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Thrombotic Microangiopathy Syndromes—Common Ground and Distinct Frontiers

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Thrombotic microangiopathies (TMAs) have in common a terminal phenotype of microangiopathic hemolytic anemia with end-organ dysfunction. Thrombotic thrombocytopenic purpura results from von Willebrand factor multimerization, Shiga toxin–mediated hemolytic uremic syndrome causes toxin-induced endothelial dysfunction, while atypical hemolytic uremic syndrome results from complement system dysregulation. Drug-induced TMA, rheumatological disease–induced TMA, and renal-limited TMA exist in an intermediate space that represents secondary complement activation and may overlap with atypical hemolytic uremic syndrome clinically. The existence of TMA without microangiopathic hemolytic features, renal-limited TMA, represents an undiscovered syndrome that responds incompletely and inconsistently to complement blockade. Hematopoietic stem cell transplant-TMA represents another more resistant form of TMA with different therapeutic needs and clinical course. It has become apparent that TMA syndromes are an emerging field in nephrology, rheumatology, and hematology. Much work remains in genetics, molecular biology, and therapeutics to unravel the puzzle of the relationships and distinctions apparent between the different subclasses of TMA syndromes.

Keywords: Thrombotic microangiopathy, Atypical hemolytic uremic syndrome, Thrombotic thrombocytopenic purpura, Complement, Autoantibody complement inhibitors

Thrombotic microangiopathies (TMAs) are a common end pathway that results in disordered coagulation and complement regulation resulting in microvascular thromboses, microangiopathic hemolysis, and multisystem organ dysfunction.[1] The broad range of disorders seen due to this pathophysiology include cerebrovascular accidents, cardiomyopathies, pulmonary embolism and hemorrhage, skin rashes, gastrointestinal disease, and liver function abnormalities.[2] Many of the TMA syndromes, but not all, result in a serious degree of acute kidney injury (AKI) and need for dialysis.[3]

The mechanisms of TMA are varied [1-5] and have been discussed in prior publications,[1] but it is important to note that not all TMAs have mechanisms that are fully understood. The inter-relations between different causes of TMAs is even less widely understood.[6-10] The most complex TMAs are complement-mediated TMAs,[11] which are the most treatable ones.[1] Other causes of TMA include von Willebrand factor (vWF)–mediated multimerization (thrombotic thrombocytopenic purpura), toxin-mediated TMA (Shiga toxin–mediated hemolytic uremic syndrome [STEC-HUS]), and vitamin deficiency–mediated TMA (vitamin B12–mediated TMA).[12] Drug-induced TMA (from various agents), malignancy-induced TMA, transplant-associated TMA, infection-associated TMA, and coagulopathy-induced TMA (such as disseminated intravascular coagulation [DIC]) are other types of TMA. Some TMAs are systemic with microangiopathic hemolytic anemia (MAHA), AKI, and thrombocytopenia. Other TMAs present as renal-limited diseases. Please see Figure 1 for representations of molecular pathology of different groups of TMAs.

The natural history of complement-mediated TMA is diverse and affected by differing triggers, predisposing genetic mutations, and presence of potentially associated autoimmune inhibitors resulting in different risk of recurrence and unpredictable and varied clinical courses.[1,2,4,5,13] Even within complement-mediated

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This research work does not contain human subject research material, as it is an individual anonymized case series. The work herein conforms with the Declaration of Istanbul.

Ethical Permission/Consent for Publication: Institutional review board permission was not applied for as it is not required for individual case reports or case series with three patients or less in our institution (University of California Los Angeles). Consent was obtained from the patient and documented, on condition that the no identifiable data be published.

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TMAs, the heterogeneous disease presentations defy a simplistic classification system.[1] See Figure 2 for molecular pathology of TMA-affiliated conditions that are increasingly shown to have links to classic TMA diagnoses.[1]

TMA DIAGNOSIS

The diagnostic process of TMA, particularly ones without clear bioassays, has been a process of rigorous investigation and elimination of other candidate diagnoses.[14,15] Typically, the clinical suspicion for a TMA increases when the picture of MAHA is observed clinically.[1,5] This involves an elevated lactate dehydrogenase (LDH) level, low haptoglobin from scavenging of free heme, schistocytes visualized on peripheral smear, and a compensatory increase in reticulocytes to replace lost red blood cells.[16] The general differential diagnosis includes ruling out vitamin B12 deficiency (which can result in a TMA),[12] ruling out TTP by checking ADAMTS13 (a disintegrin. and metalloproteinase with thrombospondin type 1 motifs, member 13) levels, ruling out STEC-HUS diarrheal cases where Shiga toxin 1 and 2 mediate endothelial injury and complement dysregulation.[1-5,12,13,17] When these other TMA disorders are ruled out, aHUS or complement-mediated TMA (CM-TMA) is generally thought to be the most likely remaining diagnosis.[18] The presence of more severe renal failure and less severe thrombocytopenia increases the likelihood of aHUS as noted in the study by Coppo and colleagues.[9] Please see Figure 3 for the diagnostic algorithm for TMA diagnosis; additional tests are listed to complete a more expanded TMA workup, which may include further diagnostic testing for CM-TMA, autoimmune hemolytic anemia, antiphospholipid antibody syndrome, and TTP.

CLINICAL SUMMARY

- An algorithmic stepwise approach is used to diagnose TMAs, and genetics and complement profiles should be used for most accurate molecular diagnosis; no biomarker exists for aHUS diagnosis.
- TMA involves microangiopathic anemia, acute kidney injury, and thrombocytopenia.
- Some TMAs demonstrate systemic symptoms such as hemolysis, anemia and acute kidney injury; others are renal limited.
- Many triggers can lead to an aHUS-/complement-mediated TMA phenotype.

A major weakness in the investigation of TMA, and aHUS in particular, is the lack of an easy-to-use and readily available bioassay to diagnose hyperactive complement and increased C5b-9 deposition.[19,20] C3 and C4 levels are acute phase reactants and can be high in acute inflammation; therefore, their levels are not always indicative of acute disease and complement activation/consumption.[19,20] CH50 is a useful adjunctive assay, but in and of itself it is not very sensitive or specific.[19,20] There are some novel markers that are irregularly available, namely C5b-9 (membrane attack complex), but this has important limitations of sensitivity and specificity in blood and urine.[19,20] The newer modified HAM assay (acidified serum lysis) is an intriguing possibility to diagnose aHUS physiology.[15] The most promising functional assay looking for membrane attack complex (MAC) deposition was described in the study by Galbusera and colleagues,[14] which moves the idea of demonstrating in vitro c5b-9 deposition forward.[21] In summary, we have made small advances to replicating in vivo pathology in a controlled in vitro assay, and aHUS diagnosis remains algorithmic for now. The future holds promise, however, for an improved set of laboratory testing.[14]

For now, bioassays looking at complement activation are complex and difficult to interpret.[22,23] Genetic testing provides an interesting option, but results are not always conclusive owing to a large number of gene variants of uncertain significance, or negative test results in patients with clear evidence of complement-mediated TMA by clinical criteria.[22,23] Patients with TMA should have complement component levels checked by antigenic assays, should receive assays looking for complement factor inhibitors, as well as be screened for alternative complement pathway mutations. As genetic and clinical data are accumulated for patients with various TMA disorders, and integrated with existing national and international registries, genetic counseling will become more informative and genetic test results will become more useful for guiding treatment of the patient.[1,5,13,17] See Supplementary Figure 1 for a schematic regarding how genetics affect alternative pathway function and can result in complement-mediated TMA.[24]

Pathology

Kidney biopsy is useful in diagnosing the syndrome of TMA. However, it is important to note that the underlying etiology cannot be determined based on the histologic features. See Figure 4 for examples of the following morphologic features. In the acute phase of TMA, fibrin-platelet thrombi may be detected in the glomerular capillaries and extraglomerular vessels including arterioles and small arteries. The granular, eosinophilic thrombi often cause occlusion and distension of the involved vessels. Fragmented red blood cells (schistocytes) may be entrapped in the thrombi or incorporated into the mesangial areas, glomerular capillary walls, and vessel walls. Endothelial cell injury may manifest as endothelial swelling, which causes luminal narrowing/obliteration and causes the glomeruli to appear "bloodless." The extraglomerular vessels often show myxoid intimal expansion, sometimes with mural incorporation of fragmented red blood cells. The acute vascular alterations are often accompanied by features of acute tubular injury/necrosis.

In chronic TMA, repeated endothelial cell injury in the glomeruli results in thickening and duplication of the glomerular basement membranes. Over time, the glomeruli show progressive ischemic collapse and scarring. Characteristic features of chronic TMA in the arteries and arterioles include concentric intimal fibrosis and

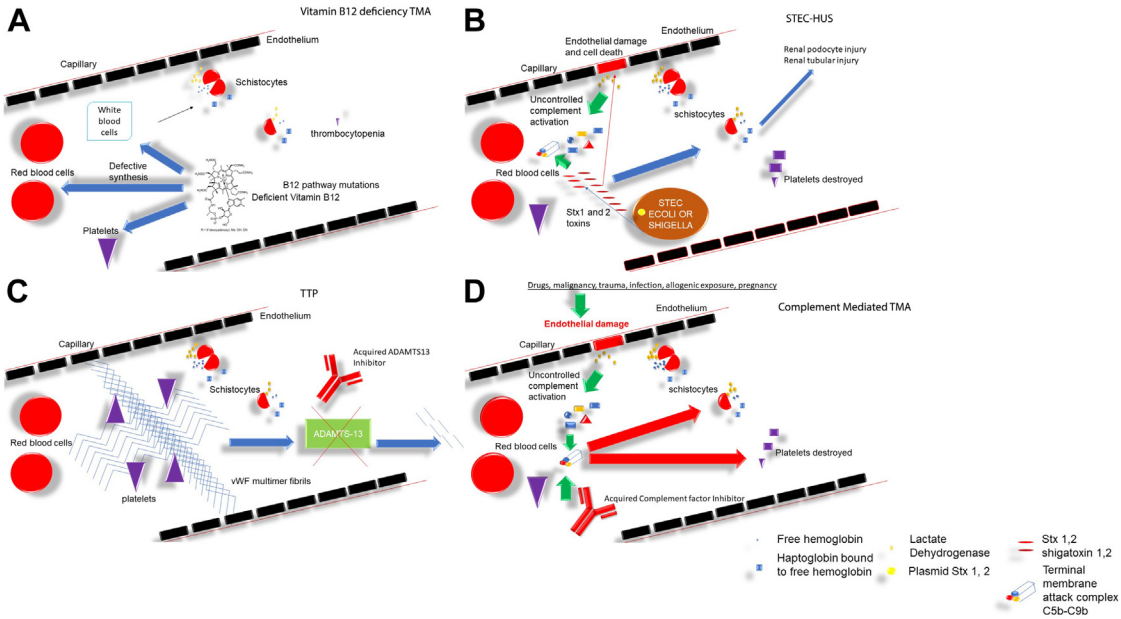

Figure 1. Hemolytic syndrome mechanisms I. (A) Vitamin B12 deficiency TMA. (B) STEC-HUS. (C) TTP. (D) aHUS. ADAMTS13, a disintegrin and metalloproteinase thrombospondin motif 1, member13, B12, cyanocobalamin; STEC-HUS; Shiga toxin *E. coli* – Hemolytic Uremic Syndrome. STx1,2; Shiga toxin 1 and 2; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura. See in figure legend for detail of figure icons. Note: Complement-mediated TMA is another designation for atypical hemolytic uremic syndrome (aHUS). (Adapted from Hanna et al, *Curr Opin Nephrol Hypertens*, © 2019 Wolters Kluwer Health, Inc, www.co-nephrolhypertens.com.[1])

smooth muscle hyperplasia which result in severe luminal narrowing or obliteration. Recanalized thrombi may also be seen. Immunofluorescence microscopy shows staining for fibrinogen in thrombi and nonspecific trapping of IgM and complement in the involved glomerular capillaries and arterioles. Electron microscopy findings include

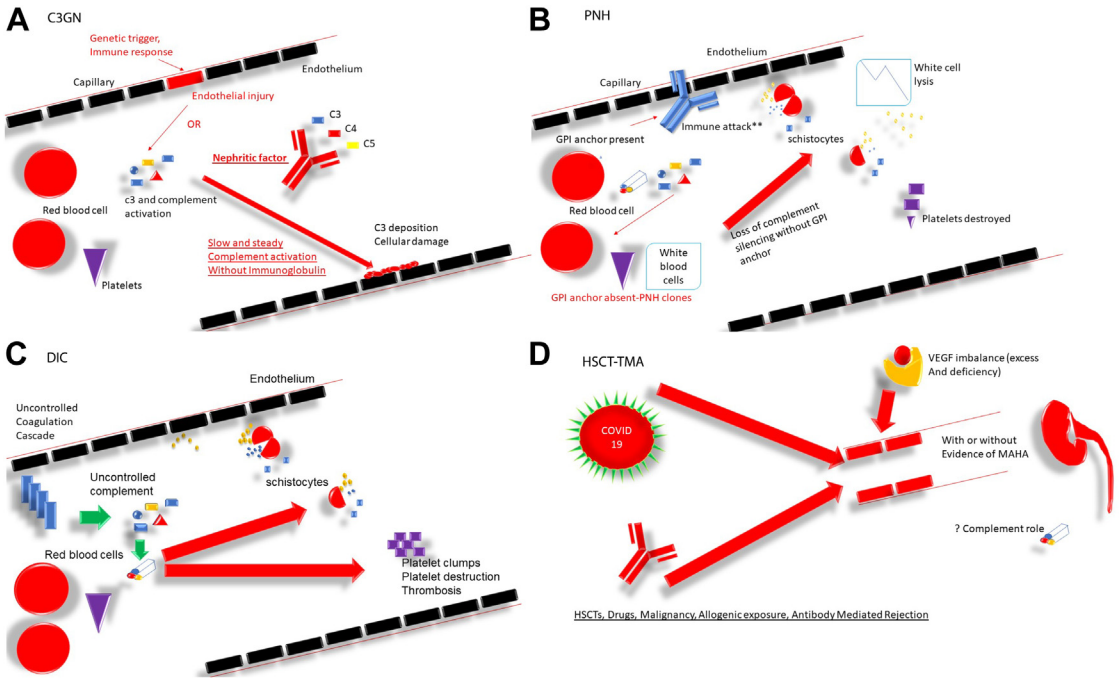

Figure 2. Hemolytic syndrome mechanisms II. (A) C3GN. (B) PNH. (C) DIC. (D) Miscellaneous TMA. C3, complement factor 3; C3GN, C3 glomerulonephritis; C4, complement factor 4; C5 complement factor 5; COVID, severe acute respiratory distress syndrome corona virus-19; DIC, disseminated intravascular coagulation; HSCT, hematopoietic stem cell transplant; PNH, paroxysmal nocturnal hemoglobinuria; TMA; thrombotic microangiopathy; VEGF, vascular endothelial growth factor.

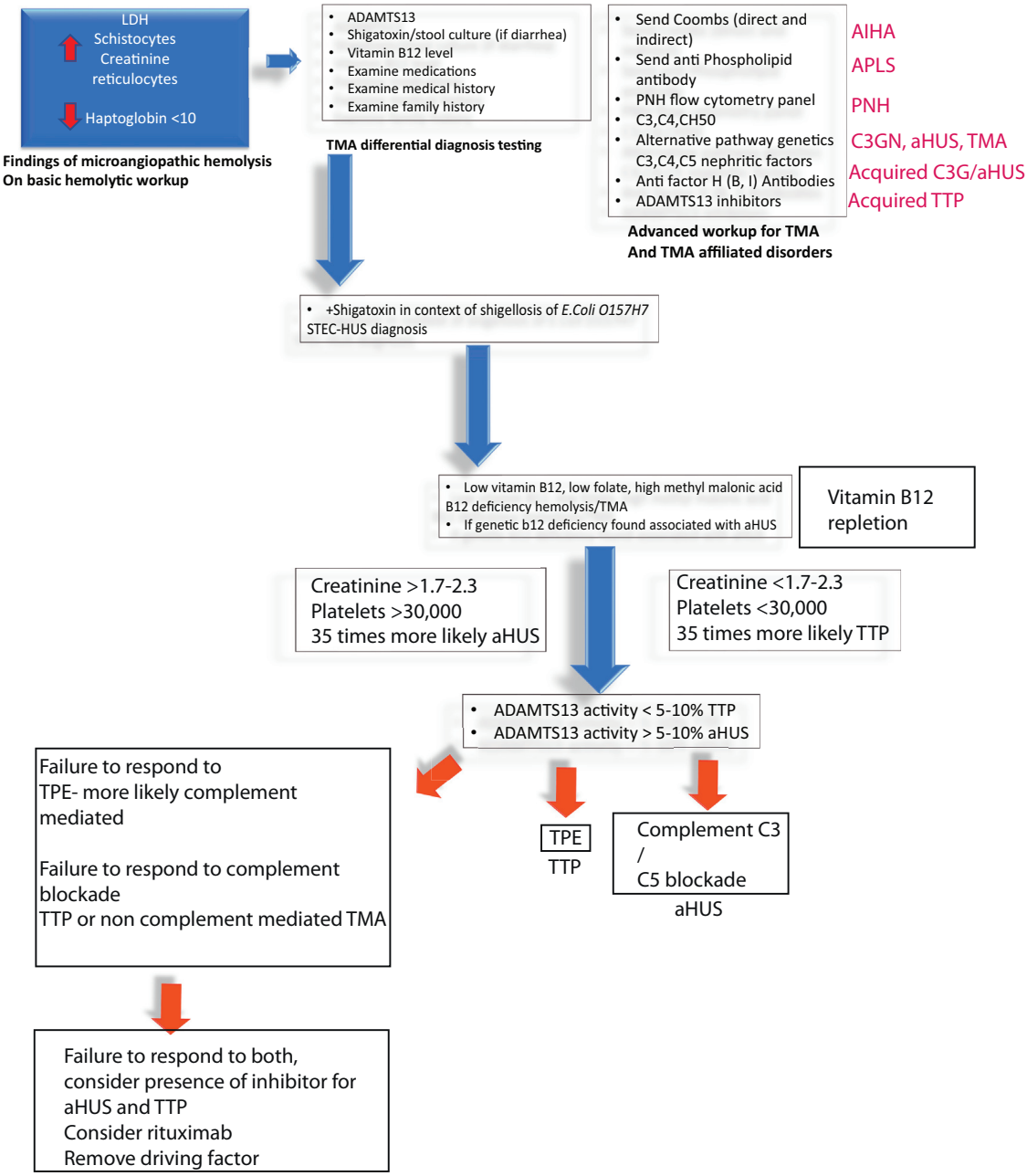

Figure 3. Algorithm for TMA syndrome diagnosis. ADAMTS13, a disintegrin and metalloproteinase thrombospondin motif 1, member 13; AIHA, autoimmune hemolytic anemia; APLS, antiphospholipid antibody syndrome; aHUS, atypical hemolytic uremic syndrome; B12, cyanocobalamin; C3,C4,C5; complement factors 3,4,5; CH50, total complement activity; C3G, c3 glomerulonephritis; LDH, lactate dehydrogenase; STEC-HUS, Shiga toxin *E. coli* hemolytic uremic syndrome (prior known as typical hemolytic uremic syndrome [tHUS]); TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

endothelial cell swelling, subendothelial space widening, and eventual duplication of the glomerular basement membranes.

In the context of onconephrology, a unique morphologic pattern of TMA has recently been described in association with anti–vascular endothelial growth factor (anti-VEGF) therapy.[5,25,26] Patients receiving monoclonal anti-VEGF antibodies tend to develop an unusual intraglomerular TMA which is thought to arise from endothelial leakage and subendothelial accumulation of serum proteins. The characteristic histologic changes include segmental glomerular capillary microaneurysms with occlusive hyaline "pseudo thrombi" which are diffusely involving the glomeruli. Notably, most of these patients do not show the classic fibrin-platelet thrombi or fragmented red blood cells on kidney biopsy.[27-29]

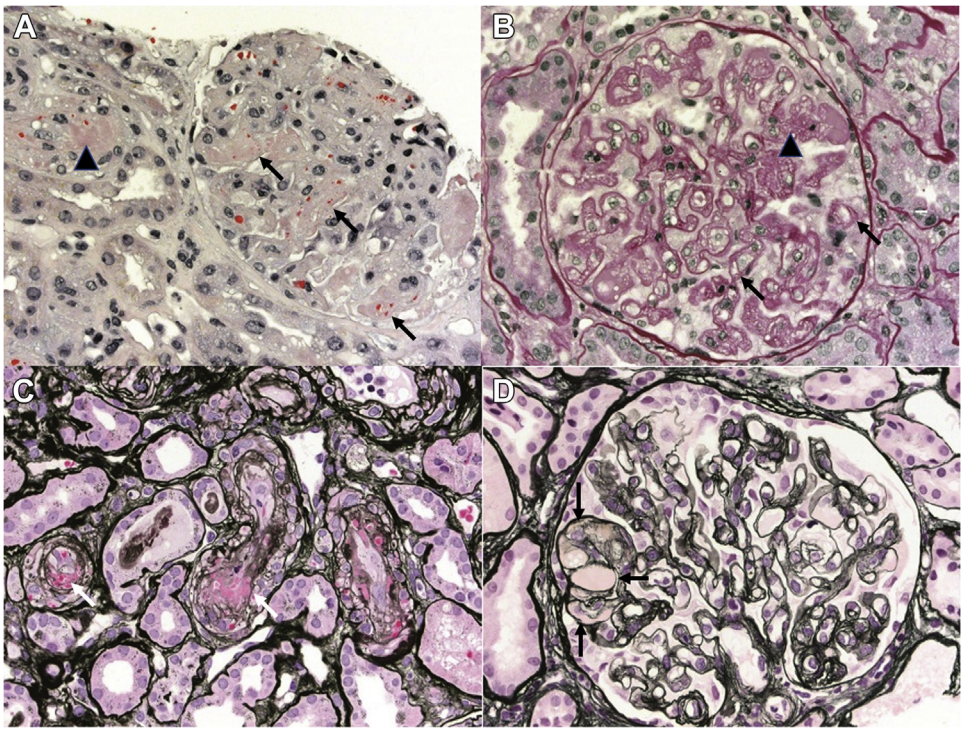

Figure 4. Pathologic findings in TMA. (A) In acute TMA, glomeruli contain eosinophilic fibrin–platelet thrombi which contain fragmented RBCs (arrows), causing occlusion and distention of the glomerular capillaries. The arteriole to the right shows pink fibrinoid change of the vessel wall and incorporation of schistocytes (arrowhead). (H&E, 400x). (B) In chronic TMA, there is remodeling and duplication of the glomerular basement membranes (arrows), and areas of mesangiolysis (arrowhead). (PAS, 400x) (C) In acute TMA, several arterioles are occluded by thrombi (arrows) and also show smooth muscle hyperplasia, fibrinoid change, and mural incorporation of schistocytes. (Jones methenamine silver, 400x) (D) Anti–VEGF-induced microangiopathy showing glomerular capillary microaneurysm formation and insudation with pale pink proteinaceous material (arrows). (Jones methenamine silver, 400x)

VARIOUS TMA SYNDROMES

TTP or ADAMTS13 Deficiency–Associated TMA

TTP is a microangiopathic process that results from buildup of vWF multimers. This occurs when ADAMTS13 activity drops below a critical level to prevent spontaneous vWF aggregation.[30,31] The aggregation of vWF results in shearing of red blood cells; this can result from congenital ADAMTS13 deficiency or the presence of an inhibitor against ADAMTS13.[30,31] See Figure 1. It is noteworthy to mention that platelet transfusion in TTP is not advised as it merely accelerates the formation of platelet clots all over the microvascular.[9,31-35] The mechanism of action also explains why platelet counts are so much lower in TTP vis a vie aHUS and other TMA presentations.[1] Severe acute kidney injury is uncommon in TTP owing to the pathophysiological mechanism involving vWF-induced MAHA and the lack of endothelial inflammation that is the hallmark of CM-TMA.

Treatment: TTP is typically treated with therapeutic plasma exchange (TPE), but cases with the presence of inhibitors require more comprehensive therapy. These inhibitors are generally encountered in acquired TTP and are removed by TPE.[30,31] This process both adds ADAMTS13 back in trans and removes any inhibitor that may be present.[36]Rituximab, an anti-CD20 murine origin monoclonal antibody, can eliminate the B-cell clone that produces the inhibitor.[30,31] A monoclonal antibody which binds vWF and prevents multimerization, caplacizumab, is an additional option that attenuates TTP.[37] Prompt treatment and accurate diagnosis by distinguishing it from other TMA syndromes yields favorable clinical outcomes.

Upshaw-Schulman syndrome. The genetic absence of ADAMTS13 is a syndrome referred to as Upshaw-Schulman syndrome, which is due to inactivating mutations in the ADAMTS13 gene that maps to chromosome 9q34.[1,37]

Treatment: The treatment for Upshaw-Schulman syndrome would involve ADAMTS13 replacement via therapeutic plasma infusion with possible use of caplacizumab.[1,37] See Figure 1.

Metabolism-Mediated TMA (cobalamin deficiency)

Acquired cobalamin. Vitamin B12 (cobalamin) deficiency is a lesser known and under-recognized cause of TMA.[12] There have even been cases of B12 deficiency resulting in MAHA in the peripartum period—which

mimics peripartum TMA.[12] The exact mechanism resulting in TMA is disordered erythropoiesis and abnormal development of the other cell lines (platelets and WBC).[1] There is generally MAHA and possible pigment injury, but not the usual level of endothelial dysfunction present in complement-mediated TMAs. Although severe renal failure is not common, it has been rarely reported with vitamin B12 deficiency–associated hemolysis/TMA.[1] Pigment injury could certainly result in renal injury from excessive hemolysis and heme-associated renal injury.[1] The distinguishing feature is generally the presence of decreased vitamin B12 level, folate level (generally red cell folate is best), and at times the finding of an elevated methylmalonic acid level. Pernicious anemia, due to the presence of intrinsic factor antibodies, accounts for many of these TMA cases, whereas TMA is less common with B12 deficiency secondary to malabsorption.[38] In a patient with ongoing hemolysis and a decreased B12 level, the clinician should be alerted to the possibility of B12-associated TMA, particularly in the absence of renal failure. See Figure 1.

Treatment: In general, the best therapeutic approach involving vitamin B12 repletion, folate repletion, Coq-10 repletion, and carnitine repletion is at times helpful.[39]

Genetic B12 pathway inborn errors. B12 pathway mutations, although certainly providing a risk for the more renally benign phenotype discussed earlier, have also been associated with a more complement-mediated TMA/aHUS type phenotype.[40] In these patients, repletion of vitamin B12 and associated cofactors (coenzyme Q10 and carnitine) may alleviate the MAHA.[40] These mutations include genes coding for cobalamin synthesis (such as methionine synthetase).[40] See Figure 1.

Treatment is difficult, given the genetic cause underlying the TMA, but generally involves vitamin B12 repletion without a confirmed role for complement blockade.[41]

Shiga Toxin–Mediated TMA

STEC-HUS is caused by the plasmid encoded proteins of *Shigella* and *Escherichia coli* 0157H7, [42,43] which are gram-negative rod species with plasmids encoding Shiga toxins 1 and 2 (STx1 and STx2).[44] These toxins result in endothelial dysfunction and complement dysregulation resulting in a complement-mediated TMA that is directly driven by the toxins. Shiga toxins 1 and 2 have direct toxicity to the podocytes and renal tubules, and this implicates complement involvement as a secondary effector of tissue damage in STEC-HUS that is different from the pathophysiological mechanism of TTP. See Figure 1.

Treatment: Conservative management has been traditionally applied, with avoidance of antibiotics inpatients with the gram-negative rod infections associated with STEC-HUS. STEC-HUS has previously been called typical hemolytic uremic syndrome in the pediatric literature.[42,43] The majority of patients improve, but some studies have been conducted looking for efficacy of both plasma exchange and complement blockade in nonresponding cases.[42,43]

COAGULOPATHY-MEDIATED TMAs

DIC is another entity which generates a common and often irreversible microangiopathic hemolytic process.[45] DIC usually presents with dysregulation of the coagulation cascade[46] and a secondary complement activation.[45] Some genetic mutations have been isolated in DIC linking back to alternative pathway dysfunction and others to coagulation cascade mutations.[46] The presence of bacterial infections, trauma, or bleeding in turn lead to unabated activation of clotting and complement.[45] The end result in MAHA is endothelial dysfunction and clotting contributing to end-organ dysfunction and extremely high mortality rates.

Treatment: Treatments have generally been supportive and aimed at inhibiting the underlying trigger for the disruption.[45]

Drug-Induced TMA

This is an expansive topic, as complement amplification and dysregulation can be caused by a variety of medications.[47] As discussed earlier in the transplant realm, calcineurin inhibitors have been known to cause TMA.[6,48] This is a difficult situation as calcineurin inhibitors are generally necessary to continue for allograft health but become contraindicated in patients who develop TMA.[6,48] Belatacept is an option in some solid organ transplant (anti CD80 and CD86), but is not currently an option for more immunogenic organs,[49] or where not studied such as liver transplantation.[49] Gemcitabine is another common cause of TMA in patients with malignancy, and some reports of successful treatment with complement blockade have been reported.[50-54] Quinine is a classic example of immune-mediated drug-induced TMA. Ultimately these are the two principal mechanisms of toxicity.[55,56] The direct toxicity route results in damage to endothelium leading to CM-TMA. The immune-mediated toxicity leads to TMA presentations driven by antibodies to drug-protein complexes.[55] Gemcitabine, for example, causes direct endothelial cell toxicity, which results in TMA caused by complement dysfunction.[57]

Both tyrosine kinase inhibitors (TKIs) and VEGF inhibitors (VEGFis) have been reported to cause TMA.[58] The mechanism is thought to be the interruption of survival signaling induced by VEGF biding to VEGF receptors on endothelial cells, which results in endothelial injury and TMA.[25] Izzedine and colleagues have postulated that systemic VEGFis are more likely to cause TMA, but TKIs have also been reported to cause the same presentation.[59] This is likely due to the fact that TKIs target the downstream mediators that are controlled by VEGF signaling.[25,26,60] Hanna and colleagues[25] and various other comprehensive studies detail the emerging and interesting findings of intravitreal VEGFi use that have been confirmed to be associated with increased hypertension and renal-limited TMAs.[61] However, the pattern seen is not necessarily the classic MAHA pattern that is most associated with ideal aHUS presentations.[25] Alternatively, collapsing focal and segmental glomerulosclerosis (FSGS)—a TMA-associated phenotype linked to glomerular hypoxia—has also been associated with VEGFis and TKI use.[25,58,61] VEGFi

systemic toxicity is well established when given intravenously; however, VEGFi toxicity when given intravitreally is a nascent topic that needs much greater levels of investigation[25,58,61] (Table 1).

Treatment: Treatment classically involves removal of the noxious agent, and if no improvement is seen, complement blockade has been tried with various degrees of efficacy.[1] TPE has also been tried with some success in drug-induced TMA.

Complement-Mediated TMA

Complement-mediated TMA, commonly called aHUS, is not easy to diagnose. The classic pattern outlined in Figure 3 that results in a diagnosis of atypical hemolytic uremic syndrome includes severe renal failure, moderate to serious thrombocytopenia (usually >30,000 platelets/uL), and confirmed MAHA.[1] This enigmatic diagnosis has been noted to be rather rare (2/500,000 incidence).[43] There is much debate regarding whether this rarity is due to the difficulty in diagnosing aHUS. aHUS may be triggered by various complement-amplifying conditions but classically presents with AKI, MAHA, thrombocytopenia with end-organ damage.[6,11,18,62,63] Making a timely diagnosis of complement-mediated TMA is life-saving and may prevent progression to end-stage renal disease[1] and the 25% mortality rate noted in the study by Legendre and colleagues,[64] making the diagnosis is paramount.[64,65] It remains very responsive to complement inhibition (currently C5, but in the future C3, factor D, and factor B[66] inhibitors are under investigation)[6,11,18,62,63]

Complement genetics are the driving force of aHUS, and likely TMA, and TMA-associated conditions as well.[22,67-73] The issue is that the penetrance of the genetic mutations is not 100%. This is because despite the disposition, complement dysfunction usually only occurs when a strong enough trigger is married to genetic susceptibility in an unhappy gathering to generate an adverse phenotype.[1,4] An elevated genetic risk of complement dysfunction is not linked to the number of mutations identified, but the severity of the dysfunction of underlying complement system components. Smaller mis-sense mutations also seem to be less problematic than large deletions or nonsense mutations that severely disrupt the protein product's function.[70]

Mutations in plasminogen, thrombospondin, vitronectin, and vitamin B12 pathway synthases have been implicated in TMA.[70] Surprisingly though, vitamin B12 pathway mutations have been implicated in complement-mediated TMA presentations,[39] as well as ADAMTS13 deficiency.[74] The identification of aHUS cases with underlying vWF mutations suggests an intimate communication of complement cascade with the coagulation cascade.[32,34,35,75] One important exception is diacyl glycerol kinase epsilon (DAGK-E) mutations that have been found to not be responsive to complement blockade for reasons that are yet unknown and could represent a separate syndrome.[76]

Treatment: Treatment has classically been complement blockade using anti-C5 agents (both long acting and short acting), although new complement-blocking agents are becoming available. Prompt treatment has been associated with favorable outcomes, and delayed treatment has been associated with increased fibrosis and less optimal outcomes owing to development of nephron loss, irreversible vascular injury, and fibrosis.[1]

It is finally noteworthy to mention that beyond c5 blockade with eculizumab, longer-acting agents such as ravulizumab are in the market.[1] Oral avocapan C5 inhibitors are being tested as steroid-sparing agents for antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis.[77] C3 blockade is being tested for a variety of complement-mediated conditions such as paroxysmal nocturnal hemoglobinuria and the TMAs of various etiologies.[1] Complement blockade is also being tried in a variety of different pathophysiological conditions such as myasthenia gravis, C3 glomerulonephritis, and other glomerular diseases.[66] Factor D and B monoclonal antibodies as well as molecules that bind other complement pathway proteins are also in the pharmaceutical pipeline.[66]

Table 1. Common Medications Causing Drug-Induced TMA

Drug	Mechanism
Aflibercept	Direct toxicity
Bevacizumab	Direct toxicity
Bortezomib	Immune mediated
Calcineurin inhibitor	Direct toxicity
Carfilzomib	Immune mediated
Dasatinib	Direct toxicity
Docetaxel	Direct toxicity
Imatinib	Immune mediated
Ixazomib	Immune mediated
Gemcitabine	Direct toxicity
Mitomycin	Direct toxicity
Oxaliplatin	Immune mediated
Pentostatin	Direct toxicity
Quinine	Immune mediated
Sorafenib	Direct toxicity
Sunitinib	Direct toxicity

SECONDARY TMA SYNDROMES

Postpartum TMA

Pregnancy is increasingly being recognized as a complement-amplifying condition, and pregnancy and childbirth are common triggers for the development of aHUS.[78] However, because of other serious obstetric complications, it may be under-recognized.[79,80]

Pregnancy represents a semiallogenic exposure, or fully-allogenic in donor egg and surrogate pregnancies.[79,81,82] If the placenta experiences ischemia or hypoxia, thromboxane molecules and endothelial toxins are secreted. This results in vasoconstriction and endothelial dysfunction and injury.[79]

There are accumulating data that complement activation, and complement dysregulation, contributes to the development of preeclampsia and HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome.[81] Thus, it remains possible that preeclampsia, HELLP

syndrome, and aHUS occur along a spectrum of complement activation and dysregulation resulting from genetic mutations in complement regulatory proteins.[81] Clinical trials are needed to investigate this approach and are currently underway (NCT04725812).[83]

Treatment: Therapy for preeclampsia and HELLP syndrome is immediate delivery if this is medically feasible. Complement blockade is indicated in cases of suspected CM-TMA related to pregnancy.

MALIGNANT HYPERTENSION–ASSOCIATED TMA

Malignant hypertension (HTN) is defined as severe HTN, often with systolic blood pressure well in excess of 200 mmHg and diastolic blood pressure in excess of 100 mmHg, with evidence of end-organ dysfunction.[84] These presentations are less common owing to the guidelines appropriately recommending intervention in hypertensive patients early with multiple agents.[71,85-88] HTN-related TMAs are still regularly seen in incident or noncompliant patients or in patients without access to care.[89,90] At times, MAHA can result[91] and is associated with the extremes of blood pressure.[89,90] The question regarding whether this is an effect of the HTN (due to sheer stress) and endothelial dysfunction from the severely elevated arterial pressures is ongoing.[89,90] Timmermans and colleagues described the increased C5b-9 deposition in renal biopsies of patients with malignant HTN, which suggests a role for complement dysregulation in some cases of malignant HTN.[89,90] The patients described were not only those with classical malignant HTN–associated TMA but also those with intractable HTN.[91-95] See Supplementary Figure 2.

Work by various pathologists also continues to link features of hypertensive nephrosclerosis and TMA associated with HTN to abnormalities in the complement system.[96] At this time, the final verdict is unknown, but it may well emerge that complement may be a cause of secondary HTN. In the extreme, these defects can produce MAHAs and aHUS-like presentations.[96] The current guidance is to control the hypertension first, and if the TMA does not resolve to consider underlying complement dysfunction.[1] There is a distinct possibility that HTN may be provoked by complement abnormalities, which in turn worsen HTN and further dysregulate the complement system in a positive feedback loop.[97] This interplay that shows the bidirectionality of complement dysregulation in this situation is displayed in Supplementary Figure 2.

Treatment: Therapy involves lowering blood pressure, and if renal function and MAHA do not subside, complement blockade can be considered—albeit it has not been widely studied.

SOLID ORGAN TRANSPLANT–ASSOCIATED TMA

TMA is a frequently described complication of solid organ transplantation occurring both as recurrent native and de novo disease.[6,62,98] Recurrent TMA is common in patients with underlying complement-mediated TMA (aHUS) and to varying degree in TTP and other autoimmune diseases. De novo TMA can be seen with antibody-mediated rejection, immunosuppressive medications, and viral infections.[98] It is thought that in the presence of genetic susceptibility alloimmune exposure can result in complement dysregulation, a positive feedback amplification of complement and if a threshold is met—a complement-mediated TMA.[69] Interestingly, TMA is also seen in the setting of antibody-mediated rejection.[99-102]

Treatment: Therapy typically depends on a suspected degree of complement involvement, and standard therapy for rejection focuses on immunosuppression. In cases of suspected CM-TMA recurrence, then complement blockade may be indicated.

HEMATOPOIETIC STEM CELL TRANSPLANT–ASSOCIATED TMA

An especially difficult presentation of post-transplant TMA (and arguably one that is complement mediated for the majority of cases) is TA-TMA.[103,104] These presentations occur with the incredibly severe complement amplification seen in the context of hematological malignancy and allogenic exposure in an allo stem cell transplants.[103,104]

Treatment: TA-TMAs have proven difficult to treat and may not respond initially to standard doses of C5 blockade.[105] Plasma exchange, rituximab, and defibrotide have been tried with various success rates. See Figure 2. Details of this are discussed in a different chapter in this issue.

RHEUMATOLOGICAL SYNDROME–INDUCED TMA

Systemic Lupus Erythematosus–Associated TMA

An area of recent study, the myriad triggers of aHUS, is increasingly recognized to include pathological processes long taught to induce hemolysis themselves.[3] One particular example is the case of patients with systemic lupus erythematosus (SLE) that then develops refractory hemolytic anemia and thrombocytopenia.[3] Although a great deal of the hematological pathology induced by SLE is due to the immune hyperactivity that is confirmed on biopsy by "full-house staining,"[1] there have been cases where SLE activity becomes quiescent—but the MAHA and endothelial dysfunction continues.[3]

Treatment: It has been shown in the study by Park and colleagues that complement blockade may have an effect of improving renal and hematological outcomes in these complex cases.[106,107] Complement blockade is seen as an option after a thorough attempt to treat the underlying SLE.[106,107]

Catastrophic Antiphospholipid Antibody Syndrome and aHUS Overlap

Similarly, catastrophic antiphospholipid antibody syndrome (CAPS), which is a disease associated with SLE, has been associated to remain refractory to standard therapy.[108] This classically includes plasmapheresis, rituximab, and cyclophosphamide.[108] It has been increasingly postulated that complement has a role in CAPS and there have been studies performed showing some efficacy in utilizing complement blockade in these situations.[2]

Treatment: Traditional therapies targeting SLE and APLS antibodies/anticardiolipin antibodies are still the first line.[2]

In patients with refractory CAPS and an increased risk of immunosuppression, complement blockade has been attempted with reported success.[2] Further investigation of the overlap between this antibody-mediated disease and complement dysregulation is needed.[2]

Scleroderma Renal Crisis–Related TMA

Scleroderma renal crisis (SRC) is an enigma, with a terrible prognosis.[97] Despite this, the only agent in the armamentarium against this deadly disease is renal angiotensin aldosterone system inhibition (specifically with captopril).[97] Although complement blockade has been tried, it has not been uniformly successful;[96,97] plasmapheresis and antiendothelin agents are the other experimental therapies. These have not been firmly established either.[97] SRC remains morbid with a high mortality rate,[109] and often the treatment is supportive until the immune system recovers.[96,97]

Treatment: The only firmly recommended therapy is renin angiotensin aldosterone system inhibition with captopril in particular.[97] Other experimental agents include antiendothelin inhibitors and TPE.[97] There have been some theoretical investigations and clinical reports of complement activation in SRC.[109]

Cancer-induced TMAs. Malignancy is a known complement-amplifying condition, and certain malignancies can trigger TMA.[110] Mucin-producing adenocarcinomas have been known to trigger TMAs in particular.[110] These cases are challenging given the potential for both the underlying disease, therapy, and infections to all trigger a TMA response.[110]

Treatment: Complement blockade may be appropriate therapy in malignancy-induced aHUS; for chemotherapy-induced TMA, see drug-induced TMA section.[110]

OTHER MISCELLANEOUS TRIGGERS ASSOCIATED WITH TMA

Illicit drugs, trauma,[6,48] and even COVID-19 have been reported to result in TMA.[111] The patterns differ with some being complement mediated/responsive[112–119] and others not appearing to be completely complement mediated.[6,9,10] In the case of COVID-19, Sharma and colleagues found that 20% of renal biopsies in patients with COVID-19 showed TMA.[117,118]

Interestingly some other diseases not thought to be complement mediated are being linked to alternative pathway mutations or were found to inexplicably be complement responsive. This includes IgA nephropathy,[80,98] idiopathic nonischemic cardiomyopathy,[120] myasthenia gravis,[121] and age-related macular degeneration.[122] For a graphical depiction of the differential TMA syndromes and their rough relationship to each other according to current data, see Figure 2.

Treatment: Some therapeutic trials from abroad showed that complement blockade may have some preliminary evidence for efficacy in patients with SARS-CoV2; this has not yet been demonstrated in large-scale trials and as such remains under investigation.[119] See Supplementary Figure 3 for illustration of complement-mediated TMA and their relations to other TMA types.

THE TMA NOMENCLATURE: A WORK IN PROGRESS

It is important to mention that nomenclature for TMA and aHUS is undergoing constant reformation. A clinical distinction as to how aHUS cases respond to complement blockade and the need for long-standing therapy has been noted by Cavero and colleagues[6] and Olson and colleagues.[48] It is the authors' suggestion that certain cases are more trigger driven than others which have a greater genetic etiology.[6,48] Consensus conferences are badly needed to reform the language, and coding of aHUS is needed to produce a clear scientific language to buttress this burgeoning field.[1]

CONCLUSION

This comprehensive review has addressed the current state of knowledge regarding the molecular physiology and pathology, diagnosis, and therapy of TMAs. This includes complement-mediated and complement blockade responsive pathways and those that are not. The developments in pathophysiological understanding, treatment, and diagnostics are quickly emerging, and it is becoming clear that complement physiology is not a monolithic disorder or set of disorders on a differential diagnosis. Complement physiology and pathophysiology are presenting themselves as a new field of medicine that is in need of investigation and funding. See Supplementary Figure 4 for a summary of the complex interplay of phenotype and genotype that lead to the rich and varied clinical presentations of TMA.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1053/j.ackd.2021.11.006.

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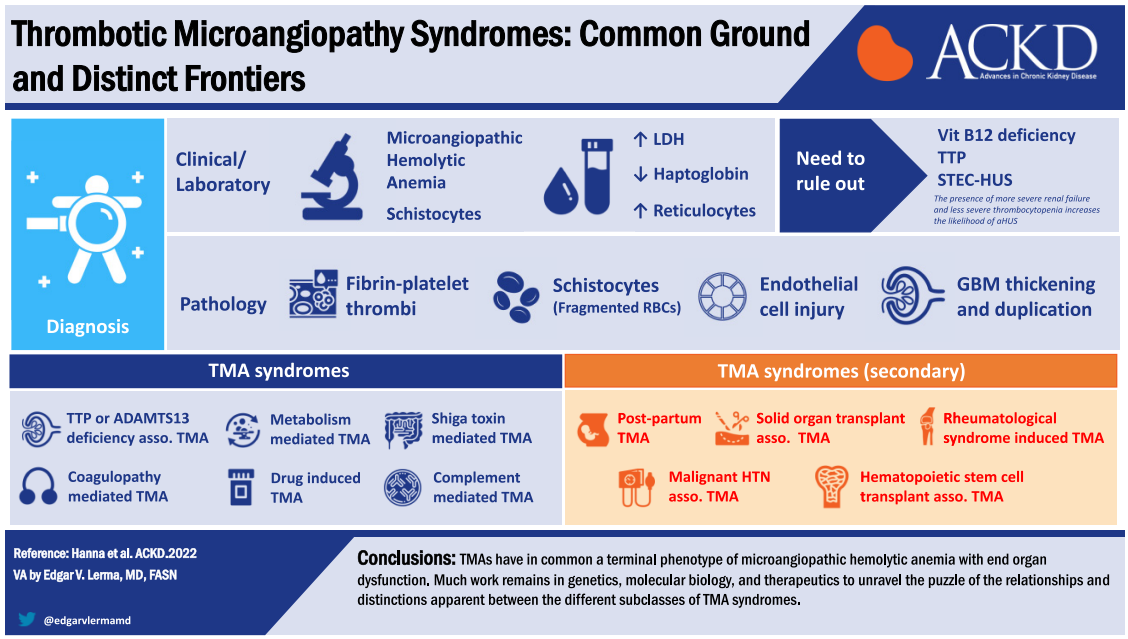
Thrombotic Microangiopathy Syndromes: Common Ground and Distinct Frontiers
ACKD
Advances in Chronic Kidney Disease
Diagnosis
Clinical/ Laboratory
Microangiopathic Hemolytic Anemia
Schistocytes
↑ LDH
↓ Haptoglobin
↑ Reticulocytes
Need to rule out
Vit B12 deficiency
TTP
STEC-HUS
The presence of more severe renal failure and less severe thrombocytopenia increases the likelihood of aHUS
Pathology
Fibrin-platelet thrombi
Schistocytes (Fragmented RBCs)
Endothelial cell injury
GBM thickening and duplication
TMA syndromes
TTP or ADAMTS13 deficiency asso. TMA
Metabolism mediated TMA
Shiga toxin mediated TMA
Coagulopathy mediated TMA
Drug induced TMA
Complement mediated TMA
TMA syndromes (secondary)
Post-partum TMA
Solid organ transplant asso. TMA
Rheumatological syndrome induced TMA
Malignant HTN asso. TMA
Hematopoietic stem cell transplant asso. TMA
Reference: Hanna et al. ACKD.2022
VA by Edgar V. Lerma, MD, FASN
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Conclusions: TMAs have in common a terminal phenotype of microangiopathic hemolytic anemia with end organ dysfunction. Much work remains in genetics, molecular biology, and therapeutics to unravel the puzzle of the relationships and distinctions apparent between the different subclasses of TMA syndromes.