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REVIEW

A new paradigm: Diagnosis and management of HSCT-associated thrombotic microangiopathy as multi-system endothelial injury

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ABSTRACT

Hematopoietic stem cell transplantation (HSCT)-associated thrombotic microangiopathy (TA-TMA) is now a well-recognized and potentially severe complication of HSCT that carries a high risk of death. In those who survive, TA-TMA may be associated with long-term morbidity and chronic organ injury. Recently, there have been new insights into the incidence, pathophysiology, and management of TA-TMA. Specifically, TA-TMA can manifest as a multi-system disease occurring after various triggers of small vessel endothelial injury, leading to subsequent tissue damage in different organs. While the kidney is most commonly affected, TA-TMA involving organs such as the lung, bowel, heart, and brain is now known to have specific clinical presentations. We now review the most up-to-date research on TA-TMA, focusing on the pathogenesis of endothelial injury, the diagnosis of TA-TMA affecting the kidney and other organs, and new clinical approaches to the management of this complication after HSCT.

1. Introduction

Hematopoietic stem cell transplantation (HSCT)-associated thrombotic microangiopathy (TA-TMA) is now a well-recognized and potentially severe complication of HSCT that can lead to a high risk of death [1]. In those who survive, TA-TMA may be associated with long-term morbidity including hypertension, chronic kidney disease (CKD), gastrointestinal or central nervous system disease, and pulmonary hypertension [2,3].

Over the past several years, there have been new insights into the incidence, pathophysiology, and management of TA-TMA. Specifically, TA-TMA can manifest as a multi-system disease occurring after various triggers of small vessel endothelial injury, leading to subsequent tissue damage in different organs. While the kidney is most commonly affected, TA-TMA involving organs such as the lung, bowel, heart, and brain is now known to have specific clinical presentations. Additionally, TA-TMA shares features with other thrombotic microangiopathies such as atypical hemolytic uremic syndrome (aHUS) and thrombotic thrombocytopenic purpura (TTP), but is now considered a separate disorder occurring post-HSCT [4].

Our limited understanding of the pathogenesis of TA-TMA for the past 30 years has prevented the evaluation of rational therapeutic interventions. In contrast, greater understanding of the roles of the complement alternative pathway in aHUS and ADAMTS13 in TTP has led to targeted therapies to improve clinical outcomes in patients with these disorders [5–7]. Recently, we observed that both the classical and alternative complement systems may be involved in TA-TMA, supporting the potential use of complement modulating therapies in patients at highest risk for the worse outcomes [8]. We now review the most up-to-date research on TA-TMA, focusing on the pathogenesis of endothelial injury, the diagnosis of TA-TMA affecting the kidney and other organs, and new clinical approaches to the management of this complication after HSCT.

2. Clinical and histologic features

TA-TMA is identified when HSCT patients present with microangiopathic hemolytic anemia, defined as de novo acute anemia and thrombocytopenia not explained by another process, elevated lactate dehydrogenase (LDH), excessive transfusion requirements, and schistocytosis in the blood. The diagnosis of TA-TMA requires a very high index of suspicion, especially in the detection of multi-organ involvement, as the diverse signs and symptoms of TA-TMA can be mistaken for other common transplant complications such as graft versus host disease (GVHD), infections, or medication-induced hypertension. TA-TMA can affect multiple organs, each of which exhibits specific features of injury.

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A tissue diagnosis can be challenging in HSCT recipients, especially children, at high risk for procedural complications. Therefore, relying on objective, organ-specific clinical criteria is critical to the timely recognition of TA-TMA after HSCT [9–11].

2.1. Kidney

The kidney appears to be the most common organ affected by small vessel injury associated with HSCT. There are several "renal" manifestations of TA-TMA, including decreased kidney function — as evidenced by a less-than-normal glomerular filtration rate (GFR), proteinuria, and hypertension [4,12,13].

It should be noted that, especially in children, serum creatinine and creatinine-based GFR estimates may not always be sensitive enough to detect renal dysfunction after HSCT because of the small body size and potentially low muscle mass of these patients [14–16]. In patients at risk for TA-TMA, kidney function should be monitored precisely and regularly. This strategy facilitates the early recognition of a decrease in GFR and thus the timely diagnosis of and treatment initiation for TA-TMA· since prompt clinical interventions for TA-TMA appear to be associated with improved outcomes [17]. Therefore, we strongly suggest adopting alternative and apparently more sensitive modalities of GFR monitoring. Nuclear medicine isotopes or other injected tracers used for measuring GFR make for more complicated, invasive, and costly assessments than serum creatinine determinations but represent the gold standard for measuring kidney function [16]. Alternatively, serum cystatin C measurements allow more accurate GFR determinations than serum creatinine measurements if appropriate formulas are used to calculate cystatin C-based GFR estimations [18,19]. However, more research is needed to determine if potential non-GFR determinants of cystatin C, such as steroid use, thyroid disease, or inflammation, impact the precision of cystatin C to estimate kidney function in the HSCT population [16]. Until more data becomes available, pediatric centers should work with their nephrology and nuclear medicine colleagues to develop protocols that extend beyond mere serum creatinine measurements to accurately and repeatedly monitor GFR in their transplant recipients.

Regular urine monitoring for proteinuria is another valuable and relatively inexpensive tool to detect the development of TA-TMA. Centers should thus use routine urinary screening for new-onset proteinuria as part of their peri-transplant care. In children with proteinuria during the daytime, this should include an assessment of a first-morning urine sample to rule out a benign orthostatic component. It may also include a more specific quantification of albuminuria, which has been associated with a higher risk of CKD and mortality among HSCT recipients [20,21]. Additionally, a spot urine protein-to-creatinine ratio (normal for patients at least 3 years of age is <0.2 mg/mg with ratios of up to 0.7 mg/mg considered normal in younger children, and nephrotic range is >2 mg/mg) can be obtained in those patients with either evidence of proteinuria on routine dipstick analysis or in those with potentially false negative urinalysis results from dilute urine secondary to high volume intravenous fluids or tubular injury after HSCT. Sequential protein-to-creatinine ratios can then be used to more precisely follow proteinuria over time. Such quantitative assessments may also offer prognostic information (see below) in those individuals who develop TA-TMA [4].

The diagnosis of renal TA-TMA requires a high degree of clinical suspicion and should be especially considered in patients requiring substantially more antihypertensive therapy than would otherwise be expected in those receiving corticosteroid or calcineurin inhibitor therapy for GVHD prophylaxis or treatment [12,22]. Accordingly, we have adopted an unwritten rule at our center stating that "HSCT recipients are allowed one antihypertensive agent for receiving steroids, and a second for their calcineurin inhibitor: TA-TMA should be strongly considered in any patient requiring more than 2 antihypertensive medications, until proven otherwise" [22]. We refer providers to consensus guidelines for the diagnosis of hypertension in children and adolescents especially since certain groups of HSCT patients, such as those with bone marrow failure syndromes and metabolic disorders, can have short stature due to their primary disease and blood pressure normal values are based on age, gender, and height [23].

If hypertension is indeed confirmed in a transplant recipient, it should be treated expeditiously. In pediatric HSCT recipients, especially those diagnosed with TA-TMA, blood pressure should accordingly be maintained at least below the 95th systolic and diastolic percentages for age, gender, and height and below 140/90 in adult patients [22,23]. Regarding the treatment of hypertension in HSCT recipients, several aspects are worth consideration. First, if the hypertension is at least in part due to TA-TMA, addressing this underlying cause obviously represents a highly reasonable first choice in management. Second, treating these patients with classes of antihypertensive agents that appear to target the underlying pathophysiological mechanisms of their elevated blood pressure is intuitive: In patients on steroids, prescribing diuretics to counter steroid-induced fluid and sodium retention and using vasodilators to antagonize steroid-associated vasoconstriction appears reasonable, as does the latter treatment for patients on calcineurin inhibitors due to their vasoconstrictive properties [24]. In addition, there appears to be a role for antagonists of the renin–angiotensin system (RAS) in patients with TA-TMA and hypertension as the endothelial inflammation seen in this patient population appears to activate the RAS [25]. At our center, we especially prefer the use of angiotensin receptor blockers (ARBs), such as losartan, in this setting because they may target the RAS more broadly than angiotensin converting enzyme inhibitors. It is important to note that agents blocking the RAS should be used with caution in subjects with significant acute kidney injury, as commonly occurs in some subjects with TA-TMA. Therefore, they may offer a more favorable risk/benefit profile when used to treat the chronic complications of TA-TMA including proteinuria and/or hypertension. In patients with TA-TMA accompanied by both hypertension and significant acute kidney injury, vasodilating agents (in particular calcium channel blockers) may represent a relatively safe first line class of agents to treat their acute hypertension early in the disease process.

Renal dysfunction, proteinuria, and hypertension may also be observed in transplant recipients who do not develop TA-TMA [26]. Alternative etiologies, other than TA-TMA, in this patient population include, but are not limited to, exposure to nephrotoxic and pro-hypertensive medications and infections such as BK virus nephropathy [27,28]. Because of the complexity introduced into the care of transplant recipients by this plethora of findings and differential diagnoses, only repeated and diligent assessments by experienced clinicians will therefore result in a high likelihood of accurately diagnosing (or ruling out) TA-TMA and thus optimizing outcomes.

In view of these challenges, it is not surprising that the most reliable modality to diagnose TA-TMA is histological. Unfortunately, an autopsy diagnosis remains a more common way of obtaining such histological proof than would be desired. In patients who have evidence of renal dysfunction, a kidney biopsy is another valid approach to be considered if there is concern for TA-TMA, although this procedure carries an obviously increased risk of bleeding and other complications in these transplant recipients with their often present thrombocytopenia and hypertension [22].

In our experience, a carefully planned and performed kidney biopsy facilitates the diagnosis of TA-TMA and guides medical management, especially in those patients without irreversible complications. Histopathologic findings of TA-TMA are not limited to the demonstration of microthrombi in the glomeruli, but may also include characteristic patterns of C4d deposition in the renal arterioles, as previously described [29]. If kidney biopsy is considered in HSCT recipient, a careful determination of the risk and benefit of a kidney biopsy is critical, as is the performance of the procedure by an experienced team in a setting where the patient can be carefully monitored.

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