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Review

Thrombotic Microangiopathy in Solid Organ Transplantation

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Abstract

Thrombotic Microangiopathy (TMA) is a syndrome characterized by microangiopathic hemolytic anemia (MAHA) and thrombocytopenia. The presence of schistocytes on peripheral smear, a negative Coombs test, elevated lactate dehydrogenase, increased reticulocyte count and low haptoglobin are often the clues for MAHA. The microvascular process often targets vasculature in kidneys, brain, gastrointestinal system, heart, and skin. A timely diagnosis and treatment are often crucial to prevent severe end organ damage and death. TMA is classified into primary and secondary forms. Primary TMA includes TTP and complement mediated or atypical hemolytic uremic syndrome (aHUS), often related to a mutation or deficiency and clinically expressed in the setting of a precipitant condition. Secondary TMA is a manifestation of underlying disorder and can occur in clinical scenarios associated with autoimmune disease, malignancy, infections, SOT (Solid Organ Transplant), pregnancy, HSCT (Hematopoietic Stem

Cell Transplantation), medications, or methylmalonic acidemia. Transplant associated TMA (TA-TMA) can be complement mediated or aHUS and could be related to the ischemic reperfusion injury, induction regimen, calcineurin inhibitor (CNI) use, mammalian target of rapamycin (MTOR) inhibitor use, or could be infection related. Cost, access, and turnaround time are often the limitations for certain TTP and complement specific testing. Treatment should not be delayed while waiting for such tests. Treatment must be individualized based on the underlying cause of TMA. Terminal complement blockade utilizing monoclonal antibodies directed against C5 complement is the treatment for complement mediated TMA. C5 inhibitors have also been used successfully in treatment of secondary HUS cases where, unlike aHUS, defects in complement cannot be demonstrated. Such treatment has demonstrated improvement in renal function, MAHA and platelet counts.

Keywords
Schistocytes; thrombotic microangiopathy; hemolytic uremic syndrome

1. Introduction

Thrombotic microangiopathy (TMA) is characterized by non-immune intravascular hemolysis and ischemic organ dysfunction. Clinical presentation is often variable, non-specific and depends on the etiological cause and the organ affected. TMA often targets the microvasculature in kidneys, brain, gastrointestinal system, heart, and skin [1, 2]. It is crucial to diagnose and initiate treatment in a timely fashion to prevent severe end organ injury and death.

TMA post lung transplantation is under reported compared to TMA post hematopoietic stem cell transplantation (HSCT) or renal transplant.

2. Incidence, Epidemiology and Types

TMA is to be suspected if there is evidence of thrombocytopenia and microangiopathic hemolytic anemia (MAHA). The presence of schistocytes on peripheral smear, negative Coombs test, elevated lactate dehydrogenase, increased reticulocyte count and low haptoglobin are often the clues for MAHA [2]. Though schistocytes are supportive of the diagnosis, lack of them does not rule out the diagnosis, especially when there is a clinical suspicion or other findings are present. TMA is a continuum process and schistocytes might not always be present on initial evaluation and may need frequent assessment [3].

TMA is classified into primary and secondary forms. The onset of TMA syndromes can be sudden or gradual. Despite being so diverse, TMA syndromes have common clinical and pathological features. Clinical features being the triad of MAHA, thrombocytopenia, and end organ injury while the pathological features include endothelial damage, fibrin thrombi generation and microvasculature damage [4, 5]. The degree of thrombocytopenia may vary based on the pathophysiological process. In TTP, platelet rich microthrombi predominate and the median platelet count is <20,000. In HUS, fibrin-rich microthrombi predominate and platelet counts are either <150,000 OR at least a 25% decrease from baseline.

Primary TMA includes thrombotic thrombocytopenic purpura (TTP) and complement mediated or atypical hemolytic uremic syndrome (aHUS), often related to a mutation or deficiency and clinically expressed in the setting of a precipitant condition. From a clinical standpoint, TTP often affects the brain and GI system and rarely causes acute kidney injury (AKI). Severe AKI is prominent in HUS or complement mediated TMA [4-6].

Secondary TMA is a manifestation of underlying disorder and can occur in clinical scenarios associated with autoimmune disease, malignancy, infections, Solid Organ Transplant (SOT), pregnancy, HSCT, medications, or methylmalonic acidemia [4-6].

2.1 Primary TMA

2.1.1 TTP

TTP is a rare and fatal condition. The incidence of TTP is 2-6 per million persons [7, 8]. TTP can be hereditary or acquired and is characterized by deficiency of ADAMTS-13. Hereditary TTP (Upshaw-Schulman Syndrome) is caused by ADAMTS13 mutations [4]. Acquired TTP, an autoimmune disorder, is caused by inhibition of ADAMTS13 activity by autoantibodies [5, 9]. Deficiency of ADAMTS-13 results in large von Willebrand factor (VWF) multimers which increase the risk for platelet aggregation and thrombi generation in the small vasculature. The vast majority of TTP cases are acquired or immune.

Diagnosis of TTP and cause can be achieved by measuring the levels of ADAMTS-13 activity, ADAMTS-13 Ag, and inhibitors. A plasma level of <10 IU/dL ADAMTS-13 activity confirms the TTP diagnosis. Extremely low or absent ADAMTS-13 Ag can be seen in hereditary TTP, which is a rare autosomal recessive condition [10-12]. The presence of autoantibodies against ADAMTS-13 can point towards the diagnosis of autoimmune or acquired TTP. These auto antibodies, usually IgG, play a role either by causing rapid clearance of ADAMTS-13 or by interfering with the VWF recognition [13].

While interpreting the ADAMTS 13 activity, it is important to acknowledge that these levels can be reduced, however greater than 10 IU/dL in other conditions such as pregnancy, severe sepsis, DIC, metastatic malignancy, SLE, severe liver dysfunction, aHUS and Shiga toxin (Stx)-producing Escherichia coli HUS (Stx E. coli HUS; STEC-HUS) [14, 15].

2.1.2 Atypical HUS/Complement Mediated TMA

Diagnosis of atypical HUS is often made on exclusion of all other forms of TMA. It is the result of dysregulation and uncontrolled activation of the alternate complement pathway. Presence of complement factor H antibodies (5-10% aHUS cases) or complement mutations can activate the terminal phase of complement pathway and membrane attack complex formation thereby resulting in extensive endothelial cell damage, platelet aggregations and microthrombi generation [5, 16, 17].

Assessment of soluble C5b-9 levels, complement regulatory factors such as CFH (Complement Factor H), complement factor I; MCP, membrane cofactor protein; C3, complement component C3; CFB, complement factor B can aid in the diagnosis of aHUS [18, 19].

Hereditary complement mediated TMA is a result of regulatory gene (CFH, CFI, CD46) or effector gene (CFB, C3) mutations [4]. Acquired form of complement mediated TMA can result from a

deficiency in complement factor H secondary to antibodies to the complement (10% of cases) [20, 21].

2.1.3 Shiga Toxin Mediated HUS

Shiga toxin mediated HUS is often an infection related more commonly with Shiga toxin producing bacteria, especially E. coli serotype O157:H7. Other potential infectious culprits include S. pneumoniae and Shigella. Bacterial cytotoxins can damage the vascular endothelial cells, RBC's and platelets, which in turn can amplify the complement activation. Patients can present with symptoms of severe abdominal pain or bloody diarrhea [22, 23].

Diagnosis of the infection and appropriate treatment is crucial to decrease the cytotoxin production and culminate the exaggerated complement activation process. Stool testing can aid in the identification of the Shiga toxin, especially in the acute colitis phase [24].

2.2 Secondary TMA

2.2.1 Transplant Associated TMA

TMA has been reported after solid organ transplantation, however the reported incidence has been variable given the lack of consensus on the diagnosis of transplant associated TMA (TA-TMA) [25]. TA-TMA can be complement mediated or aHUS type and could be related to the ischemic reperfusion injury, induction regimen, calcineurin inhibitor (CNI) use, mammalian target of rapamycin (MTOR) inhibitor use, or could be infection related. TMA in transplant setting can occur as a de novo event or as a recurrent disease. Recurrent disease can be seen in patients with genetic aberrations of complement system [26]. TA-TMA can occur in early post operative period or later. An accurate diagnosis can be challenging in post operative state and can be confounded by factors such as ischemic reperfusion insult, post operative hemodynamics, and sepsis. The clinical spectrum of TA-TMA can range from a limited disease, chronic organ dysfunction or systemic TMA with multi organ dysfunction. TMA after lung transplantation could be a result of atypical HUS or secondary factors such as CNI use and opportunistic infections. Systemic TMA is often associated with significant morbidity and mortality [27].

The pathogenesis of TMA post transplantation remains poorly understood. However, different mechanisms have been speculated including acquired deficiency of ADAMTS13 either in a post operative state or in the presence of inhibitor antibodies [28]. Neutrophil activation and neutrophil extracellular traps released from endothelial injury has been described, that can result in complement activation, complement factor P and C5b-9 deposition [29-31]. Acquisition of donor complement regulatory proteins appeared to increase the risk of TA-TMA [32]. Also, an association of HLA-DRB1*11 and TTP has been reported [33].

A multiple hit theory has been proposed in HSCT literature with the preexisting host factors such as underlying predisposition for complement activation or preexisting endothelial injury being the initial hit, conditioning regimen or ischemic reperfusion injury and subsequent endothelial cell activation being the second hit, and finally the alloreactivity or medication or infections being the third hit, eventually triggering the complement cascade activation [34]. Complement activation can be confirmed by significant elevations in C3b and C5b-9 [35]. Diagnosis and treatment of TA-TMA is crucial to stop the dysregulation process and halt the end organ damage [36, 37].

TA-TMA could also be related to acquired deficiency of ADAMTS13 activity. Metivier and colleagues assessed ADAMTS13 activity in lung transplant recipients with suspected TMA. 3 out of 8 patients had extremely low ADAMTS13 activity (<5%) while the remaining had low but detectable levels [38].

Hachem and colleagues reported an incidence of 3.8 cases per 100 years in their retrospective review of 262 lung transplants between January 1, 1999, and December 31, 2003. The median onset of TMA was 265 days, with as early as 17 days and as late as 4 years post transplantation. 11 out of 24 instances were isolated TMA while the rest of them occurred in the setting of other illnesses such as pneumonia, graft dysfunction, CMV infection, post-transplant lymphoproliferative disorder and reversible posterior leukoencephalopathy. They noted a higher incidence of TMA with the combination of CNI and sirolimus. Female gender, history of TMA and immunosuppressive regimen were noted to be the significant predictors of TMA [39].

Fortin et al reported that the immunosuppressive combination of cyclosporine and sirolimus has both pro-necrotic and anti-inflammatory effects on the endothelial cells [40]. There have been reports of TMA in the setting of infections in lung transplant recipients [41].

2.2.2 Drug Induced

Drug induced TMA (DITMA) can be immune mediated or nonimmune mediated, dose dependent direct endothelial cell damage [42] (Table 1).

Table 1 Potential Drug-Induced Causes of TMA.

Pharmacological Category	Drug Name
Calcineurin inhibitor	Tacrolimus
	Cyclosporine
MTOR inhibitor	Sirolimus
	Everolimus
Atypical antipsychotic	Quetiapine
Antibiotic	Sulfamethoxazole-trimethoprim
	Rifampin
Antimalarial	Quinine
Proteasome inhibitor	Bortezomib
	Carfilzomib
Chemotherapy	Mitomycin
	Gemcitabine
	Docetaxel
	Vincristine
	Pentostatin
VEGF inhibitor	Bevacizumab
	Ponatinib
	Sunitinib
Opioid	Oxycodone

Immune Mediated Mechanism: Quinine was the first drug to be implicated in the development of drug dependent antibodies binding to multiple cell antigens and endothelial cell activation [43, 44]. Subsequently quetiapine and gemcitabine were reported to be associated with acute episodes of TMA on repetitive exposure [45, 46]. Such immune mediate reaction is related to the structural elements of the drugs complementary to the epitope and the antibody [47].

Dose dependent mechanism: Drugs such as immunosuppressants, chemotherapeutic agents and VEGF inhibitors in a dose dependent fashion can cause endothelial dysfunction, prostacyclin inhibition, platelet aggregation thereby resulting in TMA [48, 49].

DITMA pathophysiology depends on the offending drug. Mitomycin, gemcitabine, interferon, quinolones are implicated in direct endothelial damage and pro thrombotic activation. Anti VEGF monoclonal drugs such as bevacizumab and tyrosine kinase inhibitors such as sunitinib and pazopanib interfere with VEGF pathway signal protein and receptor affecting the homeostasis of endothelial podocyte complex in the kidney. Carfilzomib can cause decreased CFH expression and thereby result in complement mediated TMA. Downregulation of transcription factor such as NF-KB, by agents such as calcineurin inhibitors can create a prothrombotic state, augment the oxidative stress, decrease nitric oxide concentration and VEGF production and can result in TMA [50].

2.2.3 Infections

Several infectious agents have been implicated in secondary TMA (Table 2). TMA has been reported in HIV infections [51]. Though the exact mechanism is unclear, there has been speculations that TMA could be a result of primary endothelial injury from the virus while some reports suggest ADAMTS 13 deficiency [52, 53]. There have been reports of TMA association with viral Infections such as adenovirus, BK virus, CMV, HHV6, parvovirus B19 and fungal infections such as aspergillus [54, 55]. aHUS can be triggered by SARS-CoV-2, could be a result of direct toxic effect on endothelial cells or complement activation [56]. Based on the clinical presentation and suspicious agent, appropriate testing should be deployed for accurate diagnosis and treatment of the infectious agent.

Table 2 Infections.

Pathogen Class	Organisms
Bacteria	Streptococcus pneumonia
	Legionella
	Rickettsiae
	Borrelia
	Brucella
	Ehrlichia
	Leptospira
	Rocky Mountain Spotted Fever
Viruses	Cytomegalovirus
	COVID-19
	Epstein Barr Virus
	Parvo virus B19
	Varicella Zoster
	Human Herpes Virus 6

	Coxsackie Virus
	Noro virus
	Human Immunodeficiency virus
	Influenza A
	Dengue
	Hepatitis viruses
Fungi	Aspergillus
	Blastomyces
	Cryptococcus
Parasites	Malaria
	Babesia

2.2.4 Pregnancy

TTP can occur or relapse during the first trimester of pregnancy [57]. HELLP Syndrome often associated with pre-eclampsia is characterized by MAHA, thrombocytopenia, and liver damage [58]. The onset of aHUS in immediate post-partum phase is related to the loss of complement regulators present on placental surface [59, 60].

2.2.5 Malignancy

TMA in the setting of malignancy could be related to cancer itself or could be secondary to chemotherapy. Metastatic cancer cells can cause microvascular obstruction and injury. Chemotherapy related TMA can be either from non-immune mediated dose dependent cytotoxicity or from immune mediated mechanism with development of drug dependent antibodies [61].

2.2.6 Autoimmune Diseases

Autoimmune disorders such as SLE and systemic scleroderma are associated with TMA. Diagnosis of such autoimmune conditions requires the need for extensive autoimmune panel testing [62].

2.2.7 Malignant Hypertension

Malignant hypertension can trigger an aHUS. TMA in the setting of malignant hypertension is related to direct endothelial injury. These patients can have ocular signs of hypertensive retinopathy [2, 5]. aHUS can be accompanied by malignant hypertension.

2.2.8 Methylmalonic Acidemia

Cobalamin C disease (hereditary metabolic disorders of vitamin B12), result of mutations of gene encoding the methylmalonic aciduria and homocystinuria type C protein, can result in methylcobalamin deficiency resulting in hyperhomocystinemia, decreased plasma methionine levels and methylmalonic aciduria [63]. Elevated levels of methylmalonic acid and homocysteine accumulation in blood and tissues can cause endothelial cell damage, platelet activation and coagulation activation [64, 65].

2.2.9 Coagulation Mediated TMA

Mutations of thrombomodulin, plasminogen, protein kinase C-associated protein, diacylglycerol kinase E can be associated with TMA, and are related to the role of coagulation factors in the pathogenesis of TMA. Loss of DGKE function and Protein Kinase C activation result in upregulation of pro thrombotic factors and downregulation of VEGF receptor thereby creating a prothrombotic state [66, 67].

3. Diagnosis

In the right clinical context, presence of anemia, thrombocytopenia, and schistocytes (>2 per high powered field or >1% schistocytes) on a peripheral smear is often diagnostic. TMA is often associated with other lab abnormalities such as elevated LDH (lactate dehydrogenase), low haptoglobin, increased reticulocyte count and unconjugated hyperbilirubinemia, which reflect MAHA. Direct Coombs test is negative in TMA. Often the coagulation parameters (Prothrombin Time, activated Partial Thromboplastin Time) are normal, however can be abnormal in severe clinical presentations with septic shock, DIC and end organ failure [5, 6]. DIC itself is a MAHA and often it is very difficult to define an aHUS or TTP in the setting of active DIC. While MAHA is an essential feature for TMA, it is important to be aware that at times lung transplant patients need extracorporeal support either in pretransplant, or post-transplant or both phases and such extracorporeal support use can also result in MAHA. In such cases, obtaining baseline MAHA labs could help identify the syndrome sooner.

Cost, access, and turnaround time are often the limitations for certain TTP and complement specific testing. Treatment should not be delayed while waiting for such tests. On suspicion of TMA, ADAMTS13 or TTP specific testing and complement assessment should be performed in addition to the work up for the evaluation of the secondary conditions that could be associated with TMA.

3.1 TTP Assessment

Measurement of ADAMTS-13 activity, ADAMTS-13 Ag, and inhibitors can aid in the diagnosis and the cause of TTP. A plasma level of <10 IU/dL ADAMTS-13 activity confirms the TTP diagnosis [10-13]. Genetic testing to rule out congenital TTP should be considered if ADAMTS13 activity and ADAMTS13 inhibitor levels are undetectable.

3.2 Complement Assessment

Low levels of serum complement C3, C4 can be seen in several pathologies such as aHUS (C3 consumption only in 30-50% of patients), TTP, STEC-HUS and glomerulonephritis. Elevated soluble C5b-9 levels is a finding of terminal complement pathway overactivation [68]. Properdin, an alternate pathway regular, levels are reduced in complement activation [5]. Factor B levels could indicate a pathway involved in C3 consumption. Measurement of total hemolytic complement (CH50) is used to assess the classic complement activation pathway. Low levels of CH50 are seen in congenital complement deficiencies, complement factor deficiencies, increased consumption of complements, infections, and auto immune disease processes such as SLE [5]. Low levels of alternative pathway complements (AP50 assay) can be seen in FB, FD, FH and properdin deficiencies, aHUS and STEC-HUS [5, 21, 69]. Plasma MASP2 levels can be measured to assess the lectin pathway

activation [70]. Anti CFH antibody testing (50-60% aHUS patients) and genetic mutational analysis (CFH, CFI, MCP, C3, CFB, THBD, CFH/CFHR hybrid gene, DGKE, PLG) should be considered in patients with aHUS picture [5, 21, 71, 72].

3.3 Assessment of Secondary Factors

An assessment of secondary factors associated with TMA should include work up for infections, DIC, auto immune disease and cobalamin metabolism disorders.

Infectious work-up should include assessment for viral infections such as CMV, EBV (Epstein Barr Virus), adenovirus, parvovirus B19, BK virus, HIV, bacterial infections like streptococcus, and fungal infections like aspergillus. Stool Polymerase Chain Reaction testing or cultures for Shiga toxin E. coli should be considered in patients with abdominal symptoms and diarrhea [52-55]. Elevated levels of methylmalonic acid and homocysteine accumulation in the serum and urine samples are seen in Cobalamin C disease. Such abnormal tests should be followed by MMACHC genetic testing for confirmation [5, 64]. Autoimmune testing should include antinuclear antibodies (ANA), anti-double-stranded DNA (ds-DNA) antibodies, anti-extractable nuclear Ag antibodies, anti-topoisomerase I (anti Scl-70) antibody, anticentromere antibody (ACA) and anti-RNA polymerase III antibodies, anti-cardiolipin antibody, anti-b2GP-1 antibody, and lupus anticoagulant (LA) [62, 63].

3.4 Histopathology

Histopathological confirmation is not mandatory for TMA diagnosis. Often, such a need can be particularly challenging. TMA diagnosis is often made on clinical grounds with an etiological and an exclusion approach. The classic histological signs of TMA include endothelial cell swelling, luminal fibrin platelet thrombi, and minimal or absent inflammation. Vasculature changes may include intimal swelling, proliferation, and necrosis of the arterial wall or thrombi in lumen [4, 5, 73, 74]. Positive C5b-9 staining in kidney, skin clues towards complement-mediated TMA [73]. Autopsy studies have demonstrated such histological signs in organs such as heart, lungs, and brain. If feasible, kidney, skin, GI system are the suggested sites for biopsy [73, 74].

4. Treatment

Given there are no general guidelines for treatment of TMA, treatment must be individualized based on the mechanism and underlying causative factors of disease to yield optimal patient outcomes. Prior to organ transplantation, it is ideal to minimize the risk of complement over-activation before donation, prevent hypoperfusion during the process or organ procurement, and avoid prolonged cold ischemia time [75].

4.1 Immunosuppression Considerations

In the setting of de novo TMA post-transplantation occurring secondary to immunosuppression, the offending agent should be reduced or stopped immediately. This occurs most commonly in the setting of CNI use post-transplant and the patient is typically switched to the alternative CNI or an MTOR inhibitor once deemed clinically appropriate based on TMA resolution [76]. In cases where continuation of a CNI is desired, tacrolimus can be switched to cyclosporine and vice versa. Verbiest et al. conducted a review of the literature of TMA management in non-renal solid organ transplant

recipients. Patients were converted to the alternative CNI in 63 of the cases that were analyzed and 95% of patients had positive outcomes; although it should be noted that these cases were primarily mild in terms of TMA severity [77]. As previously mentioned, switching patients from a CNI to an MTOR inhibitor can also be considered along with using an MTOR inhibitor in combination with a CNI at a reduced dose. However, this strategy carries a risk of limitations as MTOR inhibitors can promote various adverse effects such as thrombotic events and TMA. In a case report presented by Negrini et al., after a kidney transplant recipient was switched from tacrolimus to sirolimus for maintenance immunosuppression, the patient subsequently developed deep vein thrombosis, ischemic colitis, and biopsy proven TMA [78]. Additionally, it must be considered that MTOR inhibitors also demonstrate additional adverse effects such as nephrotoxicity, myelosuppression, and lower immunosuppressive potency compared to CNIs [79, 80]. As a result, patients must be monitored diligently when switched to MTOR inhibitors in this setting and the decision should be balanced with the risk of graft rejection.

In the setting of de novo TMA induced by immunosuppression, another alternative agent that can be considered is Belatacept as it has not been shown to have similar endothelial toxicity properties to those seen with CNIs and MTOR inhibitors. Belatacept is a cytotoxic T lymphocyte 4-immunoglobulin fusion protein that prevents the activation of T cells that block the CD28 costimulation pathway [75, 76]. Successful use of Belatacept as an alternative immunosuppressant in setting of post-transplant TMA was first described in case report by Ashman et al. In this case, a kidney transplant recipient experienced three episodes of drug-induced TMA associated with cyclosporine, tacrolimus, and sirolimus before the patient was transitioned to Belatacept. Once converted and after nine months of follow-up, the patient had complete TMA resolution along with no significant drug adverse events noted [81]. In a cohort of 115 kidney transplant recipients presented by Morel et al. where three-year outcomes were assessed in patients converted from a calcineurin inhibitor to Belatacept, 11 patients were identified to have a diagnosis of CNI-induced TMA. After patients were converted to Belatacept, all cases of TMA resolved along with a 92% graft survival rate at three years post-conversion [82]. While Belatacept can be considered in this setting, it must be noted that it has been demonstrated in multiple investigations to have higher rates of acute rejection, particularly in renal transplantation, when compared to traditional immunosuppression along with potential increased risk of post-transplant lymphoproliferative disorder [82-85].

While immunosuppression should be altered in the setting of acute drug-induced TMA to avoid a poor prognosis, the causative agent can be rechallenged if deemed clinically appropriate or necessary by the clinician. However, outcomes utilizing this strategy are conflicting when evaluated in different types of solid organ transplant based on available case report data [77].

4.2 Plasma Exchange

In the setting of post-transplant TMA that is unresponsive to conventional measures or associated with antibody-mediated rejection, plasma exchange (PE) or plasmapheresis (PP) can be considered along with concomitant IVIG and additional immunosuppression if indicated [75]. However, it is important to note that the use of plasma exchange in the setting of TMA induced by CNIs or MTOR inhibitors is not well established and should be considered on an individualized patient-specific basis according to the American Society for Apheresis guidelines [77]. Additionally,

randomized controlled trials are lacking on the use of plasma exchange in this setting for both hematopoietic and solid organ transplant recipients. Based on available case report data, it is challenging to draw any concrete conclusions given the heterogeneity of the findings as some case reports found withdrawal of the CNI to be the optimal choice, others found no difference between plasma exchange or CNI conversion, while others found worse outcomes in patients that were treated with plasma exchange alone [28,86-88].

Patients that develop TMA because of antibody-mediated rejection tend to respond significantly better to plasma exchange and concomitant IVIG compared to drug-induced TMA. Plasma exchange can remove HLA-specific antibodies while IVIG can further suppress alloantibodies and modulate immune response [76]. In a retrospective review of renal allograft biopsies, Satoskar et al found a TMA prevalence of 13.6% in patients with C4d positive biopsies compared to 3.6% in C4d negative biopsies. While not a statistically significant finding, they found that patients with C4d positive TMA that received plasma exchange had a lower rate of graft loss compared to those that did not [89]. In another investigation, Satoskar et al. analyzed outcomes of patients with graft dysfunction. They evaluated patient outcomes and compared two-year graft survival in patients with C4d positive AMR-associated graft dysfunction who received plasmapheresis and IVIG to those who did not receive therapy. While receipt of plasmapheresis and IVIG did not show significant improvement survival and graft function in the overall cohort at 2 years post-transplant, all patients with TMA in the study cohort who received plasmapheresis sand IVIG had functioning grafts at the two-year follow up indicating the beneficial effects of plasma exchange and IVIG in this setting [90].

As previously discussed, utilization of plasma exchange should be individualized based on the causative factor of TMA for the patient to balance the potential benefits vs. risks and adverse effects of therapy including thrombosis, bleeding, infection, and hypotension.

4.3 Complement Directed Therapy

The role of complement as a target for TA-TMA has increased based on efficacy seen in the treatment of aHUS and the similarities in activation of the complement system. Anti-complement therapies target the underlying complement-mediated vascular lesion [91]. C5 inhibitors are humanized monoclonal antibodies that bind to the complement protein C5, preventing cleavage into C5a and C5b which inhibits the formation of terminal complex C5b-9, including the formation of MAC. Eculizumab is a C5 inhibitor currently indicated for the treatment of PNH, aHUS, gMG and NMOSD. Ravulizumab, derived from eculizumab, exhibits high-affinity binding, as well as substitution of 4 amino acids in the complementary binding and neonatal Fc regions of the eculizumab backbone, leading to a terminal half-life that is approximately 4 times than that of eculizumab. Ravulizumab is currently indicated for the treatment of PNH, aHUS and gMG [92-94]. Alternative complement pathway activation plays a role in the pathogenesis of TA-TMA; therefore, suggesting the utility of eculizumab and ravulizumab in the setting of TA-TMA.

Literature on eculizumab use for TA-TMA has been historically limited to HSCT [95]. Jodele et al. described the use of eculizumab in a pediatric cohort of 64 patients with high-risk TA-TMA. The study demonstrated a response rate of 64% and 1-year survival rate of 66% after HSCT, compared with a 16.7% survival rate in a historical control cohort [96]. de Fontbrune et al. reported use of eculizumab in an adult cohort of 12 patients with TA-TMA after allogeneic HSCT with severe TMA with neurological and/or renal involvement. At a median follow-up time of 14 months,

hematological response and overall survival were 50% and 33%, respectively, demonstrating a favorable response [97].

ECULISHU, a phase 3 randomized placebo-controlled study did not show clear benefit of using early eculizumab on duration of renal replacement therapy in patients with milder presentation. However, the study excluded patients with severe complications for ethical reasons [98].

Gonzales et al. reported the use of ravulizumab for TA-TMA due to medication availability instead of eculizumab. The patient demonstrated response within 2 weeks after initiation of ravulizumab, with a total of 5 maintenance doses leading to successful complement blockade and clinical improvement [99].

Literature in solid organ transplant recipients is primarily found in renal transplant recipients, with eculizumab as the primary complement directed therapy. Eculizumab has been successfully used in de novo TA-TMA after kidney transplantation [75]. Portolés et al. described 22 patients with TA-TMA, with early (<1 month) and late (>1-month post-transplant) onset TMA. Patients responded better with a shorter time between TMA diagnosis and beginning of treatment with eculizumab [100]. Dhakal et al. describe a retrospective analysis of 26 cases, with TA-TMA occurring in 17 (65%) solid organ transplant (41 kidney, 29 small bowel, 12 liver, 12 simultaneous pancreas and kidney, and 6 combined lung and kidney) and 9 (35%) stem-cell transplant recipients. The median time to initiation of eculizumab from transplant was 63 days, with 92% of cohort recovering after eculizumab administration. 18 (95%) of patients received induction therapy, and maintenance therapy was continued in 20 (77%) patients [101].

With the treatment, a statistical difference was noted in renal recovery, with most of it occurring within the first 30 days and the median time for platelets to normalize was about 4 days. Factors such as shorter time between the clinical presentation and first dose of eculizumab, younger age, lower creatinine, and lower platelet counts were associated with better renal recovery and function with eGFR > 60 ml per min at 6 months [102].

The dosing of eculizumab and ravulizumab are not well established in TA-TMA; however, the established dosing regimen for aHUS is commonly used, including an induction phase, followed by a maintenance phase. In cases where complement directed therapy is utilized alongside plasma exchange, supplemental doses are recommended before, or within 1 hour, after plasma exchange [93, 94]. The utilization of complement directed therapy should be individualized and consider potential benefits versus risks and adverse effects including, meningococcal infection and infusion-related reactions. Administration of meningococcal vaccinations within 2 weeks of initiation, is recommended with the use of eculizumab and ravulizumab. Often patients are immunosuppressed, prophylactic antibiotics should be considered, in addition to vaccination, for the entire duration of treatment with eculizumab or ravulizumab. The duration of treatment with complement directed therapy is unknown; however, discontinuation of therapy can be considered once complications of TA-TMA have completely resolved, including resolution of hematologic markers and complement blockade determined by CH50 levels.

5. Conclusions

Thrombotic Microangiopathy (TMA) characterized by microangiopathic hemolytic anemia (MAHA) and thrombocytopenia, often targets vasculature in kidneys, brain, gastrointestinal system, heart, and skin. If unrecognized and or if left untreated can result in severe multiorgan failure and

death. Treatment should not be delayed while waiting for TTP and complement specific tests. In addition to the identification of causative factors and their treatment, terminal complement blockade should be considered especially if there is a suspicion for complement mediated TMA.

List of Abbreviations

aHUS	atypical hemolytic uremic syndrome
Anti-FH	anti-complement factor H antibodies
CFB	complement factor B gene
CFH	complement factor H gene
CFI	complement factor I gene
ADAMTS13	A Disintegrin and Metalloproteinase with a ThromboSpondin type 1 motif, member 13
ANA	antinuclear antibody
ANCA	Autoantibodies to neutrophil cytoplasmic antigens
CMV	cytomegalovirus
DAT	direct antiglobulin test
DGKE	diacylglycerol kinase epsilon
DIC	disseminated intravascular coagulation
DNA	deoxyribonucleic acid
ELISA	enzyme-linked immunoabsorbent assay
FACS	fluorescence activated cell sorting
FB	complement factor B
FH	complement factor H
FI	complement factor I
gMG	generalized myasthenia gravis
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplant
HUS	hemolytic uremic syndrome
LDH	lactate dehydrogenase
MAC	membrane attack complex
MAHA	microangiopathic hemolytic anemia
MCP	membrane cofactor protein
NMOD	neuromyelitis Optica spectrum disorder
PNH	paroxysmal nocturnal hemoglobinuria
PLG	plasminogen
STEC	Shiga toxin-producing Escherichia coli
THBD	thrombomodulin
TA-TMA	transplant-associated thrombotic microangiopathy
TMA	thrombotic microangiopathy

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Author Contributions

Sravanthi Nandavaram has written the manuscript. Rickey Evans and Hannah Twist have written the treatment section of the manuscript. Sravanthi Paluri, Ana Castellanos assisted with the editing. Andres Pelaez assisted with the reviewing and editing.

Competing Interests

The specified authors do not have any conflicts of interest to disclose.

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