Thrombotic microangiopathic syndromes associated with drugs, HIV infection, hematopoietic stem cell transplantation and cancer

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Summary

Thrombotic microangiopathy (TMA) has multiple etiologies. In the four disorders described in this review, the primary organ involved is the kidney. Drug-associated TMA can be an acute, immune-mediated disorder or the result of gradual, dose-dependent toxicity. TMA may occur in patients with advanced HIV infection, possibly mediated by angio-invasive infections. TMA following allogeneic hematopoietic stem cell transplantation may also be caused by drug toxicity; the pathogenesis may involve inhibition of vascular endothelial cell growth factor in renal podocytes. Malignancies of many types with systemic microvascular involvement may cause TMA. Recognition that these syndromes may mimic TTP is important to provide appropriate management and to avoid the inappropriate use of plasma exchange treatment.

Thrombotic microangiopathy (TMA) is recognized pathologically by thrombosis in arterioles and capillaries associated with characteristic swelling of endothelial cells and the subendothelial space [1]. TMA is recognized clinically by the results of microvascular thrombosis: microangiopathic hemolytic anemia and thrombocytopenia [2]. The initial report of microangiopathic hemolytic anemia described multiple etiologies: thrombotic thrombocytopenic purpura (TTP), malignant hypertension, cancer, and several acute renal diseases [2]. Since this original description, multiple other etiologies of TMA have been recognized: hemolytic uremic syndrome (HUS),
scleroderma, antiphospholipid antibody syndrome, drug toxicity, preeclampsia, radiation nephropathy, renal allograft rejection, hematopoietic stem cell transplantation (HSCT), and human immunodeficiency virus (HIV) infection [1]. This review focuses on four of these TMA syndromes: adverse reactions to drugs, HIV infection, HSCT, and cancer.

In this review, our opinions are based on the experience of the Oklahoma TTP-HUS Registry, a population-based cohort of 398 consecutive patients with a first episode of clinically diagnosed TTP or HUS, January 1, 1989 to December 31, 2009 [3–6]. Registry patients are identified by a request for plasma exchange treatment, the current standard treatment for TTP. Therefore adults in the Registry are described as having TTP (or TTP-HUS, if renal failure is predominant) [6]. Children are described as having HUS if renal failure is present [6]. In this review, TMA is used since it is inclusive of patients with these four syndromes associated with adverse reactions to drugs, HIV infection, HSCT, and cancer, whether or not plasma exchange is an appropriate treatment.

The four TMA syndromes discussed in this review have accounted for 94 (24%) of all 398 Registry patients (table I). Since plasma exchange is not appropriate for some patients with these syndromes, inclusion in the Registry is incomplete because treatment with plasma exchange was not requested. However, in some patients the cause of the TMA was only discovered after plasma exchange was begun for an initial clinical diagnosis of TTP, or the cause of TMA was never certain. In other patients, the cause of the TMA was initially apparent and plasma exchange was considered to be beneficial. These are the patients that were included in the Registry. This experience is common in clinical practice and emphasizes the importance of understanding the pathogenesis, evaluation, and management of these four TMA syndromes.

### Drug-associated thrombotic microangiopathy

Drug-associated thrombocytopenia is more common than drug-associated TMA. Many drugs that can cause isolated thrombocytopenia have been recognized using multiple methods for identification [7]. The causal association of drugs with TMA is more difficult to assess in published reports because both the diagnosis of TMA as well as the causal role of the drug may be uncertain [8]. In the Registry, TMA is categorized as drug-associated when a drug previously reported to be associated with TTP, HUS, or TMA was taken prior to the onset of symptoms or if there was a compelling temporal association of a previously unreported drug with the onset of symptoms. The drugs associated with TMA in the Registry are presented in table II. In addition to our experience, multiple other drugs have been reported to cause TTP, HUS, or TMA, but a causal association was often uncertain [8]. In addition to approved drugs, there have been reports that herbal remedies (Cupressus funebris [mourning cypress] and Echinacea pallida) and a diet supplement (chromium picolinate) have been associated with thrombocytopenia, hemolytic anemia, and acute renal failure, the characteristic clinical features of TMA [9].

Quinine is the most commonly identified drug, accounting for nearly half of all patients with drug-associated TMA; quinine is also the only drug for which the pathogenesis has been clearly documented. Quinine in beverages such as tonic water or Schweppes Bitter Lemon can also cause acute TMA [10,11]. Some chemotherapeutic agents (most commonly mitomycin C [12] and gemcitabine [13–15]) and calcineurin inhibitors (cyclosporine, tacrolimus [16,17]) can cause dose-dependent renal toxicity with pathologic and clinical features of TMA. For other drugs, the occurrence is uncommon, the causal association with TMA is uncertain, and if a causal association actually exists, the pathogenesis is unknown.

### Pathogenesis

Drugs may cause TMA by at least two mechanisms: an acute, immune-mediated reaction or dose-dependent toxicity. Although multiple drugs have been reported to cause TMA with an

<table>
<thead>
<tr>
<th>TMA etiology</th>
<th>Occurrence (% of all Registry patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-induced</td>
<td>52 (13%)</td>
</tr>
<tr>
<td>HIV</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>HSCT</td>
<td>23 (6%)</td>
</tr>
<tr>
<td>Cancer</td>
<td>12 (3%)</td>
</tr>
<tr>
<td>All other patients</td>
<td>304 (76%)</td>
</tr>
</tbody>
</table>

**Table I**

Occurrence of thrombotic microangiopathy (TMA) associated with drugs, human immunodeficiency virus (HIV) infection, hematopoietic stem cell transplantation (HSCT), and cancer among the 398 consecutive patients in the Oklahoma TTP-HUS Registry, 1989–2009, with a first episode of clinically diagnosed thrombotic thrombocytopenic purpura (TTP) or HUS.

**Glossary**

- DIC: disseminated intravascular coagulation
- GVHD: graft-versus-host disease
- HIV: human immunodeficiency virus
- HSCT: hematopoietic stem cell transplantation
- HUS: hemolytic uremic syndrome
- TMA: thrombotic microangiopathy
- TTP: thrombotic thrombocytopenic purpura
- VEGF: vascular endothelial cell growth factor
TABLE II
Drugs that have been associated with thrombotic microangiopathy (TMA) in the Oklahoma TTP-HUS Registry, 1989–2009.

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute, immune-mediated</td>
<td></td>
</tr>
<tr>
<td>Quinine</td>
<td>25</td>
</tr>
<tr>
<td>Dose-dependent toxicity</td>
<td></td>
</tr>
<tr>
<td>Chemotherapeutic agents</td>
<td></td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>11</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>4</td>
</tr>
<tr>
<td>Carmustine</td>
<td>1</td>
</tr>
<tr>
<td>Pentostatin</td>
<td>1</td>
</tr>
<tr>
<td>Calcineurin inhibitor</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>3</td>
</tr>
<tr>
<td>Association with TTP uncertain and pathogenesis unknown</td>
<td></td>
</tr>
<tr>
<td>Alendronate</td>
<td>1</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>1</td>
</tr>
<tr>
<td>Cocaine</td>
<td>1</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>2</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>1</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1</td>
</tr>
</tbody>
</table>

Chemotherapeutic agents and calcineurin inhibitors can cause dose-dependent renal toxicity resulting in TMA. Chronic and cumulative dose dependence of the toxicity has been documented for mitomycin C [12] and gemcitabine [13–15]. One patient has been reported with a toxic overdose of deoxycoformycin causing acute, severe TMA [29]. The calcineurin inhibitors, cyclosporine and tacrolimus, can also cause dose-dependent renal toxicity resulting in TMA. Dose dependence of the toxicity by calcineurin inhibitors has been supported by improvement of the TMA when the dose is decreased [16]. TMA may recur when cyclosporine or tacrolimus are resumed after initial recovery [17].

TMA associated with chemotherapeutic agents is not always dose-dependent. Acute and presumed immune-mediated TMA has been reported with oxaliplatin [30]. Although tests for oxaliplatin-dependent antibodies were not done in this patient, oxaliplatin-dependent, platelet-reactive antibodies have been documented in patients with acute oxaliplatin-induced thrombocytopenia [31]. Although gemcitabine-induced TMA is typically dose-dependent, one patient has been reported with acute TMA following a single dose of gemcitabine [32]; tests for gemcitabine-dependent antibodies were not done. We have seen a similar patient with acute and fatal TMA, following a second administration of gemcitabine; tests for gemcitabine-dependent antibodies have not yet been done in this patient.

Evaluation

Patients with quinine-associated TTP have a characteristic sudden and severe presentation (Table III). In patients with this presentation, a detailed search for exposure to quinine is critical. Although quinine has been the common established treatment for leg cramps for over 70 years [33] and leg cramps are very common among older patients [34], the exposure to quinine may not be initially apparent [35]. If patients are asked, "What drugs or medicines do you take?", they may not describe quinine use because they do not consider quinine tablets, which they regulate themselves and take only occasionally, as a "drug" or "medicine" [35]. Patients may also consider a quinine tablet to be unimportant and not report it because it was given to them by a friend or relative. Quinine in a beverage, such as tonic water or Schweppes Bitter Lemon, can also cause acute TMA [10,11]. If quinine exposure is excluded in patients with this characteristic presentation, another drug should be suspected as the etiology. These clinical features were the basis for our suspicion of alendronate, cocaine, and trimethoprim-sulfamethoxazole, although tests drug-dependent antibodies were negative for each of these three patients (including tests for quinine-dependent antibodies in the patient whose acute TMA followed cocaine exposure). There have been reports of TMA associated with cocaine [36] and trimethoprim-sulfamethoxazole [37], but there has
been no previous report of TMA associated with alendronate. Vancomycin is a common cause of drug-induced thrombocytopenia but has not been reported to cause TMA. In our patient, vancomycin-induced thrombocytopenia with anemia from severe pulmonary hemorrhage may have caused consideration of TMA [38]. Chemotherapeutic agents and calcineurin inhibitors cause dose-dependent renal TMA, manifested by a gradual onset of renal failure; thrombocytopenia and microangiopathic hemolytic anemia also develop gradually, parallel with the renal failure.

**Management**

For patients with quinine-associated TMA, or TMA with an acute onset that may be associated with another drug, plasma exchange is appropriate because the drug etiology cannot be certain at the time of initial presentation. Even when a drug association is apparent, plasma exchange may be used because of the severity of illness and the absence of other treatments. We do not use glucocorticoids when a drug etiology is suspected. Long-term follow-up is essential because persistent renal failure following recovery from quinine-associated TMA is common. Therefore, avoidance of quinine, or other drugs suspected of causing acute immune-mediated TMA, is the most important management.

For patients with TMA associated with dose-dependent drug toxicity, stopping the suspected drug may be all that is required. This appears to be sufficient for patients with calcineurin inhibitor-associated TMA, but patients with TMA associated with mitomycin C and gemcitabine may have persistent, severe renal failure [12,14]. Although plasma exchange has no documented benefit for patients with dose-dependent drug toxicity [39], a trial of plasma exchange treatment is sometimes requested because of the severity of illness, the similarity to TTP, and the lack of other appropriate treatments [14]. The serious risks of plasma exchange [40] must be considered in this decision. For patients with acute, severe TMA syndromes associated with chemotherapy, such as with oxaliplatin [30], gemcitabine [32], and deoxycoformycin [29], plasma exchange may be appropriate because of the uncertainty of the etiology.

**Summary**

Quinine is the most common cause of drug-associated TMA and it is the only drug that has been documented to have an immune-mediated pathogenesis. Recognition of a drug etiology is critical to avoid future exposure to the suspected drug. Although TMA associated with chemotherapeutic agents typically has a chronic, progressive clinical course, acute and potentially immune-mediated TMA may also occur with some chemotherapeutic agents.

### Table III

**Pathogenesis, presentation, history, management and outcomes of patients with quinine-associated thrombotic microangiopathy (TMA).**

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathogenesis</strong></td>
<td>Quinine-dependent antibodies are present that react with platelets and probably multiple other cells in multiple organs. Quinine-dependent antibodies persist for many years. Exposure to microgram quantities of quinine can cause acute thrombocytopenia and multi-organ failure</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td>Sudden onset of acute systemic symptoms within hours of quinine exposure (chills, fever, nausea, vomiting, diarrhea, extreme headache) followed by anuria, microangiopathic hemolytic anemia, and thrombocytopenia. Neutropenia, disseminated intravascular coagulation, and hepatotoxicity may occur</td>
</tr>
<tr>
<td><strong>History</strong></td>
<td>Quinine exposure is typically intermittent. Tablets taken for leg cramps are the most common etiology; quinine-containing beverages (tonic water, Schweppes bitter lemon, and others) can also cause TMA. Previous exposures were often associated with systemic symptoms, such as headache mimicking meningitis, that had not been attributed to quinine. There are not yet any reported associations with cinchona, the natural product from which quinine is extracted</td>
</tr>
<tr>
<td><strong>Management</strong></td>
<td>Although there is no evidence for efficacy of plasma exchange, it is appropriate because of the acute onset, the severity of the clinical course, the initial uncertainty about the etiology, and the absence of other treatment options</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>May cause death. Chronic renal failure is common</td>
</tr>
</tbody>
</table>
Human immunodeficiency virus-associated thrombotic microangiopathy

Soon after the first recognition and reports of AIDS in 1981 [41,42], case reports suggested that HUS and TTP were manifestations of HIV infection [43–46]. Subsequent case series reported a high frequency of HIV infection among patients with TTP and suggested that HIV-associated TTP was a specific entity [47,48], that HIV infection can cause TTP [49], and that TTP may be an AIDS-defining disorder [50]. However among all published case series of patients with TTP, most do not mention HIV infection [51]; among case series of TTP that do report HIV infection, the frequency ranges from 0% [52] to 83% [49]. Among patients in the Registry through December 2007, the prevalence of HIV infection was greater than the estimated prevalence of HIV infection in the population of the Registry region: 6 of 351 patients in the Registry in whom HIV status was determined had HIV infection (1.84%; 95% CI, 0.68%–4.01%) compared to the population prevalence of 0.30% [51]. However both the frequency of HIV infection among Registry patients and the estimated prevalence of HIV infection in the population were low. One additional patient has been documented to have HIV infection in 2010. Clinical observations suggest that there may be multiple reasons for the association of HIV infection with TTP and also that there may be a specific entity of HIV-associated TMA, distinct from TTP [53,54].

Pathogenesis

A specific entity of HIV-associated TMA is suggested by pathologic observations in patients with HIV infection documenting endothelial dysfunction with deposition of thrombi in the vessel wall [55]. Human herpesvirus-8 infection, which is common among HIV-infected patients, involves vascular endothelium and may contribute to the development of TMA [56]. Patients with HIV-associated TMA who do not have ADAMTS13 deficiency have multiple HIV-related complications [54]. This suggested that the entity of HIV-associated TMA is a manifestation of advanced HIV infection, [54] consistent with the decreased frequency of HIV-associated TMA following the introduction of HAART [57,58].

In addition to a specific entity of HIV-associated TMA, there are multiple other reasons for an association of HIV infection with patients who are diagnosed with TTP (table IV). Coincidental occurrence of HIV infection and TTP may be the explanation in patients with severe ADAMTS13 deficiency [54]; this appeared to be the explanation for two of the six patients with HIV infection in the Registry [51]. In these two patients, it is possible that the acute episode of TTP could have been triggered by inflammation associated with the HIV infection or an unrecognized opportunistic infection. These two patients had not received HAART. In patients treated with HAART, the acute inflammation associated with immune reconstitution may be a potential trigger for an acute episode of TTP [59]. One other Registry patient had ADAMTS13 activity of 6% with inhibitor activity of 0.9 Bethesda Units; however autopsy examination discovered systemic Kaposi sarcoma as the cause of his illness; there was no evidence for TTP [51]. In this patient and three other Registry patients, whose clinical features were attributed to HIV-associated nephropathy with malignant hypertension,

<table>
<thead>
<tr>
<th>Reason</th>
<th>Discussion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coincidental occurrence of HIV infection and TTP</td>
<td>Most reports describing a high frequency of HIV infection associated with TTP are from regions with a high prevalence of HIV infection. In regions with a low prevalence of HIV infection in the population there is also a low frequency of HIV infection among patients with TTP</td>
</tr>
<tr>
<td>Trigger event for an acute episode of TTP</td>
<td>Inflammatory conditions (infections, surgery, pancreatitis, surgery, pregnancy) can trigger the occurrence of acute episodes of TTP in susceptible patients. Inflammation associated with the HIV infection, with an opportunistic infection, or with the immune reconstitution response to HAART may trigger an acute episode of TTP</td>
</tr>
<tr>
<td>Mimic of TTP</td>
<td>Multiple HIV-related conditions may mimic an acute episode of TTP: Opportunistic infections with an angioinvasive organism, such as CMV or HHV-8 Disseminated malignancy, such as Kaposi sarcoma HIV-associated nephropathy with malignant hypertension</td>
</tr>
<tr>
<td>Cause of TMA, unrelated to TTP</td>
<td>Advanced HIV infection may be associated with endothelial dysfunction and deposition of thrombi in the vessel wall, causing the pathologic and clinical features of TMA. Infection with HHV-8 may contribute to these vessel wall abnormalities</td>
</tr>
</tbody>
</table>

TTP: thrombotic thrombocytopenic purpura.
the HIV-related conditions merely mimicked the clinical features of TTP [51].

**Diagnosis**

HIV status is documented in all Registry patients because our standard practice is to perform routine blood donor testing, including tests for HIV infection, on all patients treated with plasma exchange. Patients who have HIV infection are carefully evaluated for occult opportunistic infections and other HIV-related disorders that could mimic TTP. If the clinical features are typical for TTP, the ADAMTS13 activity is < 10%, and no HIV-related infections or other complications are apparent, then we assume that the HIV infection is coincidental, or that it may have contributed to the onset of the acute episode of TTP. However, a correct diagnosis may not be apparent until an autopsy is performed.

**Management**

Treatment of the HIV infection is the only appropriate management for patients diagnosed with HIV-associated TMA. If TTP is diagnosed, then management is the same as for all patients with TTP [6]. If an alternative explanation for the acute thrombocytopenia and microangiopathic hemolytic anemia is discovered, appropriate treatment is begun and plasma exchange is stopped to avoid its potential risks [40].

**Summary**

HIV infection may be a coincidental diagnosis in patients with TTP or it may provide an inflammatory stimulus for initiating an acute episode of TTP in susceptible subjects, similar to reports of TTP associated with infections [60], surgery [61], pancreatitis [62], and pregnancy [63]. In most patients with HIV infection in whom the diagnosis of TTP is considered, an alternative explanation for the thrombocytopenia and microangiopathic hemolytic anemia will be discovered. Finally, patients with advanced HIV infection may have a syndrome of HIV-associated TMA.

**Hematopoietic stem cell transplantation-associated thrombotic microangiopathy (TMA)**

Patients who developed clinical features of TMA following allogeneic hematopoietic stem cell transplantation (HSCT) were previously described as TTP and treated with plasma exchange [64,65]. However substantial experience failed to document effectiveness of plasma exchange treatment [66]; therefore the name of this syndrome has been changed to HSCT-associated TMA [67,68]. Use of the name, HSCT-associated TMA, helps to avoid consideration of plasma exchange and other treatments used for TTP. There are no reports of autopsies demonstrating systemic microvascular thrombosis characteristic of TTP in patients with HSCT-associated TMA, further supporting the distinction between HSCT-associated TMA and TTP [66,69]. Although many complications of HSCT may mimic TMA [70] and many diverse etiologies may contribute to TMA following HSCT [71], HSCT-associated TMA is considered to be a specific syndrome complicating allogeneic HSCT [67,68,71,72].

Our experience supports the concept that HSCT-associated TMA is a specific syndrome. We analyzed 20 consecutive autopsies of patients following allogeneic HSCT; six of the patients had been clinically diagnosed with TMA and treated with plasma exchange (Table V) [69]. In all six patients, the clinical diagnosis of TMA was confirmed by documentation of histologic TMA in the kidneys, involving 75% of the glomeruli and arterioles; only two of the other 14 patients had renal TMA (P < 0.001). Rare isolated arterioles in other organs had evidence for TMA in three of the six patients with a clinical diagnosis of TMA (pancreas in one patient, lung in one patient, and both the heart and lung in one patient); none of the other 14 patients had extra-renal TMA. These data provide pathologic support for the clinical

<table>
<thead>
<tr>
<th>Pathologic Features</th>
<th>Clinical diagnosis of TMA (n = 6)</th>
<th>No clinical diagnosis of TMA (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal TMA</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>

**Cause of death**

<table>
<thead>
<tr>
<th></th>
<th>Clinical diagnosis of TMA (n = 6)</th>
<th>No clinical diagnosis of TMA (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Aspergillus</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Candida</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Staphylococcus</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Enterobacter</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Acute GVHD</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Intracranial hemorhage</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary complications</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

Data are from 20 consecutive autopsies on patients following allogeneic HSCT, 1994–2005 [69]. These patients included six of the 23 patients who were clinically diagnosed with HSCT-associated TMA and 14 patients who were not clinically diagnosed with HSCT-associated TMA. No patients in the Registry have been clinically diagnosed with HSCT-associated TMA since 2005. GVHD: graft-versus-host disease; TMA: thrombotic microangiopathy.
diagnosis of TMA following allogeneic TMA, and emphasize that HSCT-associated TMA is essentially restricted to the kidneys [69,72]. These data also demonstrated that HSCT-associated TMA was not a cause of death. In each of the six patients with clinical and pathologic evidence of TMA, the cause of death was infection, similar to patients following allogeneic HSCT without TMA (table V) [69].

Pathogenesis
There may be multiple causes of TMA following HSCT, since TMA occurs in patients at the highest risk for complications, such as patients with an unrelated or HLA-mismatched donors, and the greatest frequency of complications, such as the occurrence of grade III–IV acute graft-versus-host disease (GVHD) and systemic infections [70]. Immunosuppressive drugs used for treatment of acute GVHD, in addition to the preparative regimens that may include high-dose chemotherapy and total body irradiation, can cause damage to the vascular endothelium with resulting microvascular thrombosis [71]. In addition to the calcineurin inhibitors, cyclosporine and tacrolimus, a potentially important etiology of HSCT-associated TMA is sirolimus, also used for GVHD prophylaxis [73]. Sirolimus, which inhibits vascular endothelial cell growth factor (VEGF), has been associated with an increased incidence of HSCT-associated TMA [73]. Bevacizumab, which also inhibits VEGF, can also cause renal TMA [74]. These clinical observations have been supported by experimental observations that VEGF inhibition, caused by gene targeting in mice to delete VEGF from renal podocytes, can cause glomerular injury resulting in TMA [74].

Diagnosis
The diagnosis of HSCT-associated TMA, like the diagnosis of TTP, requires the exclusion of alternative etiologies for thrombocytopenia and microangiopathic hemolytic anemia. In HSCT patients, who are often critically ill with multiple systemic complications, this may be impossible. A systematic review of case series of HSCT-associated TMA documented that the frequency of diagnosis of TMA following allogeneic HSCT varied by 125-fold, from 0.5% to 63.6% [66], providing evidence that the diagnosis is empirical and imperfect. To address this diagnostic dilemma, two groups have presented algorithms attempting to make the diagnosis of HSCT-associated TMA more consistent [67,68]. Both groups cited evidence for microangiopathic hemolytic anemia as the principal diagnostic criterion; thrombocytopenia, renal, and neurologic abnormalities were supporting criteria. Whether these criteria can provide reproducible and consistent clinical diagnoses has not yet been determined.

Management
Since the etiology of HSCT-associated TMA is not clear and since it has not been documented to cause death, the principal management is supportive care. Potential etiologic drugs, such as cyclosporine, tacrolimus, and sirolimus, should be discontinued. Plasma exchange should not be performed. From 1989 to 2003 we routinely treated patients with HSCT-associated TMA with plasma exchange; 23 patients with HSCT-associated TMA were enrolled in the Registry during this time. Since 2003, we have not treated any patients following allogeneic HSCT with plasma exchange. Avoiding plasma exchange is appropriate both because of lack of evidence for effectiveness [66] and, perhaps more importantly, because plasma exchange has risks of death, sepsis, and other serious complications [40]. Other treatments adapted from the management of TTP, such as rituximab [75,76], have been reported for HSCT-associated TMA. Daclizumab, a monoclonal anti-CD25 antibody, has been suggested as an alternative for calcineurin inhibitors for prophylaxis and treatment of GVHD in patients with HSCT-associated TMA [71]. Defibrotide, a polydeoxyribonucleotide that inhibits endothelial apoptosis and is effective treatment for hepatic veno-occlusive disease in patients following allogeneic HSCT [77], has also been suggested as treatment [71,78]. Whether any of these treatments are beneficial for patients with HSCT-associated TMA is uncertain.

Summary
HSCT-associated TMA is a specific complication following allogeneic HSCT. TMA is restricted almost entirely to the kidney. Drug toxicity may be the principal etiology and the pathogenesis may involve inhibition of VEGF. The mortality of patients diagnosed with HSCT-associated TMA remains high but TMA itself does not appear to be a cause of death. Therefore supportive care remains the best current management.

Cancer-associated thrombotic microangiopathy
Systemic malignancies of any type can cause both pathologic and clinical features of TMA [1,2,79–82]. Five (20%) of the 25 patients in the initial description of microangiopathic hemolytic anemia had cancer [2]. Although there are multiple etiologies for thrombocytopenia and red cell fragments in patients with systemic malignancy, such as marrow suppressive chemotherapy, sepsis, and disseminated intravascular coagulation (DIC), it is important to recognize that TMA without evidence for DIC can also occur [79–82]. In most patients with cancer-associated TMA, the cancer is apparent. In some patients, cancer has not been previously recognized or is assumed to be in remission [80,83]; these patients may be mistakenly diagnosed as having TTP. Multiple malignant disorders can cause cancer-associated TMA. Among the 10 patients in the Registry who were discovered to have systemic malignancy after plasma exchange for TTP had begun, 8 different etiologies were discovered: breast, two; lung, two;
pancreas, one; kidney, one; Kaposi sarcoma, one; non-Hodgkin lymphoma, one; acute lymphocytic leukemia, one; myelodysplasia, one [80]. Three additional patients have been treated with plasma exchange for presumed TTP in spite of clinically apparent disseminated malignancy. The critical clinical issue is to appreciate that systemic malignancies can mimic TTP so unnecessary plasma exchange can be avoided [40]. If plasma exchange treatment for TTP was begun before a systemic malignancy was discovered, it should be stopped when the systemic malignancy is discovered. If a systemic malignancy is present, the potential benefits of plasma exchange for an unlikely diagnosis of TTP must be balanced against the known risks of plasma exchange [40].

**Pathogenesis**

Previous observations in patients with systemic malignancies have documented arteriolar intimal proliferation, a characteristic histologic feature of TMA [1]. Cancer-associated TMA may occur predominantly in the lungs and appears to be associated with tumor emboli [79,83]. Microscopic intravascular tumor emboli may induce local activation of coagulation and fibrocellular intimal proliferation [81]. One of our patients [80,83], who was discovered at autopsy to have systemic metastatic breast cancer, illustrates that the TMA is not only the result of microvascular obstruction by tumor emboli but that hyaline thrombi, histologically typical of TTP, may also be present (figure 1) [83]. These may be platelet-fibrin thrombi that form

**Figure 1**

**Brain and lung pathology are from a patient with a history of breast cancer who was considered to be in remission**

She was diagnosed with thrombotic thrombocytopenic purpura (TTP) and treated with plasma exchange. Autopsy revealed microscopic breast cancer metastases in multiple organs. In some sections, tumor thrombi were apparent; in other sections, hyaline thrombi similar to the pathologic appearance of TTP were present.

1A – Brain: microvascular thrombus composed of carcinoma cells.
1B – Brain: platelet-fibrin thrombus.
1C – Lung: microvascular thrombus composed of carcinoma cells.
1D – Lung: platelet-fibrin thrombus.

Autopsy data and photomicrographs courtesy of Stephen C. Ingels, MD.

Source: Reproduced from a previous publication [83] with permission.
adjacent to tumor cell thrombi. Although severe ADAMTS13 deficiency was present in one of our 10 patients, and half of these patients had ADAMTS13 activity that was lower than normal [80], it is assumed that ADAMTS13 deficiency is not relevant to the pathogenesis of cancer-associated TMA. When ADAMTS13 deficiency occurs, it may merely be the result of systemic inflammation rather than the cause of the syndrome.

**Evaluation**

*Table VI* describes the clinical and laboratory features of 10 patients who were diagnosed with TTP and in whom systemic malignancy was only discovered after plasma exchange had been begun. These clinical features, which are not typical for TTP, should cause suspicion for systemic malignancy. However none of these clinical features provides an absolute distinction; their importance is to encourage a careful evaluation for the presence of a previously unsuspected systemic malignancy. The most important diagnostic test may be a bone marrow biopsy, since marrow involvement may be the major cause of thrombocytopenia and microangiopathic hemolytic anemia [80–82]. However, in three of our 10 patients, the bone marrow biopsy was normal. In these three patients TMA was the result of

### Table VI

**Characteristics of patients with a clinical diagnosis of thrombotic thrombocytopenic purpura (TTP) that suggest cancer associated thrombotic microangiopathy (TMA).**

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Clinical features</strong></td>
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<tr>
<td>Older age, male gender</td>
<td>7 of 10 patients with systemic malignancy were men; mean age of the 10 patients was 56 years; 80% of patients with TTP were women; mean age was 41</td>
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<tr>
<td>Previous diagnosis of cancer</td>
<td>Although only 1 of 10 patients with systemic malignancy had a previous diagnosis of cancer, marrow involvement should be excluded with a marrow biopsy in all patients with a history of cancer</td>
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<tr>
<td>Progressive symptoms for 2 weeks or longer</td>
<td>Although patients with TTP may have symptoms for several weeks prior to presentation, a prolonged prodrome suggests an alternative diagnosis. The median duration of symptoms in the 10 patients with systemic malignancy was 21 days</td>
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<tr>
<td>Weakness</td>
<td>Although patients with TTP commonly have weakness associated with anemia, prolonged, progressive weakness is uncommon</td>
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<tr>
<td>Weight loss</td>
<td>Symptoms of TTP are rarely long enough to be associated with weight loss</td>
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<tr>
<td>Pain</td>
<td>Although patients with TTP commonly have symptoms of abdominal pain associated with nausea, vomiting, and diarrhea, other pain symptoms are rare</td>
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<tr>
<td>Respiratory symptoms</td>
<td>7 of 10 patients had cough and dyspnea; 6 of these 7 patients had abnormal chest x-rays (pleural infusion, bilateral infiltrates, congestion). Microvascular thromboses in TTP rarely involve the lung; &lt; 10% of patients with TTP had symptoms of cough. Dyspnea is rare unless associated with anemia</td>
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<tr>
<td><strong>Laboratory features</strong></td>
<td></td>
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<tr>
<td>Leukoerythroblastic reaction</td>
<td>Although nucleated red cells and immature granulocytes on the peripheral blood smear may occur with extreme hemolysis, this is uncommon in TIP</td>
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<tr>
<td>Extreme elevation of serum LDH</td>
<td>Although increased LDH is always present in TTP, extreme elevations are rare. The highest value among patients with TTP was 3783 U/L; 4 of 10 patients with systemic malignancy had values of 5865-10126 U/L</td>
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<tr>
<td>Coagulation abnormalities</td>
<td>2 of 10 patients had low fibrinogen levels attributed to liver involvement. Patients with TTP rarely have DIC resulting from systemic tissue ischemia</td>
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<tr>
<td>ADAMTS13 activity</td>
<td>1 of 10 patients had ADAMTS13 activity &lt; 10% (61, he also had HIV infection). The median value for 8 patients in whom ADAMTS13 activity was measured was 50%</td>
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<tr>
<td><strong>Treatment</strong></td>
<td></td>
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<tr>
<td>Failure to respond to plasma exchange</td>
<td>In patients with TTP, neurologic symptoms typically respond promptly, LDH decreases within 1–2 days, and platelet count increase in 3–4 days. One of the 10 patients responded, probably because of effective treatment of pneumonia and hypotension</td>
</tr>
</tbody>
</table>

Data for the 10 patients with cancer-associated TMA are derived from a previously published report [80]. Data for patients with TTP are from 65 patients with ADAMTS13 activity < 10% [6].
extensive bilateral lung cancer, metastatic renal cancer, and systemic Kaposi sarcoma that were diagnosed by open lung biopsy after a bronchoscopic biopsy had been normal, by imaging, and by autopsy, respectively [80].

Management

There is no benefit from plasma exchange in patients with cancer-associated TMA. The only appropriate management is chemotherapy treatment specific for the diagnosed malignancy, when this is possible. Since malignancies causing TMA are advanced, survival is short and chemotherapy may not be appropriate. Among our 8 patients who were diagnosed while they were living, median survival after diagnosis of the malignancy was only 3 days [80].

Summary

Systemic malignancy should be considered in the differential diagnosis of TTP. If a malignancy is suspected, a bone marrow biopsy is appropriate. If a systemic malignancy is diagnosed in a patient begin treated with plasma exchange for TTP, the plasma exchange should be stopped.

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