



**EDUCATIONAL OBJECTIVE:** Readers will recognize the urgency of diagnosing thrombotic thrombocytopenic purpura to improve the dismal prognosis

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# Thrombotic thrombocytopenic purpura: The role of ADAMTS13

## ABSTRACT

Thrombotic thrombocytopenic purpura (TTP) is an uncommon, life-threatening disease requiring prompt diagnosis and initiation of therapeutic plasma exchange to improve patient survival. However, diagnosis is often difficult because of atypical presentations and signs and symptoms that resemble other conditions. Measurements of ADAMTS13 activity, ADAMTS13 inhibitor, and ADAMTS13 autoantibody are useful for diagnosing TTP, guiding therapy, and predicting relapse.

## KEY POINTS

Symptoms of TTP are usually neurologic but can also be cardiac or abdominal. Thrombocytopenia and unexplained microangiopathic hemolytic anemia are sufficient to highly suspect the disease.

In the appropriate clinical setting, an ADAMTS13 activity level lower than 10% is highly indicative of TTP.

ADAMTS13 inhibitor and ADAMTS13 antibody assays provide more diagnostic clues. ADAMTS13 antibody is generally absent in the congenital form.

The ADAMTS13 assay can help distinguish TTP from hemolytic-uremic syndrome, which presents similarly but typically involves normal or only mildly reduced ADAMTS13 activity.

A strong clinical suspicion of TTP warrants immediate initiation of therapeutic plasma exchange without waiting for ADAMTS13 test results.

A BREAKTHROUGH in understanding the pathogenesis of thrombotic thrombocytopenic purpura (TTP) came with the discovery of ADAMTS13 (an abbreviation for “a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13”), a plasma protein that cleaves von Willebrand factor, which interacts with platelets to promote blood clotting. If ADAMTS13 is lacking, unusually large multimers of von Willebrand factor can accumulate and trigger intravascular platelet aggregation and microthrombosis, causing the signs and symptoms of TTP.<sup>1-3</sup>

This knowledge has practical applications: we can now measure ADAMTS13 activity, ADAMTS13 inhibitor, and antibodies against ADAMTS13 to help us diagnose TTP and distinguish it from other forms of thrombotic microangiopathy, such as hemolytic-uremic syndrome, that have similar symptoms but require different treatment.

Using case studies, this article describes typical presentations of acute and relapsing TTP; the role of laboratory testing, including the ADAMTS13 assay; how to distinguish TTP from other conditions that present similarly; and how to manage this condition.

## ■ A HIGH RISK OF DEATH WITHOUT PLASMA EXCHANGE

TTP is characterized by disseminated microthrombi composed of agglutinated platelets and von Willebrand factor in small vessels. Tissue damage by microthrombi can cause thrombocytopenia (platelet deficiency), microangiopathic hemolytic anemia (loss of red blood cells caused by destructive conditions in small vessels), and multiorgan failure.<sup>1</sup>

Untreated TTP has a mortality rate of

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### Case 1. A middle-aged woman with transient neurologic symptoms

A 50-year-old woman presents to the emergency department with transient right-sided weakness, headache, and altered mental status. Laboratory results (**Figure 1, Table 1**) show microangiopathic hemolytic anemia with a moderate increase in schistocytes (red blood cell fragments) on the blood smear, thrombocytopenia, and no signs of acute kidney injury. Severely decreased ADAMTS13 activity and a positive inhibitor test confirm the diagnosis of TTP.

Plasma exchange is started immediately. After daily plasma exchange for 16 days and prednisone therapy (125 mg intravenously per day for 3 days, 60 mg orally with tapering to 10 mg per day for 12 days), her clinical symptoms resolve, and her laboratory results return to normal and remain stable for 20 months.

**Comment.** This describes an acute episode of acquired idiopathic TTP. The patient's neurologic symptoms and abnormal laboratory findings related to microvascular involvement improved with prompt diagnosis and therapy.

### Case 2. A woman with a history of TTP

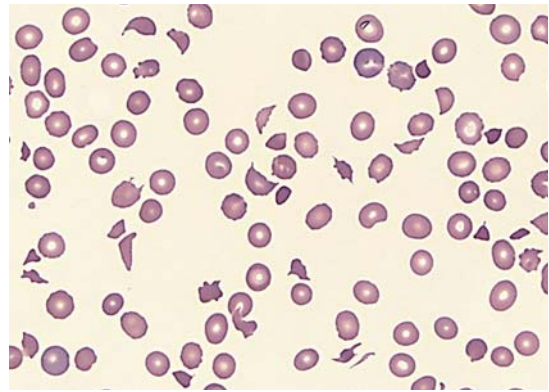
A 15-year-old girl is diagnosed with TTP when she presents with microangiopathic hemolytic anemia, thrombocytopenia, and neurologic symptoms. She is treated with plasma exchange for 3 weeks and splenectomy at another institution.

Then, 15 years later, at age 30, she returns with neurologic symptoms related to a recent left parietotemporal stroke and an old infarct. She has no signs or symptoms of anemia, thrombocytopenia, or hemolysis (**Table 1, Relapse 1**). ADAMTS13 activity is decreased, but levels of ADAMTS13 inhibitor and autoantibodies are normal. She does not undergo plasma exchange, and remains on clopidogrel 75 mg/day.

Now, 8 years after this last episode, she returns with muscle weakness and dysarthria and is found to have a right middle cerebral artery territory infarct on magnetic resonance imaging and a movable mass on the mitral valve. Immediately after cardiac surgery to remove the mass (which is found on pathologic study to be an organizing thrombus), she develops acute-onset severe thrombocytopenia and microangiopathic hemolytic anemia with numerous schistocytes. TTP is confirmed, with severely decreased ADAMTS13 activity and a positive inhibitor (**Table 1, Relapse 2**).

Treatment is started with daily therapeutic plasma exchange for 6 days, prednisone 90 mg with tapering to 40 mg/day for 7 days. Severely decreased ADAMTS13 activity and positive inhibitor continue over the following 5 months despite therapy. She is given rituximab 375 mg/m<sup>2</sup> weekly for 4 weeks. Her symptoms eventually stabilize, her ADAMTS13 inhibitor values fall, and her ADAMTS13 activity slowly rises to normal levels.

**Comment.** This scenario is consistent with chronic relapsing TTP with atypical presentations such as chest or abdominal pain or stroke, and with or without anemia or thrombocytopenia. Therapeutic plasma exchange and prednisone may not resolve clinical symptoms or laboratory abnormalities, so additional therapy with rituximab may be required.



**FIGURE 1.** Peripheral blood smear showing microangiopathic hemolytic anemia with numerous schistocytes and thrombocytopenia (Wright-Giemsa, x 500).

about 90%.<sup>1</sup> As shown in **Case 1, Case 2, and Table 1**, rapid diagnosis and prompt initiation of daily therapeutic plasma exchange can improve this grave outlook.<sup>4</sup>

### ADAMTS13 DEFICIENCY CAN BE ACQUIRED OR CONGENITAL

Two major forms of TTP with ADAMTS13 deficiency and microvascular thrombosis are recognized:

**Acquired TTP**, the more common form, peaks in incidence between ages 30 and 50.<sup>2,5</sup> It more often affects women, particularly during and after pregnancy (its estimated prevalence is 1 in 25,000 pregnancies), and African Americans.<sup>6</sup> Acquired TTP may be:

- **Primary** (idiopathic or autoantibody-mediated), associated with severely decreased ADAMTS13 and the presence of ultra-large von Willebrand factor multimers, or
- **Secondary** (23%–67% of cases), arising from a variety of conditions, including autoimmune disorders (eg, systemic lupus erythematosus, rheumatoid arthritis), solid organ or hematopoietic cell transplant, malignancy, drugs, and pregnancy (**Table 2**).<sup>1,5–8</sup> Secondary TTP has a worse prognosis than idiopathic TTP.<sup>5,9</sup>

**Congenital TTP** (Upshaw-Shulman syndrome) is a rare autosomal-recessive disease caused by compound heterozygous or homozygous mutations of the *ADAMTS13* gene, producing nonfunctional ADAMTS13 protein. Patients have severely deficient ADAMTS13

TABLE 1

## Two cases of thrombotic thrombocytopenic purpura

	Case 1	Case 2		Reference range
		Relapse 1	Relapse 2	
Age	50	30	38	
White blood cell count, $\times 10^9/L$	16.09	14.16	13.39	3.7–11.0
Hemoglobin, g/dL	5.7	13.6	10.7	11.5–15.5
Platelet count, $\times 10^9/L$	10	272	32	150–400
Schistocytes	Moderate	0	Moderate	
Lactate dehydrogenase, U/L	2,403	219	718	100–220
Creatinine, mg/dL	0.8	0.8	0.78	0.70–1.40
Fibrinogen, mg/dL	330	253	155	200–400
Activated partial thromboplastin time, seconds	28.7	29.1	26	23.0–32.4
Prothrombin time, seconds	10.9	10	10.9	8.4–13.0
ADAMTS13 activity, %	5	11	< 5–9 <sup>b</sup>	$\geq 68$
ADAMTS13 inhibitor, BU <sup>a</sup>	0.5	< 0.4	1.8–8 <sup>b</sup>	$\leq 0.4$
ADAMTS13 antibody, U/mL	18	4	NA	< 19
Treatment	Plasma exchange, prednisone	None	Plasma exchange, prednisone, dipyridamole, rituximab	
Follow-up	Recent ADAMTS13 activity > 114, platelets 240	Yes	4 months later: ADAMTS13 activity 87, platelets 474	

<sup>a</sup> Bethesda Unit (normal reference range  $\leq 0.4$  BU)

<sup>b</sup> Fluctuated during admission

activity but usually do not develop autoantibodies. There is a high risk of chronic, relapsing episodes; identified triggers include pregnancy and heavy alcohol intake.<sup>2,10</sup> About half of patients with congenital TTP have an early onset, usually presenting with acute TTP between birth and age 5, and about half have a late onset, usually remaining without symptoms until age 20 to 40.

### THE CLINICAL PICTURE OF TTP IS NOT ALWAYS CLASSIC

TTP is primarily diagnosed clinically, but diagnosis is often difficult because of various

nonspecific symptoms. Typical TTP presents with the “classic pentad”:

- Severe thrombocytopenia (70%–100% of patients)
- Microangiopathic hemolytic anemia with multiple schistocytes (70%–100%) (Figure 1)
- Neurologic involvement (50%–90%)
- Renal abnormalities (about 50%)
- Fever (25%).

However, the entire picture often does not emerge in a single patient.<sup>2,6</sup> Waiting for the entire pentad to develop before diagnosing TTP can have grave clinical consequenc-

**The ADAMTS13 assay is imperative for early correct diagnosis, but waiting for results should not delay initiation of plasma exchange**

es,<sup>1,2,5</sup> and the presence of thrombocytopenia and unexplained microangiopathic hemolytic anemia are considered clinically sufficient to suspect TTP.<sup>5</sup>

Neurologic symptoms usually fluctuate. They can include mild abnormalities such as weakness, dizziness, headache, blurred vision, ataxia, and transient mental status changes, as well as severe abnormalities including stroke, seizure, and coma.<sup>2,6</sup>

Most patients have normal findings on computed tomography and magnetic resonance imaging at the onset of neurologic symptoms or with a history of TTP. Some patients (8%–39%) show reversible acute brain lesions, including ischemic changes.<sup>11–13</sup>

Other signs and symptoms may result from multiorgan failure due to microthrombosis; ischemia in retinal, coronary, and abdominal circulations; and unconjugated hyperbilirubinemia.<sup>2</sup>

**Atypical presentations.** About 18% of patients have cardiac involvement from microvascular occlusion, with arrhythmia, angina, or congestive heart failure. Abdominal pain and pancreatitis occur in 5% to 13%, and visual disturbances in 8% to 10%.

Patients with an atypical presentation may not have laboratory evidence of microangiopathic hemolytic anemia, but an ADAMTS13 assay will show severely decreased activity. Therapeutic plasma exchange can improve atypical symptoms.<sup>2,3,10,14,15</sup>

#### ■ ADAMTS13 ASSAY IS KEY TO DIAGNOSIS

Laboratory evidence typically includes hemolytic anemia (reticulocytosis, schistocytes, elevated indirect bilirubin, reduced haptoglobin, elevated lactate dehydrogenase) and thrombocytopenia.<sup>3</sup> There are no significant abnormalities in prothrombin time, international normalized ratio, activated partial thromboplastin time, fibrinogen, or D-dimer level.

Measuring the levels of ADAMTS13 activity, ADAMTS13 inhibitor, and ADAMTS13 antibody is becoming standard to confirm the diagnosis of TTP, to determine if it is congenital or acquired, and to distinguish it from thrombocytopenic conditions such as hemolytic-uremic syndrome, idiopathic thrombocytopenic purpura, and heparin-induced thrombocytopenia.<sup>4,5</sup> A newer ADAMTS13

assay based on fluorescence energy transfer (FRET) technology with a synthetic amino acid-von Willebrand factor peptide substrate has a faster turnaround time and less test variability.<sup>6,16,17</sup> This FRET assay can give the result of ADAMTS13 activity within 2 hours. In comparison, the assay based on multimeric von Willebrand factor takes 2 to 3 days, and mass spectrometry to measure the cleavage products of a synthetic von Willebrand factor molecule takes about 4 hours.<sup>3,10,16</sup>

About two-thirds of patients with the clinical diagnosis of idiopathic TTP have ADAMTS13 activity levels lower than 10%.<sup>5,14,18</sup> In the appropriate clinical setting, this threshold level is highly sensitive (89%–100%) and specific (99%–100%) in differentiating TTP from other thrombotic angiopathies.<sup>2,3,18</sup>

Note: The ADAMTS13 assay was needed for early correct diagnosis in **Case 1** and **Case 2**.

#### Inhibitors provide more clues

Autoantibodies can be classified according to whether they inhibit ADAMTS13 activity.

**Neutralizing inhibitors.** Most cases of acquired, idiopathic TTP with severe ADAMTS13 deficiency are related to circulating autoantibodies that neutralize ADAMTS13 activity. This ADAMTS13 inhibitor level is obtained by measuring residual ADAMTS13 activity after mixing equal amounts of patient plasma with normal pooled plasma. ADAMTS13 inhibitor is detectable in 44% to 93% of patients with severely deficient ADAMTS13 activity.<sup>3,6,19</sup>

**Nonneutralizing inhibitors.** From 10% to 15% of patients with TTP with severe ADAMTS13 deficiency lack ADAMTS13 autoantibodies measured by enzyme immunoassay but have nonneutralizing immunoglobulin G (IgG) or IgM autoantibodies. In such cases, ADAMTS13 deficiency may be related to increased antibody-mediated clearance or other unknown mechanisms.

Neutralizing inhibitors and nonneutralizing inhibitors may be present simultaneously in some patients.<sup>3,10,19,20</sup>

#### Blood factors affect ADAMTS13 activity

Specimen factors can affect ADAMTS13 activity and antibody levels.

Hemoglobin is a potent inhibitor of AD-

The classic pentad often does not emerge in a single patient



AMTS13, so an elevated plasma level of free hemoglobin (> 2 g/dL) can reduce ADAMTS13 activity, as can hyperbilirubinemia (> 15 mg/dL).

High levels of endogenous von Willebrand factor, lipids, thrombin, or other proteases that may cleave ADAMTS13 can also reduce ADAMTS13 activity.<sup>3</sup> Conversely, recent plasma exchange or transfusion can mask the diagnosis of TTP because of false normalization of ADAMTS13 activity. In addition, ADAMTS13 autoantibody can be detected in other immune-mediated disorders (eg, systemic lupus erythematosus, antiphospholipid syndrome), and hypergammaglobulinemia, as well as in 10% to 15% of healthy individuals.<sup>19</sup>

### ■ CONSIDER OTHER CONDITIONS

Before diagnosing TTP, other conditions causing thrombocytopenia and hemolytic anemia should be excluded by taking a careful clinical, laboratory, and medication history (Table 2). Of these conditions, the most challenging to differentiate from TTP—and often indistinguishable from it at presentation—is hemolytic-uremic syndrome (Table 3).

#### Hemolytic-uremic syndrome

Hemolytic-uremic syndrome presents with a triad of thrombocytopenia, acute renal failure, and microangiopathic hemolytic anemia, with increased lactate dehydrogenase levels. Renal dysfunction from ischemia or tissue injury by microvascular thrombi predominates. Hemolytic-uremic syndrome most often occurs in children and is often related to hemorrhagic enterocolitis caused by infection with *Escherichia coli* O157:H7 or *Shigella* species (90%–95% of cases).<sup>1,2,5</sup>

From 5% to 10% of cases of hemolytic-uremic syndrome are atypical. These cases are not associated with diarrhea, and many are caused by genetic mutations that result in chronic excessive complement activation. Implicated genes regulate complement regulator factor H (20%–30% of cases) or CD46 (10%) and other cofactors, or autoantibodies against factor H (10%), which affect the alternate complement pathway.<sup>6,21–23</sup>

Initial therapeutic plasma exchange is commonly undertaken for atypical hemolytic-uremic syndrome, particularly for patients at

TABLE 2

### Differential diagnosis of thrombotic thrombocytopenic purpura

Hemolytic-uremic syndrome
Atypical hemolytic-uremic syndrome
Disseminated intravascular coagulation and sepsis
Idiopathic thrombocytopenic purpura
Evans syndrome
Malignant hypertension
Solid organ or bone marrow transplant
Severe vasculitis
Pregnancy (preeclampsia, eclampsia, HELLP syndrome)
Human immunodeficiency virus infection
Liver disease
Heavy alcohol intake
Disseminated malignancy
Drugs (eg, clopidogrel, ticlopidine, cyclosporine, mitomycin C, tacrolimus, quinine, gemcitabine)
Combined chemotherapy
Total body irradiation
Malfunctioning prosthetic cardiac valve
Cocaine use

HELLP = hemolysis, elevated liver enzymes, and low platelet count

risk of rapid progression to end-stage renal failure. But despite such treatment, about 60% of these patients die or develop permanent renal damage within 1 year.<sup>2,3,24</sup>

Eculizumab, a monoclonal antibody against complement component C5, has been approved by the US Food and Drug Administration for atypical hemolytic-uremic syndrome and may improve quality of life.<sup>25–27</sup>

### ■ PLASMA EXCHANGE IS THE MAINSTAY OF THERAPY

In 2012, the British Society for Haematology published revised guidelines for managing TTP and other thrombotic microangiopathies.<sup>28</sup>

Acquired idiopathic TTP with reduced ADAMTS13 activity requires immediate

TABLE 3

**Thrombotic thrombocytopenic purpura vs hemolytic uremic syndrome**

	<b>Thrombotic thrombocytopenic purpura</b>	<b>Hemolytic-uremic syndrome</b>
<b>Ischemia, tissue injury</b>	Multiorgan	Renal
<b>Presentation in children</b>	Few cases (early onset of congenital TTP)	Most cases; usually accompanied by bloody diarrhea (except in atypical hemolytic-uremic syndrome)
<b>ADAMTS13 activity</b>	Markedly reduced	Normal or mildly reduced in almost all cases
<b>Recurrence</b>	Common	Rare
<b>Therapeutic plasma exchange</b>	Good response	Poor response when associated with <i>Escherichia coli</i> infection May help in atypical hemolytic-uremic syndrome
<b>Sequelae</b>	Approximately 80% of patients showing complete response without sequelae	Permanent renal damage in 30% (rate higher in atypical hemolytic-uremic syndrome)

**Neurologic symptoms usually fluctuate and can be mild or severe**

therapeutic plasma exchange. Daily plasma exchange combines plasmapheresis to remove circulating ultralarge von Willebrand factor-platelet strings and autoantibodies against ADAMTS13, and infusion of fresh-frozen plasma to replace ADAMTS13.<sup>18</sup> This procedure is the mainstay of therapy and brings 70% to 90% of patients with idiopathic TTP to remission.<sup>1,2,5,6</sup> However, the optimal duration of daily plasma exchange and the number of procedures required is highly variable according to clinical condition. Therapeutic plasma exchange can also cause plasma-related adverse reactions.<sup>9,28</sup> Congenital TTP requires plasma infusion or exchange depending on the patient's severity of ADAMTS13 deficiency.

Corticosteroids are used in combination with daily therapeutic plasma exchange, although evidence from controlled trials of their efficacy in this setting is lacking. Patients with severely decreased ADAMTS13 activity or low titers of ADAMTS13 autoantibodies tend to respond to the therapy.<sup>5,8,29</sup>

An ADAMTS13 assay with a short turnaround time can help guide the decision to

initiate therapeutic plasma exchange. However, if there is a strong clinical suspicion of TTP, plasma exchange should be initiated immediately without waiting for test results.<sup>5,30</sup> Monitoring ADAMTS13 activity or inhibitor during initial plasma exchange therapy has had conflicting results in several studies and is generally not recommended for patients with acquired TTP.<sup>8,30,31</sup>

### ■ RELAPSE IS COMMON

About 20% to 50% of patients with idiopathic TTP experience a relapse (**Case 2**). Most relapses occur within the first 2 years after the initial episode, with an estimated risk of 43% for relapse at 7.5 years.<sup>5,9</sup>

Factors that predict a higher risk of relapse include persistently severely decreased ADAMTS13 activity, positive inhibitor, and high titers of autoantibodies to ADAMTS13 during symptomatic TTP. During clinical remission, persistence of autoantibodies also indicates increased risk.<sup>1,3,5,6,9</sup>

Patients who have a relapse and whose disease is refractory to therapeutic plasma exchange (10%–20% of cases) have been treated with cor-

ticosteroids, splenectomy, or immunosuppressive agents (cyclosporine, azathioprine, or cyclophosphamide) with varying rates of success. Rituximab (monoclonal anti-CD20) has recently been used as second-line therapy in refractory or relapsing immune-mediated TTP or idiopathic TTP with

neurologic or cardiac symptoms associated with a poor prognosis. Therapy including rituximab results in improved response and progression-free survival.<sup>32</sup> Other potential therapies, including recombinant active ADAMTS13, are under investigation.<sup>9,23,28,30,33,34</sup>

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