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Review Article

Complement in Pathophysiology and Treatment of Transplant-Associated Thrombotic Microangiopathies

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ABSTRACT

Transplant-associated thrombotic microangiopathy (TA-TMA) is a form of microangiopathy specifically occurring in the context of hematopoietic stem cell transplantation. Similarly, to other microangiopathies, TA-TMA is characterized by hemolytic anemia, thrombocytopenia, and organ failure due to endothelial injury. Although its clinical association with medications (eg, calcineurin inhibitors), immune reactions (eg, graft vs host disease) or infectious complications is well established, the pathophysiology remains largely unknown. Recent data have highlighted the role of complement in the pathophysiology of TA-TMA, which are frequently associated with a functional impairment (either inherited or acquired) of the endogenous regulation of the complement classic and alternative pathway. This manuscript will review the data supporting the involvement of complement in the pathophysiology of TA-TMA, as well as the clinical data supporting the use of anticomplement agents in this rare condition.

Introduction

Transplant-associated thrombotic microangiopathy (TA-TMA) is a form of microangiopathy specifically occurring in the context of hematopoietic stem cell transplantation (HSCT). Similarly, to other microangiopathies, TA-TMA is characterized by hemolytic anemia, thrombocytopenia, and endothelial injury related organ failure. Although its clinical association with medications (eg, calcineurin inhibitors), immune reactions (eg, graft versus host disease) or infectious complications is well established, the exact pathophysiology remains under investigation. Recent data have highlighted the role of complement in the pathophysiology of TA-TMA, which are frequently associated with a functional impairment (either inherited or acquired) of the endogenous regulation of the complement classic and alternative pathway.

Significant effort was made in recent years by researchers and physicians to better understand complement role in TA-TMA. New insights and published data peeked an interest in TA-TMA in transplant community with the hope for potential clinical interventions for this transplant complication that has a significant impact on short and long-term outcomes.

This article will review the data supporting the involvement of complement in the pathophysiology of TA-TMA, as well as the clinical data supporting the use of anticomplement agents in this rare condition.

TA-TMA Presentation and Outcomes

TA-TMA occurring in HSCT recipients brings particular challenges due to the overall complexity of these patients with a multitude of coinciding clinical problems and paucity of normal laboratory studies observed during bone marrow recovery after therapy induced aplasia, toxic therapy effects, and immune-mediated reactions due to donor graft [1-6]. On the other hand, transplantation process offers a unique opportunity to prospectively study and treat TA-TMA and associated multiorgan dysfunction syndrome (MODS) that occurs due to systemic endothelial injury. In the effort to improve TA-TMA diagnosis, multiple clinical and laboratory criteria had been adopted from the other microangiopathies like thrombotic thrombocytopenic purpura and atypical hemolytic uremic syndrome that had been challenging to interpret in complex transplant settings. With increased awareness about this complication and its clinical presentations, we came to understand that studying the HSCT patient population in a prospective manner can aid prompt recognition of TA-TMA diagnosis. HSCT is a planned procedure, with a predictable period of

Disclosures: S.J. has US patents pending for compositions and methods for treatment of HSCT-associated thrombotic microangiopathy.

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high risk of complications where clinically available tests and monitoring could be used to recognize and differentiate TA-TMA from other common transplant complications and can lead to improved diagnostic and therapeutic options resulting in better outcomes.

Clinical Outcomes

With improved recognition of TA-TMA, this HSCT complication is shown to have a significant effect on multiple organ functions often leading to microangiopathy-associated MODS requiring intensive care support [7-9]. Large pediatric studies have reported that TA-TMA is significant risk factor for pediatric intensive care unit (PICU) outcomes [10,11]. Cardiac and renal complications due to TA-TMA had been associated with increased mortality in HSCT recipients. TA-TMA associated renal dysfunction accounts for large part of renal injury after HSCT. Cho et al [12,13] reported a 29% incidence of TA-TMA ($n = 148$) with $<20\%$ survival in patient with "definite" TMA with acute kidney or neurologic injury, and concluded that TA-TMA should be treated as soon as it is suspected, to avoid irreversible organ damage, since therapeutic interventions only had benefit if initiated early. Oran et al reported 55 of 66 patients with HSCT with TA-TMA (83%) dying at a median of 3 months after TA-TMA diagnosis. Median survivals from TA-TMA diagnosis for nonresponders to interventions was 1.07 months vs 7.5 months in responders to therapeutic interventions ($P = .0001$). Survivals at 6 months was 0% and 50.7% for TA-TMA nonresponders and responders, respectively [14]. Jodele et al [15] reported an overall TA-TMA incidence of 39% (39/100) with 11 of these 39 patients (28%) having high-risk TA-TMA associated with MODS in a 100 patient prospective observational study. PICU admissions for MODS were much higher in children with TA-TMA as compared to those without TA-TMA (46% vs 15%, $P = .01$). The overall survival rate for patients with TA-TMA with MODS who did not receive TMA targeted therapy was 9% (1/11) with 2/11 (18%) patients alive at 6-months from TA-TMA diagnosis. Similar rates are consistently reported from others showing $<20\%$ survival with TA-TMA and MODS with most patients dying within 6-month of TA-TMA diagnosis [13,14,16].

TA-TMA Associated MODS

A high index of suspicion and prospective monitoring is needed to identify TA-TMA and associated MODS. Organ failure due to complement-mediated endothelial injury with TA-TMA can be similar to other common HSCT complications like infections, graft versus host disease (GVHD), or medication side effects, like hypertension. TA-TMA exhibits particular organ injury patterns that could be recognized with careful attention to clinical features and dynamic monitoring of ill patient keeping TA-TMA in the differential diagnosis.

Kidney Injury

Even though acute kidney injury is common after HSCT, symptoms of renal impairment like nephrotic range proteinuria and hypertension along with complement activation were identified as early diagnostic signs of TA-TMA in prospective studies. Transplant recipients with TA-TMA often have nephrotic range proteinuria with a spot urine protein-to-creatinine ratio (urine pr/cr) >2 mg/mg without clinical presentation of nephrotic syndrome (urine pr/cr ratio up to <0.2 mg/mg is normal for adults and <0.7 mg/mg for younger children). A spot urine protein-to-creatinine ratio can serve as a readily accessible and useful biomarker when TA-TMA is suspected and for therapy response monitoring. In contrast, serum creatinine can be a very late and insensitive in detecting impaired renal function in recipients with HSCT, especially in young patients, who have low muscle mass and thus low creatinine generation rates. For these reasons, an elevation of serum creatinine is not required anymore for TA-TMA diagnosis [15]. Laskin et al [17], in a prospective 94 patient cohort showed that pediatric equations including Cystatin C performed better than those including only creatinine. Patients with high-risk TA-TMA presenting with complement activation had a median Cystatin C GFR decline of 75% from pre-HSCT baseline, indicating severe kidney injury with TA-TMA, with 36% of patients progressing to ≥stage 3 chronic kidney disease. Due to the complexity of the clinical presentation, renal symptoms should be correlated with other TA-TMA signs and dynamically monitored. Proteinuria and Cystatin C-based GFR for monitoring of acute kidney injury is being adopted in clinical practices caring for stem cell transplant patients. Arteriolar complement C4d deposits indicating classic complement pathway involvement had been documented in recipients with HSCT with histologic evidence of TA-TMA on kidney biopsies and autopsies [18,19]. C4d immunohistologic stains serve as an additional diagnostic option for complement-mediated endothelial injury for TA-TMA diagnosis when a tissue sample is available.

Cardiac and Pulmonary Injury

Significant pulmonary vascular injury has been shown in biopsy and autopsy specimens in patients with TA-TMA [20]. Clinically, lung TA-TMA presents as hypoxemic respiratory failure with acute progression to pulmonary hypertension (PH) and right sided cardiac failure [21]. Cardiac echocardiography using a PH protocol can identify vascular injury associated with TA-TMA as early as 7 days after HSCT [22]. In the prospective TA-TMA study ($n = 100$) by Jodele et al, PH was diagnosed exclusively in the TMA group. These patients had high-risk disease features including complement activation. Respiratory failure and pericardial effusions were also strongly associated with TA-TMA ($P < .01$) [15]. In a separate prospective screening study of 227 patients, Dandoy et al [22] showed similar findings confirming that clinically significant pericardial effusions after HSCT were associated with TA-TMA ($P < .01$) [23].

Gastrointestinal injury

There is a growing body of literature documenting TA-TMA effect on bowel injury. The most prominent clinical features are intestinal bleeding and intractable pain in patients with TA-TMA associated endothelial injury document in tissue biopsies. El-Bietar et al proposed 8 histologic features aiding in recognition of intestinal TA-TMA and differential diagnosis from intestinal GVHD [23]. Complement C4d deposits were shown to be present in TA-TMA affected bowel vessels in patients who later developed "steroid-refractory GVHD" [24].

CNS Injury

Neurologic symptoms like confusion, headaches, hallucinations, or seizures can be observed in up to half of all patients with TA-TMA. CNS injury most commonly occurs due to acute uncontrolled TA-TMA associated hypertension, including posterior reversible encephalopathy syndrome that may result in CNS bleeding. Patients with long-standing complement-mediated endothelial injury, like those with sickle cell disease, are at the highest risk to develop TA-TMA with neurologic symptoms or posterior reversible encephalopathy syndrome [25].

Blood Stream Infections

In a prospective analysis ($n = 374$) examining the incidence, risk factors, and outcomes of HSCT recipients that developed blood