THE ROLE OF INNATE IMMUNE MECHANISMS IN THE PATHOGENESIS OF THROMBOTIC THROMBOCYTOPENIC PURPURA

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Background: The protease catalyzing the maturation of von-Willebrand factor (ADAMTS13) plays critical role in the pathogenesis of thrombotic thrombocytopenic purpura (TTP). Genetic (mutations of *ADAMTS13*) and autoimmune (inhibitory autoantibodies against ADAMTS13) risk factors contribute to the development of TTP but direct triggers are needed to exacerbate acute disease.

Aim: The aim of our recent studies was to identify innate immune mechanisms associated with acute TTP, therefore, complement activation and neutrophil activation were investigated in the setting of acute TTP.

Patients: Multiple EDTA-plasma and serum samples of 38 TTP patients were investigated together with samples of 20 healthy controls.

Method: ADAMTS13 activity and anti-ADAMTS13 inhibitory antibodies were measured by the VWF-FRET73 assay. Complement parameters (C3, Factors H, I, B and total alternative pathway activity) together with complement activation fragments (C3a) or complexes (C1rs-INH, C3bBbP, sC5b9) were measured by ELISA or RID. A stable complex of PMNE-proteinase-inhibitor was measured by ELISA (Calbiochem, Merck-Millipore, Darmstadt, Germany).

Results: Increased levels of C3a, and SC5b9 were observed in TTP during acute episodes, as compared to healthy controls. Decreased complement C3 levels indicative for complement consumption occurred in 15% of acute TTP patients. The sustained presence of anti-ADAMTS13 inhibitory antibodies in complete remission was associated with increased complement activation. Furthermore, acute TTP was also associated with increased PMNE levels, increased PMNE levels and deficient ADAMTS13 activity together characterized hematologically active disease. PMNE concentration inversely correlated to disease activity markers platelet count ($r= -0.349$, $p=0.032$) and hemoglobin levels ($p= -0.382$ $p=0.018$). There was positive correlation between PMNE levels and complement activation markers C3a and Bb.

Conclusions: Activation of two important arms of innate immunity, the complement and neutrophils, was shown in acute TTP, and there was positive correlation between the two. Our

data support previous observations that neutrophil extracellular traps (NETs) may be released in acute TTP, NETs may activate complement and potentially contribute to the pathophysiology of this disease. These results support the ‘multiple hit’ model of the pathogenesis of TTP.

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