The Journal of Rheumatology 2023;50:730–40
doi:10.3899/jrheum.220752
First Release February 1 2023

The Journal of Rheumatology

Review

The Role of Complement in Autoimmune Disease-Associated Thrombotic Microangiopathy and the Potential for Therapeutics

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ABSTRACT. The complement system is a tightly regulated, cascading protein network representing a key component linking the innate and humoral immune systems. However, if misdirected or dysregulated, it can be similarly damaging to host-tissue. The role of complement dysregulation on vascular endothelial cells has been well established in atypical hemolytic uremic syndrome (aHUS), a thrombotic microangiopathy (TMA) characterized by microangiopathic hemolytic anemia, thrombocytopenia, and target organ injury. Yet, a great deal of complexity exists around the role of complement in TMA associated with other diseases. A further complicating factor is the cross-talk between complement, neutrophils, and coagulation pathways in the pathophysiology of TMA. Advancements in the understanding of the etiopathogenesis of aHUS paved the way for the successful development of anticomplement therapies (complement C5 inhibitors), which have revolutionized the treatment of aHUS. Therefore, a clearer understanding of the role of the complement system in TMA associated with other conditions will help to identify patients who would benefit from these therapies. This review aims to provide an assessment of the nature and extent of complement involvement in TMA associated with autoimmune diseases such as systemic lupus erythematosus, antiphospholipid syndrome, and scleroderma renal crisis. Defining the role of complement in TMA in these conditions will help to guide timely diagnosis and management.

Key Indexing Terms: antiphospholipid syndrome, complement, neutrophil activation, systemic lupus erythematosus, systemic sclerosis, thrombotic microangiopathy

Thrombotic microangiopathy (TMA) is a well-known clinicopathologic entity characterized by microangiopathic hemolytic anemia, thrombocytopenia, and organ injury.[1-3] The pathological features of TMA are endothelial cell damage and microthrombi formation in small blood vessels, leading to a partial or complete obstruction of the vessel lumina.[1-3] Acute kidney injury is a common prominent feature of the disease, owing to the susceptibility of the glomerular circulation to endothelial damage.[2,4,5] Extrarenal manifestations (occurring in up to 38% of patients) may include strokes, seizures, and/or involvement of the cardiovascular, pulmonary, or gastrointestinal systems[2,4-6] Early recognition is important because TMA is associated with significant mortality and morbidity, including end-stage kidney disease, although prompt initiation of supportive and specific management can transform disease outcomes.[2,7] There are several underlying pathophysiological mechanisms associated with TMA.[7-9] A TMA is called "primary" when a genetic or acquired defect in a complement protein is identified (as in atypical hemolytic uremic syndrome [aHUS]) or "secondary" when occurring in the context of another disease process or factor such as infection, autoimmune disease, malignancy, or drugs.[10] This distinction is not absolute because genetic defects in complement proteins have been identified in secondary TMA.[10] Differentiating between a primary complement-mediated process and one triggered by secondary factors is critical since the former is nonresponsive to supportive therapy and has a high risk of recurrence.[10] This review aims to provide an assessment of the nature and extent of complement involvement in the underlying pathophysiology of TMA associated with autoimmune diseases that will help to stratify patients for targeted therapy.

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Accepted for publication February 14, 2022.

Complement pathways

The complement system is a tightly regulated, cascading protein network that performs multiple roles in homeostasis and disease prevention and is a key component of both the innate and the humoral immune systems.[8,11-14] Numerous stimuli can drive the activation of the complement system, including apoptotic debris, pathogens, and antibody–antigen complexes, in addition to ischemia–reperfusion injuries associated with organ transplantation.[4,13] Complement plays a crucial role in host defense against foreign bodies by promoting phagocyte-mediated clearance of cell debris through activation of an inflammatory response, opsonization of pathogens, and lysis of susceptible bacteria and cells.[11,12,15]

Activation of the complement system occurs through the classical (CP), lectin (LP), or alternative (AP) pathways. The CP is initiated by the binding of antibody to antigen, the LP is initiated by the binding of lectin to an oligosaccharide, and the AP is initiated by the binding of one of its components to a pathogen, without need for prior contact/exposure.[16] The AP is thus constitutively active and turns over continuously, generating small amounts of autoactivated C3 (the so-called C3 tick-over that represents a thioester-hydrolyzed form of C3, termed C3[H_2O]).[16] Central to all 3 pathways is the formation of C3 convertase, which cleaves complement component C3 to C3a and C3b. If C3b deposits on a microbe or foreign debris, the system can be rapidly amplified by engaging 2 proteases, factors B and D, along with a stabilizing protein properdin to create the powerful AP C3 convertase. Contained within the AP is an efficient feedback or amplification loop for generating large amounts of C3b for opsonization of pathogens, leading them to be recognized, engulfed, and destroyed by phagocytes. The addition of C3b to C3 convertase in all 3 pathways generates C5 convertase, which leads to the activation of the terminal complement pathway. In the terminal pathway, 2 types of C5 convertase (C4bC2C3b and C3bBbC3b) can cleave the C5 protein into anaphylatoxin C5a and the larger C5b component, resulting in the formation of the membrane attack complex (MAC, C5b-9; Figure 1).[11] This complex penetrates membrane bilayers to form pores that disrupt the osmotic barrier, leading to swelling and cell lysis.[11,12]

The misdirection or dysregulation of the complement system can lead to indiscriminate host inflammation and tissue injury.[4,15,17,18] Thus, nearly half of the components of the complement system are responsible for the stringent regulation of the arsenal.[19] Disruption of this delicate balance, for example, by inherited or acquired deficiencies in its activating or control proteins, is increasingly implicated in disease pathology.[10] Insights gained from genetic studies over the past decade have established that modulation of complement inhibitory activity predisposes an individual to TMA.[10] Although understanding of the complement system is increasing, a lack of clarity remains around the etiology, triggers, and scope of complement activation, as well as the relationship of these factors in the various types of TMA. Determining the underlying cause can be a challenge but is important for directed therapy.

Mechanisms of complement activation in TMA

Complement dysregulation. Complement dysregulation stems from intrinsic genetic factors, due to abnormalities in genes encoding complement components and regulatory proteins, or due to acquired defects in the complement system (such as autoantibodies). A classic example of a "primary" TMA resulting from complement dysregulation is aHUS. In this disease, a loss-of-function mutation in a regulator (such as factor H, factor I, or membrane cofactor protein) or a gain-of-function mutation in a complement component (such as C3 or factor B) predispose patients to endothelial damage (Figure 2). Sometimes, a genetic defect, namely a homozygous deletion in factor H-related proteins 1 and 3, is associated with the development of acquired factors, such as factor H autoantibodies.[2] These autoantibodies can occur in patients with aHUS and may inhibit the regulatory function of factor H. The presence of factor H autoantibodies varies between different ethnic populations and has been reported in 11% of US patients, 9% of European patients, and 56% of Indian patients with aHUS.[20-22]

However, TMA can also occur in response to or following certain conditions or "triggers," including systemic infections, pregnancy, solid organ or hematopoietic stem cell transplantation, certain metabolic disorders, or cancer, as well as in autoimmune diseases such as systemic lupus erythematosus (SLE).[2,4,23] TMA occurring in the setting of any of the above conditions is often thought to be a result of "short-lived" complement overactivation secondary to the associated condition, and is therefore called a "secondary" TMA. However, genetic abnormalities of the complement system have been reported in approximately 10% to 60% of patients with a secondary TMA.[2,10] In such situations, the complement system may be initially activated in response to the associated condition (such as infection or SLE) but may evolve into dysfunctional control owing to an underlying, and potentially unrecognized, genetic abnormality. Such patients in whom a complement mutation is identified in the presence of concomitant autoimmune disease can be considered to essentially have aHUS or primary TMA, with the autoimmune condition functioning as a trigger.

TMA occurring because of an underlying genetic etiology progress despite removal of the precipitating cause, with poor long-term outcomes in the absence of timely treatment.[24,25] Therefore, making the distinction between a primary TMA resulting from underlying genetic complement dysregulation leading to overactivation and a secondary TMA involving transient complement overactivation is critical, but can be challenging for clinicians.[2] Patients in whom the clinical course of an assumed secondary TMA is unusually aggressive and unresponsive to conventional treatment should be considered for treatment with anticomplement therapy. Additionally, genetic testing and/or complement biomarker assessments should be pursued to establish complement involvement in the disease in greater detail. Several real-world cases have been published that illustrate how sequential and systematic analyses can help to determine disease etiology, pathogenic mechanisms, prognosis, and duration of therapy based on individual risk assessment.[26,27]

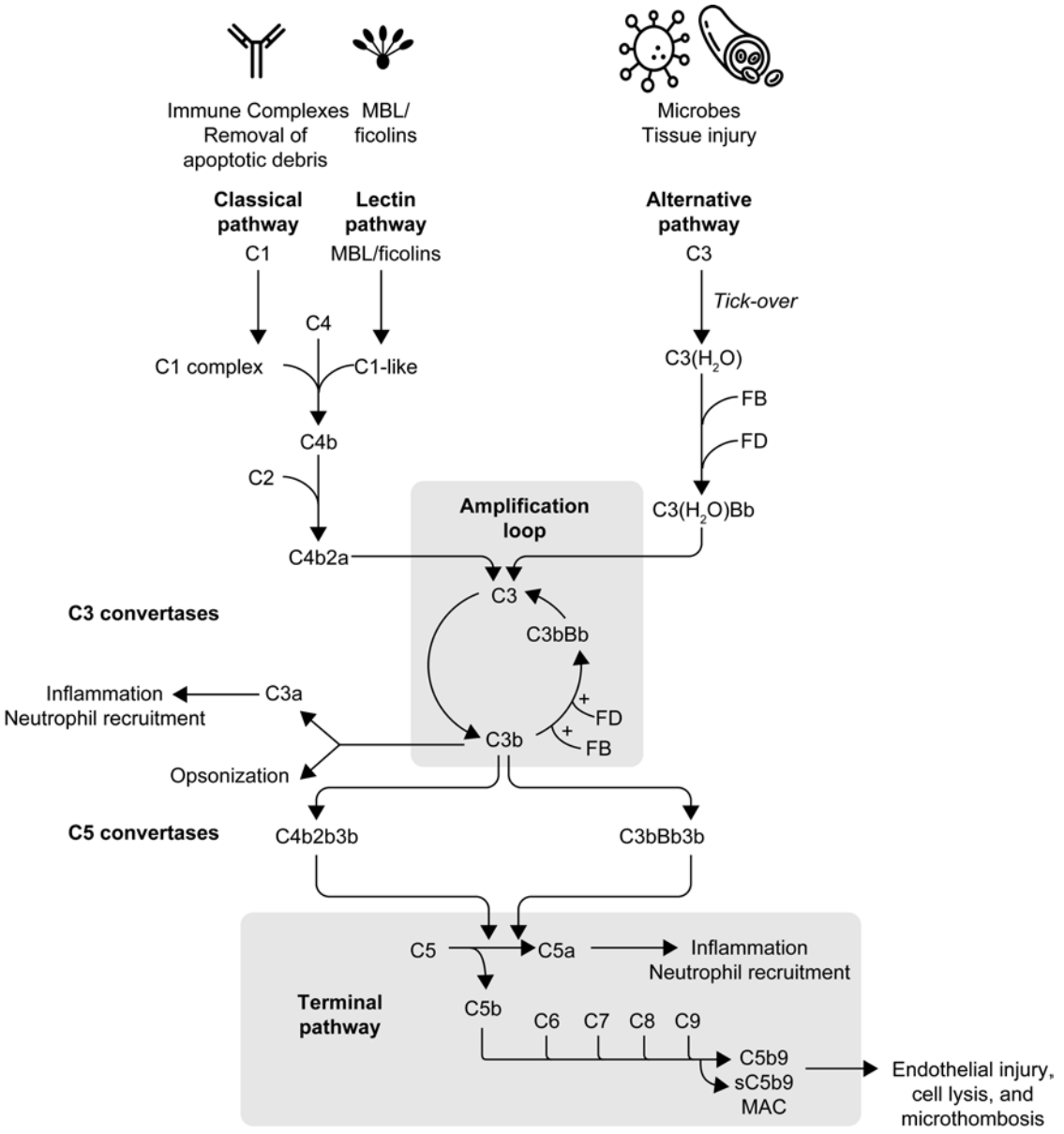

Figure 1. Activation of the complement system. This figure was adapted from Lemaire et al.[8] C1 complex consists of C1q, C1r, and C1s. FB: factor B; FD: factor D; MAC: membrane attack complex; MBL: mannose-binding lectin.

Neutrophil activation. The proinflammatory complement cleavage products C3a and C5a activate a range of immune cells, including neutrophils, mast cells, monocytes/macrophages, basophils, eosinophils, and T and B cells (Figure 3).[28] This proinflammatory response is very potent, and leads to increased expression of inflammatory cytokines such as tumor necrosis factor-α and interleukin (IL)-1β and IL-6.[28] Activated neutrophils create large chromatin structures known as neutrophil extracellular traps (NETs), formed through a type of programmed cell death known as NETosis, which is further stimulated by a number of inflammatory cytokines.[29,30] NETs incorporate complement components such as C3 cleavage products, properdin, and complement factor B, which can form a C3 convertase leading to exuberant AP complement activation (Figure 3).[28,31,32] C3a and C5a anaphylatoxins released during neutrophil-driven complement activation can act to further amplify proinflammatory neutrophil responses, such as additional NET formation, enhanced CD11b expression, and oxidative burst, again illustrating the multifaceted interaction between neutrophils and the complement system.[31-35] NETs also play a role in non-AP mediated complement activation and the generation of the MAC.[32]

Importantly, NETs have been shown to be directly cytotoxic and act as a scaffold for thrombus formation, activating coagulation and eventually forming part of the resulting thrombi.[32-34] NETs have been implicated in the development of thrombophilic conditions such as antiphospholipid syndrome (APS), suggesting that NET formation may exert secondary effects

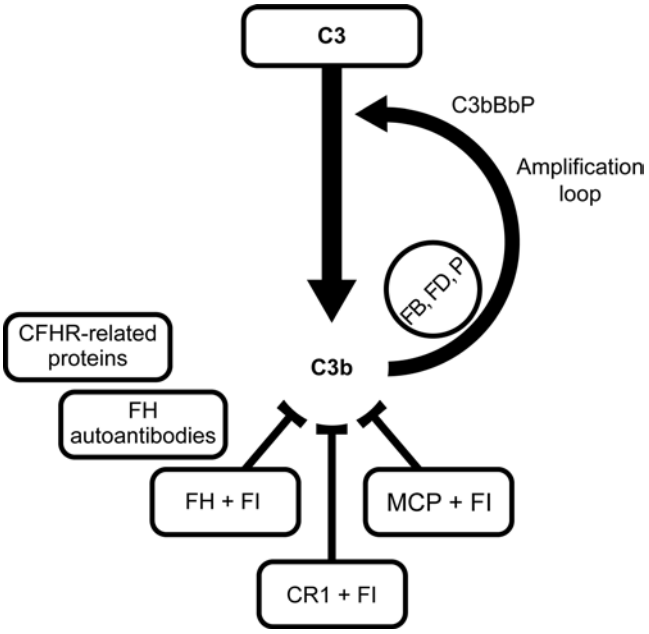

Figure 2. Etiopathogenesis of aHUS. This figure was published in the paper from Java.[104] The relationship between aHUS and CR1 is hypothetical owing to CR1 being a well-known regulator of CP and AP.[103] aHUS: atypical hemolytic uremic syndrome; AP: alternative pathway; CFHR: complement factor H-related; CP: classical pathway; CR1: complement receptor 1; FB: factor B; FD: factor D; FH: factor H; FI: factor I; MCP: membrane cofactor protein; P: properdin.

such as cell injury and death, in addition to triggering complement activation.[32,33] Further, autoantibodies targeting NETs, identified in conditions such as APS and coronavirus disease 2019 (COVID-19), may potentially impair NET clearance and enhance ongoing complement activation.[33,34] Anti-NET antibodies may act to shield NETs from degradation by DNase, and may themselves be associated with venous thrombosis in patients with APS.[33] NETs may also be stabilized by complement components such as C1q, further preventing DNase-mediated clearance.[35] This complex interplay between the complement components, inflammatory mediators, and coagulation proteins results in endothelial injury and a hypercoagulable state leading to TMA.[29,33]

Autoimmune disease-associated TMA

Systemic lupus erythematosus. SLE is a multisystem complex disorder distinguished by the presence of autoantibodies to multiple nuclear antigens, including DNA and ribonucleoproteins, leading to complement activation, inflammation, and tissue injury.[36] Virtually any organ may be affected, leading to diverse clinical presentations.[36,37] TMA in SLE has been reported in < 1% to 9% of affected patients, with multiple mechanisms leading to the pathogenesis and autoimmunity observed in the disease.[38-40]

Deficiencies or low gene copy number of the early CP components are the strongest genetic risk factors for SLE,[36,41]

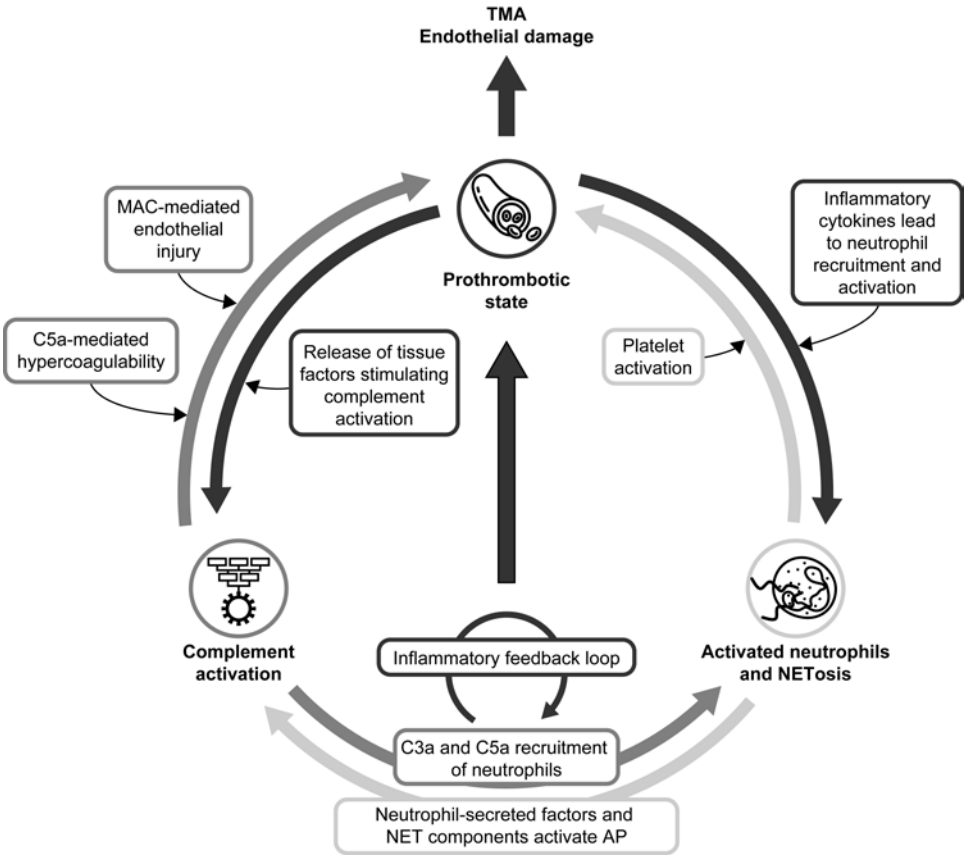

Figure 3. Mechanism of the interplay between complement activation and immune hyperinflammatory reactions. Sourced from Java et al.[28] Complement activation generates the anaphylatoxins C3a and C5a and leads to neutrophil recruitment. Activated neutrophils generate NET lattices in a type of cell death known as NETosis, which contain components that activate the alternative pathway and generate an inflammatory feedback loop. Additionally, the MAC causes endothelial damage, with injured tissue releasing inflammatory cytokines that further stimulate NETosis. Injury to the endothelial tissues results in the creation of prothrombotic factors, compounded by C5a-mediated release of proteins that promote a hypercoagulable state. AP: alternative pathway; MAC: membrane attack complex; NET: neutrophil extracellular traps; TMA: thrombotic microangiopathy.

because severe forms of the disease are observed in patients with defects in C1q, C2, or C4.[41] Notably, homozygous mutations of C1q, C1r, or C1s leading to a complete absence of the protein demonstrate the highest genetic penetrance for SLE, with 88% of patients displaying SLE or lupus-like disease.[42] C4 deficiency due to low copy numbers of the gene has also been identified as a risk factor for the development of SLE.[43]

These factors are also potential mechanisms for the generation of autoantibodies that bind to host proteins or deposit within tissues as a component of immune complexes,[36] and further trigger activation of the complement system.[36,44] Autoantibodies against C1, C5, and factor H have been reported in SLE.[41,45] Factor H autoantibodies can also arise in patients with SLE, in association with genetic deletions in factor H-related protein 1 (similar to aHUS).[45]

Further, increased levels of complement split products, C3dg, iC3b, and C4d, have been observed in SLE and may function as biomarkers.[46] The ratios of C3dg to C3 and iC3b to C3 also appear to correlate with active disease.[46] B-cell-bound C4d and erythrocyte-bound C4d may further indicate active SLE, whereas affected patients display low levels of C3 and/or C4 complement proteins.[46] Complement-related gene variations, including mutations in factors H, I, and B, CD46, and factor H-related proteins 1 to 3, have been reported in patients with lupus nephritis (LN)-associated TMA.[47] This suggests that the presence of an underlying genetic predisposition may lead to TMA development in the setting of ongoing complement activation in SLE.[45,47]

It may seem paradoxical that both a deficiency of the complement system and its excessive activation are both associated with the pathophysiology of SLE.[36,41] However, this can be reconciled when considering that the excess apoptotic debris following a CP component deficiency serves as a source of nuclear autoantigens for autoantibody formation and binding.[48-50] The resultant immune complexes cannot be cleared, leading to proinflammatory cytokine production and interferon-α (IFN-α) secretion by plasmacytoid dendritic cells.[51,52] IFN-α is a hallmark cytokine in SLE, the level of which correlates with disease activity.[51,52]

NETs have also been under scrutiny because of their role in disease pathogenesis. IFN-α stimulates NET production, with NETs in turn triggering further IFN-α secretion by plasmacytoid dendritic cells.[53] Notably, neutrophils in patients with SLE undergo accelerated NETosis, possibly owing to elevated IFN-α.[54,55] Some patients with SLE have a DNase deficiency that leads to impaired degradation of NETs, with the ensuing defect in clearance correlating with the development of LN and associated TMA.[37,56]

The presence of TMA on renal biopsy portends a poor prognosis when associated with LN.[57] It has been reported to be an independent risk factor for poor long-term renal outcomes, with 80% of patients with LN and TMA developing end-stage kidney disease within 5 years of diagnosis.[58] Therefore, although long-term immunosuppressant therapy remains the mainstay of SLE management, complement inhibition represents a promising therapy for a subset of patients with TMA.

Antiphospholipid syndrome. APS is characterized by the development of antiphospholipid antibodies that bind to endothelial cells and trigger thrombosis. The condition is associated with substantial morbidity and may involve virtually all organ systems,[36,59,60] resulting in stroke, skin ulcerations, nephropathy, seizures, and cognitive decline.[61] Primary APS is diagnosed when other associated conditions are absent, occurring in over 50% of patients.[60] APS may also occur in the context of autoimmune diseases such as SLE.[60] Among patients with SLE, TMA was found in 67% of those with concurrent APS, but only in 32% of those without APS.[62] Approximately 1% of patients with APS may develop catastrophic APS (CAPS), which is fatal in more than half of cases, manifesting as small vessel thrombosis in 3 or more organs within the span of a week.[63,64]

Mounting evidence suggests that the complement system plays a critical role in the pathogenesis of thrombosis in APS, with activation of the complement cascade due to antiphospholipid antibodies causing cellular injury and promoting coagulation via multiple mechanisms.[59] In murine models of thrombotic APS, C9 deposition has been reported on the vascular endothelium, indicating the presence of the MAC.[59] Further, antiphospholipid antibody-induced thrombosis was markedly attenuated in C6-deficient rats or animals treated with a C5 inhibitor.[65] Investigators have also reported lower plasma C3 and C4 levels and elevated levels of complement activation fragments, particularly Bb and C3a, in patients with APS compared with control individuals.[66,67] Increased serum MAC has been detected in patients with CAPS, with clinical improvement after treatment with eculizumab correlating with a reduction in serum MAC and normalization of serum C3 and C4.[68,69] Complement activation is more commonly observed near to the occurrence of a thrombotic event, with 68.5% of samples from patients with APS collected within 1 year of thrombosis showing evidence of complement activation.[59] Although these findings and the benefits of complement inhibition support a role for complement in APS,[70,71] the exact mechanisms of complement activation in the disease and its correlation with vascular events remains incompletely understood.

NETs have been implicated in the pathogenesis of APS, and may aggravate thrombosis through activation of the coagulation cascade and inhibition of anticoagulant factors.[61] Antiphospholipid antibodies themselves promote NET formation, and compared with control individuals, patients with APS have been reported to harbor increased levels of low-density granulocytes, which are prone to exaggerated NETosis.[61] Moreover, NETs formed in APS appear resistant to degradation.[33,61] Anti-NET antibodies (particularly IgM), which may act by stabilizing NETs, are also markedly increased in patients with APS.[33]

Although specific biomarkers of APS disease activity are lacking, numerous potential candidates exist for examination, such as NET load, complement activation products, and, in some patients, anti-NET antibodies. When considering disease therapy, the current standard of care for APS is limited to anticoagulation and immunosuppression.[61] The variability of treatment effectiveness in APS and reports of recurrent thrombosis

despite standard treatment suggest that a subset of patients might benefit from treatment beyond anticoagulation.[61]

Scleroderma renal crisis. Scleroderma renal crisis (SRC) represents a life-threatening complication of systemic sclerosis (SSc) and is characterized by the sudden onset of hypertension, TMA, and acute kidney injury.[72] The underlying pathological mechanisms of SRC include vascular injury, autoantibody production, and fibroblast dysfunction, although the complement system has also been implicated as a factor in development of the disease.[73] Whole exome sequencing in patients with SRC identified an association with complement genetic variants, similar to those observed in other forms of TMA, such as aHUS, or TMA associated with other conditions (eg, 35-66% of patients with malignant hypertension-associated TMA have been shown to have mutations in complement genes that produce C3, factor I, CD46, or factor H proteins).[74,75] Renal deposition of C1q, C4d, and C3b has been observed in SRC, suggesting involvement of the CP, which may be driven by autoantibodies.[72,76,77] In addition, reduced levels of C3 and factor B have also been noted, suggesting AP activation.[72,77] These data suggest that complement activation plays a role in SRC and the associated TMA.[74,77,78]

Similar to APS and SLE, emerging evidence suggests that microparticles released from activated platelets stimulate neutrophils to induce NETosis, leading to abundant NET burden in patients with SSc.[79] Neutrophils have previously been implicated in extrarenal manifestations of SSc such as pulmonary arterial hypertension and digital ulcers.[79,80] Currently, angiotensin-converting enzyme inhibition represents a highly effective therapy for SRC[81]; however, complement inhibitors may represent a potential treatment option for refractory cases of TMA in SRC, owing to the fact that they more directly address the primary cause of SRC.[72,81,82] Early identification and aggressive treatment is critical to avoid loss of kidney function and other complications.[77]

Diagnosis and treatment of autoimmune disease-associated TMA

Complement dysregulation and activation play a role in the development of TMA in autoimmune diseases, although defining the extent of complement involvement may be challenging. For some patients, highly complex, multifactorial, and incompletely understood interactions occur across complement activation, coagulation pathways, and neutrophil processes,

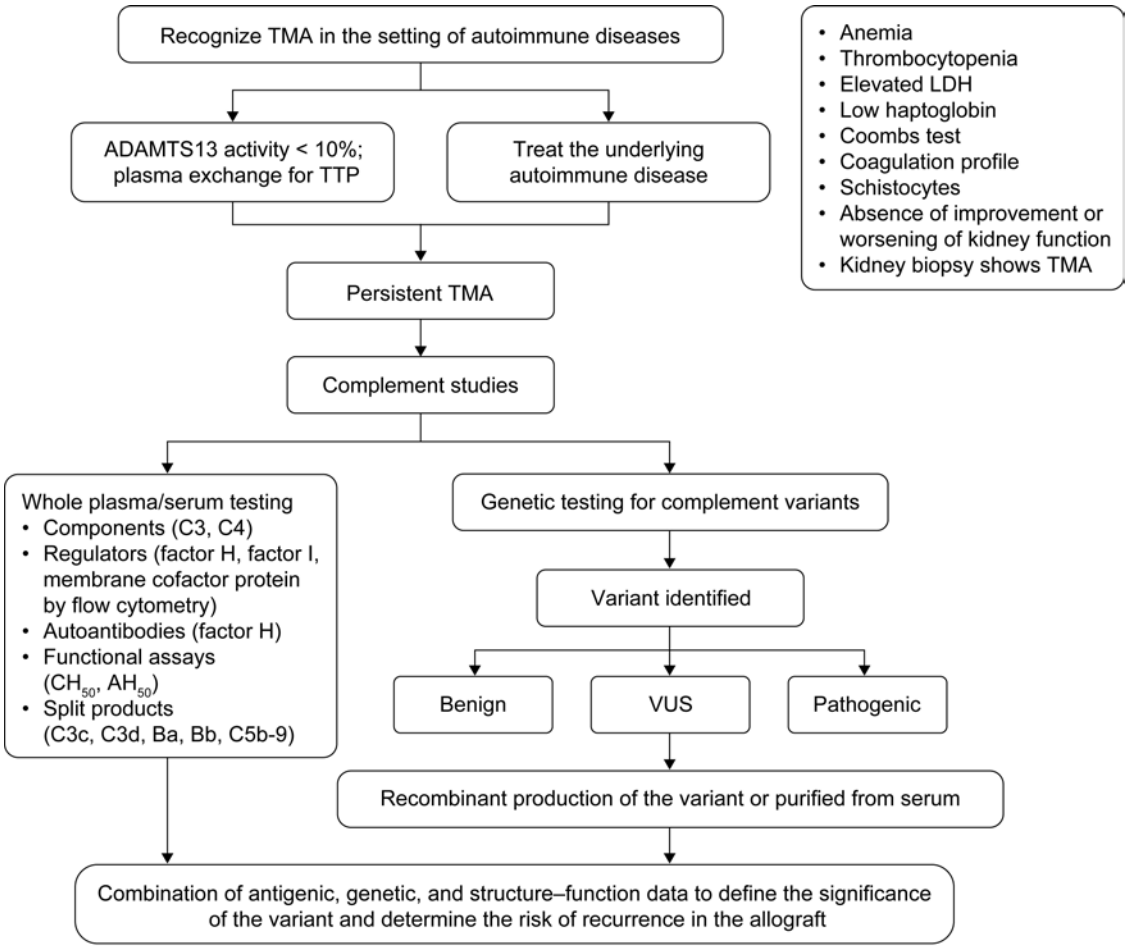

Figure 4. Diagnostic work-up. ADAMTS13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; LDH: lactate dehydrogenase; TMA: thrombotic microangiopathy; TTP: thrombotic thrombocytopenic purpura; VUS: variant of uncertain significance.

adding to the challenge. However, a thorough systematic work-up will help to delineate the underlying disease etiology and determine treatment.

Diagnostic work-up. Prompt identification of TMA is vital to minimize organ damage and improve patient outcomes (Figure 4). To begin with, thrombotic thrombocytopenia purpura should be ruled out through the assessment of ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity. Laboratory tests (complete blood count, comprehensive metabolic profile, reticulocyte count, lactate dehydrogenase, haptoglobin, direct Coombs test, and coagulation profile) and/or biopsy (when feasible) should be performed to evaluate organ damage and confirm the presence of TMA.[83] Functional hemolytic assays, such as CH50 and AH50, as well as testing for antigenic levels of complement proteins should be used to evaluate the presence of a quantitative defect.[10,84] Further, evaluation for underlying genetic variants in complement proteins should be conducted. The clinically validated aHUS next-generation sequencing-based panel consists of 15 genes (*ADAMTS13, C3, CD46, CFB, CFH, CFHR1, CFHR2, CFHR3, CFHR4, CFHR5, CFI, DGKE, THBD, MMACHC,* and *PLG*). Variants are reported according to Human Genome Variation Society nomenclature and classified based on the guidelines established by the joint consensus of the American College of Medical Genetics and Genomics, and the Association for Molecular Pathology. If identified, interpretation of variants may require additional functional assays, biomarker testing, or, in select cases, recombinant protein production followed by structure–function assessment of the variants.[83] As the technologies allowing examination of molecular phenotypes at the tissue-level improve, future understanding of the effect of complement activation in specific organs will provide valuable insights into both homeostatic and pathogenic mechanisms. Combined genetic, antigenic, functional, and structural evaluations will help to define the role and extent of complement involvement in TMA in autoimmune diseases and will further facilitate the stratification of patients for targeted therapy.[10,85]

Treatment. In TMA associated with autoimmune diseases, it is a reasonable first step to treat the underlying condition or precipitating factor.[86] Patients who do not respond to conventional therapy or who have unusually aggressive TMA should be considered for treatment with a complement inhibitor. There are 2 C5 inhibitors that are currently available: eculizumab and ravulizumab.[31] Both eculizumab and ravulizumab have received approval from the US Food and Drug Administration and European Medicines Agency for use in patients with aHUS.[87-90] Both therapies offer meaningful patient benefit and improved disease outcomes in aHUS as demonstrated in clinical trials, with extensive real-world evidence also illustrating the efficacy and safety profiles of these therapies in this condition (Figure 5).[91-99] Several other drugs primarily targeting the AP are also in development. These novel complement inhibitors include crovalimab (anti-C5), pegcetacoplan (anti-C3), iptacopan (anti-factor B), danicopan (anti-factor D), and avacopan (anticomplement C5a receptor 1).[2,100] Blockade of the LP through inhibition of mannose-binding lectin-associated serine protease 2 is also being investigated (eg, narsoplimab)[15] and inhibitors of the initial stages of the CP and LP are also available or undergoing clinical trials.[100] The role of C5 fragments in amplifying neutrophil responses further suggests that C5 inhibitors may be a potential benefit in both complement- and neutrophil-mediated inflammatory diseases. Prospective, randomized controlled trials are required to investigate the utility of anticomplement therapies in TMA associated with autoimmune diseases in more detail, to provide insights on which patients to treat and for how long in this complex and challenging area.[101,102] Further improvements in the understanding and awareness of the mechanisms underlying complement involvement in different diseases will be of great benefit to clinicians, both in identifying affected patients and in selecting appropriate therapies.

ACKNOWLEDGMENT

The authors fulfilled the International Committee of Medical Journal Editors authorship criteria, and all drafts (including the final draft) were critically reviewed, extensively edited, and approved by the authors. Article preparation was sponsored by Alexion, AstraZeneca Rare Disease. Editorial support was provided by Alexandra Kisbey-Ascott, of Oxford PharmaGenesis, Oxford, UK, and was funded by Alexion, AstraZeneca Rare Disease. Radha Narayan, PhD, of Alexion, AstraZeneca Rare Disease, reviewed early drafts of this publication for scientific/medical accuracy.

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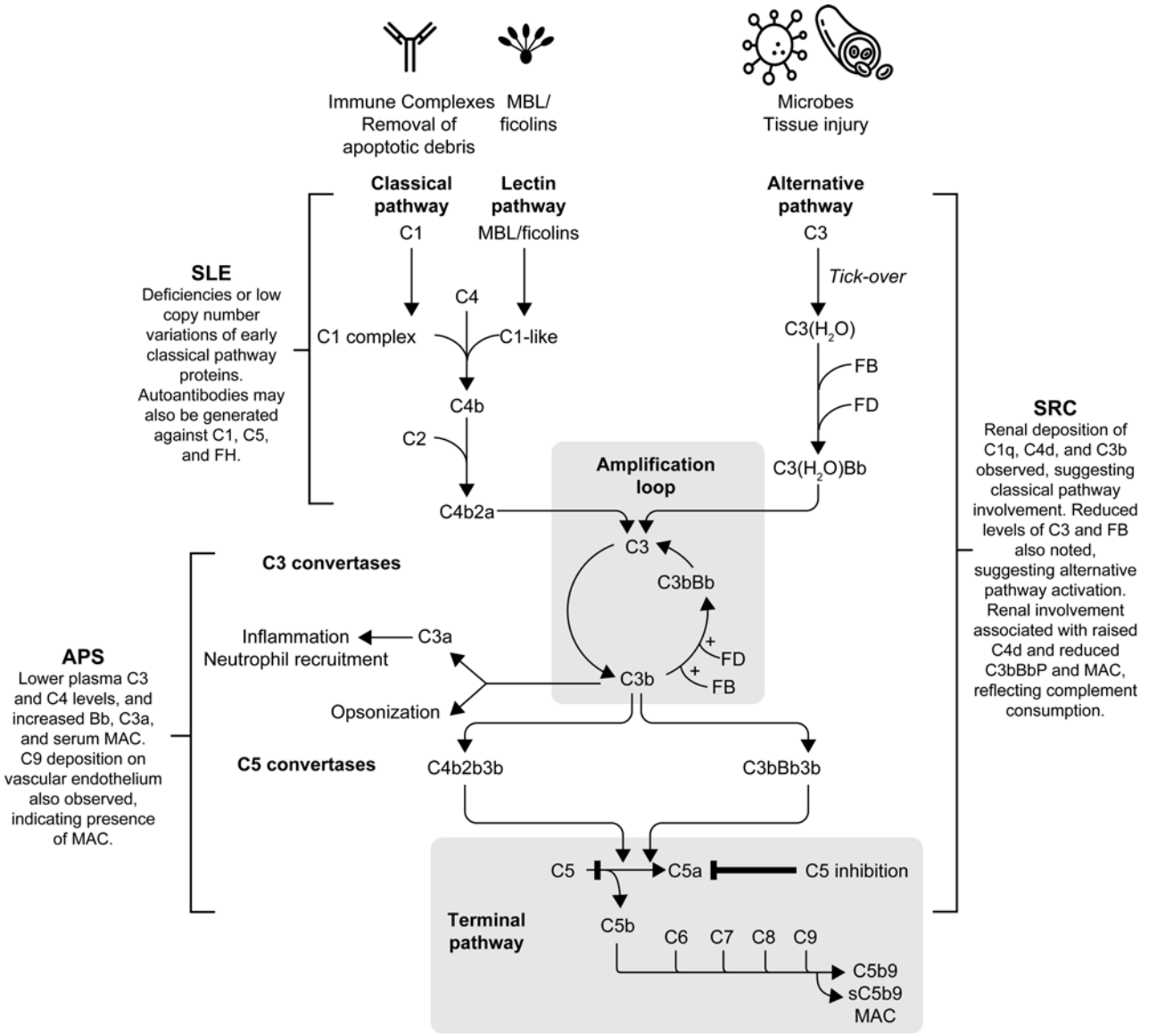

Figure 5. Effects of autoimmune diseases SLE, APS, and SRC, and action of the C5 inhibitors eculizumab and ravulizumab on the complement system. This adapted figure was originally published in Lemaire, Mathieu, et al. Inherited kidney complement diseases. *Clinical Journal of the American Society of Nephrology* 16.6 (2021): 942–956.[8] Blacks bar indicate the point of action of C5 inhibitors, which specifically inhibit C5 cleavage to C5a and C5b, preventing C5a-mediated inflammation and the formation of the MAC. APS: antiphospholipid syndrome; FB: factor B; FD: factor D; FH: factor H; MAC: membrane attack complex; MBL: mannose-binding lectins; P: properdin; SLE: systemic lupus erythematosus; SRC: scleroderma renal crisis.

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