Acquired thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are appropriately at the top of a clinician’s differential when a patient presents with a clinical picture consistent with an acute thrombotic microangiopathy (TMA). However, there are several additional diagnoses that should be considered in patients presenting with an acute TMA, especially in patients with nondeficient ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity (>10%). An increased awareness of drug-induced TMA is also essential because the key to their diagnosis more often is an appropriately detailed medical history to inquire about potential exposures. Widespread inflammation and endothelial damage are central in the pathogenesis of the TMA, with the treatment directed at the underlying disease if possible. TMA presentations in the critically ill, drug-induced TMA, cancer-associated TMA, and hematopoietic transplant–associated TMA (TA-TMA) and their specific treatment, where applicable, will be discussed in this manuscript. A complete assessment of all the potential etiologies for the TMA findings including acquired TTP will allow for a more accurate diagnosis and prevent prolonged or inappropriate treatment with plasma exchange therapy when it is less likely to be successful. (Blood. 2017;129(21):2857-2863)

Introduction

The term thrombotic microangiopathies (TMAs) typically refers to a group of diseases that share occlusive microvascular or macrovascular disease, often with intraluminal thrombus formation, but may also be used to refer to the clinical findings of a microangiopathic hemolytic anemia and thrombocytopenia.1 Although TMA is commonly associated with entities such as thrombotic thrombocytopenic purpura (TTP) and atypical hemolytic uremic syndrome (aHUS), it also occurs as a complication from systemic illness or certain medications. Historically, plasma exchange therapy (PEX) was the empiric therapy for all patients presenting with an acute TMA, and this may still be the first step for the treatment of a suspected diagnosis of TTP. However, recent evidence has shown that when TMA occurs as the result of a systemic illness, the ADAMTS13 activity is typically normal or mildly deficient, and patients do not respond to PEX.2 In these cases, the treatment should be directed toward treating the underlying disease or stopping the offending drug. In the following review, we will discuss specific etiologies of TMA that should be considered after acquired TTP has been ruled out by nondeficient ADAMTS13 activity (>10%) and alternatives to a diagnosis of aHUS are being considered (Table 1).

TMA in the critically ill patient

Pathogenesis

Patients with TTP and HUS can present seriously ill. There are other etiologies, however, more frequently seen in the hospital and intensive care unit (ICU), such as sepsis, DIC, and malignant hypertension, that may also cause TMA. Although different contributing factors may lead to TMA findings in these patients, they share a proinflammatory component. Neutrophil extracellular traps (NETs) are part of the human immune response and are released by neutrophils in these clinical settings. Their main task is to trap organisms and then kill them by myeloperoxidase, neutrophil elastase, reactive oxygen species, and other enzymes. NETs are also prothrombotic; they initiate factor XII activation, activate tissue factor pathway, and promote platelet activation and aggregation. The ineffective clearance or excessive production of NETs can lead to the clinical finding of TMA in these disorders.3 In at least 1 study, a deficiency in DNAase1 activity in patients presenting with a TMA was responsible for the impaired degradation of NETs.4 Neutrophils also release nucleosomes during inflammation. The DNA and histones contained on nucleosomes are also prothrombotic, inducing fibrin deposition, platelet aggregation, and adhesion. Fuchs et al demonstrated elevated levels of DNA-histone complex in patients with TMA.5

In addition to the contribution of NETs, DNA, and histones, an uncontrolled activation of the coagulation system and impaired-fibrin degrading potential, as seen in DIC and critically ill patients, can lead to widespread fibrin-platelet clots in the microvasculature. In sepsis, bacterial toxins will activate complement, endothelial cells, platelets, coagulation factors, and the fibrinolytic system. Thus, a consumptive coagulopathy, TMA, and multiorgan failure can occur.6,7 ADAMTS13 activity and antigen are moderately decreased in patients with severe sepsis when compared with patients with organ failure as a result of other causes and healthy subjects. In the same study, lower ADAMTS13 activity correlated with acute renal failure, shock, and disease severity only in patients with sepsis and not in patients with organ failure from other etiologies. This may be caused by consumption of ADAMTS13 (as evidenced by the negative correlation found between ADAMTS13 activity and von Willebrand factor [VWF] antigen in patients with sepsis), and ADAMTS13 inhibition by IL-6.
Table 1. Etiologies of TMA beyond TTP and HUS

| TMA in the critically ill
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>DIC</td>
</tr>
<tr>
<td>Malignant hypertension</td>
</tr>
<tr>
<td>TMA in pregnancy</td>
</tr>
<tr>
<td>Drug-induced TMA</td>
</tr>
<tr>
<td>Cancer-associated TMA</td>
</tr>
<tr>
<td>Hematopoietic stem cell trans TMA</td>
</tr>
<tr>
<td>Cobalamin C defect</td>
</tr>
<tr>
<td>DGKE deficiency</td>
</tr>
</tbody>
</table>

(only seen in patients with sepsis, not organ failure from other etiologies).Bernardo et al showed that IL-6 inhibits ultralarge VWF cleavage by ADAMTS13 under flow, but not static conditions, which may also explain the clinical correlation seen only in patients with sepsis.

TMA can also be seen in patients that present with malignant hypertension. The mechanism that triggers TMA in this setting is poorly understood, but elevated blood pressure may lead to sustained endothelial damage, which can overstimulate the renin-angiotensin-aldosterone system, leading to the TMA findings.

Clinical presentation and diagnosis

Critically ill patients that present with TMA will have a different clinical phenotype than the one seen in equally ill patients with TTP or aHUS; because of concurrent consumption in coagulation factors, patients tend to have more bleeding and macrovascular complications. In a retrospective study of 55 patients diagnosed with TMA in the ICU, 51% of patients had macrovascular complications, including deep venous thrombosis and cerebral artery thrombosis. A retrospective study evaluating the clinical characteristics of patients with malignant hypertension who developed thrombotic microangiopathy found that these patients had higher systolic and diastolic blood pressure when compared with those in whom TMA did not develop. They also had higher aldosterone levels, which correlated with an elevated lactate dehydrogenase (LDH).

The ADAMTS13 activity and complement biomarkers may also give important information to rule out TTP and may also be of prognostic value. Farkas et al studied different laboratory abnormalities in patients with TMA associated with different systemic illness including sepsis, solid organ transplantation, malignancy, and autoimmune diseases, and compared them with control patients and healthy subjects. The patients in the TMA group had decreased ADAMTS13 activity (median activity 33.5%, range 16%-47%), marked complement activation (increased C3a), and consumption (lower C3 and C4, and lower Factors H, I, and B levels). Thirty-day mortality was associated with decreased platelet number, lower albumin concentration, and increased C-reactive protein and IL-6 levels. Patients with increased complement activation as evidenced by higher sC5b-9 and C3a levels, also had higher mortality rates.

Treatment

There is currently no specific directed therapy when the TMA occurs in the setting of systemic illness, other than supportive care and aggressive treatment of the underlying condition. This would also include aggressive blood pressure control and broad-spectrum antibiotics when clinically indicated.

TMA in pregnancy

Hemolysis, elevated liver enzymes, and low platelet count (HELLP) is part of the clinical spectrum of preeclampsia (proteinuria and hypertension), and both are a leading cause of maternal and neonatal morbidity and mortality. The type of hemolysis seen in HELLP is microangiopathic, as evidenced by schistocytes on the peripheral smear and a negative Coombs test. The pathologic lesion seen in the kidneys of patients with HELLP rarely has TMA features and more commonly will have glomerular endotheliosis and acute tubular necrosis. However, liver biopsies done in patients with HELLP show the classic fibrin thrombi seen also in patients with TMA.

Although the etiology of HELLP and preeclampsia is not fully understood, it has been linked to elevated circulating antiangiogenic factors soluble Flt1 (sFlt1) and endogline. sFlt 1 reduces the concentration and activity of vascular endothelial growth factor (VEGF), leading to endothelial dysfunction, hypertension, and proteinuria. The complement system also plays a role as a mediator of systemic inflammation in these diseases. C3a and C5a have effects on the vascular bed, and C5a is a potent chemotactic factor with the ability to activate leukocytes. When neutrophils are exposed to C5a in vitro, they release polymorphonuclear elastase, a marker of neutrophil activation. Women with severe preeclampsia have higher levels of factor C5a and SC5b-9 at delivery and 1 day postpartum, when compared with women with normal pregnancies and women with cesarean deliveries after a normal gestation. Some patients with HELLP will have complement genetic mutations as seen in aHUS patients. In a case series of 11 patients with HELLP, 4 had complement mutations and 3 had low serum C3 and Factor B levels but without genetic mutations. In a larger study of 22 patients, only 3 had complement genetic mutations. Although the complement system is dysregulated in preeclampsia and HELLP, its contribution is still being studied and seems to be one of many predisposing factors rather than the main triggering event.

Clinical presentation and diagnosis

HELLP will occur in 10% to 20% of patients with severe preeclampsia (hypertension and proteinuria). However, 15% to 20% of HELLP cases are not preceded by hypertension or proteinuria. Most patients present at between 28 and 36 weeks of pregnancy, although one third of patients will present postpartum. It is challenging to differentiate HELLP from TTP, aHUS, and other etiologies that may also cause a microangiopathic hemolytic anemia and thrombocytopenia, including acute fatty liver during pregnancy, systemic lupus erythematosus, antiphospholipid syndrome, and severe sepsis. TTP has a similar time of presentation as HELLP, during the second and third trimesters of pregnancy. However, aHUS is more common in the postpartum period. HELLP is much more common in this scenario than TTP or aHUS (1/1000 for HELLP vs 1/200 000 pregnancies for TTP and aHUS). Subtle differences may aid in making the correct diagnosis; severe headache, visual symptoms, and hyperreflexia are more common in severe preeclampsia and HELLP, whereas transient focal abnormalities and mental status changes are more characteristics of TTP. Declining renal function despite blood pressure control and delivery of the fetus should also raise the suspicion for aHUS. The thrombocytopenia seen in HELLP will be less severe than what is seen in TTP and is usually more than 50 000 × 10^9/L. Higher transaminases are also more commonly associated with HELLP than with TTP or...
aHUS.24 At the end of a normal pregnancy, the ADAMTS13 median activity was 71% in 1 study. In contrast, ADAMTS13 was decreased but not severely deficient in women with HELLP syndrome, with a reported mean of 31%.25,26 Interestingly, the French Thrombotic Microangiopathies Reference Center found a higher incidence (24%) of congenital TTP in pregnant patients presenting with their first TTP episode.27

Treatment

The treatment of a pregnant patient with preeclampsia and HELLP consists of aggressive blood pressure control and delivery as soon as possible. If there is no improvement in clinical status, platelets and LDH 2 to 3 days after delivery, one must reconsider the diagnoses of TTP and aHUS and treat accordingly.

Drug-induced thrombotic microangiopathy (DI-TMA)

Pathogenesis

There are 2 proposed mechanisms to explain how drugs may trigger a TMA. In immune-mediated DI-TMA, the drug will induce the formation of antibodies against different cell types, including platelets, neutrophils, and endothelial cells, causing microvascular injury and platelet consumption. These antibodies are drug-dependent and will cause TMA only in the presence of drug, even at small doses.28-30 The first and most common drug associated with an immune-mediated reaction is quinine.31 The second mechanism is through a direct, toxic effect. Although the mechanism is not fully understood, decreased expression of VEGF seems to play a role. Sartelet et al reported decreased renal expression of VEGF in patients with sirolimus-induced TMA. This finding was not seen in patients with TMA from other etiologies and the VEGF levels returned to normal when sirolimus was stopped.32 A murine model with conditional gene targeting to delete VEGF from renal podocytes also resulted in a thrombotic glomerular injury.33

Diagnosis

A detailed history is often the key to the diagnosis of a DI-TMA. Patients may not spontaneously report the use of over-the-counter medications or supplements (treatment of muscle cramps or tonic water, both sources of quinine). Proof of drug-dependent antibodies can confirm the cause, but the absence of these does not rule it out,29 as was the case of a recently reported DI-TMA caused by proteasome inhibitors carfilzomib and bortezomib.34,35 Patients with immune-mediated DI-TMA will usually have a relevant history of exposure to a drug known to cause this condition. They will present with systemic symptoms and acute kidney injury on their first exposure to the suspected drug. In contrast, toxic-mediated DI-TMA patients can present acutely or after a prolonged exposure.36 The most common drugs associated with immune-mediated DI-TMA are quinine, oxaliplatin, and quetiapine, whereas the most common drugs associated with toxic mechanism are cyclosporine, tacrolimus, sirolimus, bevacizumab, interferons α and β, and mitomycin.28,29 Gemcitabine is the only medication that has been associated with both immune-mediated37 and toxic mechanisms.38 Illicit drugs, specifically cocaine and IV use of oxymorphone (OPANA ER), have also been reported to cause a DI-TMA.39-41

TMA in patients with cancer

Microangiopathic hemolytic anemia and thrombocytopenia was initially described in patients with cancer almost 40 years ago.40 It can present as a manifestation of metastatic disease and bone marrow involvement, or because of a medication used in the cancer treatment, as described previously.

Cancer-related TMA

Several factors contribute to endothelial injury in cancer patients. Tumor emboli and intraluminal fibrin thrombi can lead to red blood cell fragmentation, usually in patients with known metastatic disease, although there have been reports of patients that have TMA as their initial presentation.40 Secondary myelofibrosis, rapid tumor growth, and abnormal angiogenesis can directly injure the endothelial cells in the narrow vessels, resulting in the release of ultralarge VWF multimers. The most common types of cancer associated with this type of TMA are gastric and breast, specifically mucin-producing adenocarcinomas.48,49

DI-TMA in patients with cancer

Several chemotherapy agents have been described to cause DI-TMA, by either immune-mediated mechanisms or direct, toxic effect, as described previously. With recent advances in the treatment of cancer with targeted agents, TMA has also been reported with different immunotoxins, immunotherapy, anti-VEGF therapy (appears to be a class effect), and imatinib.50 In the case of immunotoxins and immunotherapy, the mechanism triggering TMA includes upregulation of cytokines (monocyte chemoattractant protein-1, tumor necrosis factor-α, IL-1β, and IL-6). This can create a proinflammatory environment that stimulates the secretion of VWF and glomerular infiltration with macrophages.50 VEGF inhibitor–induced TMA has been

Downloaded from https://ashpublications.org/blood/article-pdf/129/21/2857/1400690/blood743104.pdf by guest on 04 September 2020
extensively described. In animal models, inhibition of VEGF has been shown to interfere with the maintenance of normal fenestrated endothelium in the glomerular microvasculature, compromising the integrity of the glomerular filtration barrier.33

Clinical presentation
When evaluating a patient with microangiopathic hemolytic anemia and thrombocytopenia, with normal or mildly deficient ADAMTS13, a cancer history if present and the treatment received need to be considered. Compared with patients with acquired TTP, patients with cancer-associated TMA may have new or exacerbated hypertension, greater pulmonary involvement (dyspnea, cough, abnormal chest radiograph), or a leukoerythroblastic reaction on peripheral smear.51,52

Treatment
Treatment of cancer-associated TMA remains limited to the treatment of the underlying malignancy to the extent that is possible and the removal of any drugs associated with TMA. PEX has not been shown to be beneficial to patients with a cancer-associated TMA.7

Hematopoietic stem cell transplant–associated TMA
Hematopoietic stem cell transplant–associated TMA (TA-TMA), a syndrome of multifactorial endothelial injury that damages the kidney and other organs after HCT,53 remains a major cause of morbidity and mortality among transplant recipients. Initially recognized in 1980,54 it has been difficult to characterize and reach unifying diagnostic criteria.55 TA-TMA commonly affects the kidneys and results in transfusion-dependent anemia and thrombocytopenia; however, it can also present with multisystem organ injury that includes: pulmonary hypertension, intestinal TMA, posterior reversible encephalopathy syndrome (secondary to uncontrolled hypertension), and polyserositis.56

Pathogenesis
Although not universally accepted,53,54,56 TA-TMA should be viewed as a unique form of TMA, distinct from TTP and aHUS. The multi-system injury seen in TA-TMA has several triggers that are unique to this population (immune dysregulation caused by infections, chemotherapy, and graft-versus-host disease [GVHD]), leading to endothelial injury and complement activation. Elevated serum NET levels, measured by an enzyme-linked immunosorbent assay, either at 4 weeks after transplantation or as early as the day of transplantation, has also been associated with a significantly increased risk of TA-TMA.57 Similar to aHUS, TA-TMA has been associated with genetic mutations of the complement system in ~65% of patients.58 Understandably, this raises the question of whether TA-TMA is a distinct disorder from aHUS, or similar conditions with differing triggers for the activation of complement. The most common are copy number variants in genes CFHR3-CFHR1 and acquired complement dysregulation through the formation of neutralizing autoantibodies to Factor H.59

Incidence and risk factors
Because of the different diagnostic criteria used by different groups, the reported incidence of TA-TMA varies widely, from 0% to 74%. There are multiple risk factors associated with TA-TMA including patient-specific factors (older age, female gender), donor factors (HLA-mismatch, unrelated donor), conditioning regimen (high-dose busulfan, total body irradiation), GVHD, medications to prevent GVHD (calcineurin inhibitors [CNIs]), and opportunistic infections. Interestingly, none of the studies could identify a difference in TA-TMA between myeloablative and reduced-intensity conditioning regimens, as well as between the different indications for transplant.55,60-62

Diagnosis
Like other forms of TMA, there is no single test to confirm the diagnosis of TA-TMA. Since the initial description of the disease, different diagnostic criteria have been proposed.63-66 The diagnosis may be more challenging in TA-TMA when compared with other etiologies of TMA because there are other complications of HCT such as GVHD, sepsis, and cytomegalovirus viremia that may have similar clinical presentations. Jodele et al published diagnostic criteria based on a prospective study of 100 children and young adults. It was noted that patients typically present with hypertension (more severe than expected with CNIs or steroid therapy, usually requiring >2 antihypertensive medications), proteinuria (random urinalysis protein concentration of >30 mg/dL), and LDH elevation. Patients with elevated sC5b-9 and proteinuria at diagnosis had worse outcomes (84% mortality rate at 1 year after HCT compared with complete recovery in patients without these markers).66 It is also recommended to obtain a measurement of the ADAMTS13 activity to exclude the diagnosis of acquired TTP.

Treatment
Treatment of TA-TMA remains supportive. When feasible, discontinuation of drugs that have been associated with TMA, especially CNIs, is recommended. Aggressive treatment of GVHD and ongoing infections is also key for improvement of TA-TMA. The disease has significant phenotypic diversity where some patients respond promptly with discontinuation of CNI and others progress despite CNI discontinuation.

There is limited and conflicting evidence on the efficacy of PEX to treat TA-TMA,63,67 with reported response rates of <50% and mortality rates of >80%.63,68 Eculizumab has been shown to reverse end-organ damage and restore hematologic parameters in children and adults, without a higher incidence of bacterial infections.69,70,71,72 Dakhal et al2 published the results of a MEDLINE search of all case reports of TA-TMA and solid organ transplantation–associated TMA treated with eculizumab until November of 2014. They identified 26 cases, 53% of which were men, with a median age of 33 years. Nine cases of TMA were associated with HCT, and 17 occurred after solid organ transplantation. Ninety-two percent of patients had a hematologic response after a median of 2 weekly treatments (range 1-18). After 52 weeks of follow-up, 92% of patients were alive and doing well.

Several questions remain regarding appropriate role of complement inhibition in TA-TMA, as well as the required dose and length of therapy for this off-label use of eculizumab. Prognostic guidelines for use of eculizumab and pharmacodynamics monitoring derived from single-center prospective studies in pediatric patients have been published.66 Although the data are preliminary and from single-center studies, the lack of other effective treatment options argues that it would be reasonable to consider eculizumab for patients with TA-TMA, especially in patients with proteinuria and elevated sC5b-9 at the time of diagnosis.73 A randomized study evaluating a novel complement inhibitor in TA-TMA is currently ongoing in the United State and Europe (www.ClinicalTrials.gov, #NCT02763644).
Cobalamin C defect TMA

Despite its rarity, cobalamin C defect TMA needs to be identified as a distinct TMA etiology with a specific therapy. It is caused by homozygous or compound heterozygous mutations in the gene encoding the methyl malonic aciduria and homocystinuria type C protein (MMACHC), which is vital in the intracellular cobalamin pathway. The mechanisms to explain how MMACHC mutations cause renal and pulmonary vascular injury are not known, because increased homocysteine alone does not lead to these problems. Although it is more commonly seen in neonates, there have been 2 case reports in adults. Patients may present with pulmonary artery hypertension, kidney failure, hyperhomocysteinemia, decreased methionine, and normal vitamin B12 levels. Recovery is typically complete after starting treatment, which includes high-dose hydroxycobalamin, betaine, and folinic acid.

Diacylglycerol kinase ε (DGKE) deficiency TMA

Loss of DGKE function occurs from recessive mutation in the gene encoding DGKE. It results in enhanced signaling through arachidonic acid–containing diacylglycerols and enhanced activation of protein kinase C. Because DGKE is expressed in endothelial cells, platelets, and podocytes, excessive DAG signaling can result in a prothrombotic state and kidney failure. Patients usually present in the first year of life with hematuria, proteinuria, and hypertension. The treatment remains supportive, because PEX and complement inhibition have not proven to be beneficial.

Summary: clinical approach to “non-TTP/HUS” TMA patients

The differentiation of TTP, aHUS, and TMA from other etiologies can be challenging. Although a delay in a potentially lifesaving treatment such as PEX must be avoided, it is also important to avoid exposing patients to the risks of PEX, where they are less likely to benefit. The first and most important step to making a diagnosis is to take a detailed history including concurrent illnesses and medications, including herbal medicines and over-the-counter products. In a patient who has been in the intensive care unit for several days or weeks, with multiorgan failure or systemic infections, our suspicion for TTP and aHUS is much lower compared with a patient that presents initially with a similar clinical picture. In these clinical scenarios, the TMA may be more likely explained by their underlying illness. A clinical history of hypertension, metastatic malignancy, concurrent chemotherapy or immunotherapy, and allogeneic stem cell transplant, which can also lead to TMA findings, also have to be considered as possible explanations for the TMA presentation.

In the absence of a clear explanation for the TMA, or while waiting the results of the ADAMTS13 activity, empiric therapy with PEX should be initiated. During this initial course of PEX, the continued clinical evaluation for other potential etiologies of the TMA should be considered. In many of these disorders, the ADAMTS13 activity will be below “normal” or even very low (10%-20%) but not severely deficient (<10%), which typically characterizes acquired TTP. In a patient who responds poorly to PEX with no other clear explanation for the TMA findings, a diagnosis of aHUS might then become more plausible on the differential diagnosis as an explanation for the TMA. It is also not uncommon for the diagnostic evaluation to continue after the patient has recovered (ie, as an outpatient), where additional studies including complement mutation analyses may add to the diagnostic evaluation.

Authorship

Contribution: C.M., S.V., and S.R.C. contributed to the writing and editing of the manuscript.

Conflict-of-interest disclosure: S.R.C. has received grant funding and honoraria from Alexion, the maker of eculizumab, which is discussed in the manuscript. The remaining authors declare no competing financial interests.

Correspondence: Spero R. Cataland, Department of Hematology, Ohio State University, A361 Starling Loving Hall, 320 W 10th Ave, Columbus, OH 43210; e-mail: spero.cataland@osumc.edu.

References


65. He HD, Bhat YS, Yang SA, Lee Y, et al. Validation of recently proposed consensus criteria for thrombotic microangiopathy after allogeneic


68. Batts ED, Lazarus HM. Diagnosis and treatment of transplantation-associated thrombotic microangiopathy: real progress or are we still waiting? Bone Marrow Transplant. 2007;40(8):709-719.


