

Thrombotic Microangiopathy: Differential Diagnosis, Pathophysiology and Therapeutic Strategies

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Abstract

Several disease states manifest as thrombotic microangiopathies (TMA), most prominently thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). The recent discovery of the von Willebrand factor cleaving protease ADAMTS-13 (a disintegrin and metalloprotease with thrombospondin type 1 motif), found to be deficient in TTP, has helped separate these entities. In contrast, HUS is caused by direct endothelial damage by bacterial toxins, while in familial cases inappropriate complement activation through deficient factor H appears to be a major pathogenetic mechanism.

Although enormous progress has been made towards understanding these syndromes, the diagnostic tools and therapies used have hardly changed in the last 20 years, with the standard of care remaining plasma exchange in most cases. In this review, we will cover the multiple etiologic factors for TMAs, with the resultant differential diagnoses, as well as provide insight into the latest pathophysiologic findings and possible implications for treatment.

Key Words: Thrombotic microangiopathy, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, von Willebrand factor, ADAMTS 13, plasma exchange.

Introduction

FIRST COINED IN 1952 (1), the term “thrombotic microangiopathy” (TMA) defines a pathologic alteration of the microvasculature, with detachment or swelling of the endothelium, amorphous material in the subendothelial space, and luminal platelet aggregation leading to compromise of the microcirculation (2).

There is a wide array of disease states that can present with a microangiopathic phenotype, the laboratory features of which almost uniformly include thrombocytopenia and hemolytic anemia with evidence of red blood cell fragmentation. The two most prominent diseases associated with thrombotic microangiopathy are thrombotic thrombocytopenic purpura (TTP) and hemolytic

uremic syndrome (HUS). The former was first described by Eli Moschcowitz in 1925 as “an acute febrile pleomorphic anemia with hyaline thrombosis of the terminal arterioles and capillaries” (3) (in a case of a 16-year-old girl, who succumbed to her disease within 2 weeks). In 1955, Conrad Gasser gave the first account of the latter syndrome, reporting on 5 children with hemolytic anemia, thrombocytopenia and acute renal failure (4).

Decades after these first clinical observations, pathophysiologic insights have allowed us to differentiate these two phenomena on a molecular basis.

In this work, we will give an overview of the differential diagnosis, showing the variety of etiologies of microangiopathic anemia, review the latest findings in the pathophysiology of TTP and HUS, and discuss the current treatment options as well as some promising newer therapeutic approaches.

Epidemiology and Etiologic Factors in the Development of TMA

Idiopathic TTP is a rare disease, with about 500–2000 new cases diagnosed in the US each year; it exists in an acute form as well as a much

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Adapted from a Grand Rounds presentation to the Department of Medicine, Mount Sinai School of Medicine, New York, NY on November 11, 2003, and updated as of October 2004.

rarer chronic relapsing variant. Women are affected about twice as often as men. HUS is slightly less common and shows a more balanced gender distribution, yet still has a female preponderance (5, 6). Apart from these idiopathic types, thrombotic microangiopathy has been associated with the use of a multitude of drugs, as well as with pregnancy, metastatic cancer, HIV and bone marrow transplantation (Table 1).

Drugs

As early as 1865, quinine was reported to cause purpura (7), and now both TTP and HUS are well-documented adverse effects of this drug. In a recent study, 14 of 132 patients with either TTP or HUS had been taking quinine, with the disease severity being the same as in idiopathic cases (8). Ticlopidine, an antiplatelet agent, was used as an adjunct in the treatment of TTP until it was discovered to cause the disease itself and was withdrawn from the market (9, 10). The similar agent, clopidogrel, has been associated with cases of TMA, albeit with a much lower risk (11).

Other groups of drugs documented in the development of TMA are the immunosuppressants cyclosporine and tacrolimus (12–15) as well as the cytotoxic cancer medications mitomycin C and gemcitabine (16, 17). Cisplatin and carboplatin have thus far been reported in a small number of cases of TMA (18–20).

Malignancy

Not only cytotoxic therapy but also the presence of cancer itself can cause TMA; tumors implicated are adenocarcinomas of the breast, gastrointestinal tract, prostate, and lung (21, 22).

HIV

HIV infection has been reported to portend a risk of developing TMA. The response of HIV-as-

sociated TMA treatment is similar to that of the idiopathic forms (23, 24). Current data suggest a role for direct endothelial damage by HIV (25).

Autoimmune Disorders

There have been occasional associations of TMA with systemic lupus erythematosus (SLE) (26, 27), ankylosing spondylitis (28), Sjögren's syndrome (29), polyarteritis nodosa (30), polymyositis (31), and Graves' disease (32). Given the paucity of the reports, however, one cannot draw firm conclusions about a causative context in these syndromes.

Bone Marrow Transplantation

In addition to the effect of cytotoxic drugs (16–20), the procedure of performing bone marrow transplantation has been identified as a cause for TMA, more frequently with allogeneic transplants than with autologous procedures. Procedure-related endothelial damage, in addition to medication effects, is thought to be an initiating factor (33, 34). Advanced age and female gender appear to be independent risk factors for post-transplant TTP (35).

Pregnancy-Associated TMA

The incidence of both TTP and HUS increases in pregnancy (36, 37), when they are often difficult to distinguish from hemolysis, elevated liver enzymes and low platelet count (HELLP), and severe pre-eclampsia (38).

Shiga Toxins

Shiga-toxin-producing *Escherichia coli* are the most common cause of HUS in children, although other bacteria have been reported (39, 40). In adults most cases of HUS are idiopathic; however, the pathogenesis of inherited HUS, as well as cases of sporadic HUS, have been tied to a deficiency in factor H (41, 42).

Idiopathic TTP

Some progress has been made in understanding idiopathic TTP, with the discovery of the von Willebrand Factor cleaving protease providing profound insights into the underlying pathology (43, 44).

Clinical Features and Differential Diagnosis

The classic pentad of TTP is defined as microangiopathic hemolytic anemia with schistocyto-

TABLE 1

Etiologic Factors in Thrombotic Microangiopathy

Medications
Stem cell transplantation
HIV infection
Pregnancy
Autoimmune diseases
Malignancy
Shiga toxins
Idiopathic enzyme deficiency

sis (at least 3 cells per 100); severe thrombocytopenia (usually less than 10,000/mm³); often fluctuating neurologic deficits secondary to central nervous system ischemia; fever; and renal abnormalities, including hematuria and/or proteinuria. However, only a minority of patients have fever, and renal involvement is not required for the diagnosis (6). Overt cerebral ischemia occurs in 50–75% of patients, making the presence of thrombocytopenia and schistocytes on the peripheral blood smear the sine qua non of the diagnosis (45, 46). A striking laboratory feature is a serum lactate dehydrogenase elevation that is often out of proportion to the degree of hemolysis, the source probably being hypoxic tissues in addition to lysed erythrocytes (47).

HUS, on the other hand, presents with similar, but milder blood count abnormalities, the main organ manifestation, however, being renal abnormalities, often severe enough to necessitate hemodialysis (48). The disease has been described in two variants. Diarrhea-associated HUS occurs predominantly in young children below the age of two years in epidemic outbreaks of *E. coli* O157:H7-related colitis (39). This form is usually self-limited, in contrast to idiopathic HUS, which commonly progresses to end-stage renal disease despite aggressive treatment (48).

Several similarly serious conditions can mimic TTP or HUS (Table 2), including disseminated intravascular coagulation (DIC) (49), the distinction of which is based on laboratory studies and the patient's history. Severe infections such as aspergillosis and cytomegalovirus have been reported to cause TMA as the result of vascular damage (50, 51). The need for antimicrobial treatment rather than plasma exchange dictates correct diagnosis of these disorders. Another fulminant illness that can be confused with TTP or HUS is the catastrophic antiphospholipid antibody syndrome (CAPS), in which widespread micro- and macrovascular thromboses with platelet consumption can occur. The detection of antiphospholipid antibody

and prolonged activated partial thromboplastin time (aPTT) help distinguish CAPS from idiopathic TMA (52, 53).

Among more common diseases, malignant hypertension can produce a clinical picture of TTP or HUS. However, the history of longstanding hypertension (a diastolic pressure above 130 mm Hg) and a retinal examination usually suffice to distinguish it (54, 55).

Although neither TTP nor HUS is specific to pregnancy, the incidence of both is increased in this setting (36, 37). These entities may be difficult to distinguish from other pregnancy-specific causes of microangiopathy, such as HELLP and severe pre-eclampsia (38). Usually, microangiopathic hemolysis is more severe in TTP and HUS than in the latter two disorders. Secondly, TTP develops relatively early in pregnancy, the mean onset time being after about 23 weeks, while pre-eclampsia and HELLP are usually encountered in the third trimester (56), and HUS occurs postpartum in 90% of the cases, with a median time to onset of 26 days (36). In contrast to cases of pre-eclampsia and HELLP, delivery does not ameliorate the course of pregnancy-associated TTP or HUS (37).

Systemic vasculitis has been reported to cause microangiopathic anemia, but in the vast majority of cases the dermatologic and orthopedic manifestations of this disease will guide one to the correct diagnosis (57).

Pathophysiology

Idiopathic TTP

The pathologic substrate of TTP is a thrombotic plaque in the microcirculation, composed mainly of aggregated platelets, with a small amount of fibrin (Table 3, 58). Although pivotal work by Brain has provided insight into the process of microangiopathic red cell fragmentation *in vivo* and *in vitro* by altered vascular surfaces and resultant rheologic disturbances (59, 60), the underlying biochemistry of the fulminant platelet aggregation remained unknown until the discovery of unusually large von Willebrand factor (vWF) multimers in TTP provided an important clue (61). A further milestone was reached with the discovery of defective degradation of vWF by a newly described metalloprotease (43, 44).

von Willebrand Factor

Mature vWF is composed of an aggregated subunit of 270 kD, assembled into multimers rang-

TABLE 2

Conditions Which Mimic Thrombotic Microangiopathy

Disseminated intravascular coagulation (DIC)
Infections (aspergillosis, Rocky Mountain spotted fever)
Pregnancy-induced thrombocytopenias (pre-eclampsia, HELLP)
Vasculitis
Intravascular devices (prosthetic heart valves)
Malignant hypertension

DIC = disseminated intravascular coagulation; HELLP = hemolysis, elevated liver enzymes and low platelet count

TABLE 3
Pathology and Mechanisms of Thrombotic Microangiopathies

Pathology	Mechanism	Disease
Systemic platelet thrombi	Inability to degrade large multimers of von Willebrand factor	Thrombotic thrombocytopenic purpura
Predominantly renal platelet-fibrin thrombi	Shiga toxins causing endothelial damage	Classic hemolytic uremic syndrome
	Factor H deficiency and complement activation	Familial hemolytic uremic syndrome
Systemic and renal thrombi	Drugs and stem cell transplantation with endothelial damage	Features of thrombotic thrombocytopenic purpura and hemolytic uremic syndrome

ing from 500–10,000 kD. It is synthesized in megakaryocytes and endothelial cells, where it is stored in the Weibel Palade bodies (62). The multimers form filaments as long as 1300 nm (approximately the diameter of a platelet), and globular structures with a diameter of about 300 nm (63). vWF has functions in both platelet aggregation (64) and stabilization of factor VIII (65), and the size of the multimer directly correlates with its ability to support platelet aggregation by establishing strong bonds with the platelet glycoprotein Ib-IX-V complex (66).

Unusually Large vWF Multimers and Shear Stress

In 1982, Moake et al. found unusually large multimers of vWF (ULvWF) in the plasma of patients with chronic relapsing TTP (61). They demonstrated in serial measurements that, between episodes of active TTP, the ULvWF forms were present in the patients' plasma, whereas during an exacerbation of the disease they seemed to be cleared from the circulation, probably by consumption in the platelet thrombi. This observation led to the hypothesis of an inability of TTP-plasma to adequately degrade large vWF multimers (61).

Increased shear forces in the microcirculation have been shown to promote platelet aggregation, which can be mediated by platelet-derived vWF as well as by exogenous large vWF multimers. At high shear stress, platelets release vWF, which in concert with its exogenous counterpart binds to the exposed GPI-IX-V complex on the platelet, thus contributing to further apposition of a growing thrombotic lesion as the circulation becomes more compromised (67, 68). Shear-dependent platelet aggregation can be abrogated by inhibitors of

vWF, lending further evidence to its crucial role in this setting (69). Globular vWF molecules on endothelial surfaces can be uncoiled under shear stress (70). This tensile stretching of ULvWF appears to be necessary for degradation by vWF-cleaving protease, suggesting their roles in forestalling uncontrolled platelet aggregation under shear stress (71).

vWF-Cleaving Protease (ADAMTS-13)

In 1996, Tsai and Furlan independently purified a plasma protease that cleaves vWF in a shear-dependent manner, creating the 140 kD and 176 kD fragments found in normal plasma (72, 73). Shortly thereafter, four patients, including two brothers, with chronic relapsing TTP were shown to have either substantially reduced or absent activity of the vWF-cleaving protease, without any inhibitors detected (74). This observation linked vWF-cleaving protease deficiency to the hereditary form of TTP, Upshaw-Shulman syndrome for the first time (75). The case of a patient with antibodies to vWF-cleaving protease and TTP suggested that acquired TTP might be an autoimmune disease (76). In the same year, two seminal studies showed that patients with TTP had severe deficiency of vWF-cleaving protease, whereas patients with HUS had normal levels. In most cases of non-familial TTP, an immunoglobulin G (IgG)-antibody to the protease was identified, supporting the notion of an autoimmune process. Of interest was the finding that patients with familial as well as non-familial HUS had normal protease levels, separating this entity from TTP on a pathogenetic level (43, 44).

The protease was identified as a member of the ADAMTS (a disintegrin and metalloprotease with

thrombospondin type 1 motif) metalloprotease family (77). By means of genome-wide linkage analysis, the responsible gene was mapped to chromosome 9q34 (78). Thus far, more than 30 different mutations in the gene for ADAMTS-13 have been described in patients with the familial form of TTP, and none of these patients had an unmutated protease gene (79).

Although there are several conditions or situations with less pronounced reductions in ADAMTS-13 activity, namely DIC, idiopathic thrombocytopenic purpura (ITP), sepsis, SLE, heparin-induced thrombocytopenia (HIT), leukemia, cirrhosis, uremia, postoperative period, and the postnatal phase (80–83), evidence points towards a severe deficiency (less than 5%) of ADAMTS-13 to be specific for TTP (84). Difficulties in utilizing the protease activity as a diagnostic test remain, highlighted by a recent study finding that in a large series of clinically diagnosed TTP, the levels of ADAMTS-13 varied greatly between patients. Only 16 of 36 patients with idiopathic TTP and 2 of 10 with the pregnancy-associated form had severely depressed ADAMTS-13 activity (less than 5%). None of the other cases (stem cell transplant, drug-related, bloody diarrhea, HUS, HIV, and autoimmune diseases) were found to have such low enzyme levels. These results suggest that, at least for nonidiopathic TTP, alternative models of pathogenesis should be devised (85).

TTP Associated with Drugs and Stem Cell Transplantation

The mechanisms leading to drug-induced microangiopathy are poorly understood and most patients do not suffer from profound ADAMTS-13 deficiency (85). However, severe deficiency has been reported in cases related to ticlopidine (86) and clopidogrel (87). In both clinical settings, it was also possible to detect ADAMTS-13-inhibiting antibodies (86, 87). This contrasts with quinine-associated TTP, in which the formation of antibodies against platelets and endothelial cells was detected, suggesting a role for endothelial damage in promoting the thrombotic process (8).

Patients developing TTP after stem cell transplantation generally have normal ADAMTS-13 levels (88). Cyclosporine, widely used in the setting of allogeneic transplantation, can damage endothelial cells (89) and release tissue factor into the circulation (90). In concert with the graft-versus-host effect on the vascular integrity, cyclosporine is a major contributing factor to post-stem-cell-transplant TMA (88). To the contrary, in autologous transplantation, an autoimmune mech-

anism is believed to be at play, underlined by the positive response of the disease to cyclosporine, revealing the drug's dual effects (91). Apart from being a powerful immunosuppressant, however, cyclosporine can also increase nitric oxide production, which might also contribute to its beneficial effect in this particular setting (92).

Hemolytic Uremic Syndrome

Although the clinical distinction between TTP and HUS can be challenging, the differing histopathologies (93) and pathophysiologic pathways recommend HUS as a separate disease entity (94). In contrast to TTP, the pathologic lesion in HUS is a predominantly fibrin-containing thrombosis, largely confined to the renal circulation, yet present in other tissues in a fraction of cases (93).

The two thus far elucidated pathomechanisms leading to endothelial damage are toxin production by bacteria (40) and inappropriate activation of the complement system by deficient factor H (95).

Shiga Toxins and Endothelial Damage

Several strains of *E. coli*, most commonly O157:H7, produce shiga-like toxins, also known as verotoxins (for their lethal effect on Vero cells—African green monkey kidney cells), that are directly toxic to endothelial cells (96, 97). Once the toxin has entered the circulation it is bound to the surface of polymorphonuclear leukocytes (PMN) and transferred to glomerular endothelial cells, which have a 100-fold higher affinity for the toxin than for PMNs (98). The B subunit of the verotoxin binds to globotriaosyl ceramide (Gb3) on the endothelial cell membrane, leading to internalization of the A subunit. What follows is a breakdown of cellular protein synthesis from inactivation of the ribosome, and cell death in most cases (97). Sites of verotoxin-induced tissue damage coincide with areas of high Gb3 expression, especially the kidney (2). Once the stage has been set by endothelial damage, upregulation of cytokine production, PMN activation and enhanced oxidant injury potentiate the damage done, leading to a weakening of antithrombotic mechanisms (99). In addition to fibrin deposition, the appearance of ULvWF multimers contributes to local platelet aggregation (100), and the ensuing narrowing of the arteriolar lumen leads to renal dysfunction (101).

Defective Factor H and HUS

Factor H is a regulatory protein that inhibits complement activation via the alternative pathway

by preventing the formation of the C3bBb complex and accelerating the dissociation of Bb from C3 convertase. By modulating complement activation, factor H plays an important role in attenuating the inflammatory response to local vascular insults (102). For HUS, activation of both the classical and alternative complement pathways has been well documented, with resolution if the disease remits (103). In cases of familial HUS, C3 levels were consistently depressed independently of the disease activity, and normal levels of C4 ruled out activation of the classic pathway (104). So far, studying families with cases of familial HUS has provided insight into several function-altering mutations of factor H associated with HUS, demonstrating autosomal dominant as well as recessive inheritance (42, 105–107). Since only 2–7% of patients exposed to verotoxin-producing *E. coli* progress to overt HUS, a genetic predisposition has long been suspected. Recent descriptions of polymorphisms in the promotor and coding regions for factor H have been described. There is speculation as to whether these might give rise to heightened susceptibility to environmental factors (94).

Therapy and Prognosis

For decades TTP was an almost uniformly lethal disease, until plasma infusion therapy was shown to have some clinical benefit (108), but the real breakthrough came with the introduction of plasma exchange, with long-term remission rates of 80–90% (45, 46). A randomized trial clearly demonstrated superiority of plasma exchange versus infusion, both in remission induction and long-term follow-up (45). It is believed that, while plasma transfusion provides the absent or defective vWF-cleaving protease, concomitant plasmapheresis removes autoantibodies against ADAMTS-13, ULvWF multimers and other potentially detrimental factors from the circulation. Supporting this notion, exchange has successfully been employed with cryosupernatant, which does not contain larger vWF polymers, in patients not responding to regular plasma exchange (109). Recurrent episodes in chronic relapsing TTP can successfully be treated with plasma- or cryosupernatant only, in retrospect understood due to the deficiency of ADAMTS-13 in the absence of an inhibitor (110–112). It is generally agreed that once the diagnosis of TTP is suspected, plasma exchange should be started as soon as possible. If delays are unavoidable, the therapy can be started with fresh frozen plasma infusions until definitive therapy can be arranged. The duration of therapy is variable, since responses can take up to one month

to become manifest and the exchange needs to be continued for about one week in excess of a complete remission, in order to avoid early relapse. Since fragmented red cells may not be cleared from the circulation for a few days, the platelet count and serum LDH are the most reliable laboratory parameters to assess treatment success. It is prudent to include steroids, since it was shown that prednisone can by itself induce remission in TTP, albeit at a very low rate (108).

Since not all TMA is TTP, it is not surprising that the response to exchange therapy is not universal, as seen in the case of stem-cell-transplantation-related TMA, which carries a mortality of 80%, and for which the effect of plasma exchange could not be distinguished from that of cyclosporine discontinuation (113, 114).

Recent data suggest that ADAMTS-13 level at diagnosis predicts the response to exchange and survival. In a prospective analysis, patients with idiopathic TTP and ADAMTS-13 levels below 5% had a mortality of 15%, in stark contrast to patients with stem cell transplantation-, cancer-, drug- or pregnancy-related TMA, whose mortality was as high as 59%. Of note, none of these patients had ADAMTS-13 levels below 5% (115). Plasma exchange is also indicated in non-shiga-toxin-associated HUS, the efficacy being lower than for TTP, with relapse rates between 29 and 82% (45, 46, 116).

Childhood *E. coli*-associated HUS does not warrant plasma therapy, since it usually resolves spontaneously (116). Nevertheless, it is not a benign disease, with a mortality of 3–5% and a similar proportion of patients developing end-stage renal disease (117).

Although there are some anecdotal reports on beneficial effects of intravenous immunoglobulin (IVIG) on TMA, a controlled study with 44 patients could not confirm any improvement from adding IVIG to plasma exchange (118–120).

The role of splenectomy was never studied in a controlled fashion, but the experience reported thus far supports its role in relapsed TTP and refractory cases (121–123). Protein A immunoabsorption, designed to remove IgG from the circulation, has produced remissions in patients resistant to plasma exchange, but no comparative studies exist (124). Other immune-modulating approaches have employed cyclophosphamide- and azathioprine-containing regimens; however, the low number of successfully treated cases prohibits any firm conclusions (125, 126).

Another cytostatic drug, vincristine, has been applied not for its immunotoxic effect, but to exploit its microtubule-destabilizing property for platelet stunning (127).

Emerging Treatments

The humanized monoclonal antibody to CD20, rituximab, holds promise in cases of resistant TTP, by decreasing antibody production (128, 129). A prospective trial is underway to evaluate its role in TTP. Although there is still controversy as to whether severe ADAMTS-13 deficiency is specific for TTP (130, 131), it will be interesting to evaluate the role of recombinant ADAMTS-13 (132) as treatment at least for hereditary TTP. Such studies should help lead to more disease-specific therapy and reduction of the high burden of toxicity and infection risk associated with the current standard of care.

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