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A review of thrombotic microangiopathies in multiple myeloma

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ABSTRACT

Patients with multiple myeloma (MM) are susceptible to developing thrombotic microangiopathies (TMAs), an etiologically diverse group of syndromes which include atypical hemolytic uremic syndrome (aHUS) and thrombotic thrombocytopenic purpura (TTP). The TMAs are characterized by thrombocytopenia and microangiopathic hemolytic anemia (MAHA), and are associated with a high mortality risk and irreversible end-organ damage when treatment is delayed. In MM patients, TMAs may be triggered by specific chemotherapies, bone marrow transplantation (BMT), and progression of underlying disease. Because many characteristics of TMAs overlap with sequelae of MM and its treatments, diagnosis requires a high index of suspicion. Furthermore, our understanding of optimal treatments for these entities is rapidly evolving and clinical practice guidelines do not yet exist. Historically, consideration of a diagnosis of TMA has prompted initiation of therapeutic plasma exchange. In this review, we present an overview of the MM-related TMAs, an approach to workup and diagnosis, and argue for initial empiric MM-related TMA treatment with eculizumab rather than plasma exchange.

1. Introduction

MM, the second most common hematologic malignancy, accounts for 2.1% of all cancer deaths. In the United States, there are roughly 131,000 people living with MM and an estimated 32,110 new cases will be diagnosed in 2019. The median age at diagnosis is 69. In the past decade, novel agents have become frontline treatments, markedly improving disease prognosis [1]. The five-year survival rate has steadily increased, currently 52.2% [2]. Despite the rapid evolution of treatment paradigms, MM remains incurable. As patients with MM progress through their disease, they can receive a multitude of subsequent treatment regimens, each of which is associated with unique risks and toxicities.

Patients with MM frequently encounter risk-inducing scenarios for the development of TMAs, including proteasome inhibitor (PI) treatment, bone marrow transplantation (BMT), and progression of underlying disease. TMAs incur a high mortality risk [3–7]. Survivors often suffer long-term morbidity such as chronic kidney, cardiovascular, pulmonary, gastrointestinal, and central nervous system disease [8]. These effects undoubtedly impact quality of life.

The TMAs constitute a broad spectrum of disease, ranging in severity from asymptomatic to life-threatening, generally thought to be unified by features of endothelial damage, dysfunctional platelet aggregation and widespread microvascular thrombosis, and MAHA. In the context of MM, early recognition of TMAs is challenging, as signs and symptoms of TMAs overlap with sequelae of MM. At initial MM diagnosis, anemia is present in 73% of patients, thrombocytopenia in 5%, and serum creatinine >2 mg/dL in 19% [9]. Worsening of these features can be easily overlooked as features of progressive disease. Diagnosing a TMA in a patient with MM requires a high degree of clinical suspicion.

The current understanding of MM-related TMAs is incomplete and muddled. Historically, their diagnostic paradigms have fluctuated and evolved over time, and disease categorizations have been inconsistent amongst case reports. Widely adopted diagnostic criteria do not yet exist for these diseases. Given the challenge of diagnosis and overlap with MM features, there has been difficulty in formulating treatment guidelines for the MM population. Despite the uncertainty in this field, promising new treatments are emerging as the underlying disease mechanisms are better understood. These advances can be applied to the MM patient population and allow us to propose a new treatment algorithm for suspected TMAs in MM that includes the empiric use of eculizumab, a terminal complement pathway inhibitor.

2. Pathophysiology

MM-related TMAs are driven by a loss of homeostasis in either of the following two critical systems: von Willebrand factor (VWF)-mediated

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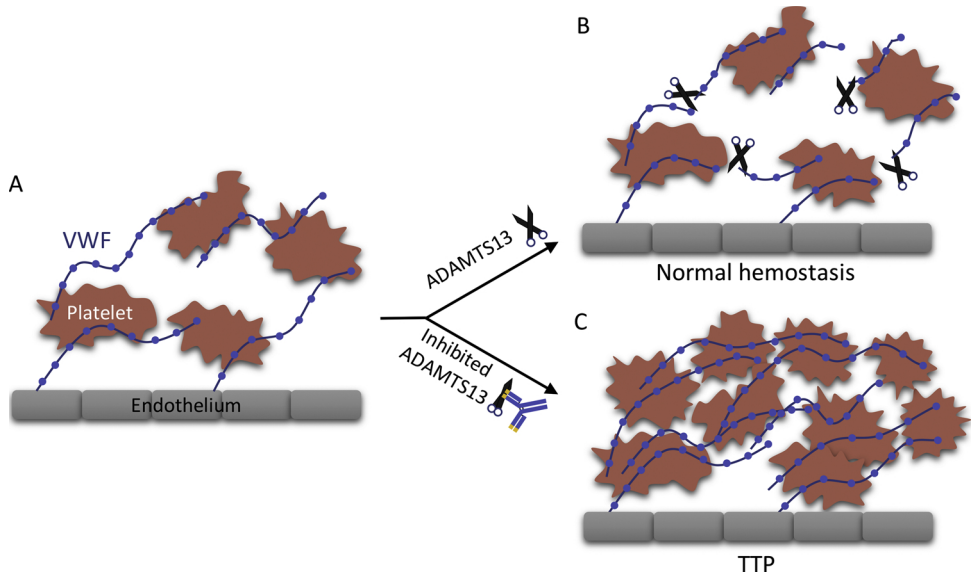

Fig. 1. Generation of microthrombi via VWF dysfunction. A) VWF multimers bind platelets on an endothelial surface. B) Normal hemostasis relies on ADAMTS13 mediated cleavage of VWF multimers. C) Loss of ADAMTS13 activity enables uncontrolled thrombus formation via VWF-platelet aggregation, resulting in TTP.

platelet adhesion and the alternative complement pathway. VWF dysfunction mediates thrombotic thrombocytopenic purpura (TTP) [10], and uncontrolled complement activation mediates atypical hemolytic uremic syndrome (aHUS) [11] and transplant associated (TA)-TMA [12].

2.1. VWF dysfunction

VWF mediates hemostasis through platelet aggregation and initial clot formation. VWF is initially secreted by endothelial cells as ultra-large multimers, which bind platelets on endothelial cell surfaces and at sites of vascular injury. VWF-mediated platelet adhesion is enhanced by factors which stretch the VWF multimer. These include 1) rapid flow rate, 2) greater number of multimers, 3) tethered VWF, and 4) platelet-bound VWF. Thrombus growth is limited by ADAMTS13, which cleaves VWF multimers in the blood. In acquired TTP, inhibition of ADAMTS13 enables unregulated VWF-dependent platelet adhesion (Fig. 1), resulting in sequestration of platelets and thrombocytopenia [13]. Inhibition has been shown to be mediated by IgG antibodies [14], which can be removed with therapeutic plasma exchange. The VWF-platelet aggregates form partially occlusive microvascular thrombi capable of fragmenting red blood cells. Lesions affect all tissues, but occur predominantly in organs that have vasculature with high pressure and high shear forces, such as the heart, pancreas, kidney, and brain [10].

2.2. Uncontrolled complement activation

Complement is a component of the innate immune system, which promotes inflammation and microbial killing [15]. Complement acts in the plasma via 1) opsonization of pathogens for phagocytosis by neutrophils and macrophages, and 2) direct lysis of target cells through the formation of membrane pores called membrane attack complexes (MACs). Complement is activated by classical, lectin, and alternative pathways. Whereas the classical and lectin pathways recognize targets via antibody-mediated immunity or recognition of pathogen-associated molecular patterns, respectively, the alternative pathway spontaneously and continuously attacks all cell surfaces. All host cells exposed to the plasma utilize defense mechanisms to subvert attack, which often depend on complement system downregulation. Non-host molecules, such as microbial fragments virus envelopes, are preferentially targeted. Alternative complement pathway homeostasis can be disrupted by the imbalance of various activating and regulating factors (Fig. 2). When activation overwhelms regulation, host cells become susceptible to complement attack. The most vulnerable cells are those continuously exposed to plasma: red blood cells, platelets, leukocytes, and endothelial cells [12]. Uncontrolled complement activation mediates aHUS and TA-TMA. The terminal complement inhibitor, eculizumab, mitigates these deleterious effects by blocking MAC generation and preventing direct lysis [16].

3. MM-related TMA subcategories

Within the broad categories of VWF dysfunction and uncontrolled complement activation, distinct TMA subcategories exist: carfilzomib-induced aHUS, bortezomib-induced aHUS, bortezomib-induced TTP, TA-TMA, MM-induced aHUS, and MM-induced TTP (Table 1). These TMA subcategories represent distinct disease entities, each with a specific prognosis and treatment of choice.

3.1. Proteasome inhibitors

The proteasome inhibitor (PI) medication class is known to trigger TMA development [17,18]. Carfilzomib and bortezomib, PIs commonly used in MM treatment, are associated with development of aHUS [19–21] and non-idiopathic (i.e., secondary) acquired TTP [22–25], respectively. PI-induced TMAs occur in the absence of MM progression. Non-idiopathic TTP has a mortality rate of 59% [6] and aHUS has a mortality rate of up to 26% [7].

Carfilzomib, an irreversible PI approved for relapsed or refractory MM, carries the highest risk of PI-associated TMA development [18]. Carfilzomib-induced aHUS occurs in patients who have tolerated at least one treatment cycle. The precise mechanism of carfilzomib-induced aHUS is not known, but may involve proteasome-mediated down-regulation of alternative pathway inhibitory genes [20].

Bortezomib, a reversible proteasome inhibitor, is also associated with TMA development. These TMAs tend to occur within one month of starting bortezomib [18,26]. Although case reports have generally been categorized as non-idiopathic TTP, it is important to note that only mild to moderate reductions in ADAMTS13 activity (12–36%) have been reported [18,22,24,26], an inhibitor of ADAMTS13 has not yet been observed [23,24], and bortezomib has successfully been utilized as salvage therapy to treat TTP, suggesting a non-VWF mediated pathway [27–29]. Thus, the existing case reports do not fit well into traditional TTP definitions that require an ADAMTS13 activity level $<10\%$ or the

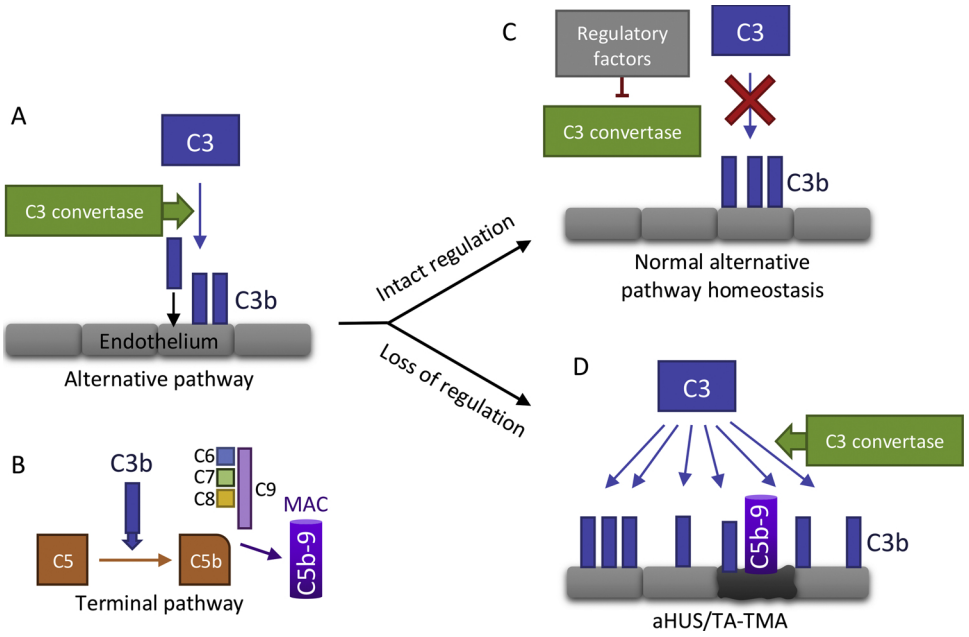

Fig. 2. Endothelial damage via alternative complement pathway dysregulation. A) Alternative pathway function: C3 convertase catalyzes conversion of C3 to C3b, which binds to endothelial and other plasma-exposed cells. B) Terminal pathway: C3b catalyzes conversion of C5 to C5b. C5b joins C6-C9 to create C5b-9, the membrane attack complex (MAC). Eculizumab binds C5, preventing generation of C5b. C) Regulatory factors (e.g., complement factor H and its related proteins) maintain alternative pathway homeostasis. D) Complement-mediated TMAs (e.g., aHUS and TA-TMA) occur when uncontrolled alternative pathway activation results in damage to host cells (e.g., red blood cells, platelets, leukocytes, and endothelial cells).

Table 1
TMA subcategories. MM-related TMA triggers and associated subcategories are arranged according to their respective pathophysiology.

Pathophysiology	Trigger	TMA subcategory
Complement overactivation	Carfilzomib	Carfilzomib-induced aHUS
	Bortezomib	Bortezomib-induced aHUS
	BMT	TA-TMA
	MM progression	MM-induced aHUS
VWF dysfunction	Bortezomib	Bortezomib-induced TTP
	MM progression	MM-induced TTP

presence of an inhibitor, suggesting these cases may have been erroneously classified as TTP instead of an alternate TMA.

3.2. Transplant associated

The incidence of TA-TMA has not been defined in a reliable fashion and reports are highly variable. Discrepancies amongst studies may be related to institutional diagnostic criteria, patient characteristics, and transplant types. Although the precise incidence is not clear, one meta-analysis of five cohorts supports an incidence of 13.6% (range 1.6–76%) for allograft and 6.8% (0–27%) for autograft HSCT [30]. In patients with MM, development of TA-TMA has been specifically associated with combined autografting-allografting [31,32]. Although histologically identical and mechanistically similar to aHUS, it is currently considered a distinct clinical entity [12]. Disease development generally occurs within 6 months of transplant [33]. In one study, the median time of onset was 44 days, with a range of 13–319 days [34]. Reports of mortality are variable, but generally in the 70–80% range [3–5].

The major risk factors influencing TA-TMA development include grade 3–4 acute GVHD, no total body irradiation, unrelated donor or haplo, and female sex [33]. Patients with proteinuria (≥30 mg/dL) and elevated markers of complement activation (elevated sC5b-9) have the highest risk of mortality [35]. Many additional risk factors (Table 2) and prognostic indicators (Table 3) have been identified.

3.3. MM-induced TMAs

Case reports highlight the development of MM-induced TTP [36–40] and aHUS [41,42], which are unrelated to treatment. In rare instances, TMA development has been described as the initial presenting feature of MM [39,42]. One retrospective study investigated the association between TMAs and monoclonal gammopathy by evaluating for the presence of monoclonal gammopathy in a cohort of patients with TMA ($N = 146$). They found a high prevalence of patients with M-protein (13.7%, $N = 20$). Furthermore, among patients age ≥50, the prevalence of monoclonal gammopathy was ~5-fold greater than expected for this population (21% vs. 4.2%) [43].

Treatment of the underlying plasma cell disorder can improve the TMA [41,44]. Although no pathophysiologic mechanism has been identified, there is an association amongst plasma cell disorders and TMA development that has been postulated to be mediated by endothelial damage effected by monoclonal immunoglobulin [43] or hyperviscosity [39]. Unfortunately, given the paucity of reported cases, the efficacy of standard TMA treatments is not currently known.

4. Clinical features

Recognizing the development of a TMA in a MM patient is challenging, as many features of TMAs overlap with those of MM. Although onset of symptoms varies from insidious to explosive, the diagnosis of TMA is often considered when a patient's worsening renal function appears out of proportion to MM-related kidney disease. Additionally, extrarenal manifestations often go overlooked as components of the TMA presentation. In this section, features of TMAs are explored in the context of MM and its treatments.

4.1. Renal manifestations

TA-TMA and aHUS often present with severe acute kidney injury, whereas TTP is notable for its relatively mild renal involvement. Renal manifestations may include elevated creatinine, proteinuria, oliguria, and hypertension. Although the presence of new proteinuria is a standard screening tool for some TMAs [8], since most patients with secretory MM have proteinuria at baseline, albuminuria is a more specific feature of TMAs amongst MM patients. Similarly, hypertension carries a lack of specificity. Therefore, it is new or worsening hypertension, unrelated to medication side-effects (e.g., corticosteroids, calcineurin inhibitors, carfilzomib), which represents a concerning feature in the MM population.

Table 2
Risk factors for development of TA-TMA.

Category	Risk factor
BMT features	Nonmyeloablative conditioning, higher patient age, prior HCT, unrelated donor, major or minor ABO mismatch, 1/6 HLA-antigen mismatch, no total body irradiation
Calcineurin inhibitors	Cyclosporine, tacrolimus
Rapamycin inhibitor	Sirolimus
Viral infections	CMV, adenovirus, parvovirus, B19, HHV-6, BK virus
Other	Female sex, chemotherapy, grade 3-4 acute GVHD

Table 3
Poor prognostic indicators in TA-TMA.

Age ≥ 18 years
TMA index (LDH/platelets ratio) ≥ 20
Hemoglobin < 8 g/dL
Platelets $< 20 \times 10^9$/L
Unrelated or haploidentical donors
Proteinuria ≥ 30 mg/dL
Elevated serum C5b-C9 levels
Schistocyte count > 5-10/HPF
TMA without sirolimus exposure
Elevated serum creatinine

4.2. Extrarenal manifestations

Beyond the hematologic dysfunction, extrarenal manifestations are widespread, involving the brain, lungs, gastrointestinal tract, and others. TTP and TA-TMA are both notable for neurologic symptoms [4,45], which may include confusion, headaches, hallucinations, and seizures. The most common neurologic complication of MM is peripheral neuropathy, which is present in up to 20% of patients at diagnosis and seen in up to 75% of patients over the course of treatment [46]. Central neurologic manifestations of MM are rare. Therefore, new central neurologic features, most specifically new onset seizures, are suggestive of an alternate cause and possible TMA in patients with MM.

Pulmonary manifestations are rare in TTP [10] and are more commonly seen in TA-TMA. These include pulmonary hypertension and hypoxia [47,48]. MM does not impact the lungs directly, with the exception of case reports which have demonstrated rare pulmonary plasmacytomas [49]. However, MM patients are at increased risk for recurrent pulmonary infections, possibly due to a reduction in functional serum globulins [50]. Additionally, specific MM treatments (e.g., lenalidomide, bortezomib, and carfilzomib) are associated with the development of pneumonitis [51–53]. Since dyspnea and hypoxia are nonspecific and may be related to pneumonitis or infection, new-onset pulmonary hypertension is the most concerning feature for TA-TMA.

Abdominal pain, intestinal bleeding, diarrhea, vomiting, or ascites are common gastrointestinal manifestations. In patients post-BMT, these symptoms may be misattributed to or occur in conjunction with GVHD [54]. Diarrhea occurs in 30% of aHUS cases [55], and has been observed as a presenting symptom of carfilzomib-induced aHUS [20]. Gastrointestinal manifestations are not particularly unique to TMAs in MM patients, but can be easily misattributed to other causes.

Other manifestations include fever, which is relatively uncommon in MM patients (0.7%) [56], and polyserositis, including pericardial effusion, pleural effusions, and/or ascites [12]. Although heart failure is a known complication of carfilzomib (7.2%), this medication has not been associated with pericardial effusion [57]. Pericardial effusion is the most unique serositis observed with TMAs in MM, and therefore the most specific.

The extrarenal TMA manifestations, although variable and nonspecific, are useful diagnostic features of MM-related TMAs. New-onset seizures, pulmonary hypertension, and pericardial effusion are particularly concerning, as these features tend to overlap least with MM sequelae and treatment side-effects.

5. General diagnostic approach

Once clinical suspicion for TMA is established, a rapid evaluation must be undertaken given the high morbidity and mortality associated with delayed treatment. The critical steps to a comprehensive workup include assessing for hemolysis, excluding alternative MAHAs, and distinguishing complement-mediated TMAs (i.e., TA-TMA and aHUS) from TTP.

5.1. Initial workup

Significant progression of MM is unlikely with the presence of stable SPEP and free light chains. Hemolysis can be initially evaluated by the presence of depleted haptoglobin, elevated LDH, and elevated indirect bilirubin. Labs consistent with hemolysis necessitate the evaluation of a peripheral blood smear. The Blood and Marrow Transplants Clinical Trials Network (CTN) has established that the presence of ≥2 schistocytes per HPF is consistent with MAHA [58], and should prompt a rapid and comprehensive workup, including consideration of TMA [59] (Table 4).

Next steps include ruling out alternative diagnoses. Most importantly, ADAMTS13 activity and inhibitor assays must be sent immediately to assess for TTP. DIC and autoimmune hemolytic anemia should be quickly ruled out by establishing the presence of normal fibrinogen, normal D-dimer, normal coagulation studies, and negative direct/indirect Coombs tests. If diarrhea is present, stool should be tested with bacterial PCR to rule out shiga-toxin producing organisms. To assess for the presence of a separate secondary TMA or infectious MAHA, rheumatologic serologies (e.g., ANA, ANCA, anti-Scl-70, anticentromere, anti-cardiolipin, lupus anticoagulant) and infectious studies (e.g., HIV, HCV, HBV, CMV, HIV, adenovirus, human herpesvirus-6, human parvovirus B19, *Aspergillus*) may be considered, however, these studied are unlikely to be helpful in the MM population.

Table 4
Initial workup in suspected MM-associated TMA.

Category	Element
General labs	Acute anemia, thrombocytopenia, acute kidney injury, hyperbilirubinemia
DIC labs	Fibrinogen, D dimer, PT/INR, aPTT
MM specific labs	Kappa/lambda free light chains, SPEP
Initial TMA labs	Schistocytes on peripheral blood smear, depleted haptoglobin, elevated LDH, negative direct/indirect Coombs test
Subsequent TMA labs	GI bacterial PCR (i.e., shiga toxin, *Campylobacter*, *Shigella*, *Salmonella*), ADAMTS13 activity and inhibitor assays, C5b-9 levels
Imaging	Transthoracic echocardiography (elevated right ventricular pressure, pericardial effusion)

TMA is a pathologic term [60], and tissue biopsy can cement the diagnosis in some cases. However, histologic diagnosis is impractical in the acute setting. Patients are at high risk for procedural complications and treatment decisions need to be made before pathology results become available. Most importantly, although specific TMA-type histologic changes may be seen in renal [17,41] and intestinal [54] biopsies, current histopathologic techniques are unable to reliably differentiate amongst TMA subtypes [61]. Management is therefore based upon clinical and laboratory features.

5.2. Distinguishing complement-mediated TMAs from TTP

Widely accepted diagnostic criteria do not yet exist for the MM-related TMAs and their classical diagnostic paradigms have traditionally relied on processes of exclusion. This poses a clinical dilemma in MM patients who are often at risk for several TMA subcategories simultaneously. Regardless, clinical context and features of disease should be used to help differentiate complement-mediated TMAs from TTP in order to guide treatment.

Although the clinical picture of aHUS is nonspecific (e.g., MAHA, thrombocytopenia, and acute renal failure) [62], features of historical TA-TMA diagnostic criteria [12] can be useful in differentiating complement-mediated TMAs from TTP. The most recently proposed TA-TMA definition [8] includes terminal complement activation (i.e., elevated sC5b-9), a feature which is not present in TTP. Acute renal failure is common in complement-mediated TMAs [7,8,63,64], yet infrequently seen in TTP [65,66]. Creatinine doubling has been suggested as a diagnostic criterion [63], and may be useful in differentiating TA-TMAs from TTP. Due to its lack of specificity, however, creatinine doubling may have greater utility as a prognostic indicator [8,64,59].

The “classic pentad” of TTP includes features of neurologic symptoms and fever [26,66,67], which are nonspecific and infrequently present in early stages of disease [68]. Although ADAMTS13 activity level is often used to confirm a diagnosis of TTP [69], moderate deficiency is nonspecific [70] and can be seen in sepsis [71], aHUS [13], post-BMT conditioning [72,73], and malignancy [6]. An undetectable or severely reduced ADAMTS13 activity level (<5-10%) is highly specific for TTP [14,74,75] and, more importantly, predictive of responsiveness to plasma exchange [6]. Furthermore, anti-ADAMTS13 antibodies, seen in >90% of cases of acquired TTP with ADAMTS13 activity <5% [75], provides further confirmation of disease.

The prolonged turnaround time needed to obtain the ADAMTS13 activity level at most institutions has led to the derivation of the PLASMIC score, a seven point clinical prediction tool validated in stratifying patients with TMA according to risk of severe ADAMTS13 deficiency. The PLASMIC score assigns one point for each of the following: Platelet count $<30 \times 10^9$/L, hemolysis variable (i.e., reticulocyte count >2.5%, or haptoglobin undetectable, or indirect bilirubin >2 mg/dL), no active cancer, no history of solid-organ or HSCT, MCV < 90 fL, INR < 1.5, and creatinine <2 mg/dL. A score of 0–4 predicts low risk (0–4%), a score of 5 predicts intermediate risk (5–24%), and a score of 6–7 predicts high risk (62–82%) of severely reduced ADAMTS13 activity (<10%) [76]. The tool has been externally validated, demonstrating good performance [77].

However, the utility of the PLASMIC score in the MM population is not well understood. Due to their underlying malignancy, 1 point is automatically deducted. Many will lose additional points for elevated baseline creatinine or history of HSCT. The majority of MM patients with a TMA are therefore likely to receive a low (0–4 points; 0–4% risk) or intermediate PLASMIC score (5 points; 5–24% risk) by virtue of their underlying MM rather than the acute process. Although most patients will be predicted to have a low risk of TTP, the specificity of this tool in the MM population is uncertain.

6. Treatment recommendations

Rapid treatment initiation improves mortality, prevents development of irreversible end-organ damage [78], and minimizes interruption of myeloma treatment. Amongst the MM-related TMA subcategories, there are two potential disease entities requiring non-complementary treatment action. Uncontrolled complement activation requires eculizumab treatment, whereas severely reduced ADAMTS13 activity necessitates plasma exchange. Unfortunately, treatment decisions must be made before these features can be fully interrogated. Therefore, clinical context drives initial management decisions.

6.1. Immediate treatment considerations

Two distinct treatment modalities exist: eculizumab and therapeutic plasma exchange. The terminal complement pathway inhibitor, eculizumab, has recently been proven effective in mitigating progression of complement-mediated TMAs [8]. Earlier initiation of eculizumab treatment is associated with superior renal outcomes [78] and prevention of irreversible organ damage [8,79]. Eculizumab is generally very well tolerated [80]. Its use, as in genetic terminal complement deficiency [81], increases the patient’s risk for meningococcal infections [82]. Vaccination against *Neisseria meningitides* is mandatory before eculizumab is administered and patients treated with eculizumab <2 weeks after immunization warrant prophylactic antibiotics (e.g., oral penicillin or macrolide) for 2 weeks [83].

Plasma exchange, the mainstay of TTP treatment, has historically been performed in a rapid, empiric manner. Its use has dramatically reduced mortality in idiopathic TTP [68,84] and delayed initiation of plasma exchange (≥6 days) has been associated with treatment failure [85–87]. Unfortunately, plasma exchange offers no clear mortality benefit in cases of non-idiopathic TTP (e.g., bortezomib or MM-induced) [4–6,36,42,73,88] or complement-mediated TMAs [3,8,30,34,45,80,84,89,90]. Furthermore, the use of plasma exchange is known to cause major complications in ˜30% of patients treated for TMAs [91]. Since plasma exchange removes circulating antibodies, including eculizumab, concurrent use is not recommended [8,12,20,83].

Eculizumab is now FDA approved and considered first-line for the treatment of aHUS [83]. It has been effectively used to treat PI-induced aHUS [20,21] as well as other forms of drug-induced TMA [92]. Amongst the battery of treatments historically used to treat TA-TMA (e.g., plasma exchange, defibrotide, rituximab), over the past five years eculizumab has emerged as the most-effective treatment available. TA-TMA case reports consistently demonstrate eculizumab’s ability to halt and reverse end-organ damage [93], whereas cohort and prospective studies demonstrate favorable hematological response and survival rates compared with plasma exchange [94,95] and highlight eculizumab’s effectiveness in patients refractory to plasma exchange [79].

Due to the lack of utility and substantial risk of harm, we recommend against the empiric use of plasma exchange for the MM-related TMAs. For patients with active PI use or post-BMT, we recommend rapid treatment with empiric eculizumab (single 900 mg dose) within 24 h of presentation, prior to the return of ADAMTS13 activity level (Fig. 3). Supportive care should be provided. The decision to continue eculizumab or initiate plasma exchange can be made once the ADAMTS13 activity level is known.

An offending PI should be immediately and permanently discontinued, as a more severe TMA may occur upon re-challenge [18]. Cyclosporine, if present, should be discontinued [34], as it may worsen nephrotoxicity [96], and potentially be replaced with mycophenolate or methylprednisolone [79]. TMA-associated hypertension, mediated by activation of the renin angiotensin system (RAS), should be aggressively managed, preferably with an angiotensin receptor blocker, or alternatively with a calcium channel blocker in the setting of renal involvement, in order to prevent complications [8].

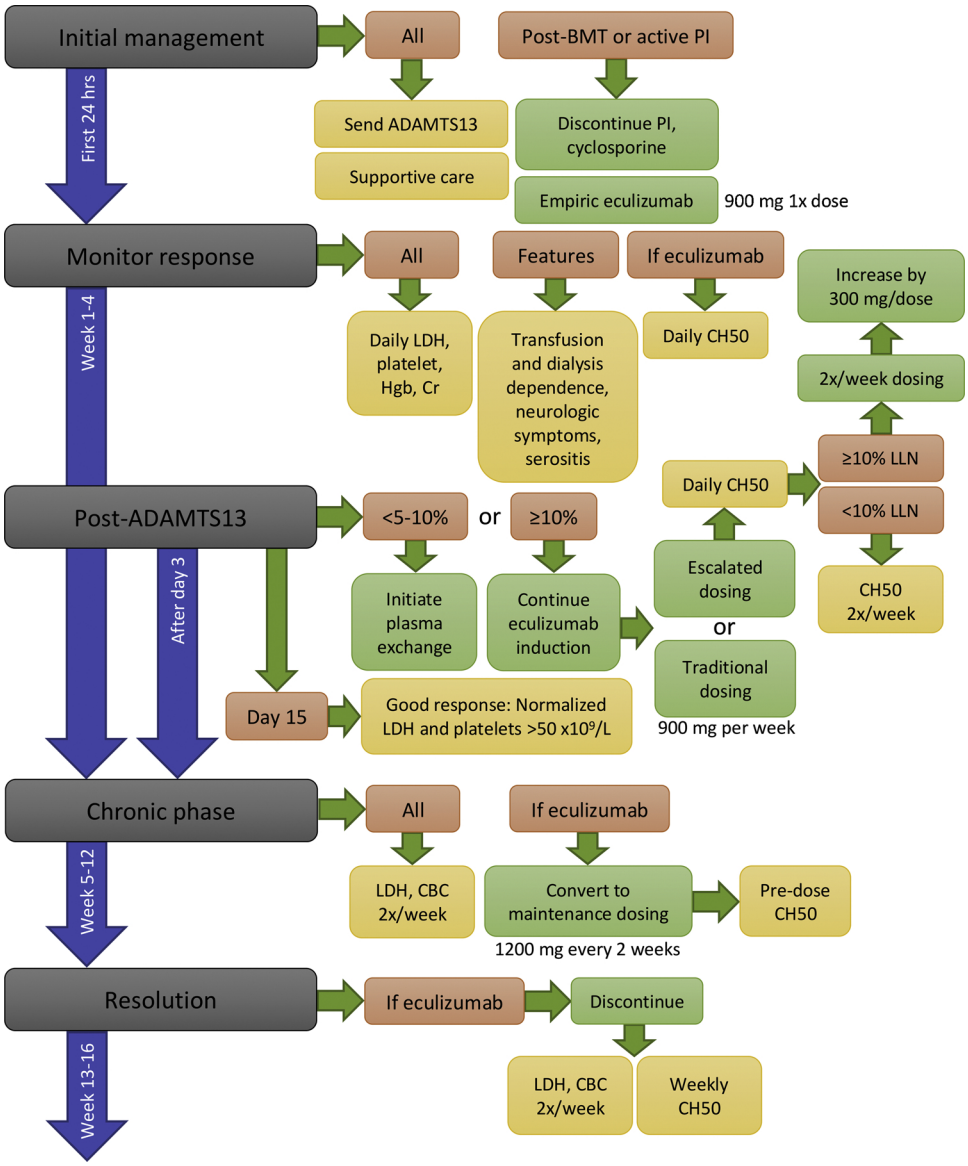

Fig. 3. MM-related TMA treatment recommendations. Within the first 24 h, an ADAMTS13 activity level must be sent and empiric eculizumab (900 mg 1x dose) monotherapy should be given to post-BMT patients and those on active PI treatment. PIs and cyclosporine should be discontinued. If ADAMTS13 level is <5-10%, daily plasma exchange should be initiated. Otherwise, eculizumab induction dosing should be continued. Monitor TMA markers and features daily. If eculizumab is initiated, dosing can be continued per traditional induction dosing (900 mg per week) or escalated dosing based on complement activity monitoring. If a dose-escalation strategy is chosen, monitor CH50 level daily to guide eculizumab dosing, with dose escalation as early as day 4 or 5 if the level is not adequately suppressed (≥10% LLN). After 4 weeks of eculizumab induction treatment, convert to maintenance dosing (1200 mg every 2 weeks). CH50 may be monitored before each dose. Discontinue eculizumab after ~4 maintenance doses.

6.2. Post-ADAMTS13 activity result

Further treatment decisions can be made once the ADAMTS13 activity level returns. If it is only slightly to moderately reduced (≥10% activity), eculizumab monotherapy should be continued. In the event of severely reduced level (<5-10% activity), TTP is the likely diagnosis. A detectable ADAMTS13 inhibitor provides further evidence. Eculizumab treatment should be discontinued.

Once the diagnosis of TTP is confirmed, eculizumab treatment should be discontinued. Plasma exchange and corticosteroids are the mainstays of treatment. Rituximab may be considered as adjunctive front-line treatment [97,98] and is commonly utilized in refractory TTP [66]. Alternatively, caplacizumab, an anti-VWF immunoglobulin fragment which inhibits interaction between VWF multimers and platelets, was recently FDA approved to treat acquired TTP [99,100].

6.3. Monitoring response

In all patients, the trajectory of disease must be assessed daily using the LDH/platelets ratio [101], hemoglobin, and creatinine. If present, transfusion dependence, neurologic symptoms, and serositis should be monitored as well. By day 15, patients with normalized LDH and platelets $>50 \times 10^9$/L are considered "good responders" [33].

Eculizumab is traditionally initiated with 900 mg weekly induction dosing for 4 weeks followed by 1200 mg given every 2 weeks as maintenance dosing [78]. Higher or more frequent eculizumab dosing may be considered to ensure therapeutic complement blockade, as therapeutic effect is more difficult to achieve in critically ill patients [83]. Although there are no well validated assays to guide monitoring of eculizumab dosing, there is some data in TA-TMAs supporting the use of total complement hemolytic activity (CH50) as a guide for eculizumab dose escalation. In contrast, there is evidence in aHUS patients that CH50 is not a good correlate for disease activity [102,103].

If available, CH50 monitoring can be considered and may be measured daily while the dosing strategy is determined, then twice weekly thereafter. Maximal CH50 suppression is expected within 2–3 days of initial dose administration, and a goal level <10% of the lower limit of normal (LLN) indicates adequately suppressed complement activity [8]. An escalation of eculizumab dosing may be considered if the CH50 level increases above the 10% of the LLN threshold prior to the subsequent day 7 dose. First, the induction dose frequency can be increased to twice weekly. A second dose may be given as early as day 4 or 5. If this strategy is insufficient, subsequent eculizumab doses may be increased by 300 mg/dose increments until CH50 is adequately suppressed in a

Table 5
Potential MM-related TMA susceptibility factors. Amongst patients who develop MM-related TMAs, it is necessary to determine mutation frequencies and phenotypes of genes which have been implicated in the development of aHUS, TA-TMA, and TTP. MM patients harboring specific mutations may only incur risk with exposure to particular treatments.

Category	Type	Specific test
Complement	Level	C3 and C4, factor B, Bb fragment, soluble C5b-9, FH, IF
	Autoantibodies	Anti-FH autoantibodies
	Mutation	*CFH-CFHR5* region, *DAF* (*CD55*), *MCP* (*CD46*), *CFI*, *CFB*, *C5*, *CFD*, *C3*, *THBD, ADAMTS13*
Other gene	Mutation	*DGKE* (diglyceride kinase epsilon), *PLG*, and *MMACHC* (methylmalonic aciduria and homocystinuria type C protein)

consistent fashion. Once CH50 is consistently suppressed, it may be checked twice weekly [8,79]. While the dosing adjustments of eculizumab have been developed using pharmacokinetic data, there is no clinical outcome data and dosing adjustments must be at the discretion of the treating provider.

Once the patient's TMA parameters (e.g., platelet count, hemoglobin, LDH, and creatinine) normalize, generally after 4–6 weeks, eculizumab should be advanced to a traditional maintenance dosing schedule with 1200 mg given every two weeks. During maintenance therapy, the following labs should be monitored twice weekly: CBC with differential, and LDH. The CH50 level can be monitored prior to maintenance eculizumab doses to ensure adequate suppression.

The question of when to withdraw eculizumab is controversial. In patients with TA-TMA, withdrawal of eculizumab can be trialed after ˜4 maintenance doses [8,79]. In patients with PI-induced aHUS, a similar maintenance strategy is advisable, although successful withdrawal has been reported following three induction doses [20]. Following eculizumab withdrawal, relapse can be monitored with twice weekly LDH, CBC with differential; and weekly CH50 for 4 weeks [8]. Most patients remain in remission. In the event of relapse, rapid re-initiation of eculizumab has proven effective [80].

7. Future research

The majority of patients who develop complement-mediated TMAs harbor predisposing susceptibility factors [62,104], and specific mutations have been associated with disease phenotypes [105]. However, given that clinical outcome data comes predominantly from pediatric literature and the pre-eculizumab era [106,104,107], its applicability to the current MM patient population is limited.

7.1. Predisposing mutations

Mutations have been most frequently observed in factor H (*CFH*), factor I (*IF*), and membrane cofactor protein (*MCP*) genes [108] (Table 5). Anti-FH autoantibodies, which mimic the phenotype of *CFH* mutations [109], have also been observed [110]. The overall penetrance of predisposing mutations is 50% by age 50 [111] and, although less well studied, older cohorts demonstrate lower frequencies of classic mutations (e.g., *CFH*, *THBD, IF*, and *MCP*) [105,112]. Since MM generally presents after the 6th decade of life [9,56], the mutation frequencies in this population are almost certainly skewed compared to the studied populations. The mutation frequencies present in the population of patients with MM-related TMAs is currently unknown, and warrants further investigation. Mutations historically considered benign may pose increased risk in the context of PI treatment [20] or BMT [104]. Pharmacogenetic studies are critically needed to aid in pre-treatment risk-stratification.

7.2. Rapid ADAMTS13 activity testing

Most institutions do not have access to rapid, on site ADAMTS13 activity assays. However, newer fluorescence energy transfer-based assays now enable accurate, point-of-care testing in as little as 60–90 min [113]. Widespread implementation of in house testing would likely promote appropriate and efficient use of plasma exchange.

7.3. Eculizumab withdrawal

The necessary duration of eculizumab treatment is not known In complement-mediated TMAs, the. In cases of aHUS, the rate of relapse upon eculizumab withdrawal is roughly 30% [114]. Unfortunately, no validated biomarker currently exists to predict the success of eculizumab withdrawal [83]. It is possible that a marker of endothelial damage or alternative pathway activity could be used to gauge underlying disease activity and help guide withdrawal of eculizumab. At this time, the serum-induced C5b-9 endothelial deposition assay shows promise as a predictor of relapse [103].

8. Conclusions

The MM-related TMAs are challenging to recognize, diagnose, and treat. Since many features overlap with MM and its treatments, clinicians must remain vigilant of these diseases. In MM, TMA triggers include PI use, BMT, and progression of underlying disease. The pathogenesis is driven by uncontrolled alternative complement pathway activation and VWF dysfunction, which result in complement-mediated TMAs and TTP, respectively.

Initial treatment decisions are often plagued with uncertainty, as an evaluation of the complement system and ADAMTS13 activity require several days to complete. However, suboptimal treatment increases morbidity and mortality. For treatment of MM-related TMAs, we feel that the risks of empiric plasma exchange outweigh the benefits and recommend against its initial use. In patients with active PI use or post-BMT, we recommend empiric therapeutic complement inhibition with eculizumab monotherapy. Once ADAMTS13 activity level returns, the decision to start plasma exchange or continue eculizumab can be made.

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