in the peripheral blood smear are supposedly more characteristic of TTP, but their presence is not diagnostic.

Scleroderma renal crisis can present like TTP, but because it is unlikely that a patient with known scleroderma would have a second rare disease, it is best to treat it as scleroderma, which does not require plasma exchange or plasma infusion.

In general, if the diagnosis is uncertain, the safest course is to treat the patient with plasma exchange, then try to establish the diagnosis, because TTP is fatal if not promptly treated. Although plasma exchange is probably overused, it is more innocuous than untreated TTP.

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ADDRESS: *Mark A. Crowther, MD, Division of Hematology, McMaster University, St. Joseph's Hospital, 50 Charlton Avenue East, Hamilton, Ontario L8N 4A, Canada; e-mail crowther@mcmaster.ca.*