Hematopoietic Stem Cell Transplantation-Associated Thrombotic Microangiopathy: Pathophysiology and Differentiation from Graft versus Host Disease

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Transplant-associated thrombotic microangiopathy (TA-TMA) is a severe and often fatal complication of allogeneic hematopoietic stem cell transplantation (HSCT), often associated with or preceded by graft-versus-host disease (GVHD). Diagnostic criteria proposed by an International Working Group include all of the following: (1) > 4% schistocytes on blood smear; (2) thrombocytopenia $< 50 \times 10^9$/L or > 50% reduction from previous count; (3) increased serum lactate dehydrogenase; (4) decrease of hemoglobin concentration; and (5) decreased serum haptoglobin.[1] The group proposed the name TAM (transplant-associated microangiopathy) for the condition but the designation of TA-TMA has been more widely accepted.[2]

Shortly after the discovery of the von Willebrand factor-cleaving protease, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13), and its severe deficiency as the diagnostic hallmark of acquired or congenital thrombotic thrombocytopenic purpura in the late 1990s, it became evident that TA-TMA was not associated with severe ADAMTS13 deficiency. Instead, endothelial cell injury induced by chemotherapy, radiotherapy, calcineurin inhibitor treatment, GVHD caused by donor cytotoxic T cells, and infections was evoked as pathogenetically most relevant. Recently, variants in several genes involved in complement activation pathways were reported to strongly predispose to TA-TMA.[3]

Gavriilaki et al,[4] in this issue of *Thrombosis and Haemostasis*, set out to elucidate the pathogenesis of TA-TMA. Over 3.5 years, they consecutively recruited 10 patients developing TA-TMA, 10 being diagnosed with GVHD and 10 control HSCT patients, and studied complement activation markers, extracellular deoxyribonucleic acid (DNA) and DNA-myeloperoxidase (MPO) complexes as remnants of neutrophil extracellular traps (NETs), soluble thrombomodulin and soluble vascular cell adhesion molecule-1 as endothelial injury parameters, and thrombin–antithrombin (TAT) complex as marker of coagulation activation.

The sC5b-9, DNA and DNA-MPO, and TAT complex levels were found to be significantly higher in the patients with TA-TMA compared with the controls, whereas those with GVHD showed values not different from controls. In contrast, soluble thrombomodulin was similarly increased over control levels in both TA-TMA and GVHD patients.

The data are interpreted to suggest that complement activation, neutrophil activation with NETs release, and coagulation activation may all contribute to the pathogenesis of TA-TMA. How exactly the various overactive defense systems interact and influence each other remains to be investigated. Whether complement activation or NET markers will become useful diagnostic tools to distinguish TA-TMA from GVHD remains to be studied in much larger prospective cohorts of HSCT patients.

Conflict of Interest

B.L. reports personal fees from Baxalta/Shire/Takeda, Ablynx, Siemens, Bayer, Alexion, and Roche, outside the submitted work. In addition, B.L. has a patent Von Willebrand factor-cleaving protease issued.

References

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