

## THROMBOTIC MICROANGIOPATHY (TMA) IN ATYPICAL HEMOLYTIC UREMIC SYNDROME (AHUS) VERSUS THROMBOTIC THROMBOCYTOPENIA PURPURA (TTP)

TMA is a general category consisting of abnormal deposition of thrombi in microvessels throughout the body and is associated with many disorders. (e.g. aHUS, HIT, DIC, TTP and many more). However, there are substantial differences between the compositions of the vesicular obstructions in most of these TMA's. In TTP for example, the obstructions are usually platelet clumps with little or no fibrin, while in aHUS, the opposite is true where you can find fibrin clots along with complement proteins and little or no platelet deposition. Yet the sequelae of these diseases have many similarities that cause them to be clinically linked. Clinically, these clumps in the microvascular supply can cause significant organ damage to Lungs, Liver, Brain, Gastrointestinal Tract and Kidneys. The clumps are also associated with hematologic trauma to RBCs such that hemolysis and or schistocytes can be found along with physiologic changes in blood pressure, decreased haptoglobin, hemoglobin, platelet levels and changes related to the specific organ dysfunction mentioned earlier such as neurological symptoms due to brain dysfunction, .

Recent publications have shown some interesting differentiation for TTP and aHUS disorders due to the TMA so that better and quicker diagnosis can be made to prevent death and morbidity associated with the organ dysfunction.

In TTP, the current findings show a strong association of this disorder with a severe decrease in ADAMTS13 (a zinc metalloprotease) which is used to decrease the ultra large or high molecular weight vonWillebrand (VWF) multimers found and released from the Weibel-Palade bodies in endothelial cells. The ultra-large VWF when released can be broken down to lower molecular weight polymers when the VWF is exposed to high shear stress found in the microvascular circulation (arterioles and capillaries). In the absence of ADAMTS13 these high molecular weight polymers have a strong attraction for platelets and cause thrombocytopenia and clumping. Levels of ADAMTS13 >10% are usually sufficient to correct the obstructed circulation and can be obtained by plasma transfusion in patients that have a congenital deficiency of ADAMTS13 (Upshaw-Schulman Syndrome, with levels <0.1 U/ml). In patients with an autoantibody against this enzyme, more frequent transfusions are needed along with immunosuppressive therapy to correct the deficiency.

In aHUS, the etiology is very different. The clumping is not related to VWF, but rather the activation of Complement components (mainly in the alternate pathway either inherited or acquired) and coagulation. The differentiation between the TTP and aHUS can be seen when the levels of ADAMTS13 are >5%. Renal impairment may be associated with elevated blood pressure and/or abnormal urinalysis and/or elevated Creatinine. The clumps in the kidneys have fibrin and Complement associated within them and there are marked decreases in the levels of many Complement components e.g. C3, C4, regulatory Factor H(CFH), control Factor I (CFI), Factor B(CFB) and CD46 (membrane cofactor protein, MCP). Plus, in a case of autoimmunity or a congenital deficiency, there can be Factor H autoantibody or deficiency which will reduce the Factor H levels that regulate the alternate pathway of Complement activity. New immunosuppressive therapies are being

tested which inhibit the activation of the Complement system and prevent end-stage renal disease and death.

In short for these two TMAs, TTP can be diagnosed by performing an ADAMTS13 assay with inhibitors usually after correcting the thrombocytopenia by plasma infusion. aHUS can be diagnosed by performing Complement Assay Profiles after determining a lack of response by a plasma infusion or ADAMTS13 levels >10% without any inhibitors. Plasma exchange therapy can be a useful way to reduce the Complement activation.