Review article

The Differential Diagnosis and Treatment of Thrombotic Microangiopathies

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Summary

Background: Thrombotic microangiopathies are rare, life-threatening diseases whose care involves physicians from multiple specialties. The past five years have seen major advances in our understanding of the pathophysiology, classification, and treatment of these conditions. Their timely diagnosis and prompt treatment can save lives.

Methods: This review is based on pertinent articles published up to 17 December 2017 that were retrieved by a selective search of the National Library of Medicine's PubMed database employing the terms "thrombotic microangiopathy," "thrombotic thrombocytopenic purpura," "hemolytic-uremic syndrome," "drug-induced TMA," and "EHEC-HUS."

Results: The classic types of thrombotic microangiopathy are thrombotic thrombocytopenic purpura (TTP) and typical hemolytic-uremic syndrome (HUS), also known as enterohemorrhagic *Escherichia coli*-associated HUS (EHEC-HUS). There are a number of further types from which these must be differentiated. The key test, beyond a basic hematological evaluation including a peripheral blood smear, is measurement of the blood level of the protease that splits von Willebrand factor, which is designated ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13). The quantitative determination of ADAMTS13, of ADAMTS13 activity, and of the ADAMTS13 inhibitor serves to differentiate TTP from other types of thrombotic microangiopathy. As TTP requires urgent treatment, plasmapheresis should be begun as soon as TTP is suspected on the basis of a finding of hemolysis with schistocytes and thrombocytopenia. The treatment should be altered as indicated once the laboratory findings become available.

Conclusion: Rapid differential diagnosis is needed in order to determine the specific type of thrombotic microangiopathy that is present, because only patients with TTP and only a very small percentage of those with atypical hemolytic-uremic syndrome (aHUS) can benefit from plasmapheresis. The establishment of a nationwide registry in Germany with an attached biobank might help reveal yet unknown genetic predispositions.

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The term thrombotic microangiopathy describes an etiologically very heterogeneous group of diseases (Table 1), which in the presence of endothelial damage can lead to thrombosis of small and micro vessels, both arterial and venous. Microangiopathy can lead to secondary consumption of platelets and mechanical hemolysis. Thrombotic microangiopathy is defined by the triad of Coombs-negative hemolytic anemia with evidence of schistocytes in the blood, thrombocytopenia (microangiopathic hemolytic anemia), and ischemic end-organ damage. Depending on the vascular systems involved, renal failure, neurological symptoms, cardiac complications, respiratory failure, visual disturbances, pancreatitis, intestinal ischemia, and (less commonly) skin changes may occur (1, 2). Mortality is high if untreated, with reports published prior to the advent of effective therapy of 72–94% (3, 4). Recognizing thrombotic microangiopathy and initiating plasmapheresis within 4 to 8 hours is essential for successful therapy (recommendation grade 1 B) (5). Plasmapheresis helps to reduce mortality of thrombotic thrombocytopenic purpura (TTP) to approximately 10–20% (3, e1). A diagnostic and therapeutic algorithm, as well as a classification of thrombotic microangiopathies, are shown in Figure 1, Table 1, eTable 2, and eTable 3, and the relevant differential diagnoses, in eTable 1. The establishment of a nationwide disease registry in Germany with a biobank would now be desirable.

Methodology

A selective literature search in the PubMed (NLM) database was carried out up to (and including) December 17, 2017, based on the following keywords: "thrombotic microangiopathy," "thrombotic thrombocytopenic purpura," "hemolytic uremic syndrome," "drug-induced TMA," and "EHEC-HUS."

Pathophysiology

The ultimate outcome of all thrombotic microangiopathies is ischemia in the terminal vascular bed of organs. In 1926, Elias Moschkowitz first reported a fatal thrombotic microangiopathy in a 16-year-old female patient who presented with anemia, fever, hemiparesis, and coma (6). This case is recognized as the first description of a TTP. Autopsy revealed multiple intravascular thrombi especially in the heart, but also in the kidneys and brain. Because of the important role of the von Willebrand factor (vWF)-cleaving protease

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ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13), TTP is diagnosed by detection of thrombotic microangiopathy—that is, the presence of schistocytes (red blood cell fragmentation) in blood, hemolysis, and thrombocytopenia—with simultaneously reduced levels of ADAMTS13 and, if necessary, detection of anti-ADAMTS13 antibodies (5). The latter inhibits the vWF-cleaving protease and leads to uncontrolled thrombosis of small and micro blood vessels in almost all organs. This results in the clinical picture of an immune-mediated, acquired thrombotic thrombocytopenic purpura (aTTP) (*Figure 2*). In contrast, in hemolytic uremic syndrome (HUS), thrombus formation almost always occurs in the kidneys, although it may affect other organs in some patients. Further, in HUS, endothelial damage with complement activation and increased vWF release results in vascular occlusion. However, ADAMTS13 levels are normal in HUS (7).

Laboratory diagnostics

Typically, microangiopathic hemolytic anemia is characterized by reduced levels of haptoglobin, reticulocytosis, and greatly increased concentrations of lactate dehydrogenase (LDH). Detection of schistocytes in a blood smear is easy to perform and is the most important laboratory test for diagnosis, which should always be initiated promptly, even at night, if thrombotic microangiopathy is suspected (recommendation grade 1 A) (*Table 2*) (5). Tests essential for differentiating TTP from other forms of thrombotic microangiopathies are quantitative detection of the vWF-cleaving protease ADAMTS13 and measurement of the activity levels of ADAMTS13 and the ADAMTS13 inhibitor. ADAMTS13 activity is determined in citrated blood samples prior to any treatments with plasma therapy or blood transfusion (recommendation grade 1 B) (5). As the results of the ADAMTS13 diagnosis are generally not available within hours, TTP must be suspected from a constellation of hemolysis with schistocytes and thrombocytopenia, due to the urgency of initiating plasmapheresis. A diagnosis of TTP is confirmed if the ADAMTS13 level is <10% (5).

Thrombotic thrombocytopenic purpura (TTP) Immune-mediated, acquired thrombotic thrombocytopenic purpura

Clinically, patients with TTP often present with non-specific prodromes, such as flu-like symptoms or diarrhea. The highly variable clinical features range from general weakness to stroke or sudden cardiac death. Amarosi et al. (4) described the symptom pentad of TTP, the incidence of which was analyzed in a registry study of 78 patients (8): fever (10%), neurological disorders (headache, confusion, neurological deficits, and seizures; up to 80%), hemolytic anemia (100%), and thrombocytopenia (100%). On the other hand, renal impairment ($\geq$ stage 3) is relatively rare (9%) (8). Severe hemolysis and marked thrombocytopenia with clinical symptoms usually only appear a certain time

after disease onset, when a large cross-section of vessels have been affected by consumption of platelets and mechanical hemolysis. Therefore, thrombogenesis in a few organs relevant for end-organ perfusion, such as in the brain stem, can lead to severe neurological symptoms very early in the course of the disease. If ADAMTS13 levels and inhibitor titer are measured repeatedly, the effectiveness of immunosuppressive therapies in chronic recurrent disease can be monitored (9). In immune-mediated acquired aTTP, the risk of recurrence is associated with low levels of ADAMTS13; however, at an individual patient level, having a low level of ADAMTS13 cannot predict recurrence. The interindividual variations in protease levels are very high (10). Thus, in addition to low levels of ADAMTS13, additional factors are needed to trigger a clinical manifestation of aTTP.

Congenital thrombotic thrombocytopenic purpura (Upshaw–Schulman syndrome)

In addition to the acquired form of TTP, an extremely rare form of congenital thrombotic thrombocytopenic purpura (cTTP) exists, termed the Upshaw–Schulman syndrome, in which the levels of ADAMTS13 are genetically reduced. In other words, the liver makes less ADAMTS13. More than 100 mutations have been described for this. Depending on the underlying mutation, the patients can become clinically symptomatic in early childhood (about 50–60% of cases) or first in adulthood, in their third to fourth decade of life, despite having low levels of ADAMTS13 for years (11).

Therapy of thrombotic thrombocytopenic purpura

Historical case reports of patients with TTP receiving either no treatment or non-specific treatment reveal a mortality of 72–94%. In a randomized, non–placebo controlled study, a Canadian working group (3) compared plasma infusion with plasmapheresis and demonstrated that plasmapheresis is superior in terms of 6-month mortality (with 37% mortality after plasma infusion compared to 22% after plasmapheresis). Current guidelines recommend plasma exchange within the first 4 to 8 hours if TTP is suspected (recommendation grade 1 B) (5, 12). Plasma exchange increases ADAMTS13 activity in the blood and should eliminate ADAMTS13 neutralizing antibodies. For aTTP, a combination with steroids is recommended to control antibody-producing B cells; however, this goal is not usually sustainable (recommendation grade 1 B) (5, 13). Compared to historical controls, rituximab ($4 \times 375 \text{ mg/m}^2$) shortens the duration of treatment, reduces the risk of recurrence (10% versus 57%), and increases the duration of remission (with a median of 27 months versus 18 months) (14). Although rituximab is not approved for treatment of TTP (off-label use), it is currently the drug of choice for the long-term control of immune-mediated aTTP (recommendation grade 1 B) (5).

As with aTTP, patients with cTTP (Upshaw–Schulman syndrome) require plasmapheresis—possibly

TABLE 1

Classification of thrombotic microangiopathies (based on Brocklebank V, et al. [7])

Disease	Laboratory constellation, pathogenesis	Frequency	Clinical characteristics	Therapy
aTTP	ADAMTS13 <5%, usually ADAMTS13 inhibitor is detectable	Incidence 3.1 per million/year (USA) (8, 12)	Focal neurologic signs, convulsive seizures, renal involvement	Plasmapheresis, steroids, rituximab (off-label use)
cTTP: Upshaw–Schulman syndrome	ADAMTS13 deficit, autosomal recessive	Very rare, fewer than 1 per million/year (USA) (31)	Initial diagnosis in >50% in childhood, in adult females pregnancy may be a trigger	Acute phase: plasmapheresis followed by plasma infusion in chronic phase.
HELLP, (pre-)eclampsia	Elevated transaminases, normal ADAMTS13, complement factor mutations?	HELLP: 0.5–0.9% of all pregnancies TMA: 5–10% of all patients with severe eclampsia (32)	Seizures, hypertension	Cesarean delivery
TMA in autoimmune diseases	SLE, CAPS, ADAMTS13 occasionally reduced: TTP	CAPS: 14% incidence of TMA (33) SLE: 8–15% TMA in the biopsy (34)	Renal involvement , polyserositis	Plasmapheresis, immunosuppression if ADAMTS13 <10%: as for aTTP
Metastatic cancer	Leukoerythroblastic hemogram ADAMTS13 >10%	Unknown	Cancer in case history, often bone marrow involvement	Treatment of underlying disease
Cobalamin C defect	Homozygous or compound heterozygous MMACHC mutation	Rare, can occur in children and adult patients	Clinical aHUS	Hydroxycobalamine, folic acid
Coagulation cascade–dependent TMA	Thrombomodulin mutations	Very rare, children <1 year	Clinical aHUS	Experimental eculizumab
	DGKE mutations			Plasmapheresis, eculizumab if recurrence
	Plasminogen mutations			Experimental eculizumab
Drug-induced TMA				
– Antibody-mediated, dose independent	Ticlopidin: ADAMTS13 antibody Quinine: Endothelial cell antibodies	Ticlopidin: 1:5000 treated patients (Japan) (5, 24) Quinine: 3.7% of TMA cases in the TTP-HUS registry (USA) (23)	Renal failure, liver toxicity	ADAMTS13 antibody positive: plasmapheresis, discontinue medication
– Dose-dependent endothelial damage	Tacrolimus, CSA, mitomycin C, gemcitabine, bevacicumb	Mitomycin C: 2–10% (35) Tacrolimus: 1–4.7% (35) Gemcitabin: 0.4% (36) per treated patient	Liver failure, clinical HUS	Supportive therapy, discontinue medication, experimental (off-label) use of eculizumab (36)
TA-TMA	Endothelial cell damage, complement activation, elevated sC5b-9	10–40% all patients with allogenic PBSCT (USA) (37)	Renal failure, convulsive seizures, hypertension, heart failure	Supportive therapy, (eculizumab, off-label use)
HIV-TMA	ADAMTS13 normal, late-stage, rare: reduced ADAMTS13, ADAMTS13 inhibitor–positive	0.3% of the HIV-positive population (USA) (38)	Focal neurologic signs, seizures, renal involvement	Plasmapheresis, HAART (5)
Atypical HUS/ complement-mediated HUS	Activation of the alternative complement pathway, factor H antibody; mutations: factor H, MCP, factor I, C3	0.42 per million adults/year (UK) (39)	Chronic TMA recurrence	Eculizumab, if factor H antibodies are present: additional immunosuppression and plasmapheresis
STEC-HUS	<i>Escherichia coli</i> /Shigella/ citrobacter (Shiga toxin)	6–8 per million children/year (USA, EU) 100–170 per million children/year (Latin America) (16)	Usually affects children, renal failure, bloody diarrhea	Supportive therapy
SP-HUS	<i>Streptococcus pneumoniae</i> (neuraminidase), Thomsen-Friedenreich antigen	Cumulative 10-year incidence of 1.2 per 100 000 children (New Zealand) (40)	Sepsis/meningitis with <i>Streptococcus pneumoniae</i>	Antibiotic therapy, supportive therapy

aHUS: atypical hemolytic uremic syndrome; aTTP: immune-mediated, acquired TTP; ADAMTS13: a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13; C5b-9: soluble terminal complement complex; CAPS: catastrophic antiphospholipid syndrome; CSA: cyclosporin A; cTTP: congenital thrombotic thrombocytopenic purpura; DGKE: diacylglycerol kinase E; EU: European Union; HAART: highly active antiretroviral therapy; HELLP: hemolysis, elevated liver enzyme levels, and low platelet levels; HIV: human immunodeficiency virus; HUS: hemolytic uremic syndrome; MCP: membrane cofactor protein; MMACHC: methylmalonate aciduria and homocystinuria type C protein; PBSCT: peripheral blood stem cell transplantation; SLE: systemic lupus erythematosus; TA-TMA: transplant-associated thrombotic microangiopathy; TMA: thrombotic microangiopathy; UK: United Kingdom; USA: United States of America

FIGURE 1

Algorithm for diagnosis and therapy of thrombotic microangiopathy (modified according to Brocklebank et al. [7])

ADAMTS13: a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13; aHUS: atypical hemolytic uremic syndrome; G/L: Giga per liter; DIC: disseminated intravascular coagulopathy; GI: gastrointestinal; HELLP: hemolysis, elevated liver enzyme levels, and low platelet levels; HUS: hemolytic uremic syndrome; LDH: lactate dehydrogenase; CNS: central nervous system; SP-HUS: *Streptococcus pneumoniae*; STEC: Shiga toxin-producing *Escherichia coli*; Susp.: suspicion of; TMA: thrombotic microangiopathy; TTP: thrombotic-thrombocytopenic purpura

followed by long-term treatment with repetitive plasma infusions—if they sustain organ damage. Asymptomatic patients with no signs of hemolysis and normal platelet counts may undergo watchful waiting without plasma infusions (15). Immunosuppressive therapy is not useful in cTTP, as there are no autoantibodies to be targeted.

Hemolytic uremic syndrome

Thrombotic microangiopathy with a primary finding of kidney failure is termed hemolytic uremic syndrome (HUS). The most common form is HUS following infection with Shiga toxin-producing *Escherichia coli* (STEC), which is typically accompanied by bloody diarrhea (Table 1). This form is called EHEC-HUS (enterohemorrhagic *E. coli*, EHEC) or STEC-HUS. HUS following a respiratory infection with *Streptococcus pneumoniae* (SP-HUS) is very rare. If none of these infections is present, there is a suspicion of an atypical hemolytic uremic syndrome (aHUS), also referred to as complement-mediated HUS (cmHUS) (7). In children, about 80–90% of all HUS cases are EHEC-induced, with only about 5–10% of cases attributable to aHUS (16). SP-HUS is even rarer, accounting for less than 5% of the cases (16).

Pathophysiologically, all forms of HUS have complement-mediated endothelial cell damage, which mainly affects the capillary area of the kidney. If HUS is due to a transient trigger, such as Shiga toxin of enterohemorrhagic *Escherichia coli*, an infection with

Streptococcus pneumoniae, or medications, spontaneous remission generally occurs with supportive therapy after the trigger has been removed. However, in the cases of a genetic defect or an acquired dysregulation of the complement or coagulation system, thrombotic microangiopathy may lead to damage of the affected organs (usually the kidney) even after the trigger (infection, surgical intervention, use of medication) has been controlled or in the absence of a trigger. Examples for this include complement-regulatory defects due to mutations of factor H, factor I, factor B, C3, or membrane cofactor protein (MCP), or to autoantibodies to factor H (1). Under physiological conditions, asymptomatic mutations of the complement regulatory genes can lead to clinical manifestation of thrombotic microangiopathy following a triggering event. Triggers can include for instance malignancy, pregnancy, stem cell transplantation, use of medication, or infection. In rare cases, mutations are present in genes involved in the coagulation system, such as those for diacylglycerol kinase E (DGKE) and thrombomodulin, or involved in cobalamin (B12) metabolism, leading to defects described predominantly in children (<1 year) (1, 16).

Typical hemolytic uremic syndrome

In 1955, Conrad Gasser coined the term hemolytic uremic syndrome (HUS) for patients with renal failure following bloody diarrhea (17). In the 1970s, an association between HUS and Shigella infections was

TABLE 2

Laboratory testing for the differential diagnosis of thrombotic microangiopathy (recommendation grade IA-IB) (5)

Laboratory	Parameter	Suspected diagnosis
Mandatory		
Hematology	Complete differential blood analysis (smear, increased schistocytes fraction)	Microangiopathic anemia
Clinical chemistry	Creatinine, protein excretion in urine LDH, haptoglobin levels	HUS Hemolysis
Coagulation	Quick ↓, PTT ↑, fibrinogen ↓, (D-dimer ↑)	Hyperfibrinolysis, DIC
Microbiology/ virology	Shiga toxin in stool or blood Blood culture Test for HIV, hepatitis B/C	EHEC-HUS SP-HUS HIV-associated TMA
Pregnancy test (for women of childbearing age)	Beta-HCG	HELLP, eclampsia
Immunology	Coombs' test positive	Autoimmune hemolytic anemia, Evans syndrome
	ADAMTS13 antigen ↓, ADAMTS13 activity ↓, positive for ADAMTS13 inhibitor	aTTP
	ADAMTS13 antigen ↓, ADAMTS13 activity ↓, negative for ADAMTS13 inhibitor	cTTP
Special indications		
Immunology	sC5b-9↑, C3↓, C4↓, anti-H-antibody positive	aHUS
Bone marrow puncture	Cytology and histology of bone marrow	Bone marrow carcinosis
Renal biopsy	Immunohistochemistry	Complement-dependent nephropathy, aHUS
Skin biopsy	Immunohistochemistry	TMA
Molecular genetics	ADAMTS13 mutation	Congenital TTP (Upshaw–Schulman syndrome)
	Mutation of factor H, factor I, MCP, C3, DGKE, thrombomodulin, MMACHC, plasminogen	aHUS

ADAMTS13: a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13; aHUS: atypical hemolytic uremic syndrome; aTTP: immune-mediated, acquired thrombotic thrombocytopenic purpura; beta-HCG: beta-human chorionic gonadotropin; cTTP: congenital thrombotic thrombocytopenic purpura; DGKE: diacylglycerol kinase E; DIC: disseminated intravascular coagulopathy; EHEC: enterohaemorrhagic *Escherichia coli*-associated HUS; HELLP: hemolysis, elevated liver enzyme levels, and low platelet levels; HUS: hemolytic uremic syndrome; LDH: lactate dehydrogenase; HIV: human immunodeficiency virus; MCP: membrane cofactor protein; MMACHC: methylmalonate aciduria and homocystinuria type C protein; PTT: partial thromboplastin time; SP-HUS: *Streptococcus pneumoniae*-induced hemolytic uremic syndrome; TMA: thrombotic microangiopathy

described (18). The most common Shiga toxin-producing pathogen is EHEC of serotypes O157:H7 and O104:H4 (16). In an intestinal infection, the Shiga toxin passes the gut wall and enters the bloodstream. Shiga toxin binds to endothelial cells of the kidney via CD77 (cluster of differentiation, CD; also called globotriaosylceramide, Gb3), causing the cells to die and release vWF. Thrombosis of the renal vessels (as well as in other vascular areas in some patients) leads to the end-organ damage characteristic for thrombotic microangiopathy. The complement system is activated in the process, such that further endothelial cells are destroyed. Renal failure requiring dialysis is common, with a rate of up to 50% (19, 20). A proportion of patients (20%) experience permanent renal insufficiency (RI), although end-stage RI is rare (3%) (19, 20). Therapy is limited to treating kidney failure and management of fluid balance. Antibiotic therapy is controversial (16).

In *Streptococcus pneumoniae*-associated HUS (SP-HUS), neuraminidases induce exposure of the Thomsen-Friedenreich antigen of erythrocytes, causing thrombotic microangiopathy (16).

Atypical hemolytic uremic syndrome

A small proportion of patients with HUS (5–10%) do not have bloody diarrhea. In these cases, there is a suspicion of an atypical hemolytic uremic syndrome (aHUS), also called complement-mediated HUS (cmHUS). Diagnosis of aHUS requires exclusion of both STEC-HUS (typical HUS, with Shiga toxin detection in stool or blood) and ADAMTS13-mediated thrombotic microangiopathy (TMA) (TTP, with ADAMTS13 levels <10%) (Figure 1). Diagnostically indicative is finding evidence of thrombotic microangiopathy in renal biopsy. Pathophysiologically, aHUS is based on a dysregulation of the alternative complement pathway (eFigure). Inherited defects in

FIGURE 2

Pathophysiology of thrombotic thrombocytopenic purpura (TTP)

a: Normal blood flow in a healthy capillary;

b: Circulatory disturbance, with microthrombus and schistocyte formation after endothelial damage in thrombotic microangiopathy.

von Willebrand Factor (vWF) is secreted from endothelia as an ultra-large vWF multimer (ULvWF multimer) and binds to the endovascular endothelia by P-selectin. Platelets (thrombocytes) aggregate via GPIIb/IIIa (glycoprotein, GP), and the formation of platelet-rich thrombi is initiated. The ULvWF multimers are physiologically cleaved by ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13), which reduces the formation of thrombi (a). Inactivity of ADAMTS13 leads to uncontrolled thrombogenesis with ischemia in dependent end organs; in the classical immune-mediated, acquired thrombotic thrombocytopenic purpura (aTTP) (affecting >90% of all TTP patients), ADAMTS13 is inactivated by antibodies (b). A thrombus can occur in all organs; those less affected are the liver and lungs. The mechanical fragmentation of red blood cells (erythrocytes) in partially occluded blood vessels and the presence of vWF fibrils are believed to be responsible for the formation of schistocytes *in vivo*

complement regulation occur more frequently than acquired changes, with the most common being factor H mutations (20–30% of all aHUS patients) (19). Because of these mutations, a trigger such as infection or pregnancy can activate the alternative complement signaling pathway. Acquired forms of aHUS are very rare and can involve an antibody against factor H (6–10% of all aHUS patients). The treatment of choice for aHUS is the complement inhibitor eculizumab, a monoclonal antibody against C5 (*eFigure*). Binding of eculizumab to C5 disrupts the terminal pathway of complement signaling and thereby reduces endothelial injury (21). In both of two prospective phase 2 trials, renal function improved (≥ 1 stage, 45–65%) and hematologic parameters (88–90%) normalized, after 26 weeks of eculizumab therapy in patients with aHUS (22). Meningococcal vaccination is obligatory prior to initiating therapy with eculizumab.

Secondary hemolytic uremic syndrome

In addition to these now well-defined entities, there are a number of diseases that are less clearly classified. These diseases are referred to as secondary thrombotic microangiopathies or secondary HUS. The common consequences are endothelial cell damage with consecutive thrombus formation and complement activation (16). Triggers are tumors, stem cell transplantation, use of medications, pregnancy, autoimmune diseases, kidney disease, or malignant hypertension (*eTable 2*).

Drug-induced hemolytic uremic syndrome

Drugs can trigger thrombotic microangiopathy in two ways: i) dose-independent antibody formation, for instance against platelets and endothelial cells with quinine (23), against thrombocytes with oxaliplatin (11), and against ADAMTS13 with ticlopidine resulting in TTP (24); and ii) associated with a dose-dependent toxic endothelial damage after use of gemcitabine, bevacicicab, mitomycin C, interferon, cyclosporin A, or tacrolimus. Gemcitabine is the only drug for which both mechanisms are described (25). Treatment of drug-induced TMA (DI-TMA) is to avoid exposure to the drug. If antibodies against ADAMTS13 are detected, therapy as for aTTP is indicated.

Transplant-associated thrombotic microangiopathy

Thrombotic microangiopathy that occurs after stem cell transplantation is referred to as transplantation-associated thrombotic microangiopathy (TA-TMA). Pathophysiologically, complement activation is suspected. Causes likely include endothelial cell damage due to conditioning, drug side effects (calcineurin inhibitors), chronic graft-versus-host (GvHD) response, and infections. TA-TMA has an unfavorable prognosis, with no standard treatment established and plasmapheresis not indicated (recommendation grade 1 A) (5, 26).

Pregnancy

Thrombocytopenia associated with elevated LDH levels in pregnancy can potentially be caused by one of the common pregnancy-related conditions: the HELLP syndrome (hemolysis, elevated liver enzyme levels, and low platelet levels), acute pregnancy-induced fatty liver, or pre-eclampsia. Pregnancy is a much less frequent trigger for aHUS (1:25 000 pregnancies) or for TTP (1: 200 000 pregnancies) (27, 28). While aHUS usually occurs postpartum (80%), TTP occurs equally in both pre- and postpartum (28). Assessment of a peripheral blood smear is mandatory. Schistocytes indicate a pregnancy-induced thrombotic microangiopathy. If schistocytes are not present and if other findings indicate a pregnancy-related disease, an immediate cesarean delivery is indicated. If a thrombotic microangiopathy is confirmed, plasmapheresis initiation should not be delayed to wait for the ADAMTS13 result. However, the ADAMTS13 result can subsequently differentiate between TTP and aHUS. Both diseases may be congenital; pregnancy may merely be the trigger (28).

Cancer-associated thrombotic microangiopathies

In advanced cancer, drug-induced thrombotic microangiopathy may occur, such as after use of bevacicumb, mitomycin C, or gemcitabine. In case of extensive metastasis to the bone marrow and/or drainage of tumor cells into the vasculature, thrombotic microangiopathy may develop, sometimes accompanied by hyperfibrinolysis. The prognosis is unfavorable, with a median overall survival of only 4 to 5 months (29). To ensure the diagnosis, a bone marrow histology can be performed. Plasmapheresis is ineffective (recommendation grade 1 A) (5).

Autoimmune diseases with thrombotic microangiopathy or similar clinical pictures

In antiphospholipid syndrome, arterial and venous thrombosis occurs in young patients, often in pregnancy. Prolonged activated partial thromboplastin time (aPTT) and the detection of antibodies to phospholipid-binding proteins are typical. Uncontrolled thrombogenesis in the so-called catastrophic antiphospholipid syndrome has features of microangiopathic hemolytic anemia. Some data also suggest an uncontrolled activation of the classical complement pathway with potential efficacy of complement inhibitors (30). Renal diseases associated with vasculitis, such as mesangio-proliferative glomerulonephritis/C3 glomerulopathy and anti-neutrophil cytoplasmic antibodies (ANCA), may also be associated with thrombotic microangiopathy and must be diagnosed serologically and biotically (7).

Malignant hypertension

In severe hypertension, thrombotic microangiopathy may result from endothelial cell damage. Distinguishing between primary thrombotic microangiopathy with subsequent hypertension, and malignant hypertension with subsequent thrombotic microangiopathy, is difficult. Control of hypertension often improves thrombotic microangiopathy (7).

Key messages

- Thrombotic microangiopathies are systemic diseases that can manifest in all vascular systems but are mainly in the central nervous system, intestine, and kidneys.
- A combination of thrombocytopenia and hemolysis should lead to a suspicion of thrombotic microangiopathy.
- Diagnostically indicative tests are the morphological evaluation of blood smears and the determination of the von Willebrand factor–cleaving protease a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13 (ADAMTS13).
- Levels of ADAMTS13 activity of <10% define thrombotic thrombocytopenic purpura (TTP) and differentiate it from other thrombotic microangiopathies. The standard therapy even for suspicion of TTP is plasmapheresis.
- In hemolytic uremic syndrome (HUS), ADAMTS13 activity is >10%. The standard therapy for atypical (complement-mediated) HUS is complement blockade with eculizumab.

Conflict of interest statement

Dr. Bommer has received consultant honoraria and study support (third-party funds) for clinical studies from Ablynx and speaking honoraria from Alexion Pharmaceuticals and Sanofi Genzyme.

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Dr. Kuchenbauer and Dr. Bohl declare that no conflict of interests exists.

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► Supplementary material

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eTables, eFigure:
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Supplementary material to:

The Differential Diagnosis and Treatment of Thrombotic Microangiopathies

by Martin Bommer, Manuela Wölfle-Guter, Stephan Bohl, and Florian Kuchenbauer

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eTABLE 1

Differential diagnoses of thrombotic microangiopathy

Disease	Pathophysiology	Differences from TMA	Therapy
Vitamin B12 deficiency, pseudo-TTP	Vitamin B12 deficiency with appearance of schistocytes and neurological symptoms, high homocysteine levels with defective endothelium	Reduced levels of reticulocytes, extremely high LDH levels (>5000 U/L), elevated levels of methylmalonate	Vitamin B12 substitution
Acute pregnancy-induced fatty liver	Hereditary defects of fat metabolism with liver failure	Nausea, abdominal pain, hypoglycemia, elevated transaminases, increased bilirubin levels, reduced ATIII, reduced coagulation factors	Child birth, supportive therapy
Hyperfibrinolysis with DIC	Fibrin consumption e.g. for APL, prostate cancer, gastric cancer	Reduced fibrinogen, blasts with Auer rod formation in PB (APL), leukoerythroblastic blood hemogram	Specific therapy
Heart valve-induced hemolysis	Mechanical fragmentation of red blood cells with consumption of platelets	Medical history Cardiac valve prosthesis, valve defect TEE	Correction of defective heart valve
Endocarditis	Bacteremia with sepsis with a valve vegetation	Blood culture, TEE	Targeted antibiotic therapy
Evans syndrome	Immune thrombocytopenia with Coombs-positive autoimmune hemolysis	Coombs' test, lack of schistocytes	Immunosuppression
Sepsis with DIC	Consumption coagulopathy	Blood culture, procalcitonin	Sepsis therapy, antibiotic therapy
Catastrophic anti-phospholipid syndrome	Arterial and venous thrombi, secondary endothelial damage	Prolonged aPTT, cardiolipin antibody, aβ2GPI-Ab	Heparin, possibly plasma-pheresis, (eculizumab)
Malaria, babesiosis	Intracellular parasites with hemolysis and thrombopenia	Morphology of peripheral blood	Antiparasitic therapy
Hemorrhagic fever, viral infections	Dengue virus, filoviridae, hantavirus	No hemolysis, clinical history of exposure	Supportive therapy

aβ2GPI-Ab: anti-beta2-glycoprotein I antibody; APL: acute promyelocytic leukemia; ATIII: antithrombin III; aPTT: activated partial thromboplastin time; DIC: disseminated intravascular coagulopathy; LDH: lactate dehydrogenase; PB: peripheral blood; TEE: transesophageal echocardiography; TMA: thrombotic microangiopathy; TTP: thrombotic thrombocytopenic purpura

eTABLE 2

ADAMTS13 activity >10%: atypical hemolytic uremic syndrome, secondary hemolytic uremic syndrome / thrombotic microangiopathy

Indication for continued plasmapheresis should be rigorously examined						Discontinue plasmapheresis		
Very rare HUS form (e.g. for children <1 year)	Complement-mediated HUS		Infections	Autoimmune diseases	Drug-induced TMA		Disseminated cancer	Malignant hypertension
	DGKE mutations	Plasminogen mutations			Dose dependent, endothelial cell damage	Dose independent, antibody mediated		
DGKE mutations	Atypical hemolytic uremic syndrome	TA-TMA	HIV, CMV, influenza H1N1, parvovirus B19	SLE, catastrophic antiphospholipid syn- drome (CAPS), ANCA pos. vasculitis, MPGN	Dose dependent, endothelial cell damage	Dose independent, antibody mediated	Prostate, breast, or lung cancer with bone marrow carcinoma- tosis, intravascular tumor cells	Known hypertension, echocardiography: hypertensive heart disease
Plasminogen mutations	Elevated sC5b-9, anti-CFH Ab	PBSCT, organ transplantation						
Cobalamin defect	Mutations: C3, factor H, factor I, factor B, thrombomodulin			Rarely: ADAMTS13 reduced	Mitomycin C, gemcitabine, bevacicuumab, calcineurin- inhibitors	Chinidin, oxaliplatin, ticlopidin		
No standard therapy is available	Eculizumab	Discontinue calcineurin inhibitors	Antiviral therapy (e.g. HAART)	CAPS: anticoagulation, plasmapheresis	Discontinue medication		Treatment of the underlying disease	Antihypertensive therapy
Cobalamin defect: Vitamin B12 substitution	Anti-CFH positive: additional plasma- pheresis	(Eculizumab off-label use)	If ADAMTS13 anti- bodies are detected: therapy as for aTTP	SLE: immunosuppression	If ADAMTS13 antibodies are detected: therapy as for aTTP			

ADAMTS13: a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13; ANCA: antineutrophil cytoplasmic antibodies; aTTP: immune-mediated, acquired thrombotic-thrombocytopenic purpura; CAPS: catastrophic antiphospholipid syndrome; CFH: complement factor H; CMV: cytomegalovirus; DGKE: diacylglycerol kinase; HAART: highly active antiretroviral therapy; HIV: human immunodeficiency virus; HUS: hemolytic uremic syndrome; MPGN: membranoproliferative glomerulonephritis; PBSCT: peripheral blood stem cell transplantation; SLE: systemic lupus erythematosus; TA-TMA: transplant-associated thrombotic microangiopathy; TMA: thrombotic microangiopathy

eTABLE 3

**ADAMTS13 activity <10%:
thrombotic thrombocytopenic purpura**

aTTP	Suspected cTTP/ Upshaw–Schulman syndrome
Anti-ADAMTS13 inhibitor positive	Anti-ADAMTS13 inhibitor negative, mutation analysis
Continue plasmapheresis, steroids, rituximab (off-label use)	Plasma infusion if acute organ damage, plasmapheresis

ADAMTS13: a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13;

aTTP: immune-mediated, acquired thrombotic thrombocytopenic purpura;

cTTP: congenital thrombotic thrombocytopenic purpura;

TTP: thrombotic thrombocytopenic purpura

eFIGURE

The complement system is part of the innate immune system and consists of a series of plasma proteins that activate a cascade of effector proteins. The final step is the formation of the membrane attack complexes (MAC) (C5b–9) with lysis of the target cell. Regulation occurs predominantly via inhibitors, including factor H, factor I, and the membrane cofactor protein (MCP). While more than 80 mutations have now been identified, factor H mutations are the most common. The majority of mutations are heterozygous. Some people who are carriers of a mutation will never get the disease, and there is a high interindividual variability for age of the first manifestation. Defects of one of the above-mentioned proteins leads to uncontrolled complement activation with endothelial damage, resulting in thromboses in terminal vascular beds. The close pathophysiological relationship between the complement system and the coagulation system is already known from studies of patients with paroxysmal nocturnal hemoglobinuria, which is considered to be one of the most serious acquired thrombophilic diatheses