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Acquired autoimmune thrombotic thrombocytopenic purpura

BY VINCENT M. VACCA, JR., MSN, RN

Abstract: Acquired autoimmune thrombotic thrombocytopenic purpura (TTP)—the most common form of TTP—is a life-threatening hematologic disease characterized by hemolytic anemia and thrombocytopenia. Acquired autoimmune TTP can cause signs and symptoms of neurologic and other organ involvement, with mortality approaching 90% if the disease is not promptly recognized and treated. Since the introduction of plasma exchange in 1991, the acquired autoimmune TTP survival rate has increased to 78%.

Keywords: acquired autoimmune TTP, ADAMTS13, hemolytic anemia, plasma exchange, rituximab, thrombocytopenia, thrombotic thrombocytopenic purpura, von Willebrand factor

ALMOST 100 YEARS AGO, Dr. Eli Moschowitz described a 16-year-old girl who had developed a constellation of signs and symptoms, including pallor, fever, petechiae, hematuria, and coma. (See *Widespread petechiae*.) Within 2 weeks of presentation, she died from her disease.^{1,2} At autopsy, her organs were found to be damaged by arteriolar and capillary thrombi composed primarily of platelets. Because of his

work in this case, the disease was named Moschowitz disease. Advances over the following decades in understanding the pathologic appearance of the affected organs led to renaming Moschowitz disease to thrombotic thrombocytopenic purpura (TTP).^{1,2} The pathophysiology of this disorder was not completely understood, and no reliable diagnostic test for TTP existed until 1966 when researchers defined a classic



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pentad of clinical findings of TTP, which include:¹⁻³

- microangiopathic hemolytic anemia (MAHA)
- thrombocytopenia
- severe neurologic findings, such as fluctuating altered mental status
- fever
- acute renal failure.

However, less than 10% of patients with TTP present with the full pentad.³ Presentation of four, or even three, of the classic five clinical findings is sufficient to diagnose TTP and begin empirical treatment with plasma exchange (PEX).⁴ PEX is the principal treatment for acquired autoimmune TTP and has reportedly reduced mortality from approximately 90% to between 10% and 20%. The pathogenesis of TTP involves autoantibodies that act against von Willebrand factor (vWF) cleaving metalloproteinase, known as a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13 (ADAMTS13). Deficiency of ADAMTS13 is responsible for the microvascular thrombosis,

hemolytic anemia, and organ damage associated with TTP. The autoantibodies against ADAMTS13 are effectively removed by PEX.^{5,6} Many patients with a history of TTP experience a relapsing-remitting course.^{1,2}

Although acquired autoimmune TTP is not the only form of this disease, it is the most common.⁷ This article focuses on the acquired autoimmune form of TTP.

Epidemiology

Acquired autoimmune TTP has a known annual incidence of 3 to 11 cases per million people, affecting up to 10,000 people in the US and Europe annually. In the US, the peak incidence of acquired autoimmune TTP occurs in the fifth decade of life. Acquired autoimmune TTP is more common in women as compared with men at a ratio of 2-3.5:1. It also affects women particularly during and after pregnancy, with an estimated prevalence of 1 in 25,000 pregnancies.^{2,4,8} Pregnancy-associated acquired autoimmune

TTP typically occurs in the late second or third trimester, with a median onset at 23 weeks gestation.⁹

Etiology

Acquired autoimmune TTP may also present in patients with other autoimmune disorders such as systemic lupus erythematosus, Sjögren syndrome, Hashimoto thyroiditis, rheumatoid arthritis, psoriasis, and celiac disease.^{2,8} Solid organ or hematopoietic cell transplant and malignancies are also recognized as acquired autoimmune TTP triggers.^{2,8} Acquired autoimmune TTP is considered a hematologic emergency because even with appropriate treatment the mortality still ranges from 10% to 20%.^{2,3}

Pathophysiology

TTP is a primary thrombotic microangiopathy manifested by thrombocytopenia, hemolytic anemia, and thrombosis. In 1982, Moake and colleagues reported the presence of an ultra-high-molecular-weight form of von Willebrand factor (UHVvWF). A procoagulant molecule, UHVvWF is responsible for platelet adhesion in patients experiencing an acute episode of TTP. The underlying pathophysiology of acquired autoimmune TTP is inhibition and inactivation (deficiency) of a protease identified as ADAMTS13.⁴ ADAMTS13 is responsible for cleaving, or breaking, UHVvWF into smaller units, which reduces platelet adhesion. In 1998, ADAMTS13 deficiency was identified as the defining feature of TTP and became a key criterion for the diagnosis of acquired autoimmune TTP. Since then, acquired autoimmune TTP is defined as a thrombotic microangiopathy syndrome resulting from a severe ADAMTS13 deficiency caused by development of immunoglobulin G autoantibodies against ADAMTS13.^{1,10-12}

When ADAMTS13 fails due to insufficient quantity and activity, the increase in circulating UHVvWF

Widespread petechiae



Patient's leg showing widespread petechiae with a platelet count of 11,000/ μ L. Petechiae do not blanch with pressure because they represent minute hemorrhages; they may accumulate preferentially in dependent areas such as the lower legs because of hydrostatic pressure. Petechiae may also present initially on the palate and tongue, so examination of the gingiva, oropharynx, and retinas is indicated in a patient with thrombocytopenia because concern for risk of intracranial bleeding is greater if petechiae are present above the level of the neck. Generally, the platelet count will be under 30,000/ μ L in a patient presenting with petechiae. Platelet counts un-

der 10,000/ μ L are associated with spontaneous bleeding and warrant immediate intervention.

Source: Weksler BB, Schechter GP, Ely S. *Wintrobe's Atlas of Clinical Hematology*. 2nd ed. Philadelphia, PA: Wolters Kluwer; 2018.

promotes platelet adhesion, particularly at sites of vascular injury and at arteriole-capillary junctions. As red blood cells (RBCs) pass through narrowed partially obstructed arteriole-capillary junctions, they are subjected to shear stress, leading to cell rupture within blood vessels. This produces hemolytic anemia, an RBC fragmentation with schistocyte formation, which can be seen on a peripheral blood smear.¹² (See *A closer look at schistocytes*.) Reduced blood flow due to thrombosis and subsequent cellular injury results in the end-organ damage associated with acquired autoimmune TTP.^{1,11,12}

In acquired autoimmune TTP, microthrombi are composed of UHvWF and platelets, but very little fibrin. Thrombi are present in all tissues, but the lungs and liver are less affected than other organs because of lower shear forces in these low-pressure systems.² Tissue damaged by microthrombi can cause thrombocytopenia, MAHA resulting from destruction and loss of RBCs in small blood vessels, and subsequent multiorgan dysfunction and failure resulting from ischemia.⁸ Despite widespread thrombosis, tissues typically exhibit minimal necrosis, suggesting that blood vessel occlusion and ischemia are not persistent or severe enough to cause necrosis. Recovery from acquired autoimmune TTP following appropriate and timely treatment with PEX is possible.²

Signs and symptoms

Acquired autoimmune TTP can cause widespread signs and symptoms. The consequences of acquired autoimmune TTP-associated platelet thrombi may damage many organ systems, including the neurologic, cardiac, renal, and gastrointestinal (GI) systems.¹³ The initial presentation may be very nonspecific and can include weakness, headache, confusion, nausea, vomiting, and diarrhea.

An infection may precede an acute episode of acquired autoimmune TTP. The more common findings are profound thrombocytopenia, usually less than 30,000/mcL (normal, 150,000 to 450,000/mcL) and evidence of MAHA, with multiple schistocytes visible on peripheral blood smear.¹⁴ These findings are associated with signs and symptoms such as cutaneous and mucosal bleeding, weakness, and dyspnea, and can lead to the diagnosis of acquired autoimmune TTP. The brain is affected in up to 60% of cases with a broad range of signs and symptoms, from a headache and impairment of mental status to acute ischemic stroke, seizures, and coma.² Chest pain and elevated troponin I levels may be present in 25% of patients.² Dysrhythmias and heart failure may occur, but myocardial infarction in acquired autoimmune TTP is rare. Mesenteric ischemia is found in approximately 25% of patients diagnosed with acquired autoimmune TTP.² GI tract involvement can include abdominal pain, nausea, vomiting, and diarrhea. Varying degrees of renal dysfunction are often present; however, impairment requiring renal replacement therapy is not typical and, if present, may suggest another disorder, such as hemolytic uremic syndrome (HUS).² The low platelet count in acquired autoimmune TTP is a marker of susceptibility to potentially significant damage in the brain and kidneys, so correcting it quickly is critical.¹⁵

Although patients with known or suspected acquired autoimmune TTP may present with various signs and symptoms resulting from widespread thrombosis, thrombocytopenia, and anemia, the most common initial sign is nonblanchable, hemorrhagic skin lesions that result from the leakage of red blood cells into the skin, known as purpura.¹⁶ Other signs and symptoms associated with acquired autoimmune TTP include:¹⁶

A closer look at schistocytes

Schistocytes are red cell fragments that may be present in microangiopathic hemolysis and other causes of mechanical hemolysis. Schistocytes are smaller than red blood cells and lack central pallor.



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- stroke, seizures, transient focal neurologic signs such as motor or sensory abnormalities, diplopia, and aphasia
- throbbing headache
- cardiac dysrhythmias
- dyspnea
- renal impairment
- fever
- fatigue.

Diagnostic studies

Testing for ADAMTS13 activity and autoantibodies directed against ADAMTS13 is standard to diagnose acquired autoimmune TTP and distinguish it from other disorders presenting with similar signs and symptoms that require and respond to different treatments.^{3,8} (See *Testing for TTP*.) ADAMTS13 levels are used to determine whether the pathogenesis of the patient's TTP is congenital or of an acquired autoimmune origin, and is also used to distinguish it from other thrombocytopenic disorders such as HUS, idiopathic thrombocytopenic purpura, and heparin-induced thrombocytopenia.⁸

About two-thirds of patients with the clinical diagnosis of acquired autoimmune TTP have ADAMTS13 activity levels significantly lower than

normal (normal, greater than 66%) and elevated ADAMTS13 autoantibody level (greater than 140 U/mL, normal, less than 12 U/mL). These measurements are both highly specific for acquired autoimmune TTP and sensitive in differentiating acquired autoimmune TTP from similar disorders such as HUS, disseminated intravascular coagulation, and other microangiopathies.^{5,8} (See *Microangiopathies associated with TTP*.)

Treatment

For patients who are acutely ill with known or suspected acquired autoimmune TTP, PEX is indicated before test results are reported because the treatment effectively removes the autoimmune antibody ADAMTS13 inhibitor and proinflammatory cytokines and replenishes the deficient active ADAMTS13. The UHvWF molecules revert to the size found in normal plasma when patients are treated with PEX. Clinical improvement typically occurs within 3 to 5 days following initiation of PEX.^{2,9,20,21}

If left untreated, acquired autoimmune TTP is progressive, with

irreversible renal failure, neurologic deterioration, and 90% mortality. PEX has been the recommended treatment for acquired autoimmune TTP since the publication of the randomized clinical trial documenting its effectiveness in 1991.^{4,15} PEX has been shown in clinical trials to be superior to plasma infusion in normalizing platelet counts and reducing mortality.¹⁵ All currently available plasma preparations are equivalent in terms of their effectiveness and outcomes in acquired autoimmune TTP.^{9,12,17,19} PEX should be initiated within 4 to 8 hours of presentation and as soon as possible in life-threatening cases. PEX should continue daily for a minimum of 2 days after the platelet count has been increased to greater than 150,000/mcL.^{18,22} In refractory disease, a twice-daily PEX should be considered.

Of note, platelet transfusion is contraindicated in acquired autoimmune TTP because of the potential presence of antibodies causing extensive thrombus formation. Antiplatelet therapy and splenectomy are ineffective and not recommended.^{2,18}

Erythropoietin and folic acid administration can be considered in addition to PEX to provide support for erythropoiesis.^{19,21} Glucocorticoids are often started simultaneously with PEX. Steroids are used initially to achieve relatively rapid immunosuppression. The proposed benefits of adding steroids to the treatment regimen include:¹⁵

- they provide coverage for other diagnoses and can be discontinued if not needed because the results of the ADAMTS13 assay are usually delayed.
- they are helpful if the patient has a poor response to initial therapy with PEX.
- they are indicated for patients whose platelet counts do not increase with several days of PEX or whose thrombocytopenia recurs as PEX is decreased.

Recent data demonstrate the efficacy of glucocorticoid administration as an adjunct to PEX therapy to efficiently suppress the production of ADAMTS13 autoantibodies, which supports its routine use as an adjunct to PEX in the acute treatment of acquired autoimmune TTP.²³

Rituximab is currently recommended in the British Society for Haematology guidelines as an alternative to immunoglobulin for refractory or recurrent TTP. Rituximab is a monoclonal antibody with action against CD19 and CD20 B cells that suppresses autoantibody production. Rituximab has been shown to improve mortality associated with TTP. Anecdotal reports and small studies involving a total of 42 patients have been published on the use of rituximab for TTP; complete remission occurred in 90% of cases. Despite the small study size, investigators found significantly improved relapse-free survival rates with rituximab treatment. However, there is also evidence to support immediate use of rituximab in acute TTP to reduce exacerbation, refractoriness, number of PEX sessions, and possibly length of hospital stay.^{2,12,15,17} When

Testing for TTP^{2,5,6,17-19}

Test	Normal range	Findings in TTP
Peripheral smear	Hemoglobin, 13.5 to 17.5 g/dL; hematocrit 41% to 53%; schistocytes and reticulocytes, 0.5% to 1.5%	Hemolytic anemia with hemoglobin and hematocrit lower than normal levels; multiple schistocytes and reticulocytes present
Haptoglobin	34 to 200 mg/dL	Haptoglobin levels lower than normal due to loss of RBCs and free hemoglobin molecules
Direct bilirubin	Less than 0.3 mg/dL	Elevated from destruction of RBCs
Total bilirubin	0.1 to 1.2 mg/dL	Elevated from destruction of RBCs
Lactate dehydrogenase (LD)	140 U/L to 280 U/L	Elevated from destruction of RBCs
Platelet count	130,000/mcL to 400,000/mcL	Significantly lower than normal, typically in the 20,000/mcL to 30,000/mcL range

the diagnosis is confirmed to be acquired autoimmune TTP, rituximab can be used in the treatment of relapsed or refractory TTP. Because up to 50% of patients are refractory or unresponsive to first-line PEX therapy, rituximab may stop the autoantibody production by destroying ADAMTS13-specific B cells.^{2,12}

Outcomes

For individuals with acquired autoimmune TTP, there is a significant association between the severity of acute kidney injury (AKI) and the risk of death, with greater risk among patients with more severe AKI. Although severe AKI is uncommon, AKI at the time of an acute episode of TTP may be a significant contributor to long-term risks for hypertension and premature death.²⁰

A major challenge faced by patients with acquired autoimmune TTP is the unpredictable risk of relapse, usually occurring 1 or 2 years after the first episode. In patients with low ADAMTS13 activity, the use of rituximab can reduce the risk of relapse; however, some patients experience a relapse 20 years after the initial occurrence. Long-term administration of rituximab can cause serious sequelae, such as infusion reactions, hepatitis B reactivation, pulmonary fibrosis, and progressive multifocal leukoencephalopathy, and these risks must be considered against the benefit.^{2,5,6,8,11,15,17}

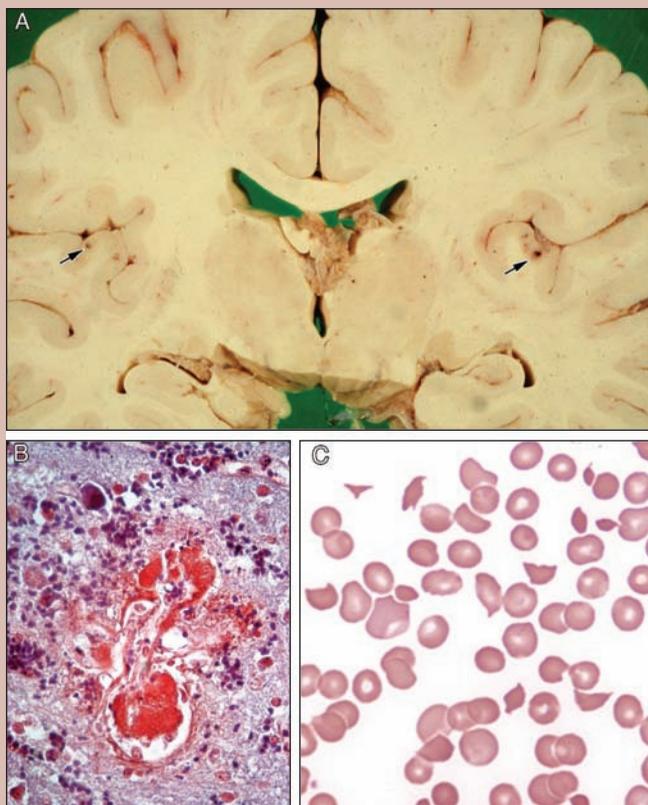
Nursing considerations

Nurses need to be aware of the urgency to provide appropriate targeted treatment, especially because they may be the first healthcare professional to encounter a patient with known or suspected acquired autoimmune TTP.

Perform a thorough physical assessment including a focus on neurologic, cardiac, pulmonary, and kidney functions, as well as skin color and condition. Be prepared

Microangiopathies associated with TTP

A: Coronal section through the brain at autopsy showing multiple small hemorrhages (arrows). B: Histologic section from the same patient shows diffuse microvascular occlusion of arterioles and capillaries. C: Blood smear from the same patient displays the microangiopathic picture with RBC fragments and profound thrombocytopenia.



Source: Image courtesy of Dr. J. Bilbao. In: Weksler BB, Schechter GP, Ely S. *Wintrobe's Atlas of Clinical Hematology*. 2nd ed. Philadelphia, PA: Wolters Kluwer; 2018.

to obtain blood specimens for ADAMTS13 activity, complete blood count (CBC) including platelet count, and vWF activity. Serum bilirubin, LD, and creatinine, as well as a urinalysis, are typically performed to evaluate the function of vital organs. If necessary, imaging studies to determine organ damage may also be performed.^{16,24}

Be prepared to assist with immediate PEX therapy because the mortality without treatment is around 80%, and with treatment, including PEX, the survival rate is around 90%.^{16,24}

Because of the potential high mortality associated with delay in diag-

nosis and treatment, if necessary, consider rapidly transferring the patient to a facility prepared to measure ADAMTS13 and ADAMTS13 antibody levels and administer PEX therapy. If treatment with PEX is planned, be prepared to assist with placement of large-bore dual-lumen apheresis or PEX catheters following facility policy, which typically includes a preprocedure time out or safety pause and adherence to a central venous catheter (CVC) placement checklist. Following confirmation of correct placement of the CVC and after PEX is initiated, monitor for signs and symptoms of potential

complications associated with PEX, including fluid overload from plasma infusion, potential allergic reactions, thrombosis of the CVC, and local or systemic catheter-associated infection.

During PEX therapy, hypotension requiring rapid nursing assessment and intervention to stabilize BP may be necessary. Monitor for signs and symptoms of hypocalcemia such as paresthesias related to the anticoagulant sodium citrate used in the procedure, because it can bind and lower ionized and possibly total calcium requiring intervention to normalize serum calcium levels.^{16,24,25}

Be prepared to administer immunosuppressants, including corticosteroids and rituximab, both of which are standard treatment options in acquired autoimmune TTP, in addition to monitoring for possible adverse reactions such as infection.^{16,24}

Although clinical improvement is expected, persistent neurologic abnormalities may be present after otherwise successful treatment of acquired autoimmune TTP. Neurologic deficits may result from stroke and may not be reversible. Persistent renal dysfunction possibly requiring

renal replacement therapy is rare, although mild renal impairment may persist for weeks to months.^{16,24}

Relapse is possible after effective treatment with PEX; to decrease the incidence of relapse, some investigators have advocated the use of rituximab as routine initial treatment together with PEX and corticosteroids.¹⁰

Over the past 20 years, the diagnosis of acquired autoimmune TTP has become more accurate and treatment has become more effective. Treatment of acute episodes of acquired autoimmune TTP may become even more effective with increasing use of corticosteroids, rituximab, and the addition of new agents, such as caplacizumab and recombinant ADAMTS13. With more effective treatments, the need for PEX and the risks of death and complications from PEX may decrease.²⁶

Be prepared to educate patients and families about long-term management of acquired autoimmune TTP. Following successful treatment, current recommendations are for the patient to be reevaluated every week for 2 weeks and, if the patient remains stable, every 2 weeks thereafter for a month. During this time, weekly blood testing to monitor the

patient's CBC and LD should be performed. If the platelet count drops or LD starts to rise, another course of PEX should be considered. If the patient remains stable for a month, the recommended frequency of follow-up is decreased. The relapse rate is reported as 13% to 36%, and recurrences have been reported after many years in remission. The National Heart, Lung, and Blood Institute website, www.nhlbi.nih.gov, is a useful resource for more information.¹⁶

Future directions

A clinical trial (ClinicalTrials.gov Identifier: NCT01554514) is underway and will study the efficacy of low-dose rituximab administered once per week for 4 weeks, along with PEX therapy, to patients with severe ADAMTS13 deficiency.¹⁷ Recently, the Study to Assess Efficacy and Safety of Anti-von Willebrand Factor Nanobody in Patients With Acquired Thrombotic Thrombocytopenic Purpura (TITAN) demonstrated the efficacy of caplacizumab, an anti-vWF antibody.¹ Caplacizumab is a humanized immunoglobulin nanobody that inhibits the interaction between UHvWF and platelets. Daily subcutaneous injections of caplacizumab resulted in faster platelet recovery in acute TTP compared with a placebo when used along with PEX. Caplacizumab is not a cure, but by preventing the interaction between UHvWF and platelets, it causes rapid reversal of the underlying pathologic mechanism, resulting in a potential to reduce early mortality. The fact that platelet normalization occurred significantly faster with caplacizumab, even in some patients who had not yet had PEX therapy, has potential clinical significance. Caplacizumab has the potential to change TTP treatment strategy. The drug is being studied further in a phase III clinical trial.^{12,15,17,19}

Bortezomib, a proteasome inhibitor, that suppresses production of

Key points

- Symptoms of acquired autoimmune TTP are usually neurologic but can also be renal, cardiac, or GI. Thrombocytopenia and unexplained MAHA are sufficient to suspect TTP.
- Acquired autoimmune TTP is diagnosed with the ADAMTS13 assay. In the appropriate clinical setting, an ADAMTS13 activity level lower than 10% is highly indicative of TTP.
- As soon as it is suspected, acquired autoimmune TTP should be treated with daily PEX until a definitive diagnosis is determined, without waiting for ADAMTS13 test results. Any delay in referring the patient for therapeutic PEX is potentially fatal. If additional treatment is indicated, as in patients with relapsing or refractory TTP, rituximab administration should be considered. An appropriate strategy is to initially add a glucocorticoid to PEX therapy and withdraw it after several days if it is determined that it is not needed.
- PEX has been shown in clinical trials to be superior to plasma infusion in normalizing platelet counts and reducing mortality. Antiplatelet therapy, platelet transfusions, and splenectomy are ineffective and not recommended. Investigators found significantly improved relapse-free survival rates associated with rituximab and complete remission occurred in 90% of cases.^{3,8,15}

autoantibodies is another promising adjunct to PEX in the treatment of refractory or relapsed TTP for patients refractory to rituximab.^{2,12,15,17,19} Another new TTP drug, which is still unnamed and under investigation, is focused on replacing the deficient ADAMTS13 with a recombinant molecule and blocking antibody production.⁸ New and developing strategies to treat TTP may become the future standard of care.^{8,15} ■

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