Seminars in Diagnostic Pathology 37 (2020) 121–126

Contents lists available at ScienceDirect

Seminars in Diagnostic Pathology

journal homepage: www.elsevier.com/locate/semdp

A New Paradigm for Renal Thrombotic Microangiopathy

Alexander J. Gallan[1,*], Anthony Chang[2]

[1] Medical College of Wisconsin, Department of Pathology, Milwaukee, WI 53226
[2] The University of Chicago, Department of Pathology, Chicago, IL 60637

ARTICLE INFO

Keywords:
Thrombotic microangiopathy
Complement
Alternative pathway
Hemolytic uremic syndrome
Kidney
Pathology

ABSTRACT

Thrombotic microangiopathy (TMA) is characterized by thrombocytopenia and microangiopathic hemolytic anemia, results from acute and/or chronic endothelial cell injury, and often manifests with kidney dysfunction. TMA can be observed in a wide spectrum of clinical scenarios, which includes but is not limited to thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, severe (malignant) hypertension, preeclampsia/eclampsia, antiphospholipid antibody syndrome, scleroderma renal crisis, drug toxicities, or metabolic disorders. These different conditions are impossible to distinguish based solely on the pathologic findings, necessitating correlation with clinical and laboratory data. For both treating physicians and pathologists, the absence of specific pathologic features for a particular etiology or association with TMA remains a great source of frustration and confusion that currently accompanies this complex topic. In this review, we introduce a new paradigm for TMA that coalesces around the important contribution of the complement system, which has potential implications for therapeutic management, disease recurrence in the kidney allograft, and genetic risks to family members.

Introduction

Thrombotic microangiopathy (TMA) is characterized by thrombocytopenia and microangiopathic hemolytic anemia (MAHA), results from acute and/or chronic endothelial cell injury, and often manifests with kidney dysfunction. TMA can be observed in a wide spectrum of clinical scenarios, which includes but is not limited to thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), severe (malignant) hypertension, preeclampsia/eclampsia, antiphospholipid antibody syndrome, scleroderma renal crisis, drug toxicities, or metabolic disorders. These different conditions are impossible to distinguish based solely on the pathologic findings, necessitating correlation with clinical and laboratory data. For both treating physicians and pathologists, the absence of specific pathologic features for a particular etiology or association with TMA remains a great source of frustration.

In this review, we introduce a new paradigm for TMA that coalesces around the important contribution of the complement system, which may begin to clarify the confusion that currently accompanies this complex topic.

Brief Overview of the Complement System

Complement is an ancient component of our innate immune system that protects us from a wide variety of pathogens, including bacteria, fungi, viruses, and parasites. The details of the complement system have been well reviewed,[1] but the alternative pathway is particularly notable, as it is constitutively active through a process called “tickover” and under tight regulation by multiple regulatory proteins. Given that infectious diseases remain the leading cause of death worldwide, the complement system has continually been honed by natural selection to achieve maximal effectiveness. Therefore, a physiologic tendency for overactivation should offer a survival advantage and be preferred over underactivation of complement. However, this represents a double-edged sword, as chronic infections (e.g. HIV or viral hepatitis) or chronic diseases (e.g. IgA nephropathy) or autoimmune disorders (e.g. lupus nephritis) can provide constant stimuli and hijack a highly efficient complement system to cause long term damage both locally and systemically. We suspect that complement may be an important explanation for the notably poor clinical outcomes in black patients with lupus and scleroderma, and perhaps also account for the higher peripartum mortality rates, as pregnancy itself and the delivery of the placenta are strong stimulants of complement.

* Corresponding author: Alexander J. Gallan, Department of Pathology, Medical College of Wisconsin, 9200 W Wisconsin Ave, Room L73, Milwaukee, WI 53226,
E-mail address: agallan@mcw.edu (A.J. Gallan).

https://doi.org/10.1053/j.semdp.2020.01.002

Proposed Model of Complement Injury in TMA

We present our working model of how complement can cause a chronic and severe microangiopathic injury in the kidneys of a patient with atypical HUS (aHUS) due to a genetic mutation. If we assume that each kidney is endowed with a million nephrons at birth, a continuous or net loss of 500 nephrons per week or 25,000 nephrons per year in each kidney since birth would result in end-stage kidneys by the age of 40. A milder form of the disease or lower rate of nephron loss would present at an older age and a more severe form would present earlier in the pediatric age group. We suspect that this injury is not continuous but rather more episodic, given that infections are a common trigger of the complement cascade, so the signs and symptoms in these patients often wax and wane. When the infection resolves and complement activation lessens, the body attempts to heal with clinical signs of improvement. This model would account for a large proportion of TMA patients that have more subtle or even an absence of clinical signs and symptoms.

Anecdotally, we have encountered black patients with sickle cell trait, two G1/G2 risk alleles for *APOL1*, and aHUS, and having any two of these three conditions is common in our experience. Heterozygosity for hemoglobin S and the G1/G2 *APOL1* risk alleles provide a survival advantage against malaria and trypanosomiasis, respectively. The prevalence of sickle cell trait and two G1/G2 risk alleles for *APOL1* is approximately 10–13% for each among black patients. Could the prevalence for aHUS approach a similar range? Instead of the concept of genetic linkage, this example represents a phenotypic linkage as each of these confers a survival advantage over an infectious agent. There is also a cognitive bias towards a parsimony of diagnoses, and aHUS in particular has taken advantage of this bias to elude our clinical suspicion.

If our theory is correct, the current focus on monogenic causes of aHUS may underestimate the polygenic forms, which have been estimated to comprise 9% of aHUS.[2] Over the course of many millenia, every mutation (and post-translational modification), which allowed the complement system to be more effective in its defense against a microorganism, would prevail and be passed on to the next generation. This would be particularly true when the average life expectancy 200 years ago was only about 30 years.

Our TMA Perspective

When a clinical and/or pathologic diagnosis of TMA is established, it is essential to exclude TTP as a potential cause. TTP results from an inherited or acquired deficiency of ADAMTS13 activity, a plasma protein that cleaves the ultralarge multimers of von Willebrand factor (vWF). Most cases are due to acquired autoantibodies to ADAMTS13, which may arise in the setting of autoimmune disorders, pregnancy, drug reaction, malignancy, and infection.[3] TTP is suspected when serum ADAMTS13 activity is less than 5-10%. Plasma exchange is an effective treatment for TTP in replacing serum ADAMTS13 and removing autoantibodies and the ultralarge multimers of vWF from circulation.

After a diagnosis of TTP has been excluded, we briefly discuss the evidence and rationale for the role of complement in the other conditions that are commonly associated with TMA. Classic (or typical) HUS is caused by Shiga toxin-producing bacteria including *Escherichia coli* O157:H7 / 0104:H4 or *Shigella dysenteriae*. Patients present with acute renal failure, MAHA, bloody diarrhea, and sometimes neurological abnormalities. Shiga toxin can bind complement factor H, resulting in overactivation of complement.[4] Also, inhibition of the mannose-binding lectin pathway of complement in an animal model of Shiga toxin-induced HUS protected kidneys from injury.[5] Similarly, numerous other bacterial, viral, parasitic, and fungal infections, including *Streptococcus pneumonia, Legionella pneumophilia*, HIV, histoplasmosis, and malaria, which all trigger complement, have been associated with TMA.

Anti-phospholipid antibody syndrome (APS) is characterized by vascular thrombosis, which can involve nearly any vessel and cause a myriad of clinical presentations. Given the wide availability of clinical assays to detect autoantibodies against cell membrane phospholipids cardiolipin, β2-glycoprotein I, or lupus anticoagulant, evaluation for APS should be done. Additionally, β2-glycoprotein I has been shown to play an in vitro role in complement activation.[6] Antiphospholipid antibodies cause fetal loss in wild-type mice, but not in those with complement deficiencies.[7] Also, APS patients theoretically could have additional autoantibodies targeting one or more complement regulatory proteins.

Pregnancy is also a complement stimulating condition, as maternal alloimmunization to the fetus occurs. Pre-eclampsia and eclampsia are characterized by elevated levels of soluble fms-like tyrosine kinase-1 (sFlt1), which antagonizes vascular endothelial growth factor (VEGF).[8] Cancer patients treated with bevacizumab, another VEGF antagonist, can develop TMA, which may be due to decreased local expression of complement regulatory proteins in the eye and kidneys.[9,10] Therefore, this provides a connection between complement and the clinical manifestations of TMA in the setting of pregnancy. HELLP syndrome is a related entity that manifests with hemolysis, elevated liver function tests, and low platelets, and emerging evidence suggests a role in complement activation.[11,12]

Malignant hypertension or hypertensive emergency can manifest with TMA in up to 50% of patients. There has been a long debate regarding whether hypertension represents the cause or effect of TMA. Arguments for the former suggest that the endothelial damage is due to sheer stress. However, a recent study found underlying mutations in complement in 6 of 9 patients with TMA and abnormal C5b-9 deposition is often found in the vasculature.[13] This topic is further discussed in the following review.[14]

Scleroderma (systemic sclerosis) is a poorly-understood autoimmune disease resulting in inflammation and fibrosis in multiple organs. Severe hypertension and acute kidney injury, known as scleroderma renal crisis (SRC), manifests in 10-15% of patients.[15] Renal biopsy findings demonstrate TMA, which often shows a predilection for the arteries rather than the glomeruli. Prominent myxoid intimal change and onion-skinning is often present. Complement deposition of C5b-9, C4d and C3 deposition in the renal vasculature have been observed.[15,16]

Atypical HUS (aHUS) is caused by a variety of genetic or acquired abnormalities in the alternative pathway of complement, resulting in overstimulation of complement and TMA.[17,18] The acute presentation can be abrupt and severe in its onset of acute renal failure, MAHA, neurologic symptoms including seizures, as well as other systemic manifestations including the cardiac, pulmonary, and gastrointestinal systems. In these cases, the renal biopsy frequently shows prominent features of acute TMA. While catastrophic presentations like this occur, a subacute or chronic, smoldering disease course is more common but more difficult to suspect clinically and easy to overlook. Outcomes have traditionally been poor in aHUS with approximately 50% of patients developing end-stage kidney disease, but contemporary treatment with complement inhibition has shown significant efficacy and improved outcomes.[19] In addition, the consideration of aHUS as a discrete entity may represent a hindrance, as this is a heterogenous disease and the contributing factor that the complement system may have varies widely depending on numerous variables. Of note, aHUS can also represent the second or even third diagnosis, which increases the likelihood of it being overlooked as a possible contributing factor.

Sickle cell disease is characterized by mutations in the β-globulin gene, leading to abnormal polymerization of red blood cells and the development of multi-organ vaso-occlusive disease. Chronic TMA is often seen in the glomeruli in addition to FSGS, including the collapsing variant.[20] The other characteristic features of sickle cell nephropathy are sickling of RBCs with vasa recta and/or peritubular capillary thrombi in the medulla where oxygen content is lower, and

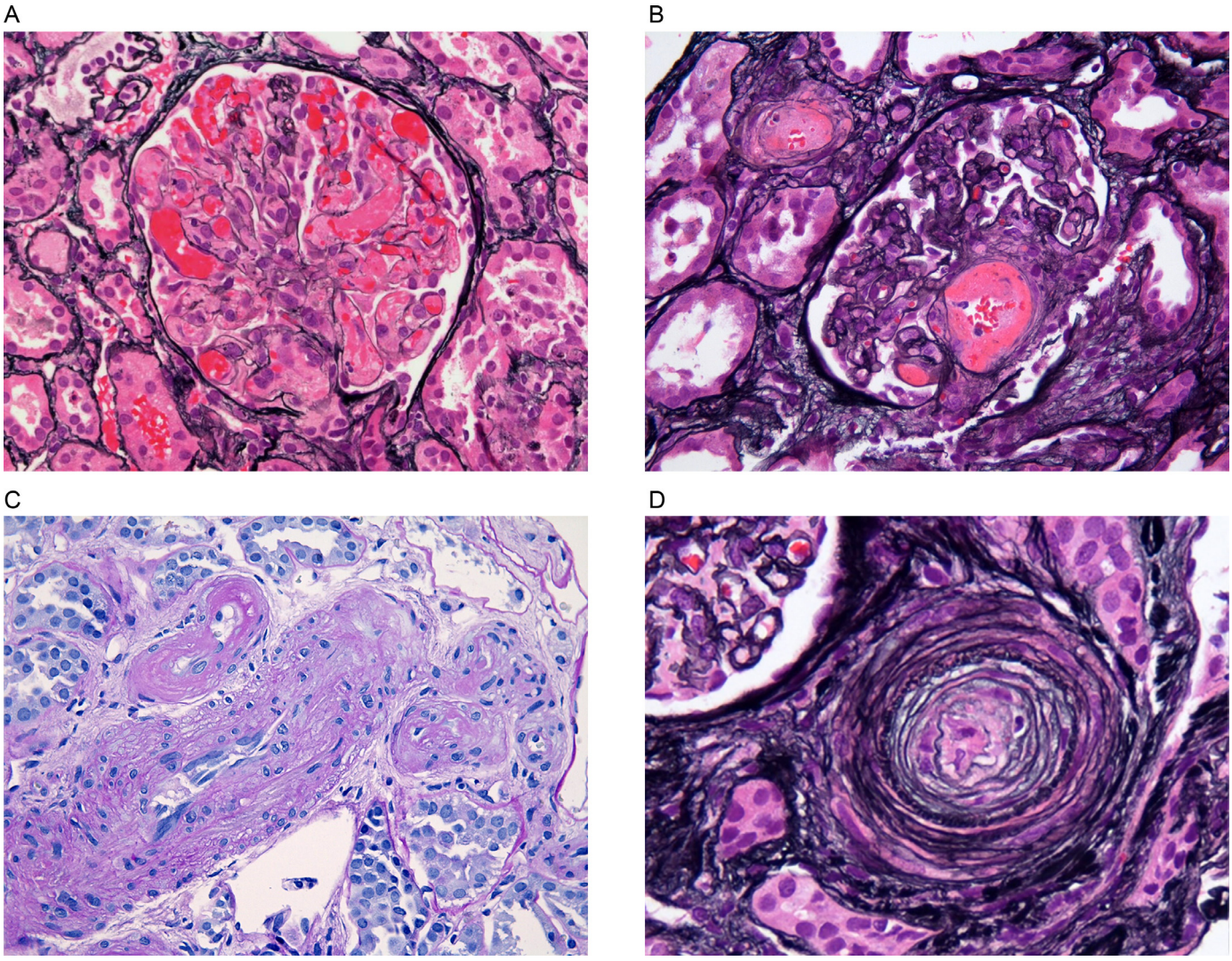

Figure 1. Light microscopic features of TMA. (A) This glomerulus demonstrates occlusion and distention of the glomerular capillaries by thrombi. Fragmented red blood cells (schistocytes) are also present (Jones methenamine silver). (B) Thrombi occlude and distend the lumens within an arteriole, the glomerular hilum, and a glomerular capillary (Jones methenamine silver). (C) A small artery demonstrates luminal narrowing due to endothelial cell swelling and intimal edema, another manifestation of acute TMA. Adjacent arterioles show severe hyalinosis, luminal narrowing, and endothelial cell swelling. Thrombi are not present (Periodic acid-Schiff). (D) This small artery demonstrates chronic features of TMA, including vessel wall thickening with intimal lamellation and luminal narrowing, imparting an "onion-skin" appearance (Jones methenamine silver).

accumulation of iron-containing hemosiderin in the renal tubular epithelial cells. We have also noted multilayering of the peritubular capillary basement membranes on electron microscopy, owing to repeated endothelial cell injury. Of note, these manifestations of sickle cell nephropathy not only occur in classic HbSS sickle cell disease, which is usually detected during newborn screening, but also in atypical hemoglobinopathies, thalessemias, and otherwise asymptomatic sickle cell trait.[21] If serum complement levels are decreased, a concurrent TMA due to aHUS can also be possible, and the rationale was discussed previously in our proposed model.

Disseminated intravascular coagulation (DIC) is characterized by thrombosis, elevated D-dimer levels, and fibrinogen consumption, which often manifests with TMA. There are numerous causes, but infections and sepsis are commonly present. We suspect that the contribution of complement in this clinical scenario has been underappreciated. However, complement inhibition may not be a first line therapeutic option if an underlying infection has not been treated and contained.

Numerous pharmacologic agents have been associated with the presence of TMA,[22] including chemotherapeutic drugs, calcineurin inhibitors, and antiplatelet drugs of the thienopyridine class (e.g. ticlopidine and clopidogrel). While some pharmacologic agents may have direct endothelial cell toxicity, generally only a small subset of patients will develop TMA. We suspect that the potential role of complement has been underappreciated in this clinical setting. It may be more likely that the patients already had a predisposition for complement dysregulation and the addition of the pharmacologic agent was the second "hit" or trigger to result in TMA.

Radiation and/or chemotherapy, often in the setting of hematopoietic stem cell transplantation, substantially increases the risk for TMA.[23] In particular, TMA that develops after stem cell transplant-associated TMA is predictive of poor clinical outcomes. A wide variety of chemotherapeutic agents have been linked to TMA, including doxorubicin, gemcitabine, cyclophosphamide, cisplatin, vincristine, mitomycin C, docetaxel, and new targeted therapies.[24] It is plausible that radiation and chemotherapy cause direct endothelial injury leading to TMA, while stem cell transplant results in a hyper-active immunologic state that results in complement activation and development of TMA, presumably in patients with underlying complement abnormalities. Complement inhibition may be a viable therapeutic option in this

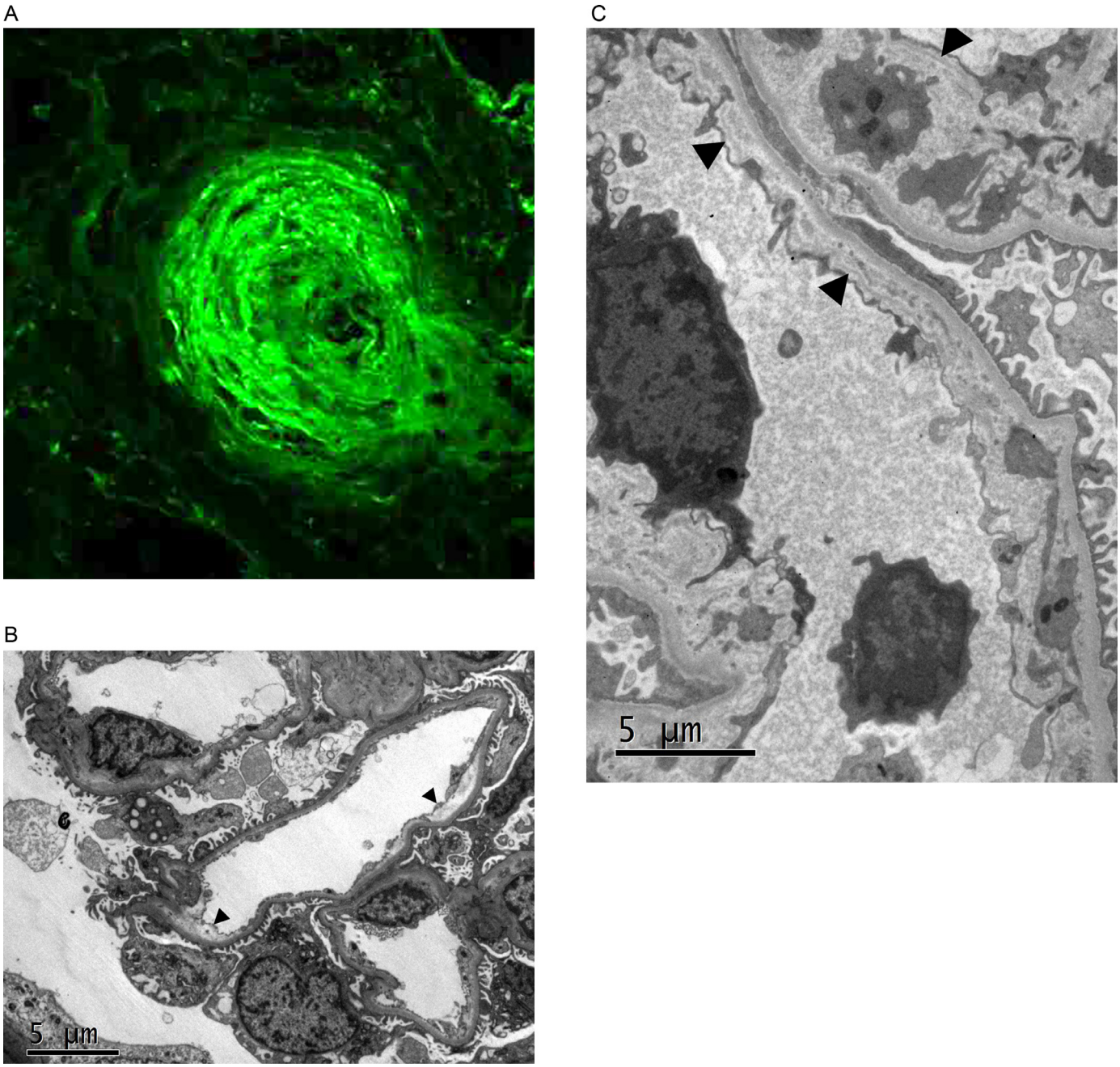

Figure 2. Immunofluorescence and ultrastructural features of TMA. (A) Immunofluorescence microscopy demonstrates strong staining for fibrinogen in this small artery, which is occluded by a thrombus. Other immunoglobulin and complement components (not shown) can also be present in injured vessels, but the staining intensity is typically much lower. (B) Endothelial cell detachment (arrowheads) from the glomerular basement membrane (GBM) is an early feature of TMA. The electron lucent material between the detached endothelial cell and GBM is the same consistency as the luminal content of the glomerular capillary (scale bar = 5 microns). (C) Duplication of the GBM (arrowheads) is a chronic feature of TMA, as the detached endothelial cell continues to secrete matrix that creates a new layer of basement membrane. There are cells and parts of cells, which can be present between the duplicated GBMs (scale bar = 5 microns).

clinical context.[25]

In kidney transplantation, TMA in the allograft is typically attributed to antibody-mediated rejection (AMR) or calcineurin inhibitor (CNI) toxicity. Active features of AMR include the presence of donor specific antibodies, peritubular capillaritis or glomerulitis, and peritubular capillary C4d deposition. CNIs utilized for post-transplant immunosuppression can cause arteriolar hyalinosis that can culminate in luminal occlusion. However, we suspect that the diagnosis of recurrent aHUS is rarely entertained. Whenever TMA is identified in the setting of transplantation, we believe that recurrent aHUS should always be given serious consideration, especially in the absence of AMR or CNI toxicity.[26,27] This is particularly true in patients whose original kidney disease was unknown, and even in some with an original diagnosis of focal segmental glomerulosclerosis (especially the collapsing variant).[28] Many of these patients were never biopsied, or biopsied when the kidney was already end stage and perhaps lacking conspicuous features of TMA. Therefore, the finding of TMA in allografts may represent recurrence of aHUS, which will result in accelerated graft loss, and impact future allografts. In heart or simultaneous heart-kidney transplantation, development of renal TMA should similarly raise concerns that aHUS may have been the original cause of cardiomyopathy and/or renal failure.

In a variety of glomerular diseases, including IgA nephropathy,[29] pauci-immune glomerulonephritis, lupus nephritis,[30] and membranous nephropathy, TMA has been well described. Renal vein thrombosis is common manifestation in the setting of nephrotic-range proteinuria, so the presence of thrombi in a kidney biopsy should raise this consideration. However, immune complexes, especially those that consist of IgG1 or IgG3, can fix complement. Therefore, it is not surprising that complement inhibition is gaining traction as a therapeutic option for a variety of glomerulonephritides. C3 glomerulonephritis is also characterized by abnormalities of the alternative pathway of complement and approximately 5% of biopsies will demonstrate histopathologic features of TMA.[31]

Pathologic Features of TMA

Endothelial cell injury induces a spectrum of pathologic features in the kidney, which we recognize as TMA. In the acute or active phase of TMA, thrombi are the most common lesion in the glomerular capillaries (Fig. 1A), arteries, and arterioles (Fig. 1B). These thrombi typically distend the vascular lumen and appear heterogenous with entrapped red and white blood cells and are best identified by hematoxylin and eosin (H&E), Masson trichrome, or Jones methenamine silver stain. The presence of thrombi can be confirmed by highlighting platelet fragments using CD61 immunohistochemistry. The thrombi (when present) also stain strongly for fibrinogen by immunofluorescence microscopy (Fig. 2A). This can mimic fibrinoid necrosis of a vessel with vasculitis or a glomerular capillary in necrotizing glomerulonephritis, but rupture of the vessel or glomerular basement membrane is not present. Schistocytes may be present within the lumen or intercalated within the vessel wall. Small or large arteries may manifest with myxoid or mucoid change of the intima (Fig. 1C), which often correlates with severe hypertension. When endothelial cell swelling occurs in the glomeruli, it can impart a “bloodless” appearance. Electron microscopy demonstrates endothelial cell swelling and detachment from the glomerular basement membrane with the presence of subendothelial electron lucent material (Fig 2B). Intraluminal fibrin tactoids may occasionally be identified. Glomeruli can frequently demonstrate ischemic changes and even the different variants of focal segmental glomerulosclerosis, including the collapsing variant.[28] In a few rare instances, we have observed only collapsing glomerulopathy in the absence of any thrombi, but the clinical presentation and other lab data were consistent with MAHA and TMA.

In its chronic phase, the repeat bouts of endothelial cell injury can manifest with duplication of the glomerular basement membrane (Fig. 2C) and multilayering of the peritubular capillary basement membranes, which are made by the injured and detached endothelial cells. Immunofluorescence microscopy is negative, but non-specific trapping of immunoglobulins between duplicated glomerular basement membranes may present a diagnostic pitfall. Thrombi are often absent in chronic forms of TMA, so some prefer the term microangiopathy with acute and/or chronic features (as applicable). Electron dense deposits are not typically identified. In the arteries, this leads to characteristic concentric “onion-skin” thickening of the vessel wall with luminal narrowing (Fig. 1D). In arterioles, we suspect that this chronic injury may be a significant contributor of subendothelial hyalinosis.

Based on our proposed injury model above, we believe that the degree of interstitial fibrosis and tubular atrophy (IF/TA) at the time of pathologic evaluation for TMA can provide an important clue regarding the underlying mechanism. If the extent of IF/TA is severe and advanced, this supports the notion that a genetic mutation involving the complement system is present. If there is minimal or mild IF/TA, especially as the age of the patient increases, the presence of autoantibodies targeting the complement regulatory proteins may be more likely and would argue against the presence of pathogenic mutations involving the complement system. The degree of IF/TA may also provide guidance regarding whether therapy in the form of complement inhibition is warranted. The likelihood of therapeutic response would diminish as the degree of IF/TA worsens, but additional studies should be conducted to confirm this speculation.

Summary

A central role for the contribution of complement is increasingly recognized in TMA. Our proposed paradigm and injury model admittedly represent an extreme view of the potential spectrum of injury due to complement, but we believe this perspective can begin to clarify the confusion that often accompanies TMA and its many complex clinical scenarios. While this review focused on renal TMA, the presence and significance of thrombi in other organs is likely overlooked and underappreciated. Our approach to TMA and many of the associated principles should be relevant to other organ systems. Increased awareness of the potential contribution of the complement system is needed to improve our diagnosis and provide additional treatment options for TMA and to advance our knowledge regarding this complex topic.

Disclosures

Alex Gallan has nothing to disclose. Anthony Chang is a consultant and on the speaker bureau for Alexion Pharmaceuticals.

Acknowledgements

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Ricklin D, Reis ES, Lambris JD. Complement in disease: a defence system turning offensive. *Nat Rev Nephrol.* 2016;12(7):383–401. https://doi.org/10.1038/nrneph.2016.70 [published Online First: Epub Date]|.
2. Noris M, Caprioli J, Bresin E, et al. Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. *Clin J Am Soc Nephrol.* 2010;5(10):1844–1859. https://doi.org/10.2215/cjn.02210310 [published Online First: Epub Date]|.
3. Sadler JE. Pathophysiology of thrombotic thrombocytopenic purpura. *Blood.* 2017;130(10):1181–1188. https://doi.org/10.1182/blood-2017-04-636431 [published Online First: Epub Date]|.
4. Orth D, Khan AB, Naim A, et al. Shiga toxin activates complement and binds factor H: evidence for an active role of complement in hemolytic uremic syndrome. *J Immunol.* 2009;182(10):6394–6400. https://doi.org/10.4049/jimmunol.0900151 [published Online First: Epub Date]|.
5. Ozaki M, Kang Y, Tan YS, et al. Human mannose-binding lectin inhibitor prevents Shiga toxin-induced renal injury. *Kidney Int.* 2016;90(4):774–782. https://doi.org/10.1016/j.kint.2016.05.011 [published Online First: Epub Date]|.
6. Gropp K, Weber N, Reuter M, et al. beta(2)-glycoprotein I, the major target in antiphospholipid syndrome, is a special human complement regulator. *Blood.* 2011;118(10):2774–2783. https://doi.org/10.1182/blood-2011-02-339564 [published Online First: Epub Date]|.
7. Girardi G, Berman J, Redecha P, et al. Complement C5a receptors and neutrophils mediate fetal injury in the antiphospholipid syndrome. *J Clin Invest.* 2003;112(11):1644–1654. https://doi.org/10.1172/jci18817 [published Online First: Epub Date]|.
8. Stillman IE, Karumanchi SA. The glomerular injury of preeclampsia. *J Am Soc Nephrol.* 2007;18(8):2281–2284. https://doi.org/10.1681/asn.2007020255 [published Online First: Epub Date]|.
9. Eremina V, Jefferson JA, Kowalewska J, et al. VEGF inhibition and renal thrombotic microangiopathy. *N Engl J Med.* 2008;358(11):1129–1136. https://doi.org/10.1056/NEJMoa0707330 [published Online First: Epub Date]|.
10. Keir LS, Firth R, Aponik L, et al. VEGF regulates local inhibitory complement proteins in the eye and kidney. *J Clin Invest.* 2017;127(1):199–214. https://doi.org/10.1172/jci86418 [published Online First: Epub Date]|.
11. Vaught AJ, Gavriilaki E, Hueppchen N, et al. Direct evidence of complement activation in HELLP syndrome: a link to atypical hemolytic uremic syndrome. *Exp Hematol.* 2016;44(5):390–398. https://doi.org/10.1016/j.exphem.2016.01.005 [published Online First: Epub Date]|.
12. Fakhouri F, Roumenina L, Provot F, et al. Pregnancy-associated hemolytic uremic

syndrome revisited in the era of complement gene mutations. *J Am Soc Nephrol.* 2010;21(5):859–867. https://doi.org/10.1681/asn.2009070706 [published Online First: Epub Date]|.
13. Timmermans S, Abdul-Hamid MA, Vanderlocht J, Damoiseaux J, Reutelingsperger CP, van Paassen P. Patients with hypertension-associated thrombotic microangiopathy may present with complement abnormalities. *Kidney Int.* 2017;91(6):1420–1425. https://doi.org/10.1016/j.kint.2016.12.009 [published Online First: Epub Date]|.
14. Zuckerman JE and Chang A. Complement and renal thrombotic microangiopathy associated with hypertension and scleroderma. Adv Chronic Kidney Dis. (In press).
15. Batal I, Domsic RT, Shafer A, et al. Renal biopsy findings predicting outcome in scleroderma renal crisis. *Hum Pathol.* 2009;40(3):332–340. https://doi.org/10.1016/j.humpath.2008.08.001 [published Online First: Epub Date]|.
16. Okroj M, Johansson M, Saxne T, Blom AM, Hesselstrand R. Analysis of complement biomarkers in systemic sclerosis indicates a distinct pattern in scleroderma renal crisis. *Arthritis Res Ther.* 2016;18(1):267. https://doi.org/10.1186/s13075-016-1168-x [published Online First: Epub Date]|.
17. Kavanagh D, Goodship TH, Richards A. Atypical hemolytic uremic syndrome. *Semin Nephrol.* 2013;33(6):508–530. https://doi.org/10.1016/j.semnephrol.2013.08.003 [published Online First: Epub Date]|.
18. Brocklebank V, Wood KM, Kavanagh D. Thrombotic Microangiopathy and the Kidney. *Clin J Am Soc Nephrol.* 2018;13(2):300–317. https://doi.org/10.2215/cjn.00620117 [published Online First: Epub Date]|.
19. Patriquin CJ, Kuo KHM. Eculizumab and beyond: the past, present, and future of complement therapeutics. *Transfus Med Rev.* 2019. https://doi.org/10.1016/j.tmrv.2019.09.004 [published Online First: Epub Date]|.
20. Nasr SH, Markowitz GS, Sentman RL, D'Agati VD. Sickle cell disease, nephrotic syndrome, and renal failure. *Kidney Int.* 2006;69(7):1276–1280. https://doi.org/10.1038/sj.ki.5000234 [published Online First: Epub Date]|.
21. Kim L, Garfinkel MR, Chang A, Kadambi PV, Meehan SM. Intragraft vascular occlusive sickle crisis with early renal allograft loss in occult sickle cell trait. *Hum Pathol.* 2011;42(7):1027–1033. https://doi.org/10.1016/j.humpath.2010.09.013 [published Online First: Epub Date]|.
22. Kreuter J, Winters JL. Drug-associated thrombotic microangiopathies. *Semin Thromb Hemost.* 2012;38(8):839–844. https://doi.org/10.1055/s-0032-1328886 [published Online First: Epub Date]|.
23. Chang A, Hingorani S, Kowalewska J, et al. Spectrum of renal pathology in hematopoietic cell transplantation: a series of 20 patients and review of the literature. *Clin J Am Soc Nephrol.* 2007;2(5):1014–1023. https://doi.org/10.2215/cjn.01700407 [published Online First: Epub Date]|.
24. Blake-Haskins JA, Lechleider RJ, Kreitman RJ. Thrombotic microangiopathy with targeted cancer agents. *Clin Cancer Res.* 2011;17(18):5858–5866. https://doi.org/10.1158/1078-0432.Ccr-11-0804 [published Online First: Epub Date]|.
25. Jan AS, Hosing C, Aung F, Yeh J. Approaching treatment of transplant-associated thrombotic Microangiopathy from two directions with Eculizumab and transitioning from Tacrolimus to Sirolimus. *Transfusion.* 2019;59(11):3519–3524. https://doi.org/10.1111/trf.15534 [published Online First: Epub Date]|.
26. Nadasdy T. Thrombotic microangiopathy in renal allografts: the diagnostic challenge. *Curr Opin Organ Transplant.* 2014;19(3):283–292. https://doi.org/10.1097/mot.0000000000000074 [published Online First: Epub Date]|.
27. Gavriilaki E, Sakellari I, Anagnostopoulos A, Brodsky RA. Transplant-associated thrombotic microangiopathy: opening Pandora's box. *Bone Marrow Transplant.* 2017;52(10):1355–1360. https://doi.org/10.1038/bmt.2017.39 [published Online First: Epub Date]|.
28. Buob D, Decambron M, Gnemmi V, et al. Collapsing glomerulopathy is common in the setting of thrombotic microangiopathy of the native kidney. *Kidney Int.* 2016;90(6):1321–1331. https://doi.org/10.1016/j.kint.2016.07.021 [published Online First: Epub Date]|.
29. Chang A, Kowalewska J, Smith KD, Nicosia RF, Alpers CE. A clinicopathologic study of thrombotic microangiopathy in the setting of IgA nephropathy. *Clin Nephrol.* 2006;66(6):397–404. https://doi.org/10.5414/cnp66397 [published Online First: Epub Date]|.
30. Song D, Wu LH, Wang FM, et al. The spectrum of renal thrombotic microangiopathy in lupus nephritis. *Arthritis Res Ther.* 2013;15(1):R12. https://doi.org/10.1186/ar4142 [published Online First: Epub Date]|.
31. Ravindran A, Fervenza FC, Smith RJH, De Vriese AS, Sethi S. C3 glomerulopathy: ten years' experience at mayo clinic. *Mayo Clin Proc.* 2018;93(8):991–1008. https://doi.org/10.1016/j.mayocp.2018.05.019 [published Online First: Epub Date]|.