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Review

New approaches in the diagnosis, pathophysiology, and treatment of pediatric hematopoietic stem cell transplantation-associated thrombotic microangiopathy

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ABSTRACT

Hematopoietic stem cell transplantation (HSCT)-associated thrombotic microangiopathy (TA-TMA) is an understudied complication of HSCT that significantly affects transplant-related morbidity and mortality. Over the past several decades, the cause of TA-TMA has remained unknown, limiting treatment options to non-specific therapies adapted from other diseases. Recent prospective studies dedicated to the study of TA-TMA have provided new insights into the pathogenesis of, and genetic susceptibility to TA-TMA, raising awareness of this important transplant complication and allowing for the identification of potentially novel therapeutic targets. Specifically, many patients with TA-TMA develop multi-organ tissue injury through endothelial damage mediated by the activation of the complement pathway, leading to rational therapeutic strategies including complement blockade. This new knowledge has the potential to favorably influence clinical practice and change the standard of care for how patients with TA-TMA are managed. In this review, we summarize novel approaches to the recognition and management of TA-TMA, using case examples to illustrate key clinical points that hopefully lead to improved short and long-term outcomes for these complex HSCT patients, who remain at significant risk for treatment-related morbidity and mortality.

Contents

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1. Introduction

Hematopoietic stem cell transplantation-associated thrombotic microangiopathy (TA-TMA) is caused by systemic vascular endothelial injury triggered by the transplantation process [1,2]. TMA affects multiple organs and occurs in about 30% of hematopoietic stem cell transplant (HSCT) recipients. Half of patients who develop TA-TMA (~15% of all transplant patients) will present with severe disease and these cases have mortality rates in excess of 80%. Recently, it has been shown that complement system activation in patients with TA-TMA is a very poor prognostic sign and implicates complement dysregulation as a key pathway in the pathogenesis of TA-TMA and its disease phenotype [3]. The original diagnostic criteria for TA-TMA used hematologic and kidney injury markers that can only detect advanced disease and therefore often delay TA-TMA diagnosis in complex transplant patients [4–7]. This delay in diagnosis significantly impacts the institution of early therapeutic measures. We have shown that HSCT patients with TA-TMA respond to a complement blocking agent (eculizumab), but therapy is often started late after multi-organ injury has already occurred [8,9]. We also observed that patients who received complement-blocking therapy early in their disease course had better responses and outcomes. There is a significant unmet medical need to recognize TA-TMA early in the disease presentation or even to proactively identify patients who are at high-risk for a severe TA-TMA phenotype prior to the start of transplantation. In the past several years, significant progress has been made in advancing our understanding of TA-TMA, guiding favorable changes in clinical practice. The objectives of this review are to summarize new advances in TA-TMA diagnosis, pathophysiology and treatment while using case studies to provide practical suggestions for clinical management.

2. Refined TA-TMA diagnostic criteria

2.1. Laboratory testing

TA-TMA is a systemic disorder that occurs when endothelial injury in patients treated with HSCT presents with microangiopathic hemolytic anemia and platelet consumption, resulting in damage to the microcirculation. This endothelial injury affects multiple organs, both over the short- and long-term after transplant. Some patients exhibit signs of TA-TMA in one particular organ, such as the kidney, lung or bowel, while others present with multi-organ involvement that can result in severe, life-threatening, acute organ failure. It is not yet understood why certain patients have a predisposition to injury of particular organs, making it important to comprehensively assess the most commonly affected organs (kidney, bowel, heart/lung) in patients with clinical concern for TA-TMA [7,10].

The diagnosis of TA-TMA requires a high index of suspicion, especially since systemic signs of TA-TMA are often mistaken for other transplant-related blood test abnormalities, particularly prior to donor cell engraftment when cytopenia is expected as part of the transplant course. In patients who are awaiting donor cell engraftment and are still transfusion dependent it is very important to assess transfusion needs. Hemolytic or consumptive processes are suspected when transfusions are required several times per week, out of proportion to what is expected before engraftment, and hemoglobin and platelet decreases are significant and acute without evidence of blood loss. It is also important to note that in case of severe TA-TMA, schistocytosis might be absent due to high vascular permeability and red blood cell extravasation into the tissues. Accordingly, it has been observed that elevated blood lactate dehydrogenase (LDH), proteinuria, and hypertension are the earliest signs of TA-TMA and should trigger more comprehensive evaluation in HSCT patients [3,11,12].

We recently proposed refined TA-TMA diagnostic and risk criteria that included proteinuria, hypertension, and elevated markers of the activated terminal complement complex (sC5b-9) that were not part of previous diagnostic criteria but were indicative of disease phenotype and clinical outcomes [3]. Taking into consideration the challenges of identifying TA-TMA in the complex transplant patient, we observed that patients exhibiting at least five of the seven diagnostic criteria listed in Table 1 were very likely to have multi-organ TA-TMA and should be further evaluated with organ-specific tests. While haptoglobin was not included in these new updated diagnostic criteria, haptoglobin serves as an important prognostic marker of overall inflammatory status. In our prospective study we showed that patients with a severe TA-TMA phenotype resulting in multi-organ failure or death had elevated haptoglobin levels at TA-TMA diagnosis. Haptoglobin as a non-specific inflammatory marker likely reflects overall tissue inflammation and may take a prolonged time to drop below normal in patients with severe TA-TMA.

In several studies, proteinuria was more informative as a TA-TMA marker of kidney injury as compared to elevations of serum creatinine, especially in patients with prolonged illness and significant muscle mass loss, in whom serum creatinine often overestimates kidney function [13–17]. Proteinuria can be assessed by simple urinalysis (random urine protein of ≥30 mg/dL), but in patients receiving high volume hydration or with significant capillary leak, random urine protein/urine creatinine ratios are often more informative, as ratios of ≥2 mg/mg have been strongly associated with a diagnosis of TA-TMA in prospective studies [3].