Acquired thrombotic thrombocytopenic purpura of unidentified pathophysiology in patients with severe disease: completing the landscape of thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura (TTP) results from a severe (activity <10 IU/dL) ADAMTS13 deficiency, typically categorized as congenital (cTTP), immune-mediated (iTTP), or acquired with an unknown mechanism (uTTP). Recently, our group proposed the term uTTP to describe acquired TTP cases with severe ADAMTS13 deficiency but without detectable anti-ADAMTS13 antibodies, that typically occur in association with other comorbidities such as cancer, severe infection, liver failure or systemic autoimmune disease. This proposal raises new questions about the pathophysiological landscape of TTP and highlights potential diagnostic gaps.[1] We understand and appreciate the comprehensive editorial of TTP classification by Knöbl[2] and we respectfully address several key points for further clarification and nuance.

Among patients classified as uTTP, who systematically exhibited features of TMA justifying an ADAMTS13 investigation, a substantial subset (20-25%) likely represents iTTP cases. These cases are typically associated with specific clinical contexts that include a history of systemic autoimmune disease, pregnancy, or mild infections; ADAMTS13 is in an open conformation, indicating an underlying autoimmune, antibody-mediated mechanism for ADAMTS13 deficiency, and clinical features are those typically observed in iTTP. In that way, anti-ADAMTS13 antibodies can be finally identified in up to 20% of those patients later during follow-up.[3] This group of patients differs significantly from uTTP cases defined by a TMA syndrome associated with specific conditions such as cancer, severe sepsis or liver failure, which tend to exhibit a closed ADAMTS13 conformation.[1] In that regard, outside of any context of TMA, rare cases of severe ADAMTS13 deficiency have been previously reported in severe sepsis, with no underlying autoimmune mechanism.[4] Our group has documented this point, reinforcing the view that severe ADAMTS13 deficiency can arise in critical diseases and results from non-immune mechanisms, particularly in the context of severe inflammation or hemodynamic stress, occurring in the absence of TMA features.[4] In those contexts, ADAMTS13 deficiency may result from a cleavage of the protein by other proteases, such as plasmin, as well as degradation or consumption. In uTTP, such mechanisms may account for a severe acquired ADAMTS13 deficiency but also for TMA features.[1] uTTP is therefore an important and specific condition occurring in non-immunologic contexts that needs to be considered in patients with features of TMA, as it expands our clinical understanding of ADAMTS13 deficiency in various pathophysiological settings. Recognizing uTTP patients provides crucial insights into ADAMTS13 activity and conformation as well as clinical background, allowing for a more comprehensive and accurate categorization and management of TTP patients. It is noteworthy that the underlying contexts in uTTP patients usually lead to their exclusion from clinical studies to ensure homogeneous patient populations, as their condition can contribute to cytopenias and directly affect prognosis, accounting for a bias where over 95% of iTTP patients with well-documented anti-ADAMTS13 antibodies are included in published studies.

The poor prognosis of uTTP usually results from the severity of the underlying condition driving severe ADAMTS13 deficiency, rather than from an inadequate treatment. These patients typically experience hemodynamic instability, severe bleeding, or active infection, where treatments with therapeutic plasma exchange, caplacizumab or rituximab may not be recommended. Furthermore, associated conditions such as neoplasia, severe infection, or liver failure significantly affect survival, emphasizing the need to urgently address the underlying condition, and not only ADAMTS13 deficiency. These statements further support the need to distinguish patients with features of TTP related to a non-immune severe ADAMTS13 deficiency from iTTP patients, for a more specific management in the acute phase but also for a more adapted long-term follow-up.[5]

In the acute phase of TTP, ADAMTS13 activity is undetectable and anti-ADAMTS13 autoantibodies are detected in 75-80% of cases. These autoantibodies can be neutralizing (i.e., inhibiting the proteolytic activity of ADAMTS13), non-neutralizing (i.e., forming antigen-antibody complexes that accelerate the clearance of ADAMTS13), or both. Approximatively 90% of anti-ADAMTS13 antibodies are of immunoglogulin (Ig) G class.[6,7] Detection of these specific immunoglobulins in iTTP is performed using Bethesda-like inhibitor assays or enzyme-linked immunosorbant assays (ELISA). Firstly, mixing inhibitor assays are prone to errors due to plasma manipulation, and serial dilutions may dissociate antibody-antigen complexes. The accuracy of this method can be impacted by several factors like antibody specificity, affinity and reaction kinetics. Additionally, mixing tests are time-consuming, require large volumes of plasma, are expensive and demonstrate low sensitivity, with discrepant results for predicting disease severity and out-

come.[7-10] ADAMTS13 specific immune complexes are found in 30% to 97% of cases[11,12] and notably, these complexes are present in 93% of the patients even during remission.[12] So far, it remains unclear whether these immune complexes play a significant role in iTTP pathophysiology, possibly through the activation of the complement system. Secondly, anti-ADAMTS13 IgG is the predominant and most clinically significant immunoglobulin class in iTTP. Although quantitative tests are more sensitive than mixing tests as they can identify both neutralizing and non-neutralizing IgG antibodies, they detect only free anti-ADAMTS13 IgG levels and may lack sensitivity in rare cases. International TTP Registries reported detectable free anti-ADAMTS13 IgG in approximatively 75-98% of TTP cases.[13-15] Additionally, plasma sample dilution is not recommended for ELISA methods, as it may reduce sensitivity and lead to imprecise values. ELISA methods for detecting IgG autoantibodies without additional dilutions are widely used and recommended in clinical laboratories; however users have to remain aware of potential false-negative results due to these limitations.[9] Our 25 years of experience in ADAMTS13 testing consistently shows that, despite rigorous protocols, severe ADAMTS13 deficiency can occur without detectable anti-ADAMTS13 autoantibodies. This is not a discrepancy but a documented reality, supported by multiple case series[13-15] and reinforced by our own experience with uTTP patients. This observation highlights the diversity of TTP pathogenesis and confirms that the absence of anti-ADAMTS13 autoantibodies does not exclude an acquired, severe ADAMTS13 deficiency.

In conclusion, these statements underline the complexity of TTP and the need to improve the bimodal classification of patients with severe ADAMTS13 deficiency. Categorizing patients as having either iTTP or cTTP provides a simple and solid model. However, there is a need to consider the subset of patients with uTTP, encompassing iTTP patients with anti-ADAMTS13 antibodies likely present but undetectable by current assays, and patients with features of TTP occurring in association with various comorbidities, resulting from severe ADAMTS13 deficiency due to an excessive degradation or an altered production, that need more specific management. Further investigations, through international collaborations using modern diagnostic tools and longitudinal data are needed to better characterize the epidemiology of patients with uTTP and our understanding of severe ADAMTS13 deficiency in this context.

We hope these insights offer valuable clarification and contribute constructively to the ongoing dialogue on TTP's classification.

Authors

Bérangère S. Joly,[1,2] Mathilde Leclercq,[3,4] Ygal Benhamou,[3,5] Agnès Veyradier[1,2] and Paul Coppo[2,6]

[1]Service d'Hématologie Biologique, Hôpital Lariboisière, AP-HP. Nord, Université Paris Cité, Paris; [2]INSERM UMRS_1138, Centre de Recherche des Cordeliers, Université Paris Cité, Sorbonne Université, Paris; [3]Département de Médecine Interne, CHU Charles Nicolle, Université de Rouen, Rouen; [4]INSERM U1234 PANTHER, Université de Rouen, Rouen; [5]INSERM U1026 EnVI, Université de Rouen, Rouen and [6]Service d'Hématologie, Centre National de Référence des Microangiopathies Thrombotiques, Hôpital Saint-Antoine, AP-HP. Sorbonne Université, Paris, France

Correspondence:
P. COPPO - paul.coppo@aphp.fr

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Contributions

BJ wrote the first version of the manuscript. AV, DS, YB and PC extensively edited the first version. All authors approved the final version.

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