EDITORIAL

The different faces of thrombotic thrombocytopenic purpura

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Today, 100 years after it was first described, thrombotic thrombocytopenic purpura (TTP) is understood as a thrombotic microangiopathy (TMA) caused by severe deficiency of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13).[1] The discovery of this enzyme and the subsequent exponential expansion of scientific research led to the establishment of two distinct types of TTP: a congenital type with mutations in the *ADAMTS13* genes, resulting in a missing or dysfunctional protein (cTTP; e.g., Upshaw-Schulman syndrome), and an acquired type, caused by autoantibodies against ADAMTS13 (iTTP).[1] Recent remarkable research, however, suggests a more complex pathophysiology: the von Willebrand factor (VWF)-ADAMTS13 axis is now understood as a dynamic, shear-dependent system, based on the binding and conformation change of both VWF and ADAMTS13, providing an autoregulatory mechanism of VWF multimeric size and thrombogenicity.[2] Current ADAMTS13 assays measure the metalloprotease activity to cleave a 73 amino-acid VWF fragment. The other functionalities of the VWF-ADAMTS13 system are not captured, which explains why some patients with clinically typical TTP have nonspecific laboratory results.

A few years ago, an article from the French TMA Reference Center challenged the TTP classification and proposed a third entity.[3] In a retrospective analysis of a large registry of TMA patients with severe ADAMTS13 deficiency, assessed from 1999 to 2013, 21.5% of patients did not have detectable anti-ADAMTS13 antibodies at admission or during the follow-up, and only transient ADAMTS13 deficiency. For these patients, the term “acquired TTP of unknown cause” (uTTP) was coined. The clinical data of these patients differed considerably from those of patients with iTTP: more had cancer, infections, or transplantation, conditions that are typically considered unlikely for TTP. This article triggered a lively discussion, as such a high number of unexplained cases of severe ADAMTS13 deficiency is not consistent with the data from other large TTP registries. Interestingly, the same group later reported on a modern TTP treatment regimen (with plasma exchange, caplacizumab and rituximab), including patients since September 2018.[4] Here, a much smaller proportion of patients had undetectable antibodies (and therefore uTTP).

Some years later, Joly *et al.*[5] published an additional comprehensive analysis of the ADAMTS13 conformation of a subgroup of patients from the French registry (patients from 2012 to 2016) and found an open ADAMTS13 conformation (typical of iTTP[2]) in only 13.6 % of uTTP patients, but even in the iTTP group only 76.7% had an open ADAMTS13 conformation. They concluded that this third entity, uTTP, has distinct clinical, epidemiological and biological features that do not fit in the usual cTTP/iTTP classification.

In this issue of *Haematologica*, the French TTP research team presents the findings on the response of uTTP to treatment.[6] A total of 273 patients from the French TTP registry were identified as having uTTP (representing 20% of the entire cohort, including patients from the last two decades). All patients had TTP with ADAMTS13 activity <10% and undetectable anti-ADAMTS13 antibodies at baseline, and many had cancer, infections, or transplantation. Only 77% of patients were treated with plasma exchange, and only a few with caplacizumab or front-line rituximab, the current standard of care. This may explain the poor overall survival of uTTP patients (30% mortality during the acute episode). Remarkably, 21% of the uTTP patients turned out to have iTTP, as anti-ADAMTS13 antibodies were found during follow-up (but with inconsistent follow-up and many missing data). This aligns somewhat with the previously reported proportion of “uTTP” patients with an open ADAMTS13 conformation, suggesting that these have iTTP. The clinical features, comorbidities, and outcomes of these patients were rather similar to those with iTTP but distinct from those with uTTP. The authors wisely recommend that all TTP patients with clinical characteristics suggesting iTTP

should initially be treated as having iTTP, regardless of the detection of anti-ADAMTS13 antibodies.

To summarize, the French TMA Reference Center identified a considerable proportion of patients with typical clinical signs of TTP and severe ADAMTS13 deficiency, but no detectable anti-ADAMTS13 antibodies. Furthermore, the majority of these patients exhibited a closed ADAMTS13 conformation and had a poor survival rate. This leaves several questions unanswered, and the authors are aware of the limitations of their studies.

The obvious first question is whether the initial finding of "severe ADAMTS13 deficiency" is reliable. The French TMA Reference Center is a government-certified national network of TMA specialists and has a high scientific reputation, so there is no doubt about integrity and data quality. Nevertheless, there are several possible intrinsic limitations that need discussion: ADAMTS13 activity was measured in a central laboratory, but different assays were in use during the study period. Older ADAMTS13 assays differ from current systems, but even today some assays have problems with a correct identification of low ADAMTS13 values.[7,8] Due to the delay between blood sampling and result reporting, treatment is initiated based on probability estimations (French or PLASMIC score) without waiting for the ADAMTS13 results. Any subsequent samples to confirm ADAMTS13 deficiency will be influenced by the therapy applied.

Anti-ADAMTS13 antibodies were measured with a commercial enzyme-linked immunosorbent assay (ELISA). These detect ADAMST13-binding IgG antibodies, but plasma mixing studies would have the advantage of being able to detect inhibiting plasma factors other than IgG autoantibodies. Patients with cancer, infections or transplantation are usually treated with multiple other medications, or have conditions that may influence ADAMTS13 or VWF. Furthermore, the ELISA may not detect very low concentrations of autoantibodies that are all bound to ADAMTS13.

In some patients with TTP, no antibodies or inhibition can be detected at diagnosis, but will rise during the course of

Table 1. Mandatory preconditions for prospective studies on thrombotic thrombocytopenic purpura.

Procedure	Reason
Prospective patient identification and collection of sufficient clinical data	Achieve good data quality
Prospective blood sampling	
Standard laboratory tests (blood and hemolysis parameters, organ function tests)	Confirmation of TMA
Laboratory studies for differential diagnosis	Alternative diagnosis?
Special laboratory tests for the ADAMTS13/VWF axis	Confirmation of TTP
Documentation of sampling time (always before therapeutic procedures)	Data quality
Correct pre-analytical procedures (avoiding sample contamination, correct plasma preparation, storage and transport conditions, etc.)	Laboratory result quality
Documentation of time to result	Impact on treatment Avoiding treatment delay
Collection of retention samples	For future analysis
ADAMTS13 activity testing	
Approved assays with sufficient sensitivity, specificity and quality control	Ensuring a reliable laboratory result
Repeated from new drawn samples, if necessary	Confirmation of initial result when inconclusive results
Possible interactions and errors to be recognized	Ensuring a reliable laboratory result
ADAMTS13 antibody testing	
Immunological assays (binding antibodies), if needed with different sample dilutions	Sensitive method to detect antibodies, may miss very low titers
Functional inhibitor assays (mixing studies with appropriate dilution steps and heat inactivation)	Detect ADAMST13 inhibition
Tests for open/closed ADAMTS13 conformation, when available	Confirmation of iTTP
Patient management and treatment	
Prospective state-of-the art-protocols	For optimal outcome
Regular assessment of the response to treatment	Guiding treatment Assessment of TTP outcome parameters[9]
Follow-up visits	
Scheduled at regular intervals	Assessment of TTP outcome parameters[9]
Assessment of clinical state and standard laboratory tests	Guiding treatment
ADAMTS13 activity and antibody measurements	Assessment of TTP outcome parameters[9] Guiding treatment
Storage of retention samples	For future analysis

TMA: thrombotic microangiopathy; ADAMTS13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; VWF: von Willebrand factor; TTP: thrombotic thrombocytopenic purpura; iTTP: acquired immune TTP.

the disease in response to treatment or the evolving autoimmune process. As regular follow-up is required in modern TTP management to assess the treatment endpoints,[9] all such patients will be detected nowadays.

Alterations of the ADAMTS13 protein, impaired synthesis, or exhaustion by very high VWF levels would not cause severe deficiency. A reciprocal relation between VWF and ADAMTS13 is long known, with a reduced, but not deficient ADAMTS13 activity in acute phase situations.

Autoantibodies (or other agents) may be directed against the ADAMTS13 cleavage site in the A2 domain of VWF. This could potentially prevent ADAMTS13 from cleaving VWF or the VWF-73 substrate. Such antibodies would not open ADAMTS13.

It is good clinical practice to confirm the reproducibility of results, particularly in controversial settings. A coordinated international effort, analyzing more recent and well-documented patients from industry-sponsored trials (Titan, Hercules, Vita) and other national registries, managed according to current guidelines with sufficient follow-up data, could provide valuable confirmatory information.

For definite confirmation, it is essential to adopt a prospective approach for future trials to identify the actual proportion of TTP patients with unexplained severe ADAMTS13 deficiency and to further analyze potential causes. As suggested by the authors, several preconditions are mandatory for such an approach to provide good data quality and avoid methodological errors (Table 1).

To conclude, the finding of a third, distinct class of non-immunological TTP is an interesting observation, although not concordant with other publications. Prospective confirmation is needed, including elaborate laboraty work, to elucidate the existence and pathophysiology of uTTP. In the meantime, management according to current iTTP guidelines is probably the best way to reduce the high mortality of these patients.

Disclosures

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