

Thrombotic Thrombocytopenic Purpura and its Look-Alikes

Joseph M. Baron, MD, and Beverly W. Baron, MD

Dr. Joseph Baron is Associate Professor of Medicine in Hematology/Oncology at the University of Chicago, where Dr. Beverly Baron is Associate Professor of Pathology and Director of the Blood Bank.

Address correspondence to:

Joseph M. Baron, MD, Associate Professor of Medicine, Hematology/Oncology Section, The University of Chicago, 5841 S. Maryland Ave., FM I-231, MC 2115, Chicago, IL 60637. Tel: (773) 702-6114; Fax: (773) 702-3002; Email: jbaron@medicine.bsd.uchicago.edu.

Abstract: The thrombotic thrombocytopenic purpura syndrome (TTP) can be mistaken for a number of other conditions, and it is important to diagnose correctly and treat appropriately. We describe the features of TTP that can help make a positive diagnosis and other conditions in the differential diagnosis with symptoms that can overlap and mimic those of TTP. We discuss TTP and its variants, hemolytic uremic syndrome, disseminated intravascular coagulation, heparin-induced thrombocytopenia, antiphospholipid syndrome, Evans syndrome, preeclampsia/eclampsia, HELLP syndrome, acute fatty liver of pregnancy, and multiorgan failure.

Thrombotic thrombocytopenic purpura (TTP) may present in its full-blown form with the classic pentad of symptoms—thrombocytopenia, microangiopathic hemolytic anemia (MAHA), impaired renal function, neurologic symptoms, and fever.^{1,2} However, in many patients the constellation of findings may be incomplete. For example, a patient might have only thrombocytopenia and MAHA, or some of the characteristic features of TTP could be attributable to other conditions. Furthermore, some patients can be without symptoms of serious illness initially, yet deteriorate rapidly and die. Thus, an accurate and timely diagnosis is especially important because prompt initiation of proper treatment is critical for a successful outcome in TTP. Likewise, the decision to omit treatment, with its potential side effects,³ is just as important if the diagnosis is not truly TTP. Accordingly, we address the issues facing the hematologist who is asked to evaluate a patient for a possible diagnosis of TTP and decide whether or not to treat. We will discuss classic TTP and the features that help make a positive diagnosis, TTP variants, and other conditions in the differential diagnosis that can mimic or overlap with TTP.

Classic TTP (Acute Idiopathic)

The diagnosis of TTP is usually raised by the presence of its 2 cardinal features, thrombocytopenia and MAHA, in the absence of other evident possible causes. Several laboratory findings can be helpful in clarifying the diagnosis and distinguishing TTP from other conditions that share these 2 features.

Serum Lactic Dehydrogenase Level

Typically, a patient's serum lactic dehydrogenase (LDH) level is very elevated in TTP, often in excess of 1,000 IU/dL (normal upper limit,

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245 IU/dL). This elevation is felt to reflect largely the extent of multiorgan ischemia caused by the thrombotic microangiopathy.⁴ Prolonged ischemia can also predispose to disseminated intravascular coagulation (DIC),⁵ which could make the underlying TTP less easily recognized. Usually LDH levels are higher in TTP than in DIC.

Schistocytes on the Peripheral Blood Smear

Assessment of the number of schistocytes per high-power field and the percentage of sheared red blood cells (RBCs) may be helpful in sorting out TTP from other types of MAHA. Schistocyte numbers exceeding 1% of RBCs favor the diagnosis of TTP.⁶ Also helpful is viewing serial blood smears, which can reveal progression of the disease process as indicated by increasing numbers of schistocytes, when other parameters are equivocal. This approach is particularly important because schistocytes can be absent from the smear in the first 24–48 hours after clinical presentation.⁵ A recent report documents 2 patients with recurrent TTP who presented with acute cerebrovascular accidents; the patients had few or no schistocytes initially but developed them later in their clinical courses.⁷ Conversely, a decline in the number of schistocytes during treatment might not occur as early in the course of improvement as a rise in platelet count or drop in serum LDH level.

ADAMTS13 Level

The von Willebrand factor (vWF)-cleaving protease ADAMTS13 is a helpful marker for the diagnosis of sporadic classic immune-mediated TTP.^{8,9} Very low to absent levels of ADAMTS13 in the presence of an immunoglobulin G-type inhibitor are believed to contribute to the impaired removal of ultra-high molecular weight vWF multimers. These multimers are felt to predispose to the propensity for intravascular platelet clumping, which is the characteristic pathogenetic mechanism of the clinical features of TTP. However, the results of these assays are often not available soon enough to influence acute decision-making regarding institution of treatment. In addition, a number of otherwise typical cases of TTP in terms of clinical features and response to treatment have been reported without low ADAMTS13 activity.¹⁰ Also, the ADAMTS13 level may be modestly subnormal (although without detectable inhibitor) in a variety of other clinical situations, such as impaired liver and kidney function, malignancy, DIC, and acute inflammation.

Chemical Markers and Tissue Biopsies

The absence of free haptoglobin and presence of hemosiderinuria help confirm the presence of intravascular hemolysis but lack specificity for TTP. Biopsies of tissues (eg, bone marrow, kidney, skin) have been used in the past to document the presence of intravascular hyaline

thrombi, but these are not done routinely today because of the usual reliance on the laboratory findings, clinical scenario, and need for urgent decisions about initiating treatment. If a tissue biopsy has been done recently for other reasons, however, it is prudent to review it with reference to the presence of such thrombi, although, even if found, they are not entirely specific for TTP.

Coexisting Autoimmune Disorders

TTP of the sporadic autoimmune type can be associated with other autoimmune disorders that alter its presentation and/or affect full recovery of platelet counts with treatment. An example is the simultaneous presence of autoimmune thrombocytopenic purpura.¹¹

Coagulation Parameters

Typically, clotting times and coagulation factor levels reflecting the integrity of the cascade are normal in TTP, as are fibrinolytic parameters. These features help distinguish TTP from DIC.

Recommended treatment of classic sporadic TTP includes therapeutic plasma exchange (TPE) and, often, corticosteroids.^{5,12,13} Management of patients with disease refractory to this approach may include splenectomy, vincristine, immunosuppressant drugs, and rituximab (Rituxan, Genentech).^{5,14}

TTP Variants

Familial TTP and chronic relapsing TTP are variants with a number of special features that can help identify them. A history of multiple acute episodes and lack of associated illness are typical in both these variants. Low ADAMTS13 levels in the familial cases are seen in the absence of inhibiting antibodies and reflect mutations in the enzyme.^{5,10} High levels of circulating ultra-high molecular weight vWF multimers between acute events may predict for a relapsing course,⁸ but clinical decisions are not made based on this finding.

Drug-induced TTP

A number of drugs have been reported to induce a TTP-like syndrome.^{5,15,16} It is important to be aware of these agents and open to the possibility that other drugs may be as-yet unrecognized causes of TTP. Among the commonly identified agents in various drug classes are cyclosporine, tacrolimus, quinine, interferon, ticlopidine, clopidogrel (Plavix, Sanofi-Aventis/Bristol-Myers Squibb), and several cancer chemotherapeutic agents including mitomycin, gemcitabine (Gemzar, Lilly), cisplatin, and bleomycin. Measurements of ADAMTS13 levels have been made in a limited number of cases. The results have been variable,

with some patients having very low levels and the presence of an inhibitor.^{5,15,16}

It may be difficult to identify a responsible drug for several reasons. First, some agents, such as mitomycin, can cause a TTP/hemolytic uremic syndrome (HUS)-like disorder weeks after discontinuation of the drug.¹⁷ Second, patients with drug-induced TTP often have complex medical situations such as solid organ transplants, cancer, and bone marrow transplant that can themselves be associated with development of thrombotic microangiopathy, thus making it very difficult to assign causality to the candidate drug. Finally, in addition to prescribed medications, abused drugs such as cocaine can induce changes similar to TTP.¹⁸ Cocaine use can be overlooked in the patient history or denied by the patient. Urine screening for metabolites might be considered under the appropriate circumstances.

It is always prudent to consider the possibility of a drug-induced mechanism of TTP and, when clinical suspicion is high, to discontinue the drug in question and initiate TPE, which can be a life-saving intervention. In cases refractory to TPE, especially those related to cancer and chemotherapeutic agents, it may be useful to try Staph protein A column treatment of the patient's plasma.¹⁹

Infection-related TTP

Although infections are more commonly associated with DIC and HUS, it is important to recognize that enteritides such as *Escherichia coli* 0157:H7 have been associated with TTP.⁵ The presence of gastrointestinal symptoms in a TTP-like setting should suggest this possible cause. A variety of systemic infections can mimic all clinical features of TTP and often the etiology of infection is not apparent until after TPE is started. Also important is the association of human immunodeficiency virus-1 (HIV-1) infection with TTP as well as autoimmune thrombocytopenia. Testing for HIV-1 should be included in the workup of TTP and appropriate antiretroviral treatment initiated if HIV-1 infection is found.

Hemolytic Uremic Syndrome

It may be difficult to distinguish HUS from TTP, but predominant renal impairment favors HUS, while neurologic features are much more common in TTP. HUS is classified as diarrhea-associated (D⁺) and non-diarrhea-associated (D⁻). Some D⁻ HUS patients have a familial disorder with deficiency of complement factor H. A low serum C3 level may be detected.⁵ The D⁺ (epidemic) type of HUS tends to occur more often in children and young adults. Clusters of patients may be seen in whom certain infectious agents, for example, verotoxin-producing

E. coli 0157:H7, are responsible. In the sporadic D⁻ forms a variety of other infections including HIV-1, *Campylobacter*, and cytomegalovirus can be associated.⁵ Patients with HUS consistently have normal ADAMTS13 levels, a feature that distinguishes them from most patients with TTP.

Many authorities do not advocate TPE for HUS, but when there is progressive deterioration in the face of supportive care and dialysis it should be considered, even though the rationale is unclear in the presence of normal ADAMTS13 levels. If the differentiation between HUS and TTP cannot be made, one usually presumes the diagnosis is TTP and treats with TPE.⁵

Disseminated Intravascular Coagulation

The key clinical features shared by DIC²⁰ and TTP are thrombocytopenia and MAHA characterized by schistocytes on the peripheral blood smear. In addition, several underlying conditions, such as certain obstetric complications and sepsis, can predispose to both DIC and TTP. In some patients, the multiorgan ischemia caused by TTP may lead to the development of DIC.

Whereas patients with TTP usually have normal clotting times indicative of an intact fibrin-generating coagulation cascade, individuals with full-blown DIC have markedly prolonged clotting times (related to clotting factor consumption) and an activated fibrinolytic system. It is to be noted, however, that DIC represents a spectrum of changes.²¹ In less advanced (more compensated) stages of DIC there may be minimal disruption of clotting times, mild thrombocytopenia, and a significant number of schistocytes—symptoms that might not be immediately distinguishable from TTP. In this phase, detection of increased fibrinolysis, as indicated by elevated D dimer levels, can help make a positive diagnosis of DIC. In more advanced DIC, schistocytes can be less evident than in TTP because of enhanced fibrinolysis of the intravascular fibrin strands felt to be responsible for the RBC shearing noted in earlier stages of DIC. Advanced DIC also is characterized by more bleeding than is usually seen in TTP. The consumptive changes in early DIC can be difficult to detect by clotting factor measurements (eg, fibrinogen and factor VIII levels) because of overshoot compensation and acute phase reactions leading to elevated levels. Serial determinations of these factor levels will often help identify downward trends as the consumptive phase accelerates.

Heparin-induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT) (type II) in the vaso-occlusive phase can mimic TTP because of thrombocytopenia and venous and/or arterial occlusions

(usually larger vessels affected than in TTP). Despite the platelet clumping leading to intravascular occlusions in HIT, there is little or no formation of schistocytes. Also, there is no marked elevation of LDH or signs of intravascular hemolysis. It is important, however, to rule out HIT as a coexisting disorder when TTP fails to show the expected rise in platelet count with TPE and steroid therapy.

It is well recognized that, once established, HIT can be sustained by ongoing exposure to very small amounts of heparin. Sometimes the source(s) of heparin exposure, such as line flushes and leaching of heparin from bonded catheters, is not immediately evident. Although the gold standard for the diagnosis of HIT remains the recovery of the platelet count following discontinuation of heparin exposure, laboratory testing can be helpful in excluding or confirming the clinical suspicion of the diagnosis.

Antiphospholipid Syndrome

Patients with antiphospholipid antibodies can have a spectrum of clinical presentations ranging from no symptoms or signs to the catastrophic antiphospholipid antibody syndrome.²² Antiphospholipid syndrome (APS) can present with some of the features seen in TTP, including thrombocytopenia and multiple vaso-occlusive events, both venous and arterial, which may affect multiple organ systems. APS can be primary (ie, occurring in the absence of a recognized associated illness or triggering drug) or secondary (eg, associated with an underlying autoimmune disorder, most commonly systemic lupus erythematosus [SLE]). As in TTP, hemolytic anemia may be present, but is more likely to be autoimmune (with positive direct Coombs test and spherocytes on peripheral blood smear accompanied by elevated mean corpuscular hemoglobin concentration) than MAHA unless there is an associated vasculitis or the catastrophic phase has supervened. In secondary cases, if the lupus anticoagulant is present, coagulation studies can reveal prolonged partial thromboplastin time, Russell viper venom time, and, uncommonly, prothrombin time. A circulating anticoagulant may be detected. These coagulation abnormalities are not expected in TTP. Another differentiating feature is the presence of anticardiolipin and β 2-glycoprotein I antibodies in APS. In some acute-phase APS cases these antibody levels are lowered due to consumption,²³ making confirmation of the diagnosis more difficult.

It is important to distinguish APS, either primary or secondary, from TTP because therapeutic interventions in APS with vaso-occlusive features would include anticoagulants. In addition, corticosteroids, cytotoxic agents, and plasmapheresis to remove antiphospholipid antibodies²⁴ might be useful, depending on the clinical situation.

Evans Syndrome

The combination of autoimmune hemolytic anemia and autoimmune thrombocytopenia as originally described by Evans and colleagues²⁵ is sometimes considered in the differential diagnosis of TTP. Evans syndrome, whether alone or as a feature of SLE, can usually be distinguished from TTP by the presence of a positive direct Coombs test, platelet-associated antibodies, and the appearance of predominantly spherocytes rather than schistocytes on the peripheral blood smear. Typically, the markers of intravascular hemolysis are absent in Evans syndrome. There may be some confusion if TTP and autoimmune hemolytic anemia coexist.²⁶

Thrombotic Microangiopathies of Pregnancy and Postpartum

There are several conditions related to pregnancy and the postpartum period^{5,27} that can mimic or overlap with TTP. These include preeclampsia/eclampsia, HELLP (hemolysis, elevated liver enzyme levels, low platelet count) syndrome, APS, DIC, acute fatty liver of pregnancy (AFLP), and postpartum HUS. It is well recognized that TTP can present at any time during gestation or after delivery. Pregnancy can precipitate a relapse in women with a prior history of TTP; fortunately, pregnancy does not seem to interfere with response to TPE. In contrast to its beneficial effect in some of the syndromes unique to pregnancy (eg, HELLP, preeclampsia/eclampsia, and AFLP), which tend to occur in the third trimester and can mimic TTP, delivery does not seem to affect the course of TTP and maternal outcome. Thus it is especially important to make an accurate diagnosis and begin treatment promptly in the setting of pregnancy because TTP is progressive and may be fatal if left untreated.

Preeclampsia/Eclampsia

Preeclampsia/eclampsia can have features that fully overlap with TTP, but its defining characteristics—hypertension, proteinuria, and edema—are not typical of TTP. In addition, decreased antithrombin III levels may be among the prothrombotic changes seen in preeclampsia; this is not a feature of TTP.⁵

HELLP Syndrome

HELLP syndrome can occur in patients with or without preeclampsia and has several distinctive features: mid-epigastric or right upper quadrant abdominal pain, nausea and/or vomiting,²⁸ elevated liver enzymes indicating parenchymal dysfunction, eye symptoms (eg, retinal detachments, vitreal hemorrhage, and cortical blind-

ness), and progressive hyperbilirubinemia.^{29,30} HELLP syndrome can be further complicated by development of DIC, abruptio placenta, acute renal failure, and pulmonary edema.⁵ Fever is not a feature of uncomplicated HELLP syndrome. Profound renal or hepatic failures are uncommon and, thus, are features that distinguish HELLP syndrome from postpartum HUS and AFLP, respectively. Typically, HELLP resolves after delivery, but sometimes corticosteroids and TPE may be needed if complete resolution has not occurred by 2–3 days postpartum. TPE for HELLP syndrome during pregnancy is ineffective.³⁰ In some patients HELLP may develop or recur postpartum. There is a risk of hepatic hematoma and rupture in patients unresponsive to treatment.

Acute Fatty Liver of Pregnancy

AFLP is a rare disorder characterized predominantly by liver dysfunction. Preeclampsia is associated in about 50% of the patients. There is usually mild thrombocytopenia; hemolysis, if present, is a minor aspect. DIC is frequently a complicating feature. In some patients a predisposing factor is a maternal/fetal genetic defect in the metabolism of free fatty acids (deficiency of long-chain 3-hydroxy acyl-coenzyme A dehydrogenase).³⁰ This abnormality can also be present in HELLP syndrome.³¹ For patients refractory despite delivery and aggressive TPE, orthotopic liver transplantation has been performed with success.³²

Postpartum HUS

HUS has been reported very rarely during pregnancy but is a well-recognized cause of subacute oliguric renal failure presenting up to 10 weeks postpartum. Some patients appear to require more TPEs and longer duration of therapy.³³

DIC and APS

DIC and APS have been reported during and after pregnancy. The differentiation of these disorders from TTP has been addressed earlier. Some unique obstetric problems predispose to DIC, for example, abruptio placenta and retained dead fetus. Appropriate obstetric interventions and blood product support are the treatments.

Vascular Injury and Mechanical Intravascular Devices

In clinical conditions predisposing to endovascular injury, such as vasculitis and malignant hypertension, alterations of the endothelial surface and generation of schistocytes can occur. In fact, patients with malignant hypertension may have all the clinical features of TTP, including thrombocytopenia. Depending upon the underlying disorder, for example, SLE, there may be accompanying

thrombocytopenia, renal dysfunction, and altered chemistries reflecting ischemia or other types of injury to several target organs. Often the accompanying clinical findings, such as severe hypertension, vasculitic rash, or angiographic changes help clarify the cause of the hematologic abnormalities. Mechanical cardiac valves, especially if complicated by jet leaks, calcified native heart valves, and intravascular hardware, such as aortic balloon pumps, can cause RBC injury, leading to formation of schistocytes and laboratory indicators of intravascular hemolysis. An accompanying decline in platelet count can occur which, coupled with the RBC changes, may suggest TTP. Usually the clinical situation is well defined and there is little diagnostic dilemma.

Multiorgan Failure

The hematologist is often asked to see patients who have multiorgan failure with complicating infections and a variety of medication effects. The complete pentad of TTP symptoms or key parts of it can be caused by several coexisting processes unrelated to TTP. In such challenging situations, making a diagnosis of TTP and introducing corticosteroids and TPE based simply on the constellation of findings without careful scrutiny of possible multiple contributing causes could be harmful.

In these patients it is particularly important to sort out and treat potentially reversible factors commonly present in patients in intensive care settings. Some examples include: 1) changing medications that may be causing thrombocytopenia, such as heparin and others²⁸; 2) treating sepsis aggressively to remove a cause of complicating DIC with schistocytes; 3) exploring drug-induced renal or nervous system dysfunction, which may be improved by change in medications; and 4) suspecting a drug-induced TTP syndrome, especially in patients with solid organ transplants or individuals receiving antineoplastic chemotherapy.

Conclusion

We have discussed the criteria for diagnosing classic TTP and a number of clinical disorders that can overlap or mimic it (Table 1). In some instances, diagnosis of another entity with similar features is not difficult. However, when the features of TTP are incomplete (eg, only thrombocytopenia and MAHA are present) or are in evolution, or several disorders coexist and mimic TTP, as in patients with multiorgan failure, it may be impossible to make a definite diagnosis. It is hoped that newer and more rapidly available testing for ADAMTS13 activity and its inhibitor⁹ will help clarify the diagnosis of TTP in some of these situations. However, inconsistent changes

Table 1. Distinguishing Features of Thrombotic Thrombocytopenic Purpura and its Look-Alikes

Disorder	Features
Thrombotic thrombocytopenic purpura (acute idiopathic)	Prominent MAHA with schistocytes and thrombocytopenia Highly elevated serum LDH level Neurologic symptoms Strongly decreased ADAMTS13 (+inhibitor) level Response to TPE, not delivery, if patient is pregnant
Hemolytic uremic syndrome	Prominent renal function impairment Association in some cases with verotoxin-producing enteric infections More likely in younger adults and children Normal ADAMTS13 level Variable response to TPE
Disseminated intravascular coagulation	Prolonged clotting times and evident fibrinolysis Clinical bleeding in advanced stage
Heparin-induced thrombocytopenia	No MAHA Antiplatelet factor 4 antibodies Heparin-induced platelet aggregation
Antiphospholipid syndrome	Antiphospholipid antibodies No MAHA; may have positive Coombs test if associated with SLE May have lupus anticoagulant with prolonged clotting times (especially PTT and RVVT) and inhibitor Response to plasmapheresis, not delivery, if patient is pregnant
Evans syndrome	Autoimmune hemolysis (positive Coombs test)
Preeclampsia/eclampsia	Hypertension Proteinuria Edema Response to delivery, not to TPE
HELLP syndrome	Liver dysfunction No fever Low antithrombin III level Response to delivery; TPE may help in refractory patients postpartum
Acute fatty liver of pregnancy	Prominent liver dysfunction No fever Response to delivery; TPE may help in refractory patients postpartum

HELLP = hemolysis, elevated liver enzymes, low platelet count; LDH = lactic dehydrogenase; MAHA = microangiopathic hemolytic anemia; PTT = partial thromboplastin time; RVVT = Russell viper venom time; SLE = systemic lupus erythematosus; TPE = therapeutic plasma exchange.

in ADAMTS13 levels in TTP (sometimes due to plasma transfusions administered prior to suspicion of TTP) and overlap of these levels with those seen in other clinical conditions still leave the burden of diagnosis in the hands of the clinician who assesses the full clinical scenario.

In those circumstances in which TTP cannot be diagnosed with confidence and there is progressive deterioration (eg, falling platelets, increasing schistocytes, and end-organ injury) it is prudent to initiate treatment with TPE without delay. Improvement in the patient's clinical status and laboratory parameters with treatment helps to confirm the diagnosis, but sometimes multiple TPE treatments are required before response is evident.⁵

References

1. Moschowitz E. An acute febrile pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries. *Arch Int Med.* 1925;36:89-93.
2. Amorosi EL, Ultmann JE. Thrombotic thrombocytopenic purpura: report of 16 cases and review of the literature. *Medicine.* 1996;45:139-159.
3. McMinn JR Jr, Thomas IA, Terrell DR, et al. Complications of plasma exchange in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: a study of 78 additional patients. *Transfusion.* 2003;43:415-416.
4. Cohen JA, Brecher ME, Bandarenko N. Cellular source of serum lactate dehydrogenase elevation in patients with thrombotic thrombocytopenic purpura. *J Clin Apher.* 1998;13:16-19.
5. Allford SL, Hunt BJ, Rose P, et al. Haemostasis and Thrombosis Task Force, British Committee for Standards in Haematology. Guidelines on the diagnosis and management of the thrombotic microangiopathic haemolytic anemias. *Br J Haematol.* 2003;120:556-573.

6. Burns ER, Lou Y, Pathak A. Morphologic diagnosis of thrombotic thrombocytopenic purpura. *Am J Hematol*. 2004;76:18-21.
7. Downes KA, Yomtavian R, Tsai HM, et al. Relapsed thrombotic thrombocytopenic purpura presenting as an acute cerebrovascular accident. *J Clin Apher*. 2004;19:86-89.
8. Moake JL. Thrombotic microangiopathies. *N Engl J Med*. 2002;347:589-600.
9. Sadler JE, Moake JL, Miyata T, et al. Recent advances in thrombotic thrombocytopenic purpura. *Hematology* (Am Soc Hematol Educ Program). 2004; 407-423.
10. Peyvandi F, Ferrari S, Lavoretano S, et al. von Willebrand's factor cleaving protease (ADAMTS-13) and ADAMTS-13 neutralizing autoantibodies in 100 patients with thrombotic thrombocytopenic purpura. *Br J Haematol*. 2004;127:433-439.
11. Baron BW, Martin MS, Suchareza BS, et al. Four patients with both thrombotic thrombocytopenic purpura and autoimmune thrombocytopenic purpura: concept of a mixed immune thrombocytopenia syndrome and indications for plasma exchange. *J Clin Apher*. 2001;16:179-85.
12. Rock GA, Shumack KH, Buskard NA, et al. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. *N Engl J Med*. 1991;325:393-397.
13. Bell WR, Braine HG, Ness PM, et al. Improved survival in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: clinical experience in 108 patients. *N Engl J Med*. 1991;325:398-403.
14. Chemnitz J, Draube A, Scheid C, et al. Successful treatment of severe thrombotic thrombocytopenic purpura with the monoclonal antibody rituximab. *Am J Hematol*. 2002;71:105-108.
15. Bennett CL, Connors JM, Carwile JM, et al. Thrombotic thrombocytopenic purpura associated with clopidogrel. *N Engl J Med*. 2000;342:1773-1777.
16. Baron BW, van Besien K, Hoffman PC, et al. Thrombotic thrombocytopenic purpura after cephalosporin administration: a possible relationship. *Transfusion*. 2003;43:1317-1321.
17. Murgo AJ. Thrombotic microangiopathy in the cancer patient including those induced by chemotherapeutic agents. *Semin Hematol*. 1987;24:161-177.
18. Keung Y-K, Morgan D, Cobos E. Cocaine-induced microangiopathic hemolytic anemia and thrombocytopenia simulating thrombotic thrombocytopenic purpura. *Ann Hematol*. 1996;72:155-156.
19. Gordon LI, Kwaan HC. Thrombotic microangiopathy manifesting as thrombotic thrombocytopenic purpura/hemolytic uremic syndrome in the cancer patient. *Semin Thromb Hemost*. 1999;25:217-221.
20. Levi M, ten Cate H. Disseminated intravascular coagulation. *N Engl J Med*. 1999;341:586-592.
21. Feinstein DI, Marder VJ, Coleman RW. Consumptive thrombohemorrhagic disorders. In: Colman RW, Hirsch J, Marder VJ, Clowes AW, George JN, eds. *Hemostasis and Thrombosis*. 4th ed. Philadelphia: Lippincott, Williams and Wilkins; 2001:1197-1233.
22. Asherson R. The catastrophic antiphospholipid syndrome, 1998. A review of the clinical features, possible pathogenesis and treatment. *Lupus*. 1998;7(suppl 2):555-562.
23. Gomez-Pacheco L, Villa AR, Drenkard C, et al. Serum anti-B2-glycoprotein-1 and anticardiolipin antibodies during thrombosis in systemic lupus erythematosus patients. *Am J Med*. 1999;106:417-423.
24. Flamholz R, Tran T, Grad GI, et al. Therapeutic plasma exchange for the acute management of the catastrophic antiphospholipid syndrome: glycoprotein I antibodies as a marker of response and therapy. *J Clin Apher*. 1999;14:171-176.
25. Evans RS, Duane RT. Acquired hemolytic anemia. I. The relation of antibody activity to activity of the disease. II. The significance of thrombocytopenia and leukopenia. *Blood*. 1949;4:1196-1213.
26. Krupsky M, Sarel R, Hurwitz N, et al. Late appearance of thrombotic thrombocytopenic purpura after autoimmune hemolytic anemia and in the course of chronic autoimmune thrombocytopenic purpura: two case reports. *Acta Haematol*. 1991;85:139-142.
27. McMinn JR Jr, George JN. Evaluation of women with clinically suspected thrombotic thrombocytopenic purpura-hemolytic anemia syndrome during pregnancy. *J Clin Apher*. 2001;16:202-209.
28. Drews RE, Weinberger SE. Thrombocytopenic disorders in critically ill patients. *Am J Resp Crit Care Med*. 2000;162:347-351.
29. Martin JN, Rinehart BK, May EF, et al. The spectrum of severe preeclampsia: comparative analysis by HELLP (hemolysis, elevated liver enzyme levels, and low platelet count) syndrome classification. *Am J Obstet Gynecol*. 1999;180:1373-1384.
30. Steingrub JS. Pregnancy-associated severe liver dysfunction. *Crit Care Clin*. 2004;20:763-776.
31. Ibdah JA, Bennett MJ, Rinaldo P, et al. A fetal fatty acid oxidation disorder as a cause of liver disease in pregnant women. *N Engl J Med*. 1999;340:1723-1731.
32. Ockner SA, Brunt EM, Cohen SM, et al. Fulminant hepatic failure caused by acute fatty liver of pregnancy treated by orthotopic liver transplantation. *Hepatology*. 1990;11:59-64.
33. Shemin D, Dworkin LD. Clinical outcome in three patients with postpartum hemolytic uremic syndrome treated with frequent plasma exchange. *Ther Apher*. 1998;2:43-48.