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Editorial

Thrombotic microangiopathy after allogeneic bone marrow transplantation: a pathologic abnormality associated with diverse clinical syndromes

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Thrombotic microangiopathy (TMA) is a pathologic term that describes a pattern of arteriolar thrombi associated with intimal swelling and fibrinoid necrosis of the vessel wall.[1] TMA is the characteristic pathologic feature of the clinical syndromes, thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS), but the same pattern of vascular damage and thrombosis occurs in other conditions such as systemic sclerosis, systemic lupus erythematosis, antiphospholipid antibody syndrome, malignant hypertension, and pre-eclampsia.[1] TMA is not itself a diagnosis and is not an etiology for a specific disorder; it is a pathologic abnormality associated with diverse clinical syndromes. Systemic TMA associated with any disorder may cause the hematologic features of microangiopathic hemolytic anemia (defined by evidence for hemolysis with fragmented red cells and a negative direct antiglobulin (Coombs') test) and thrombocytopenia. Microangiopathic hemolysis may also occur in other disorders that can cause microvascular thrombosis, such as metastatic carcinoma,[2] and the angioinvasive infections, *Aspergillus*[3] and cytomegalovirus.[4]

These observations on TMA and related hematologic abnormalities provide the background for interpretation of the article in this issue of *Bone Marrow Transplantation* by Nishida *et al*,[5] who describe apparently localized intestinal TMA after allogeneic BMT. Nishida *et al* report 16 patients following allogeneic BMT, who had bloody diarrhea and in whom intestinal pathology demonstrated arteriolar microthrombi consistent with TMA. The observation of intestinal TMA was made at autopsy in the first seven patients of their series and then by colonoscopy in the next nine patients. Although acute GVHD was the clinically suspected cause of the bloody diarrhea, the authors concluded that the etiology was a different disorder associated with TMA, because the pathologic features of TMA have not been described as part of acute GVHD.[6] They used this information to diminish, rather than intensify, immunosuppressive treatment, since immunosuppressive drug toxicity has been associated with the development of TMA. This management decision carried considerable risk since most patients had received transplants from unrelated donors, had received mismatched stem cells, and had stage III or IV aGVHD.

The strengths of this report are the pathologic observation of intestinal TMA, suggesting a novel etiology for acute bloody diarrhea following allogeneic BMT, and the suggestion of successful management by diminishing immunosuppressive treatment. The weaknesses of this report are that the data are limited to pathologic descriptions of the intestines, the pathology of other organs in the seven patients who had an autopsy is not reported, other stigmata of acute GVHD are not described, and the number of patients who also had pathologic evaluation for bloody diarrhea without finding TMA is not reported. Systemic fungal or viral infections apparently did not occur.

When TMA is described in patients following allogeneic BMT, it is often implied that TMA is equivalent to the clinical diagnosis of TTP. In the report by Nishida *et al*,[5] seven patients were treated with plasma exchange or plasma infusion, implying that the observations of TMA and the presence of red cell fragmentation were considered to be evidence for TTP. However, it is important to emphasize that TMA and TTP are not synonymous terms. The clinical diagnosis of TTP predicts a rapidly fatal illness[7] and requires urgent treatment with plasma exchange.[8] TTP and HUS in adults may be described by the comprehensive term TTP-HUS, because the clinical features of these two syndromes are not distinct from each other and the pathologic features of TMA are identical in both syndromes.[1,9] Observations that the von Willebrand factor-cleaving protease, termed ADAMTS13, may be absent in patients with TTP have provided important insight into the pathophysiology of this syndrome,[10] but have not yet provided support for management decisions.[11] Severe deficiency of ADAMTS13 has not been reported in patients diagnosed with TTP following BMT.[12]

The decision for intervention with plasma exchange treatment is difficult in most patients with TTP-HUS because the diagnostic features are not specific.[9] The diagnosis of TTP-HUS and the clinical decision regarding plasma exchange treatment are a particularly difficult dilemma in patients following allogeneic BMT. TTP has been considered to be a BMT-related complication, but case series describing patients who were diagnosed with TTP-HUS after allogeneic BMT are remarkably inconsistent. In our systematic review of all published case series, the frequency of diagnosis of TTP-HUS following allogeneic BMT varied from 0 to 64%; 28 different sets of diagnostic criteria were described in the 35 case series; mortality varied from 0 to 100%; and benefit of plasma exchange treatment could not be documented.[12] Autopsies have been reported for 35 patients who were diagnosed with TTP-HUS following allogeneic BMT; none had systemic TMA characteristic of patients with TTP.[12] The most common cause of death determined by autopsy in

these 35 patients was systemic infection, consistent with the ability of systemic fungal and viral infections to mimic all clinical features of TTP-HUS.[12]

Therefore, the actual occurrence of TTP or HUS following allogeneic BMT may be quite rare[12] and the data presented by Nishida *et al*[5] cannot be assumed to indicate a syndrome comparable to TTP or HUS. Since there is no evidence for efficacy of plasma exchange treatment in patients with suspected TTP-HUS following allogeneic BMT, there may be no benefit for early diagnosis. In contrast to previously healthy subjects with clinically suspected TTP who require urgent intervention with plasma exchange, it may be more appropriate to defer plasma exchange treatment for patients with suspected TTP-HUS following allogeneic BMT until alternative etiologies can be confidently excluded. The high frequency of severe and potentially fatal complications caused by plasma exchange[13,14] provides an additional incentive to defer this treatment.

The observations of Nishida *et al*[5] may provide new insights for management of BMT-related complications. However, this report requires systematic observations by other transplantation centers to confirm the pathologic features of TMA in patients with acute bloody diarrhea, to determine how common TMA may be among all patients with bloody diarrhea, to investigate potential etiologies for the TMA, and to establish the safety of diminishing, rather than intensifying, immunosuppressive treatment when intestinal TMA is observed and acute GVHD is apparently excluded.

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