More on the pathogenesis of thrombotic thrombocytopenic purpura. Comment on "Acquired thrombotic thrombocytopenic purpura without detectable anti-ADAMTS13 antibodies: a possible underlying autoimmune mechanism" and on "The different faces of thrombotic thrombocytopenic purpura"

In recent decades, many publications have clarified the pathophysiology of thrombotic thrombocytopenic purpura (TTP), a life-threatening disease characterized by microangiopathic hemolytic anemia, thrombocytopenia and multiorgan failure.[1] TTP is a clinical entity caused by the deficiency of ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13).[2,3] ADAMTS13, also known as von Willebrand factor (VWF) cleaving protease, is responsible for cleaving VWF multimers, thereby quenching the heightened activity of ultra-large VWF multimers in binding to Gp1b receptors on platelets. In the absence of ADAMTS13 (i.e., in TTP), ultra-large VWF multimers accumulate in plasma, resulting in the widespread formation of VWF- and platelet-rich microthrombi.[2,3]

Congenital TTP is caused by defects in the *ADAMTS13* gene, leading to decreased or absent enzyme activity.[4] In contrast, in most patients with immune-mediated TTP (iTTP), ADAMTS13 deficiency is an acquired disorder due to the development of antibodies against ADAMTS13, which promote the clearance of ADAMTS13 from the circulation or inhibit its activity.[5]

Mariotte *et al*. reported that TTP can also occur without anti-ADAMTS13 antibodies as an acquired form of unknown cause (uTTP) and unclear mechanism.[6] The same group reported that 20% of the cases in their national cohort were uTTP,[7] although 21% of them needed to be revisited because anti-ADAMTS13 antibodies were actually detected during follow-up. In the remaining cases, the absence of anti-ADAMTS13 antibodies, searched for using enzyme-linked immunosorbent assays, excluded the presence of ADAMTS13 activity inhibition, as confirmed by the Bethesda method or plasma mixing assay. Therefore, the authors suggested a non-immune mechanism involving the destruction or consumption of ADAMTS13, and concluded that the absence at baseline of detectable anti-ADAMTS13 antibodies in patients with typical features of iTTP (such as young age, cerebral involvement, severe thrombocytopenia, and severe ADAMTS13 deficiency) should not rule out a diagnosis of iTTP.

In the lively discussion surrounding these findings,[8] it is important to rememeber that anti-ADAMTS13 antibodies can circulate free or complexed with the ADAMTS13 enzyme. Lotta *et al*. reported a group of iTTP patients (37% of all acquired TTP cases) in whom reduced ADAMTS13 activity was not associated with anti-ADAMTS13 autoantibodies, and showed that these patients had ADAMTS13-specific circulating immune complexes.[9] Increasing levels of ADAMTS13-specific circulating immune complexes were found to be clinically associated with a higher number of plasma exchange procedures required to achieve clinical remission. Moreover, Mancini *et al*. reported an increased risk of recurrence in patients with circulating immune complexes detected during the acute disease phase.[10] Overall, while the majority of TTP cases are immune-mediated, secondary causes may account for 10% to 15% of all the presentations, including pregnancy-related TTP, infection-related TTP (human immunodeficiency virus, cytomegalovirus, or influenza), malignant hypertension and drug-induced TTP. All these cases are associated with severely reduced ADAMTS13 and require treatment of both the underlying TTP and of the precipitating causes.[11] Moreover, Kubo *et al*. reported a case of TTP caused by influenza A (H1N1) without anti-ADAMTS13 antibodies, which was successfully treated with plasma exchange.[12] Initially, ADAMTS13 activity was not significantly decreased and autoantibodies were negative but later ADAMTS13 activity decreased markedly.[12] To understand the role of endothelial cell perturbation, Mancini *et al*. described significant changes in the VWF-ADAMTS13 axis in patients with coronavirus disease 2019 (COVID-19), including an elevated VWF:Ag to ADAMTS13 activity ratio which was strongly associated with disease severity.[13] This imbalance enhances the hypercoagulable state of COVID-19 patients as well as their risk of microvascular thrombosis. In addition, it significantly worsens the clinical course of patients with iTTP and low ADAMTS13 activity affected by COVID19.[14]

The consensus guideline introduced by Scully *et al*. in 2017 and reports of several other groups offered a comprehensive update on the management and classification of TTP by addressing both acquired and inherited forms of TTP, including the diagnostic criteria and the importance of ADAMTS13 testing for TTP diagnosis.[11,15] A major clue to our understanding of ADAMTS13 was introduced by Roose *et al*. who showed that this protease usually circulates in an open conformation during the acute phase of iTTP but remains primarily closed during remission, with ADAMTS13

activity higher than 50% and undetectable anti-ADAMTS13 autoantibodies.[16] All in all, despite major advances in recent years in the understanding of the disease, many aspects of its pathophysiology still remain unclear. TTP remains primarily a clinical diagnosis, which must be confirmed by the presence of severely reduced ADAMTS13 activity (<10%) with or without the presence of anti-ADAMTS13 antibodies.

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