Renal Thrombotic Microangiopathy: A Review

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Thrombotic microangiopathy (TMA), a pathological lesion observed in a wide spectrum of diseases, is triggered by endothelial injury and/or dysfunction. Although TMA lesions are often accompanied by clinical features of microangiopathic hemolytic anemia, thrombocytopenia, and ischemic end-organ injury, renal-limited forms of TMA are not infrequently encountered in clinical practice. The presence of renal-limited manifestations can be diagnostically challenging, often delaying the initiation of targeted therapy. Prompt investigation and empirical treatment of TMA is warranted to reduce associated morbidity and mortality. Major advances have been made with respect to the pathophysiology of primary TMA entities, with the subsequent development of novel diagnostic tools and lifesaving therapies for diseases like thrombotic thrombocytopenic purpura and complement-mediated TMA. This article will review the clinical presentation and pathologic hallmarks of TMA involving the kidney, and the disease-specific mechanisms that contribute to the endothelial injury that characterizes TMA lesions. Diagnostic approach and both empirical and disease-specific treatment strategies will be discussed, along with the potential role for emerging targeted disease-specific therapies.

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Introduction

Thrombotic microangiopathy (TMA) is a pathologic lesion characterized clinically by the presence of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and ischemic organ injury.[1] The kidney is the most frequently injured organ, but other systems including the central nervous system, the cardiovascular and respiratory systems, and the gastrointestinal tract may also be affected.[2] The classification and nomenclature describing TMA continues to evolve in parallel with discoveries elucidating the molecular mechanisms responsible for the characteristic endothelial injury and microvascular thrombi formation.[3] For the nephrologist, an approach that facilitates timely identification of conditions requiring urgent targeted therapies is a priority.

A practical schema outlining the differential diagnosis of the underlying causes of TMA is outlined in Figure 1, with a more exhaustive list of causes in Box 1. This schema highlights fundamental mechanisms contributing to endothelial injury, including deficiency of ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) in thrombotic thrombocytopenic purpura (TTP) and alternative pathway (AP) dysregulation in complement-mediated TMA (CM-TMA; also referred to as atypical, or complement-mediated, hemolytic uremic syndrome [HUS]).[1,4-6] This schema is helpful for generating a differential diagnosis but may be simplistic with respect to molecular pathogenesis because it is increasingly recognized that the mechanisms contributing to the different TMA syndromes can overlap. Indeed, complement activation may be triggered at endothelial surfaces in the context of TTP, the ADAMTS13-mediated TMA.[7,8] Furthermore, a trigger such as infection is often identified at first presentation of CM-TMA, even in the presence of pathogenic variants in complement genes.

In this review, we will discuss the spectrum of conditions associated with TMA (Box 1) and the clinical and pathologic hallmarks, and we will provide a diagnostic approach to TMA. We will highlight the disease-specific mechanisms of endothelial injury of the commonly encountered TMA syndromes, treatment strategies (Table 1; Table S1), and investigational complement-directed therapies according to TMA etiology (Table 2).

Clinical Presentation and Pathologic Features

Endothelial injury with associated platelet activation and consumption contribute to microvascular thrombosis formation, tissue ischemia, and subsequent end-organ injury. As red blood cells (RBCs) traverse the microvasculature laden with thromboses, they become fragmented, producing the hallmarks of MAHA including schistocytes and thrombocytopenia, with low haptoglobin and elevated indirect bilirubin reflecting RBC fragmentation. Although lactate dehydrogenase (LDH) elevation is related to RBC destruction, marked elevations reflect tissue ischemia. Hematuria, proteinuria, and hypertension are common with renal involvement.

Systemic findings of TMA (ie, MAHA and thrombocytopenia) are not required for the diagnosis of TMA. Indeed, renal-limited TMA is not infrequently observed in clinical practice. For example, as we will discuss, isolated renal TMA lesions may be observed more often in the setting of glomerulonephritides (eg, antineutrophil cytoplasmic antibody [ANCA]-associated vasculitis, immunoglobulin A nephropathy), solid organ transplantation (eg, calcineurin inhibitor [CNI] or antibody-mediated rejection) and in drug-induced TMA. Although endothelial injury is central in the development of TMA, a predilection for specific vascular beds, including the renal vasculature, is observed in many TMA syndromes, and the pattern of

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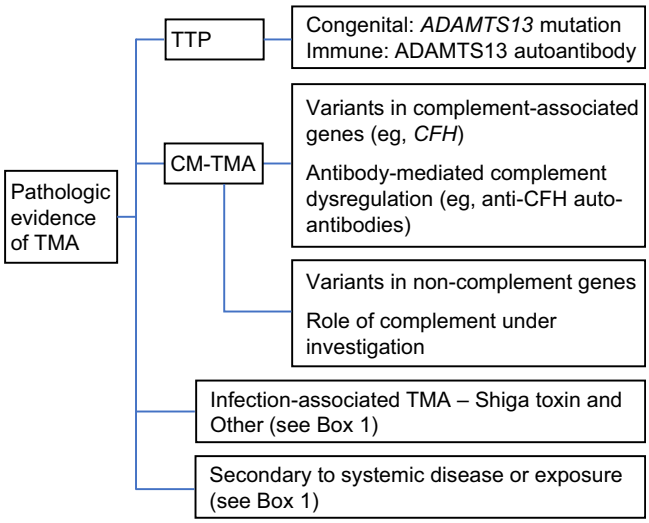


Figure 1. Schema illustrating a practical approach to the classification of thrombotic microangiopathy. Abbreviations: ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; anti-CFH, autoantibodies to CFH; *CFH*, complement factor H; CM-TMA, complement-mediated thrombotic microangiopathy; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

organ involvement may be influenced by genetic factors underlying the pathophysiology.[2]

An example of pathologic features of TMA in scleroderma renal crisis (SRC) is illustrated in Figure 2. The histologic changes of TMA are protean and variably present.[9] The changes may be quite subtle and will evolve over time; glomerular or arteriolar thrombi are pathognomonic, but these may be missed with limited sampling. In addition to microthrombi, the presence of arterial intimal edema (mucoid/myxoid change) or fibrin is also considered diagnostic. Within glomeruli, endotheliosis (particularly with pregnancy-associated syndromes) and mesangiolysis are also typical. RBC fragments may be seen in any instance. It should be noted that although the type of histologic change is not specific for any etiology, glomerular thrombi are more frequent in CM-TMA, and arteriolar changes are usually prominent in SRC and hypertension-related TMA.

In the chronic phase, glomerular capillary wall double contouring evolves from new subendothelial basement membrane formation, and arterial onion skinning from myointimal hyperplasia. With repeated cycles of acute and chronic disease activity, both acute and chronic lesions may be seen in a single sample. Of special note, the unusual appearance of marked segmental subendothelial expansion with loose and dense hyalinosis is specifically associated with vascular endothelial growth factor (VEGF) antagonist–related TMA.[10]

Pathogenesis

End-organ manifestations of TMA result from endothelial injury or dysfunction with subsequent intravascular thrombosis. Underlying endothelial health may affect susceptibility to organ dysfunction. Indeed, local intravascular production of nitric oxide by endothelial nitric oxide synthase (eNOS) promotes vasodilatation and reduces the risk of thrombosis formation.[11] VEGF regulates eNOS expression and modulates complement activation via complement factor H (CFH).[12,13] Situations in which VEGF or nitric oxide are reduced therefore predispose to TMA.

Once the endothelium becomes injured, there is activation of the coagulation system, mediated by tissue factor, inflammatory cytokines, and lipopolysaccharide. There is growing evidence implicating neutrophil extracellular traps (NETs). Although NETs are released by activated neutrophils to help combat infection, they are also released in autoimmune diseases and may contribute to endothelial dysfunction and TMA.[14] In addition to releasing antimicrobial proteins, they release scaffolding proteins that bind coagulation factors, platelets, and RBCs. Moreover, NETs contribute to thrombosis formation and can activate complement pathways.[15]

Complement activation serves an important function in host defense by linking innate and adaptive immune responses; it also maintains homeostasis by clearing immune complexes and damaged host cells.[16] Three initiating pathways ultimately lead to terminal pathway (TP) activation. The classical pathway (CP) is activated by antibody-antigen complexes binding to the C1q complex. The lectin pathway (LP) becomes activated through the binding of mannose-binding lectin or ficolins to mannose residues on microbial surfaces. Activation of the LP and CP result in proteolytic cleavage of C2 and C4 to form a C3 convertase. Conversely, the AP is constitutively active (ie, continues to "tick over") whereby spontaneous hydrolysis of C3 binds complement factor B and ultimately leads to the production of the AP C3 convertase. The C3b produced by either the LP or CP can trigger the AP through proteolytic cleavage of C3 to C3b. The AP acts as an amplification loop to significantly increase downstream TP activation. Membrane-bound C3b triggers TP activation, resulting in membrane attack complex formation and osmotic lysis of endothelial cells.[16] C3a and C5a are complement activation by-products that are important for leucocyte recruitment at the site of injury and are involved in activating the coagulation cascade.[17]

There exists cross-talk between the complement system and the coagulation cascade.[18,19] The AP is tightly regulated by membrane-bound and soluble complement regulators to prevent widespread activation and host injury via C3b deposition on host cells. Complement overactivation leads to systemic endothelial injury and thrombosis. Conversely, endothelial injury, platelet activation, and hemolysis can activate complement cascade.[20,21]

Targeting complement activation in this setting does not address the underlying disease-causing trigger for

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Box 1. Conditions Associated With TMA

- ADAMTS13-mediated TMA (TTP)
  - ◇ Congenital (cTTP)
  - ◇ Immune (iTTP)
- Complement-mediated TMA (aHUS)
  - ◇ Congenital
  - ◇ Immune
- Coagulation-mediated TMA (pathogenic variants in *PLG, THBD,* and *DGKε*)
- Metabolic (defects of cobalamin metabolism)
- Infection-associated TMA
  - ◇ Bacterial: Shiga toxin–producing *Escherichia coli*, *Streptococcus pneumoniae*, *Campylobacter jejuni*, *Klebsiella pneumoniae*
  - ◇ Viral: influenza, HIV, EBV, CMV, BK virus, parvovirus B19, SARS-CoV-2
  - ◇ Fungal: histoplasmosis
- Pregnancy-associated TMA
  - ◇ Preeclampsia
  - ◇ HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome
  - ◇ Trigger of TTP, aHUS, CAPS
- Drug-induced TMA
  - ◇ Immune mediated
    - ▪ Via drug-triggered antibodies against platelets/neutrophils: gemcitabine, oxaliplatin, trimethoprim-sulfamethoxazole, quinine, vancomycin
    - ▪ Via autoantibodies against ADAMTS13: ticlopidine
  - ◇ Non–immune mediated
    - ▪ Chemotherapy: alemtuzumab, gemcitabine, mitomycin C, vincristine, doxorubicin, pentostatin, VEGF inhibitors, tyrosine kinase inhibitors, proteasome, and checkpoint inhibitors
    - ▪ Immunosuppressive therapy: calcineurin inhibitor, sirolimus, interferon β
    - ▪ Antibiotics: ciprofloxacin, levofloxacin, metronidazole, nitrofurantoin, penicillin
    - ▪ Other: cocaine, ecstasy, estrogen/progesterone, anti-inflammatories, oxymorphone, simvastatin
- Transplant-associated TMA
  - ◇ Solid organ
  - ◇ Hematopoietic stem cell transplant
- Malignancy-associated TMA
  - ◇ Solid: breast, gastric, lung, ovarian, prostate, and urothelial cancers
  - ◇ Hematologic: Myelo and lymphoproliferative, monoclonal gammopathies (myeloma, smouldering myeloma, MGRS), and POEMS
- Autoimmune diseases
  - ◇ APS, including CAPS
  - ◇ SRC
  - ◇ SLE
  - ◇ Primary glomerulonephritis and vasculitis (observed on biopsy)
  - ◇ Sjögren syndrome, rheumatoid arthritis, dermatomyositis
- Hypertensive emergency
- Other: hemophagocytic lymphohistiocytosis, sickle cell disease, Castleman disease and variants

Abbreviations: ADAMTS13, a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13; aHUS, atypical hemolytic uremic syndrome; APS, antiphospholipid syndrome; CAPS, catastrophic antiphospholipid syndrome; CMV, cytomegalovirus, *DGKε*, diacyglycerol kinase epsilon; EBV, Epstein-Barr virus; HELLP, hemolysis, elevated liver enzymes, and low platelets; HUS, hemolytic uremic syndrome; MGRS, monoclonal gammopathy of renal significance; *PLG*, plasminogen; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes; SLE, systemic lupus erythematosus; SRC, scleroderma renal crisis; *THBD*, thrombomodulin; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic pupura.

endothelial injury, but it is not yet clear if modulation of complement activity may affect downstream injury pathways. The role of complement activation as a driving event or merely a secondary finding remains unclear in many other TMAs. Interestingly, the LP's mannan-binding lectin-associated serine protease 2 (MASP-2) is also implicated in the coagulation cascade and clot formation by converting prothrombin into thrombin and activating factor XIII.[18,22]

Approach to Common Clinical Syndromes Associated With TMA

It is of critical importance to investigate the underlying TMA etiology to offer therapy directed toward the causal pathogenic process. A thorough "ideal" general diagnostic approach is provided in Figure 3, although it is recognized that in clinical practice the full spectrum of these tests is often not readily available. Furthermore, the results of

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Table 1. Pathophysiology and Treatment According to TMA Etiology

TMA Etiology	Pathophysiology	Therapy
cTTP	Congenital *ADAMTS13* deficiency; complement activation potentially involved	Plasma infusion
iTTP	Acquired *ADAMTS13* deficiency through circulating ADAMTS13 autoantibodies; complement activation potentially involved	TPE; caplacizumab; steroids/rituximab; bortezomib if refractory
Hereditary CM-TMA	Pathogenic variant(s) in complement gene(s) (Table 3)	Eculizumab or ravulizumab; TPE vs plasma infusions; liver transplant (*CFH, CFI, CFB*)
Acquired CM-TMA	Complement dysregulation through circulating autoantibodies	Eculizumab or ravulizumab; TPE; rituximab or cyclophosphamide
Coagulation-mediated TMA (*PLG, THBD, DGKε*)	Endothelial cell dysregulation	Unknown; role of complement therapies unclear
Metabolic: cobalamin deficiency	Endothelial dysfunction mediated by hyperhomocysteinemia suspected[107]	Cobalamin
Infection-associated		
STEC-HUS	Coagulation and complement activation via Shiga toxin	Supportive
S. pneumonia; viral	Complement dysregulation implicated	Supportive, including antibiotics
SARS-CoV-2	Complement dysregulation; cytokine storm; iTTP	Supportive treatment; steroids; remdesivir; tocilizumab, baricitinib
Pregnancy-associated[a]		
TTP	Triggered by pregnancy; see cTTP and iTTP above	Plasma infusion; TPE; IS
CM-TMA	Triggered by pregnancy; see CM-TMA above and Table 3	Eculizumab; TPE if circulating autoantibodies
PET/HELLP syndrome	Anti-angiogenic imbalance; complement dysregulation	Supportive care, including delivery
Drug-induced	Immune-mediated and non–immune-mediated mechanisms	Cessation of causal drug; TPE in iTTP
Transplant-associated		
HSCT	Multiple hits required (genetic predisposition, conditioning regimen, and trigger[s])	Supportive treatment; modification of IS/chemotherapy
Kidney transplant	Multiple causes/multifactorial (recurrent or *de novo* disease, drug-induced, antibody-mediated rejection, infection)	Directed toward underlying cause (antibiotics/antivirals, modification of immunosuppression, or eculizumab/TPE)
Cancer-associated	Endothelial dysfunction; intravascular tumor emboli; coagulation and complement pathway activation	Cancer-directed therapy
Autoimmune-associated		
APS, including CAPS	Unclear but may involve genetic predisposition and circulating antibodies	Anticoagulation; IS and IVIg or TPE; if refractory, consider rituximab or eculizumab
SRC	Unclear but involves renal ischemia, activation of the RAAS and hypertension-mediated mechanical stress	ACEI; unclear role for endothelin receptor antagonist, TPE, and eculizumab
SLE	Unclear but complement activation implicated	IS; TPE for severe cases; if refractory, consider eculizumab
Hypertensive emergency	Mechanical shear stress	Blood pressure control

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; *ADAMTS13*, a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13; APS, antiphospholipid syndrome; CAPS, catastrophic antiphospholipid syndrome; *CFB/H/I*, complement factor B/H/I; CM-TMA, complement-mediated thrombotic microangiopathy; cTTP, congenital TTP; *DGKε*, diacylglycerol kinase epsilon; HELLP, hemolysis, elevated liver enzymes, and low platelets; HSCT, hematopoietic stem cell transplantation; IS, immunosuppression; iTTP, immune-mediated TTP; IVIg, intravenous immunoglobulin; PET, preeclampsia toxemia; *PLG*, plasminogen; RAAS, renin-angiotensin-aldosterone system; RTX, rituximab; SLE, systemic lupus erythematosus; SRC, scleroderma renal crisis; STEC-HUS, Shiga toxin–producing *Escherichia coli* hemolytic uremic syndrome; *THBD*, thrombomodulin; TMA, thrombotic microangiopathy; TPE, therapeutic plasma exchange; TTP, thrombotic thrombocytopenic pupura.
[a]Note that other entities (eg, CAPS) may be triggered during pregnancy.

some of these tests may not be available for days to months. Prompt initiation of targeted therapies such as therapeutic plasma exchange (TPE) or eculizumab should not be delayed. Specific diagnostic tests are described in the sections below, but in reality the priority is recognition of a clinical syndrome consistent with TMA and verification of the presence of MAHA with review of a blood film. Once MAHA is confirmed, the elimination of systemic

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Table 2. Complement-Directed Investigational Therapies According to TMA Etiology

TMA Etiology	Investigational Therapy (Target)	Identifier
cTTP	Recombinant ADAMTS13	NCT03393975 (Phase 3) NCT04683003 (Phase 3)
	Narsoplimab (MASP-2)	NCT02222545 (Phase 2)
iTTP	Recombinant ADAMTS13 Narsoplimab (MASP-2)	NCT03922308 (Phase 2) NCT02222545 (Phase 2)
Hereditary and acquired CM-TMA	Narsoplimab (MASP-2)	NCT03205995 (Phase 3) NCT02222545 (Phase 2)
	Iptacopan (Factor B)	NCT04889430 (Phase 3)
	Crovalimab (C5)	NCT04958265 (Phase 3) NCT04861259 (Phase 3)
Coagulation-mediated	No registered clinical trial	
Metabolic (including cobalamin deficiency)	No registered clinical trial	
Infection-associated		
STEC-HUS	Eculizumab (C5)	NCT02205541 (Phase 3) EUCTR2016-000997-39
SARS-CoV-2	Ruconest (C1)	NCT04705831 (Phase 4) NCT04530136 (Phase 2)
	Narsoplimab (MASP-2)	NCT04488081(Phase 2)
	Danicopan (Factor D)	NCT04988035 (Phase 2)
	AMY-101 (C3)	NCT04395456 (Phase 2)
	Eculizumab (C5)	NCT04288713 NCT04346797 (Phase 2)
	Ravulizumab (C5)	NCT04570397 (Phase 3) NCT04369469 (Phase 3)
	Vilobelimab (C5)	NCT04333420 (Phase 2/3)
	Zilucoplan (C5)	NCT04382755 (Phase 2)
Other	Ravulizumab (C5)	NCT04743804 (Phase 3)
Pregnancy-associated: PET/HELLP syndrome	Eculizumab (C5)	NCT04103489 (Phase 1) NCT04725812 (Phase 2)
Drug-induced	Ravulizumab (C5)	NCT04743804 (Phase 3)
Transplant-associated		
HSCT	Narsoplimab (MASP-2)	NCT04247906 NCT02222545 (Phase 2)
	Pegcetacoplan (C3)	NCT05148299 (Phase 2)
	Eculizumab (C5)	NCT03518203 (Phase 2)
	Ravulizumab (C5)	NCT04543591 (Phase 3) NCT04557735 (Phase 3)
	Nomacopan (C5)	NCT04784455 (Phase 3)
Solid organ	Ravulizumab (C5)	NCT04743804 (Phase 3)
Cancer-associated	No registered clinical trial	
Autoimmune-associated, excluding primary CAPS	Ravulizumab (C5)	NCT04743804 (Phase 3)
Hypertensive emergency	Ravulizumab (C5)	NCT04743804 (Phase 3)

Abbreviations: ADAMTS13, a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13; CAPS, catastrophic antiphospholipid syndrome; CM-TMA, complement-mediated thrombotic microangiopathy; cTTP, congenital TTP; HELLP, hemolysis, elevated liver enzymes, and low platelets; HSCT, hematopoietic stem cell transplantation; iTTP, immune-mediated TTP; MASP-2, mannan-binding lectin serine protease 2; PET, preeclampsia toxemia; STEC-HUS, Shiga toxin–producing *Escherichia coli* hemolytic uremic syndrome; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic pupura.

causes such as infection, malignancy, or autoimmune disease is of first importance; history and readily accessible clinical tests to exclude these causes are universally warranted early in diagnosis.

Although it is not typical for ADAMTS13-mediated TMA (ie, TTP) to present with renal-limited disease, early recognition is critical because mortality can reach 90% if left untreated.[23] Measurement of ADAMTS13 activity is now more widely available, and publicly funded drug access may require documentation of preserved ADAMTS13 activity before approval of eculizumab. Clinical risk scores (the French TMA Reference Center and PLASMIC scores) may be helpful tools to initially assess the likelihood of TTP, but do not eliminate the need for early consideration of potentially lifesaving plasma infusion or TPE.[24] These scores have limitations and thus do not replace the need for ADAMTS13 assessment.

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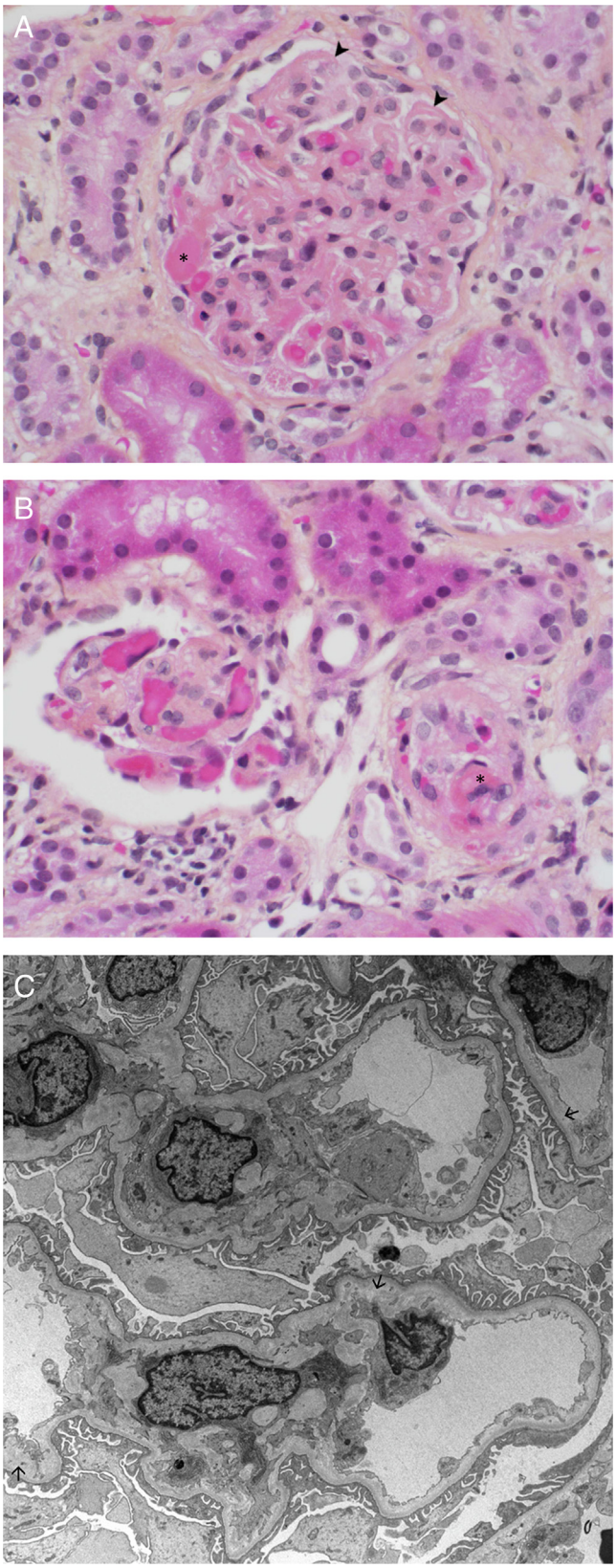


Figure 2. Kidney histopathologic findings in acute thrombotic microangiopathy with mild chronic changes. Light and electron microscopic findings of acute thrombotic microangiopathy with early features of chronicity in a patient with systemic sclerosis and normotensive scleroderma renal crisis. (A) Segmental thrombus (*) and capillary wall thickening with double contouring (arrow heads) (hematoxylin phloxine saffron [HPS], original magnification, ×40). (B) Arteriolar intimal fibrin (*) and edema with adjacent mildly shrunken glomerulus and congestion (HPS, original magnification, ×40). (C) Glomerular capillary subendothelial expansion with mild lucency and loose new basement membrane formation (arrows) (original magnification, ×4,000).

TTP

Although it is relatively unusual for TTP to present as a renal-limited TMA or with severe acute kidney injury (AKI), familiarity with its diagnosis and therapy is critical because prompt initiation of TPE is associated with a marked reduction in mortality.[23]

Pathophysiology

TTP develops in the setting of ADAMTS13 deficiency (activity < 10%). ADAMTS13 normally cleaves the highly thrombogenic von Willebrand factor (vWF). A deficiency in enzyme activity results in accumulation of ultralarge vWF multimers, followed by widespread platelet aggregation and thrombosis.[25] TTP can either be congenital (cTTP), due to homozygous or compound heterozygous variants in the *ADAMTS13* gene, or immune-mediated (iTTP), due to inhibitory autoantibodies against ADAMTS13 (majority of cases). Although cTTP normally presents during childhood, it can also present in early adulthood.[26] Complement activation may be important in the development of clinical TTP manifestations. Elevated C3a and sC5b-9 levels have been observed in patients with TTP.[27] Indeed, ultralarge vWF in the setting of ADAMTS13 deficiency activate the AP in *ex vivo* models.[8]

Diagnosis and Treatment

In the presence of TMA, it is imperative that physicians exclude ADAMTS13-mediated disease with activity assays. Limited access to timely results requires that physicians have a low threshold to initiate plasma therapy pending the test results; a clinical prediction score (as previously discussed) may be helpful in this regard.

Intermittent plasma infusion to replenish ADAMTS13 is required for exacerbations of cTTP triggered by stressors such as pregnancy or infection. A phase 1 study of recombinant ADAMTS13 has suggested it is safe and effective.[28] In iTTP, TPE and immunosuppression (steroids, rituximab) are required to remove the inhibitory autoantibodies and prevent ongoing synthesis.[29] Caplacizumab, a humanized monoclonal antibody that targets vWF and prevents its interaction with platelets, was approved for the treatment of acute TTP after 2 multicenter randomized controlled studies demonstrated rapid hematological response, fewer exacerbations, and shorter hospital stays.[30,31] It does not, however, target antibody production; consequently, disease relapses occur without targeted B-cell depletion.

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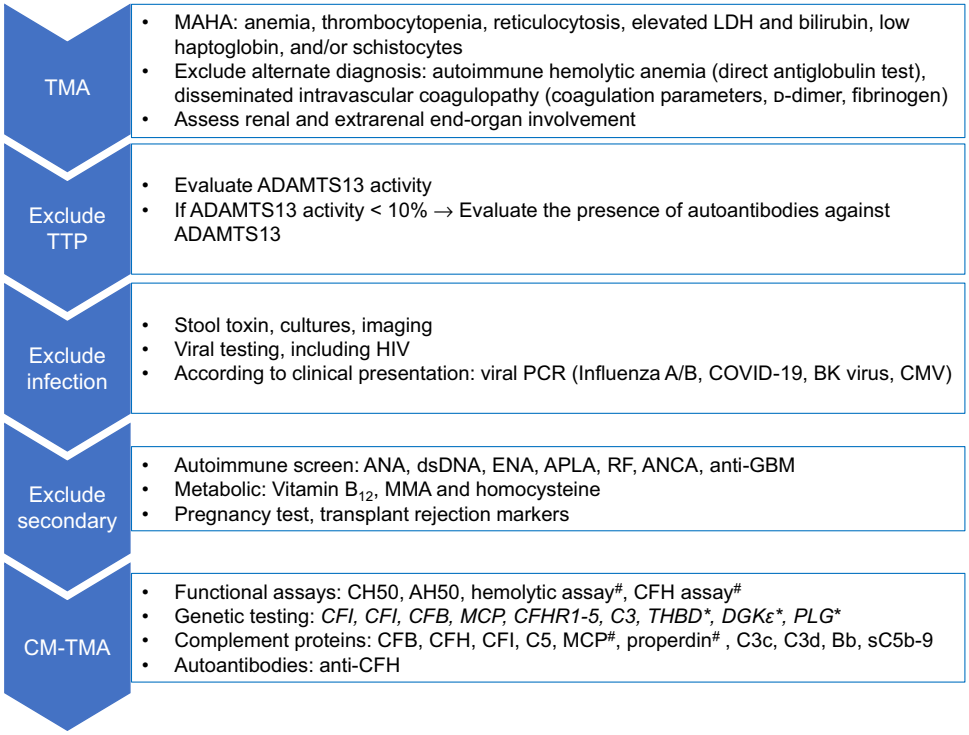


Figure 3. Complete diagnostic algorithm for thrombotic microangiopathy. This is an example of an "ideal" thorough diagnostic algorithm. Many of the tests are not widely clinically available, and some results may only be returned days to months after presentation. Further, the list of tests continues to evolve with new discoveries about pathophysiology. *Coagulation-mediated TMA. #Research-based assays. Abbreviations: ADAMTS13, a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13; ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibodies; anti-GBM, anti–glomerular basement membrane antibody; APLA, antiphospholipid antibody; *CFB/H/I*, complement factor B/H/I; CFHR1-5, complement factor H-related proteins 1-5; CM-TMA, complement-mediated thrombotic microangiopathy; CMV, cytomegalovirus; *DGKε*, diacylglycerol kinase epsilon; dsDNA, anti–double-stranded DNA antibody; ENA, extractable nuclear antigen antibodies; LDH, lactate dehydrogenase; MAHA, microangiopathic hemolytic anemia; MCP, membrane cofactor protein; MMA, methylmalonic acid; PCR, polymerase chain reaction; *PLG*, plasminogen; RF, rheumatoid factor; *THBD*, thrombomodulin; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

Complement-Mediated TMAs

Pathophysiology

CM-TMA, also referred to as complement-mediated or atypical HUS, is caused by AP dysregulation, resulting in persistent downstream terminal pathway activation. The CP and LP have also been implicated in pathogenesis based on C4d and C1q staining of kidney biopsy specimens.[32] Approximately 50%-60% cases of CM-TMA are caused by Mendelian genetic variants (Table 3); however, the absence of a detectable variant does not preclude a genetic form.[3,33,34] More variants are emerging as genetic testing increases in quality and frequency and as patient registries expand. The penetrance of familial CM-TMA is incomplete and may present with more advanced age, suggesting that a second hit is needed to unmask overt TMA.[3,34] Triggers, when identified, may be infection, pregnancy, vaccination, or surgery.[3,34] Age can help narrow the differential diagnosis: the majority of patients who develop CM-TMA are younger than 60 years.[35]

Dysregulation of complement activation may also occur as a result of development of autoantibodies that interfere with complement regulation. A prototypic example is patients documented to have autoantibodies that neutralize CFH, thereby interfering with CFH-mediated down-regulation of AP activity.[36] The high degree of homology between the gene encoding CFH and the CFH-related proteins makes this area prone to gene rearrangement events. Autoantibodies may then develop that target the products of fusion genes or gene rearrangements (Table 3).

Referral for genetic screening is increasingly important as highly targeted complement-modulating therapies emerge. Functional assays and measures of complement cascade proteins are an important adjunct to genetic testing.[37] Although not yet widely available, functional assays are ideal for monitoring disease activity and treatment response.

Treatment

Complement dysregulation is the predominant mechanism of endothelial injury in CM-TMA; treatment is directed toward restoring complement regulation. Initiation of therapy should not be delayed pending confirmation of complement dysregulation.[34] Eculizumab, a humanized

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Table 3. Frequent Genetic Variants Implicated in Thrombotic Microangiopathy

Gene	Variant	Incidence[33,108]	Posttransplant Recurrence[3]
CFH	Inactivating	20%-30%	High risk of recurrence; prophylactic eculizumab recommended
CFI	Inactivating	4%-8%	Moderate risk of recurrence; prophylactic eculizumab recommended
MCP/CD46	Inactivating	10%-15%	Moderate to high risk of recurrence
C3	Activating; increased activity or resistance to CFI regulation	2%-10%	Moderate risk of recurrence; prophylactic eculizumab recommended
CFB	Activating; increased activity or resistance to CFH regulation	1%-2%	High risk of recurrence; prophylactic eculizumab recommended
CFH-CFHR	Rearrangements resulting in CNVs, including deletions[a]	Varies by cohort (Austrian cohort, 25%; Indian cohort, up to 50%)	High risk of recurrence in the first 2 years if ongoing high anti-CFH antibody titers
THBD	Inactivating	Rare	True risk of recurrence unknown
DGKε	Inactivating	Rare	Risk of recurrence unknown

Abbreviations: *CFB/H/I*, complement factor B/H/I; CNV, copy number variants; CFH/I, complement factor H/I; *CFHR*, complement factor H–related; *DGKε*, diacylglycerol kinase epsilon; *MCP*, membrane cofactor protein; *THBD*, thrombomodulin.
[a]Deletions of *CFHR1* are possibly associated with autoantibodies to CFH that lead to inhibition of CFH carboxy-terminal function (ie, surface and C3b binding).

anti-C5 monoclonal antibody, is widely approved for CM-TMA.[6,38] The optimal duration of treatment with eculizumab remains unknown.[39,40] Indeed, discontinuation of therapy is usually possible after a 6- to 12-month course of eculizumab, with the exception of patients with high-risk variants with severe disease manifestations (eg, variants in the carboxy terminus of CFH) or very high titers of anti-CFH antibodies. TPE can be considered in patients with life-threatening end-organ injury.[41] Patients with anti-CFH antibodies may also benefit from TPE and immunosuppression (rituximab or cyclophosphamide) to clear circulating antibodies and prevent relapse.[42] Coadministration of eculizumab and immunosuppression is used to address downstream complement activation and production of anti-CFH antibodies.

Additional Primary TMA Syndromes

Screening for genetic causes of TMA may reveal potentially pathogenic variants in genes encoding proteins involved in coagulation such as thrombomodulin, plasminogen, and diacylglycerol kinase epsilon (*DGKε*). These are described in Tables 1-3. *DGKε* gene variants have also been implicated in CM-TMA. The role of complement-inhibiting therapies in these instances is unknown. Similarly, rare hereditary disorders of B_{12} metabolism that may result in TMA arise due to variants in the *MMACHC* gene (methylmalonic aciduria and homocystinuria type C). Targeted therapy focusing on restoring B_{12} metabolism is warranted in this instance; the involvement of complement in organ injury is not clear.

Infection-Associated TMA

Pathophysiology

Diverse pathogens, including bacteria, viruses, and fungi, are associated with TMA (Box 1). Infections are the most common cause of pediatric TMA, the majority of which are in the setting of Shiga toxin (Stx)–producing *Escherichia coli* (STEC). Stx translocates from the intestines and binds globotriaosylceramide 3 (Gb3) in circulation, entering endothelial cells via the Gb3 receptor, which is highly expressed in the kidney.[43] Within the cell, it inhibits protein synthesis, resulting in endothelial injury and an increase in tissue factor and vWF.[43] Activation of the AP may be mediated by binding of Stx to CFH, thereby reducing its regulatory effects.[44]

Systemic and renal TMA may also be observed in the context of infections as reviewed in Box 1. SARS-CoV-2 recently has been implicated in causing systemic TMA. The proposed mechanisms involved in systemic TMA include complement and coagulation dysregulation and widespread cytokine storm resulting in systemic endothelial injury.[45] However, in a series of patients with COVID-19 who were biopsied because of AKI or proteinuria, glomerular TMA was a rare finding compared to acute tubular necrosis or collapsing glomerulopathy.[46]

Treatment

Management of infection-associated TMA is mainly supportive, including adequate hydration, transfusions, and dialysis if needed.[43] Per the American Society for Apheresis, there is insufficient evidence to support TPE in routine management of infection-associated HUS; however, it can be considered in severe cases.[47] A favorable response to eculizumab in the setting of STEC-HUS has been reported, although it is not standard of care.[48,49]

Pregnancy-Associated TMA

Pathophysiology

Three distinct TMA etiologies are observed in pregnancy and the peripartum period: CM-TMA, HELLP (hemolysis,

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elevated liver enzymes, and low platelets) syndrome, and TTP. In addition, TMA syndromes not specifically associated with pregnancy (eg, catastrophic antiphospholipid syndrome [CAPS]) can also be triggered during gestation or the puerperium, and these should be ruled out in the appropriate clinical context. Another entity that may mimic TMA is pregnancy-associated renal cortical necrosis in the setting of disseminated intravascular coagulation arising from postpartum hemorrhage and/or sepsis.[50]

Tight control of complement activation is necessary throughout pregnancy to ensure maternofetal tolerance.[51] Women with a genetic predisposition to complement dysregulation may develop overt CM-TMA during pregnancy or in the postpartum period, triggered by inflammation, infection, and hemorrhagic complications.[52,53] The underlying pathophysiology is identical to CM-TMA as discussed earlier.

Preeclampsia and HELLP syndrome result from impaired spiral artery remodeling and placental ischemia resulting in an imbalance between the proangiogenic VEGF and placental growth factor (PlGF) and antiangiogenic circulating factors, including soluble Fms-like tyrosine kinase 1 (sFlt-1).[54] Aberrant complement activation is implicated in preeclampsia development.[55,56] Abnormal uterine doppler analysis, low circulating PlGF, and an elevated sFlt-1:PlGF ratio may aid in confirming the diagnosis.[57,58] Finally, TTP may present during pregnancy, typically during the second or third trimester; one-quarter of such cases are congenital.[59]

Treatment

Distinguishing pregnancy-associated TTP, CM-TMA, and HELLP syndrome is necessary because the treatments differ.

Similar to nonpregnant patients, cTTP and iTTP are treated with plasma infusions and TPE, respectively. Patients with cTTP may only require plasma infusions during this high-risk period.[60] In the setting of iTTP, immunosuppression typically includes steroids and azathioprine or calcineurin inhibitor.[60] Delivery is often required for refractory disease, with careful balance of pregnancy risk and fetal viability. In CM-TMA, TPE is frequently initiated pending the results of ADAMTS13 activity testing however optimal treatment is focused on complement blockade with eculizumab, which appears to be safe in pregnancy.[61] Response to complement blockade, assessed via normalization of hemolytic and renal parameters, should be monitored closely to ensure adequate eculizumab dosage.[62]

In the situation of preeclampsia and/or HELLP syndrome, urgent placental delivery is required. Failure of MAHA to resolve after delivery should lead clinicians to suspect an alternative diagnosis from preeclampsia or HELLP syndrome, such as an underlying CM-TMA.[63]

Drug-Induced TMA

Pathophysiology

Numerous drugs have been associated with TMA (see Box 1 for an exhaustive list). Diagnosis of drug-induced TMA is further suspected when resolution or recurrence of disease occurs upon cessation or retrial of the culprit drug, respectively. The exact mechanisms by which this occurs are not well established but include immune and non–immune-mediated mechanisms.[1,64] Example of immune-mediated mechanisms include the development of autoantibodies against ADAMTS13 (eg, ticlopidine), platelets (eg, quinine), or neutrophils. Non–immune-mediated mechanisms result from direct endothelial toxicity, which can arise due to dose-related toxicity (eg, gemcitabine) or aberrant angiogenesis (eg, VEGF inhibitors).

Treatment

Cessation of the offending agent is the first—and usually only—step required for resolution of TMA. Some patients develop iTTP after ticlopidine administration; TPE is warranted in this setting.[47] TPE has otherwise no clear role in nonimmune drug-induced TMA.[47] The role of complement-targeted therapies in refractory cases is unclear.

Transplant-Associated TMA

Pathophysiology

TMA can arise as a complication of solid organ transplantation or hematopoietic stem cell transplantation (HSCT). Some believe HSCT-TMA to be an endothelial variant of graft-versus-host disease.[65]

Three hits likely contribute to HSCT-TMA: (1) endothelial dysfunction or predisposition to complement dysregulation; (2) a conditioning regimen causing endothelial injury; and (3) additional insults such as infection, medications, and alloreactivity.[66] In the setting of widespread endothelial injury, there is subsequent complement and coagulation pathway activation. Interestingly, 65% of HSCT recipients with TMA are found to have a pathogenic complement variant.[67]

Among solid organ recipients (especially kidney transplant recipients), specific TMA causes include recurrent or de novo CM-TMA in the allograft, antibody-mediated rejection, drug-induced TMA, and infections (Box 1).[68] Up to 29% of kidney transplant recipients with de novo TMA have complement variants.[69] In the presence of donor-specific antibodies, TMA in antibody-mediated rejection is hypothesized to be mediated by CP activation.[70] Despite this traditional belief, recent evidence suggests that TP activation may not be responsible for cytotoxicity in a significant portion of antibody-mediated rejection cases.[71] The mechanisms implicated in drug-induced TMA in transplant include direct contributions to endothelial injury and complement dysregulation.[72,73]

Treatment

In kidney transplantation, therapy is directed toward the underlying cause, including infection or rejection.

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Switching from one calcineurin inhibitor to another, or to an alternate agent is common. Use of TPE, intravenous immunoglobulin, belatacept, and eculizumab in kidney transplant–associated TMA has recently been reviewed.[74] The role of eculizumab in treatment or prevention of recurrent CM-TMA in the kidney allograft is well established, although not available in all jurisdictions.[74]

Management of HSCT-TMA, including the roles of TPE and eculizumab for refractory disease, has recently been reviewed.[75] A recent phase 2 study investigating narsoplimab in patients with HSCT-TMA resulted in improvements in serological TMA markers and renal parameters in 60% of participants.[76]

Cancer-Associated TMA

Pathophysiology

TMA can arise in the setting of cancer or as a consequence of its treatment, and it has been reported in nearly all solid malignancies and lymphoproliferative cancers.[77-79] TMA has also been observed in patients with monoclonal gammopathies, warranting investigations directed toward underlying monoclonal proteins in adults above 50 years of age.[80] The proposed mechanisms involved in solid cancer–associated TMA include direct endothelial injury from mucin-producing adenocarcinomas, tumor embolization, and activation of the coagulation and complement systems.[78,81-83]

Treatment

Distinguishing cancer, chemotherapy, infection, and complement dysregulation as possible causes of TMA is challenging. Treatment is directed toward the underlying TMA driver (solid cancer, lymphoproliferative disorder, monoclonal protein, medication, or infection). There is no proven evidence supporting TPE or eculizumab for cancer-associated TMA. Although eculizumab may be considered in malignancy-triggered CM-TMA, consideration of the patient's overall prognosis should be factored into the decision, and often funding of medication costs is not supported by payors in this clinical context.[84]

Autoimmune Diseases

Catastrophic Antiphospholipid Syndrome

Pathophysiology

CAPS is a rare manifestation of antiphospholipid syndrome (APS), characterized by multiorgan injury from disseminated microvascular and macrovascular thrombosis within 1 week.[85] In the presence of a trigger (infection, pregnancy, surgery), binding of circulating antibodies on endothelial cells, platelets, and leucocytes results in their activation, with subsequent endothelial injury, uncontrolled coagulation, and complement activation.[86,87] Patients with CAPS are more likely to have genetic complement abnormalities compared with those with systemic lupus erythematosus (SLE) and APS without catastrophic features, further supporting complement dysregulation in disease development.[88]

Treatment

The cornerstones of therapy are anticoagulation, immunosuppression, and either intravenous immunoglobulin or plasmapheresis.[89,90] In refractory disease, use of rituximab or eculizumab has been described.[91,92]

Scleroderma Renal Crisis

Pathophysiology

Endothelial injury and subsequent arterial intimal thickening and proliferation of the arcuate and interlobar arteries characterize SRC.[93] Immune complexes consisting of scleroderma-specific autoantibodies may be involved in mediating endothelial activation.[94] Vessel narrowing and vasospasm results in reduced renal blood flow and activation of the renin-angiotensin-aldosterone system.[95] Despite activation of the renin-angiotensin system, up to 10% of patients will be normotensive at presentation.[96] Presence of endothelin 1 (ET-1) and C3b in kidney biopsy specimens, along with elevated serum C4d and sC5b-9, is potentially suggestive of a role for endothelin and complement activation in mediating renovascular injury.[97,98]

Treatment

Treatment is focused on angiotensin-converting enzyme inhibitors.[99] The role of ET-1 receptor antagonists is not well established in SRC.[100] Patients who develop SRC are at high risk of requiring kidney replacement therapy. Peritoneal dialysis may be the preferred modality given better preservation of residual kidney function, as kidney recovery can be delayed in SRC up to a year.

Systemic Lupus Erythematosus and Other Autoimmune Diseases

Pathophysiology

TMA is an infrequent complication of SLE; however, its incidence is up to 24% in patients with lupus nephritis, as it may be identified on kidney biopsy.[101] Acquired CM-TMA, iTTP, APS, and hypertensive emergency are identified in a third of cases with lupus-associated TMA.[101] Immune-complex deposition and complement activation are the likely culprits in the development of otherwise unexplained TMA in the setting of SLE.[102,103]

TMA can also be observed in patients with dermatomyositis/polymyositis and rheumatoid arthritis, and it can be observed in biopsies of patients with severe glomerulonephritis including vasculitis.

Treatment

Immunosuppression is the mainstay of treatment of TMA in autoimmune diseases. Plasma exchange is frequently initiated pending results of ADAMTS13 activity assays in

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patients with MAHA. The American Society for Apheresis supports its use in severe cases of SLE.[47] Eculizumab has been associated with favorable outcomes in patients with refractory TMA and SLE.[104]

Hypertensive Emergency

Pathophysiology

Hypertensive emergency is a recognized cause of renal TMA; it is believed to arise from mechanical shear stress to the renal microcirculation.[105] Cases of hypertension-associated TMA may in fact represent undiagnosed CM-TMA. In a recent study of 26 participants with hypertensive emergency and TMA, 69% had massive *ex vivo* endothelial C5b-9 formation.[106] Among these, 50% had pathogenic variants in complement genes. Endothelial C5b-9 formation was a risk factor for kidney failure. This supports the importance of complement testing in TMA attributed to "hypertensive emergency" to unmask complement dysregulation. If accessible, evaluation of sC5b-9 may help identify patients who should undergo genetic testing. Ongoing systemic hemolysis despite adequate blood pressure control warrants further testing.

Treatment

Aggressive blood pressure control is the cornerstone of treatment. As complement inhibitors become more widely available, these may be trialed in the future in patients with elevated complement cleavage products (without a pathogenic complement gene variant).[106]

Conclusion

In summary, TMA is a pathologic lesion identified in a spectrum of life-threatening diseases. Much remains to be learned about the disease-specific mechanisms causing TMA, but endothelial injury is a central feature of patients with TMA involving the kidney. Complement dysregulation is a causative or maladaptive feature of many syndromes associated with TMA, and a potential role for cross-talk between coagulation and complement pathways is an area of active investigation. The availability of highly targeted therapies mandates rapid and accurate diagnosis; timely genetic and functional testing are increasingly essential to make therapeutic decisions, and broader access to these tests would assist in personalizing care. Future attention and discussion should focus on overcoming financial and diagnostic barriers to equitable access to highly targeted therapies.

Supplementary Material

Supplementary File (PDF)

Table S1: Epidemiology, pathophysiology, and treatment (including investigational therapies) according to TMA etiology.

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