Consider Thrombotic Microangiopathy in Pediatric and Hematopoietic Stem Cell Transplant Patients

September 13, 2011
By Rina Meyer, MD [1] and James B. Bussel, MD [2]

The article by Dr. George is of great use to the practicing clinician, not only in the hematology-oncology setting but also in general practice or emergency medicine.

The Value of ADAMTS13 Activity in Diagnosing TTP

Although ADAMTS13 levels may be decreased in other disorders, such as pre-eclampsia[1] and idiopathic portal hypertension,[2] assessment of ADAMTS13 is still a very useful tool in the diagnosis of thrombotic thrombocytopenic purpura (TTP), or in its exclusion. Typically, patients with TTP (congenital or acquired) have severely decreased levels of ADAMTS13 (often less than 5%), whereas patients with other disorders have higher, albeit decreased, ADAMTS13 activity.[3]

In a paper by Hovinga et al, ADAMTS13 activity was determined for 396 patients. Severe deficiency was noted in 17% of these patients, including 43 with acquired TTP, 14 with congenital TTP, 10 with unspecified TMA, and 2 patients out of 15 with malignancy or chemotherapy-associated angiopathy. Although ADAMTS13 activity less than 5% was noted in 60% of patients with acute TTP, it was not found in any patients with hemolytic-uremic syndrome (HUS) or in any patients with transplant-associated TMA.[3] This study suggests that ADAMTS13 is relatively specific for primary TTP, and potentially is a useful tool in its diagnosis or exclusion. The utility of this assay may also be increased by the rapid turnaround possible with the FRETS assay, which has been shown to have accuracy comparable to that of earlier assays.[4] Additionally, although antibodies to ADAMTS13 are not uniformly positive in patients with acquired TTP, their presence also helps suggest a diagnosis.

Useful Assays in the Diagnosis of TMA

Additional studies that may provide benefit are the assay for von Willebrand factor propeptide (VWFpp), a marker of endothelial cell damage, and the assay for thrombomodulin. Ito-Habe described a study of 75 patients with TMA, 30 of whom had decreases in ADAMTS13 and 45 of whom had normal levels. Plasma levels of thrombomodulin and VWFpp were high in these patients (particularly those with nondecreased levels of ADAMTS13), especially those who had poor outcomes.[5] With further study, these additional markers may be useful adjuncts in the diagnosis of patients with TMA.

TMA in the Pediatric Setting

Although Dr. George’s work focuses on adult patients, we are also concerned about TMA in the pediatric setting. While admittedly a rare event, there are several case reports in the literature that describe TMA secondary to malignancy or autoimmune disease. For example, Rizzo et al described TMA as the first presentation of gastric adenocarcinoma in a 14-year-old with a family history of related carcinomas and a 1-month history of vague symptoms, including early satiety, fatigue, and joint pain.[6] There are two other case reports in the literature of adolescent patients with gastric adenocarcinoma who developed pulmonary disease from TMA.[7,8] In children with unexplained microangiopathy, as Dr. George suggests, an evaluation for malignancy should be undertaken. In the pediatric setting, one might argue that an evaluation for an autoimmune illness should also be performed. Muscal et al described eight children initially diagnosed with acquired TTP (with decreased ADAMTS13 and/or antibodies to ADAMTS13) who went on to develop systemic
autoimmunity. Seven of the eight patients were ultimately diagnosed with systemic lupus erythematosus, some at the time of TTP diagnosis. The majority of the patients developed immune-mediated lupus nephritis and antiphospholipid antibodies.[9] Another case report, by Patra and Scott, described a 12-year-old patient whose first presentation of diabetic ketoacidosis was concurrent with TMA.[10] These cases, along with other reports, suggest that autoimmune illness should also be considered part of the differential diagnosis in patients presenting with microangiopathy.

**Transplant-Associated TMA and Hematopoietic Stem Cell Transplant Patients**

Finally, Dr. George does not discuss an important subset of oncology patients, those undergoing hematopoietic stem cell transplant. The incidence of this disorder in transplant recipients is variable, with estimates ranging from 0.5% to 70%.[11] One large study of 1219 transplant recipients revealed an incidence of 5.9%,[12] while an autopsy study of 314 recipients demonstrated an incidence of 20%.[13] suggesting that the disease may be underdiagnosed given the multiple comorbidities and confounding factors in transplant recipients.

The pathophysiology of transplant-associated TMA is believed to be endothelial cell damage (from myriad causes, including direct cytotoxic damage, decreased vascular endothelial growth factor levels, exposure to high levels of cytokines, etc.) leading to exposure of the subendothelium with subsequent platelet activation and aggregation. Risk factors include female gender, unrelated/mismatched donors, infection (adenovirus, HHV6, BK viruria, etc), graft-vs-host disease, underlying lymphoid malignancy, and concurrent infections.[11,14] There does not appear to be a significant risk difference between reduced-intensity conditioning and myeloablative regimens, although some treatments, such as total body irradiation and fludarabine, may cause more direct endothelial damage than others.[15] Additionally, while patients who undergo allogeneic transplant are at higher risk, the disease is still found in recipients of autologous stem cell rescue.[11] Although the mortality of transplant-associated TMA is high (estimated at 60% to 90%), there are still possibilities for treatment.[14] As Dr. George points out, there is limited evidence for use of plasma exchange, although it is often attempted in the face of possible TTP. Plasma exchange does little to correct the underlying mechanisms of transplant-associated TMA, however. Given the association between TMA and calcineurin inhibitors, such as cyclosporine, tacrolimus, and sirolimus (Rapamune), changing to different immunomodulatory agents, rather than reducing doses, may be beneficial.[11] One study by Changsirikulchai et al failed to find any correlation between cyclosporine level and extent of damage due to TMA.[13] There is also evidence for the use of rituximab (Rituxan), although its mechanism of action is unclear.[11] As with malignancy-associated TMA, it is important to have a high index of suspicion for TMA in transplant patients. Early recognition may lead to greater efficacy of treatment.

**Conclusion**

Overall, Dr. George shares his valuable long-term experience in discussing several key points regarding malignancy-related TMA. His detailed reports of patients with TMA are invaluable to our understanding of this illness. It is important to remember, as he suggests, to attempt to make a diagnosis of malignancy in a patient with a history of concern before assuming that a case of TMA is primary TTP and initiating plasma exchange.

**Financial Disclosure:** The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

**References:**


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