Evaluation of Patients with Microangiopathic Hemolytic Anemia and Thrombocytopenia

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Abstract

When a patient presents with unexpected microangiopathic hemolytic anemia and thrombocytopenia, the diagnosis of thrombotic thrombocytopenic purpura (TTP) is often considered. However, many different disorders, including many different systemic infections and malignancies, can cause thrombotic microangiopathy (TMA), with the clinical features of microangiopathic hemolytic anemia and thrombocytopenia. Other etiologies include severe hypertension, preeclampsia, systemic lupus erythematosus, adverse drug reactions, allogeneic hematopoietic stem cell transplantation, and abnormalities of complement regulation. This article focuses on distinguishing TTP from other etiologies of microangiopathic hemolytic anemia and thrombocytopenia, because consideration of the diagnosis of TTP requires an urgent decision for the initiation of plasma exchange treatment. Awareness of the many etiologies of TMA is essential for the appropriate evaluation of patients presenting with microangiopathic hemolytic anemia and thrombocytopenia and the appropriate diagnosis of TTP.

Keywords
- ► microangiopathic hemolytic anemia
- ► thrombotic thrombocytopenic purpura
- ► thrombotic microangiopathy

The term "thrombotic microangiopathic hemolytic anemia," together with a shorter version, "thrombotic microangiopathy" (TMA), was first suggested by Symmers in 1952 as a name for what we now know as thrombotic thrombocytopenic purpura (TTP).[1] Symmers proposed this name because it described the "unique histological picture of widely disseminated thrombosis of the smallest-caliber blood vessels, with endothelial hyperplasia, conspicuous dilatation of many of the affected vessels, and no inflammatory reaction."[1] In 1964, Brain et al reported that the vascular lesions of TMA occurred in disorders other than TTP and documented that these lesions were the cause of hemolysis characterized by the presence of fragmented red cells. They named this disorder "microangiopathic hemolytic anemia."[2] In their report of 25 patients, the etiologies of microangiopathic hemolytic anemia, in addition to TTP, were malignant hypertension, metastatic carcinoma, systemic lupus erythematosus (SLE), polyarteritis nodosa, acute glomerulonephritis, and renal cortical necrosis. Most patients had thrombocytopenia in addition to microangiopathic hemolytic anemia.[2] Over the past 50 years, the clinical spectrum of patients with microangiopathic hemolytic anemia and thrombocytopenia has continued to increase.

Importance of Diagnosing Microangiopathic Hemolytic Anemia for Decisions on Therapy

The distinction among the disorders causing microangiopathic hemolytic anemia and thrombocytopenia became more important when effective treatment for TTP became available. In 1991, a randomized clinical trial documented that the treatment of TTP with plasma exchange (PEX) resulted in 78% survival,[3] compared with only 10% survival 25 years earlier without PEX.[4] The inclusion criteria for this clinical trial were only microangiopathic hemolytic anemia and thrombocytopenia

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without an apparent alternative etiology[3]; these continue to be the current diagnostic criteria for TTP.[5] The effectiveness of PEX treatment created urgency to diagnose TTP and to begin therapy, which in turn created urgency to exclude alternative etiologies of microangiopathic hemolytic anemia and thrombocytopenia. Therefore, the objective of this article is to address the clinical problem of distinguishing TTP from the alternative etiologies of microangiopathic hemolytic anemia and thrombocytopenia. Treatment of patients with alternative etiologies, such as infections, malignancies, and severe hypertension, requires alternate therapies.

This article describes the principal disorders that can cause microangiopathic hemolytic anemia and thrombocytopenia and which may therefore need to be considered in the differential diagnosis of TTP. In some patients, systemic infections or malignancies are the clearly apparent cause of microangiopathic hemolytic anemia and thrombocytopenia. In these patients, TTP should not be diagnosed and PEX should not be instigated. In other patients, the cause of microangiopathic hemolytic anemia and thrombocytopenia is not apparent. In these patients, TTP often becomes a principal consideration.[5] Consideration of the diagnosis of TTP requires urgent consideration of PEX, a procedure which can control TTP[3] but which also has risk for major complications.[6] This is a clinician's perspective that often becomes the clinician's diagnostic dilemma.

The Oklahoma Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome Registry

The clinician's perspective on the evaluation of patients with clinically suspected TTP is reflected in the experience of the Oklahoma TTP-hemolytic uremic syndrome (HUS) Registry. Patients are enrolled in the Oklahoma Registry when their treating clinicians determine that the probability of TTP is sufficiently great to begin PEX[5,7,8] and to justify the risk of PEX.[6] Even among patients enrolled in the Oklahoma Registry, alternative etiologies for the microangiopathic hemolytic anemia commonly occur. Sometimes an alternative etiology is recognized promptly and PEX is then stopped; sometimes an alternative etiology is not discovered until autopsy; sometimes an alternative etiology is only suspected but never confirmed. From the beginning of the Registry, on January 1, 1989, through December 31, 2011, 451 patients have been enrolled: 439 with their first episode of TTP diagnosed either by clinical features (427 patients) or by a renal biopsy demonstrating TMA (12 patients). We discuss patients diagnosed by renal biopsy separately because they often did not have clinical diagnostic features of TTP, microangiopathic hemolytic anemia, and thrombocytopenia. An additional 12 patients had PEX begun for their initial episode of TTP outside the Registry region, or were enrolled for a relapsed episode when the initial episode preceded 1989, or were treated outside of the Registry region. Beginning on November 13, 1995, through December 31, 2011, serum samples were collected immediately before beginning PEX on most patients (320/343 or 93% of consecutive patients), allowing for measurement of ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member-13) activity.[8] Data for the 320 patients who had ADAMTS-13 determinations before therapy are presented in ►**Table 1**; only 70 (22%) of these patients had severe ADAMTS-13 deficiency (activity < 10%). Therefore, 78% of patients who were enrolled in the Oklahoma Registry since 1995 have had an alternative etiology of TMA or they had TTP without severe ADAMTS-13 deficiency.

Not only are there many potential etiologies of TMA in addition to TTP, patients with a diagnosis of TTP and a documented severe ADAMTS-13 deficiency can present in extraordinarily diverse ways.[9] TTP, as well as other TMA syndromes, may present in hospitalized patients or in previously healthy people. The onset may be insidious or sudden. Patients may be critically ill or have no systemic symptoms. The only clinical features that are present in all of the microangiopathic hemolytic anemia disorders discussed here are microangiopathic hemolytic anemia and thrombocytopenia.

Terminology of the Thrombotic Microangiopathic Syndromes

Terminology is important. TMA is a descriptive term for the characteristic pathological findings of all syndromes that manifest with microangiopathic hemolytic anemia and thrombocytopenia, and is therefore the inclusive term for all disorders discussed in this article. This discussion focuses on adults in whom treatment with PEX is considered for the diagnosis termed TTP. Although some have implied that TTP is defined by severe ADAMTS-13 deficiency (activity < 10%),[10,11] we consider TTP as the appropriate diagnosis for all patients who fulfill current diagnostic criteria, which are the presence of microangiopathic hemolytic anemia and thrombocytopenia without an apparent alternative etiology, regardless of ADAMTS-13 activity.[5] Our article focuses on patients with acquired disorders as hereditary TTP caused by congenital ADAMTS-13 deficiency is extremely rare[12] and will not be discussed. Among all 462 patients enrolled in the Registry through October 31, 2012, only one family was identified with hereditary TTP (in 2012).

Some clinicians may use the term HUS when renal failure is the predominant clinical abnormality, but HUS is traditionally a pediatric term, used to describe children with TMA preceded by a diarrheal illness caused by an enterohemorrhagic infection with *Escherichia coli* (*E. coli*) O157:H7 (or other Shiga toxin–producing strains). Children with HUS are treated with supportive care and PEX is rarely used.[13] Children without a diarrhea prodrome are described as "atypical" HUS (aHUS), a term that has recently been adopted as the name for syndromes caused by complement regulatory abnormalities.[14] Microangiopathic hemolytic anemia and thrombocytopenia caused by infection with *E. coli* O157:H7 and complement regulatory abnormalities are uncommon among adults.

Disorders that Can Cause Microangiopathic Hemolytic Anemia

The principal disorders that can cause microangiopathic hemolytic anemia and thrombocytopenia, and therefore

Table 1 Frequency of severe ADAMTS-13 deficiency in patients initially diagnosed as having thrombotic thrombocytopenic purpura or hemolytic uremic syndrome in the Oklahoma TTP-HUS Registry

Patient categories	Patients	
	All	ADAMTS-13 <10%
Patients diagnosed by clinical features		
Stem cell transplant	12	1 (8%)
Pregnancy	17	3 (18%)
Drug-associated		
Quinine	20	0
Drugs causing dose-dependent toxicity[a]	13	0
Other drugs[b]	6	0
Bloody diarrhea prodrome (presumed Shiga toxin etiology)	30	2 (7%)
Additional or alternative disorder		
Autoimmune disorders	40	4 (10%)
Sepsis	25	4 (16%)
Systemic malignancy	10	1 (10%)
Severe hypertension	6	0
Other disorders	13	0
"Idiopathic" (none of the above)	119	55 (46%)
Patients diagnosed by renal biopsy		
Drug-associated		
Tacrolimus	4	0
Gemcitabine	1	0
Bloody diarrhea prodrome (presumed Shiga toxin etiology)	1	0
Autoimmune disorders		
Systemic lupus erythematosus	1	0
Scleroderma	1	0
"Idiopathic" (none of the above)	1	0
Total	320	70 (22%)

Abbreviations: ADAMTS-13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member-13; TTP-HUS, thrombotic thrombocytopenic purpura-hemolytic uremic syndrome.
Note: The table summarizes data for 320 of 343 (93%) consecutive patients who enrolled in the Registry from November 13, 1995 through December 31, 2011, and also had ADAMTS-13 activity measured immediately before their initial plasma exchange, using both fluorescence resonance energy transfer and immunoblotting assays.[8] Patient categories were assigned at the time of the initial episode in a hierarchical manner; no patient could be in more than one category.[7] In 64 of the 70 patients with severe ADAMTS-13 deficiency (activity < 10%), the TMA was attributed to TTP (postpartum, $n = 3$; presentation with bloody diarrhea, $n = 2$; previous or concurrent diagnosis of systemic lupus erythematosus, $n = 3$; previous diagnosis of Sjögren syndrome, $n = 1$; and idiopathic, $n = 55$). In the other six patients with severe ADAMTS-13 deficiency, the TMA was attributed to another etiology (sepsis, $n = 4$; systemic malignancy, $n = 1$; and sepsis following allogeneic HSCT, $n = 1$).
[a]Mitomycin C, $n = 4$; gemcitabine, $n = 4$; carmustine, $n = 1$; pentostatin, $n = 1$; carboplatin-taxol, $n = 1$; cyclosporine, $n = 2$.
[b]Alendronate, $n = 1$; clopidogrel, $n = 1$; cocaine, $n = 1$; ticlopidine, $n = 1$; trimethoprim-sulfamethoxazole, $n = 1$; vancomycin, $n = 1$.

mimic TTP, are summarized in ►**Table 2**. For each of these disorders, we have summarized data from the Oklahoma Registry (►**Table 1**) and the clinical features that may help to distinguish these disorders from TTP (►**Table 2**).

Systemic Infections

Many different systemic infections can cause microangiopathic hemolytic anemia and thrombocytopenia and therefore may mimic TTP. In the Oklahoma Registry, 31 (7%) of 415 patients (1989–2010) were initially diagnosed as having TTP and were treated with PEX, then subsequently, their illness was attributed to a systemic infection.[15] Sixteen (52%) of these 31 patients had fever, neurologic abnormalities, and renal failure in addition to microangiopathic hemolytic anemia and thrombocytopenia, comprising the complete "pentad" of clinical features that were associated with TTP in the era before effective treatment.[4] In contrast, the complete "pentad" of clinical features rarely occurs in patients in whom the diagnosis of TTP is supported by the documentation of severe ADAMTS-13 deficiency. For example, among 70 consecutive

Table 2 Etiologies of thrombotic microangiopathies that cause microangiopathic hemolytic anemia and thrombocytopenia and may mimic thrombotic thrombocytopenic purpura associated with severe ADAMTS-13 deficiency

Etiologies	Distinction from TTP
Systemic infections	Many different bacterial, viral, and fungal etiologies have been reported to cause MAHA and thrombocytopenia. Critical illness with coma, renal failure, and high fever with chills suggests sepsis rather than TTP.
Systemic malignancies	Microvascular thrombi caused by many different malignant disorders can cause pathologic lesions similar to TMA. Older age, gradual onset of symptoms, weight loss, localized pain, pulmonary involvement, and a leukoerythroblastic reaction on the peripheral blood smear suggest malignancy. A bone marrow biopsy is the essential diagnostic test.
Severe hypertension	Renal TMA caused by hypertension is indistinguishable from TTP. Severe neurologic abnormalities related to PRES may occur.
Pregnancy-related syndromes	Severe preeclampsia and HELLP syndrome may be indistinguishable from TTP. Spontaneous improvement following delivery is the most important distinguishing criterion. The distinction is difficult because pregnancy may also trigger the occurrence of acute episodes of TTP.
Systemic lupus erythematosus	SLE may have all of the diagnostic clinical features of TTP, especially in patients with lupus nephritis and hypertension. The distinction is difficult because patients with TTP have increased risk for developing SLE.
Adverse drug reactions	Multiple drugs have been reported to cause acute, severe MAHA and thrombocytopenia. An immune-mediated mechanism has only been documented for quinine and this is the most common drug etiology. Dose-dependent toxicity by chemotherapy or calcineurin inhibitors can also cause MAHA.
Allogeneic hematopoietic stem cell transplantation	A syndrome of transplantation-associated TMA has been described that is distinct from TTP and unresponsive to plasma exchange treatment.
Abnormalities of complement regulation	Genetic abnormalities of complement regulatory factors may be associated with renal TMA.

Abbreviations: ADAMTS-13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member-13; HELLP, hemolysis, elevated liver function tests, low platelets; MAHA, microangiopathic hemolytic anemia; PRES, posterior reversible encephalopathy syndrome; SLE, systemic lupus erythematosis; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

patients with severe ADAMTS-13 deficiency in the Registry, only 15 (21%) patients had fever. Most of these patients had mild fever; high fever with chills rarely occurred.[5,9,16] Furthermore, the complete "pentad" of clinical features was present in only three (4%) patients, in two of these patients the presenting clinical features were subsequently attributed to a systemic infection.[5,15,16] Although disseminated intravascular coagulation (DIC) occurring with systemic infections may cause microangiopathic hemolytic anemia and thrombocytopenia, most of these patients had no coagulation abnormalities. A systematic literature review identified 67 additional patients who had been reported to have an infection associated with TTP or HUS.[13] In some reports, the authors described the infection as mimicking TTP or HUS; in other reports, it was assumed that the patients had both TTP or HUS and a systemic infection.[15] Among all 98 patients, 41 different infectious etiologies were described, including bacterial, viral, and fungal infections.[15] The most commonly reported etiologies were angioinvasive infections: cytomegalovirus (seven patients) and aspergillus (six patients).

The Oklahoma Registry experience suggests that the systemic infections were merely mimicking TTP. Of the 31 patients with systemic infections, 21 (68%) died and 6 had autopsies with no evidence for TTP. An alternative interpretation is that a systemic infection may have "triggered" the onset of TTP, a sequence that has been documented for TTP associated with severe ADAMTS-13 deficiency following influenza A infection.[17] The concept that systemic infections may trigger the onset of TTP is consistent with observations that other conditions, such as pregnancy,[18,19] surgery,[20] and pancreatitis,[21] can apparently trigger acute episodes of TTP.

Documentation of severe ADAMTS-13 deficiency (activity $< 10\%$) is not sufficiently specific to exclude a systemic infection as the etiology of microangiopathic hemolytic anemia and thrombocytopenia. Of the 31 patients with systemic infections, 4 (13%) had severe ADAMTS-13 deficiency.[9,15] One of these four patients had an autopsy with no evidence of TTP.[15] One patient with documented bacterial endocarditis had undetectable ADAMTS-13 activity with no demonstrable inhibitor.[8] One year later, when she was asymptomatic, ADAMTS-13 activity was 92%; the following year when she remained asymptomatic, ADAMTS-13 activity was again undetectable with no demonstrable inhibitor.[9] We have no explanation for her intermittent severely deficient ADAMTS-13 activity.

Human Immunodeficiency Virus Infection

Human immunodeficiency virus (HIV) infection requires specific discussion because multiple reports have suggested that it can cause TTP.[22,23] Among Oklahoma Registry patients, the prevalence of HIV infection (1.8%, 95% confidence interval, 0.7 to 4.0%) was only slightly greater than the prevalence of HIV infection among all Oklahoma adults (0.3%).[24] Certainly, the prevalence of HIV infection among Oklahoma Registry patients was not comparable to the 83% prevalence reported for patients with TTP in South Africa, in which HIV infection was described as the "commonest cause of TTP."[23] There are multiple reasons for the diagnosis of TTP in patients with HIV infection[24,25]: (1) HIV infection may cause endothelial injury resulting in TMA, mimicking TTP; (2) HIV-associated nephropathy with malignant hypertension may cause TMA and mimic TTP; (3) acquired immunodeficiency syndrome (AIDS)-related infections or malignancies may mimic TTP; (4) HIV infection may trigger the onset of TTP in patients with severe ADAMTS-13 deficiency; and (5) HIV infection may coincidentally occur in a patient with TTP. Among the six patients with HIV infection in the Oklahoma Registry, it may have been coincidental in one patient[9,24,26] and may have triggered the onset of an acute episode of TTP in another.[24] In the other four patients with HIV, the clinical features were subsequently attributed to HIV-associated nephropathy with hypertension in three and systemic Kaposi sarcoma in one.[24]

Enterohemorrhagic Infections with Shiga Toxin–Producing Bacteria

This is the cause of the "typical" diarrhea-associated HUS in young children[13] and also, less commonly, in adults.[27] Although outbreaks are widely publicized,[28] endemic sporadic occurrence is more common.[29] TTP associated with severe ADAMTS-13 deficiency can cause hemorrhagic colitis that is pathologically indistinguishable from Shiga toxin–induced colitis, with bloody diarrhea mimicking the presentation of typical HUS.[30] Among 30 Registry patients who presented with bloody diarrhea, two had TTP associated with severe ADAMTS-13 deficiency.[9,27] Therefore, adults who present with bloody diarrhea may be appropriately treated with PEX. If stool analysis reveals *E. coli* O157:H7 or Shiga toxin, and the clinical abnormalities are resolving, PEX may be stopped. However, Shiga toxin–induced HUS has a high mortality among adults and empiric PEX may be appropriate.[27]

Systemic Malignancies

In the initial description of microangiopathic hemolytic anemia and thrombocytopenia by Brain et al in 1964,[2] 5 of 25 patients had metastatic carcinoma (gastric, 3; lung, 1; prostate, 1). A recent review of systemic malignancies as an unexpected cause of microangiopathic hemolytic anemia and thrombocytopenia described 65 patients with 19 different malignancies, suggesting that any systemic malignancy may cause microangiopathic hemolytic anemia and thrombocytopenia.[31] Although DIC occurring in systemic malignancies may cause microangiopathic hemolytic anemia and thrombocytopenia, most reported patients with malignancy associated microangiopathic hemolytic anemia and thrombocytopenia had no evidence for DIC.[31–33] In such patients without DIC, systemic microvascular tumor emboli may cause TMA and mimic both the clinical and pathologic features of TTP.[32,34] In the Oklahoma Registry, 10 patients were documented to have a systemic malignancy as the cause of their clinical features. One woman had systemic microvascular thrombi caused by breast carcinoma cells that were not detected until a microscopic analysis of autopsy tissues was performed.[31,34] One man had HIV infection and systemic Kaposi sarcoma that was documented by autopsy, in association with a severe ADAMTS-13 deficiency, but no autopsy evidence for TTP.

Clues that may suggest the presence of systemic malignancy in a patient with suspected TTP include older age and a gradual onset of symptoms with weight loss.[32] However, the onset can also be sudden.[34] Localized pain and respiratory symptoms, with an abnormal chest X-ray, are common in patients with systemic malignancies but are rare in patients with TTP associated with severe ADAMTS-13 deficiency. A leukoerythroblastic blood picture, characterized by the presence of immature granulocytes and many nucleated red cells on the peripheral blood smear, should be considered suspicious of marrow involvement by malignancy rather than TTP. With any suspicion of systemic malignancy, a bone marrow biopsy is essential.[32,34]

Severe Hypertension

Severe hypertension can cause renal TMA that is indistinguishable from the pathologic lesions of TTP.[35,36] Hypertension causing microangiopathic hemolytic anemia and thrombocytopenia is typically severe, with systolic pressures over 200 and diastolic pressures over 100, and is typically associated with severe kidney injury.[35–37] However, the threshold blood pressures that may cause TMA are not known. Severe hypertension can cause neurologic abnormalities associated with the posterior reversible encephalopathy syndrome (PRES), which may be confused with TTP.[38] The key to appropriate evaluation is recognition that severe hypertension alone can cause these abnormalities. If there are improvements of the clinical and laboratory abnormalities with the control of blood pressure, without PEX, this confirms the diagnosis. In the Oklahoma Registry, the clinical features that originally suggested the diagnosis of TTP were subsequently attributed to severe hypertension in six patients. The physicians initially managing these patients did not recognize that the severe hypertension itself could cause microangiopathic hemolytic anemia and thrombocytopenia. Nonetheless, clinicians must recognize that patients with TTP and severe ADAMTS-13 deficiency may also present with sudden onset, severe hypertension.[9]

Pregnancy-Related Syndromes

The pregnancy-related syndromes of severe preeclampsia and the HELLP (hemolysis, elevated liver function tests, low platelets) syndrome can mimic all features of TTP,[39] including severe microangiopathic hemolytic anemia and thrombocytopenia, with the possible exception of fever, which is also rare in TTP.[5,16] In the Oklahoma Registry since 1995, 17 postpartum or pregnant patients have been treated with PEX for clinically diagnosed TTP; 3 had severe ADAMTS-13 deficiency (►**Table 1**); the other 14 patients may have had severe preeclampsia or HELLP syndrome. The difficulty for evaluation is that pregnancy is also a recognized condition that can trigger the onset of acute episodes of TTP.[18,19,39] Although TTP associated with pregnancy may occur during early gestation, most occurrences of TTP are near term or postpartum, when preeclampsia and HELLP syndrome also occur. When preeclampsia proceeds to eclampsia with seizures, often associated with PRES,[39] the distinction from TTP may not be possible.

The key distinction is that pregnancy-related syndromes resolve following delivery, unlike TTP. Therefore, urgent delivery and frequent postpartum evaluations are essential. Resolution of preeclampsia and HELLP syndrome within 3 days is often described, but how long a clinician can wait following delivery to see if improvement occurs to exclude TTP depends on the severity of the abnormalities.[39] Although severe preeclampsia with microangiopathic hemolytic anemia and thrombocytopenia can first occur after delivery, continually increasing severity after delivery suggests that intervention with PEX is appropriate.

Systemic Lupus Erythematosus

SLE can mimic all clinical features of TTP. The prevalence of SLE is increased in patients with TTP associated with severe ADAMTS-13 deficiency, consistent with observations that TTP and SLE both occur predominantly in young, black women.[40,41] Among 70 consecutive Oklahoma Registry patients with severe ADAMTS-13 deficiency, 8 (11%) also have been diagnosed with SLE. SLE may precede TTP, may be diagnosed concurrently with an initial episode of TTP, or may occur years following recovery from TTP. TTP may be suspected in patients with an established diagnosis of SLE when microangiopathic hemolytic anemia and thrombocytopenia seem more severe than expected, or when unexpected neurologic or renal abnormalities occur. However, these clinical features may also be features of an acute flare of SLE, associated with lupus nephritis with hypertension.

Adverse Drug Reactions

Adverse drug reactions may cause sudden, severe TMA mediated by drug-dependent antibodies. This has been documented only for quinine, by demonstration of quinine-dependent antibodies reactive with platelets, neutrophils, and other cells.[42] The quinine etiology has also been documented by the recurrence of sudden, severe TMA with reexposure to quinine.[43–45] Many other drugs have been suspected to cause TMA; however, drug-dependent antibodies have not been documented and recurrence of TMA with recurrent drug exposure has not been reported with any drug other than quinine. In the Oklahoma Registry, 20 of 26 patients who presented with sudden, severe TMA and a history suggesting a temporal relation to drug exposure had taken quinine, either as a tablet for symptoms of leg cramps or as a beverage containing tonic water (►**Table 1**). Among the other six patients, one patient had vancomycin-dependent, platelet-reactive antibodies, from vancomycin-induced isolated thrombocytopenia, complicated by anemia (due to hemorrhage) and not TTP.

Drugs may also cause microangiopathic hemolytic anemia and thrombocytopenia by dose-dependent renal toxicity. Examples are mitomycin C,[46] gemcitabine,[47] calcineurin inhibitors (cyclosporine, tacrolimus),[48] and vascular endothelial growth factor (VEGF) inhibitors (bevacizumab,[49] sirolimus[50]). In some patients, the TMA may be irreversible. In the Oklahoma Registry, patients with suspected drug-associated, dose-dependent TMA were often only detected by renal biopsy (►**Table 1**), and often did not have microangiopathic hemolytic anemia or thrombocytopenia. The evidence for a causal effect of the six drugs listed in ►**Table 1** as a cause of dose-dependent renal toxicity is based only on the patients' history of the drug exposure, temporally related to the onset of symptoms. Among these 12 patients, only 2 had a strongly supportive history: 1 patient had received a greater than usual dose of pentostatin immediately before the sudden onset of TMA[51] and 1 patient had transient dyspnea, weakness, and hallucinations following his first exposure to gemcitabine and the sudden onset of TMA following his second exposure.

Allogeneic Hematopoietic Stem Cell Transplantation

In the past, TMA associated with allogeneic hematopoietic stem cell transplantation (HSCT) was referred to as TTP,[52] implying a requirement for PEX. More recently, this syndrome has been considered to be distinct from TTP, and PEX is rarely used.[53,54] Diagnostic criteria for a potentially distinct syndrome following allogeneic HSCT have been proposed and the name has been changed to transplantation-associated TMA.[55,56] Empirical PEX is still occasionally requested because patients are critically ill and there is no known effective treatment for transplantation-associated TMA. In the Oklahoma Registry, one patient with this diagnosis had severe ADAMTS-13 deficiency, but she had systemic aspergillosis and acute graft-versus-host disease, with a total serum bilirubin concentration of 64 mg/dL, which probably invalidated the ADAMTS-13 assay.[8] She had PEX without apparent benefit.

Congenital Deficiency of Complement Regulatory Proteins

These disorders were initially described in the rare families with hereditary aHUS.[14] Mutations causing deficiencies of complement factor H, factor I, membrane cofactor protein (CD46), and other proteins were identified that allowed unrestrained activity of C5a, which in heterozygous subjects, was associated with an increased risk for developing aHUS. Interest in these disorders increased when a drug that inhibits C5a (eculizumab) was documented to benefit these patients[57] and this drug was FDA approved in 2011. In the past year since FDA approval, eculizumab has been marketed aggressively and it has been used empirically in patients with a variety of TMA syndromes, with case reports of its possible benefit. However, our understanding of the most appropriate use of eculizumab is limited by the very limited availability of genetic testing for mutations in complement regulatory proteins and by the absence of assays to document increased C5a activity.

Conclusions

Many different disorders can cause microangiopathic hemolytic anemia and thrombocytopenia. In patients with no clinically apparent etiology, diagnosis of TTP and treatment with PEX is appropriate. But because treatment with PEX is associated with the risk for major complications, thorough evaluation of these patients is required to exclude potential alternative etiologies of microangiopathic hemolytic anemia and thrombocytopenia.

Conflicts of Interest

Dr. George serves as a consultant for Baxter, Inc. for the development of rADAMTS-13 as a potential treatment for thrombotic thrombocytopenic purpura and as a consultant for Alexion, Inc. for the development of eculizumab as a treatment for acquired hemolytic uremic syndrome. Dr. Charania has no conflicts. The authors have no conflict with this topic or these data.

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