A third form of thrombotic thrombocytopenic purpura?

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In this issue of *Haematologica* a highly provocative letter by B.S. Joly *et al.*, on behalf of the French Reference Center for Thrombotic Microangiopathies (CNR-MAT), reiterates the existence of a so-far largely disregarded - not to say «scotomized» - form of acquired thrombotic thrombocytopenic purpura (TTP).[1] In the hundred years since its first description by Moschcowitz in 1924, TTP has attracted the interest of numerous clinicians and researchers; the development of our knowledge on the pathophysiology and more recently new therapeutic advances in this previously mostly fatal disease are a major success story of modern scientific medicine.[2]

TTP specialists usually distinguish two pathophysiologically distinct forms of TTP: (i) a very rare hereditary or congenital TTP (cTTP) or Upshaw-Schulman syndrome caused by biallelic mutations of the *ADAMTS13* gene leading to a severe constitutional deficiency of the von Willebrand factor-cleaving metalloprotease ADAMTS13 and (ii) an acquired, autoimmune TTP (iTTP) associated with autoantibody-mediated severe ADAMTS13 deficiency.[3,4]

Whereas in plasma from healthy subjects, from patients with hemolytic uremic syndrome or from patients with sepsis, the ADAMTS13 circulates in a closed conformation whereby the two CUB domains interact with the spacer domain, in plasma from patients with acute iTTP, the ADAMTS13 adopts an open conformation allowing cryptic epitopes in the spacer domain to be recognized by specific monoclonal antibodies.[5] Thus, an open ADAMTS13 conformation, i.e. a conformation index >0.5, was suggested to be a specific hallmark of acute acquired, autoantibody-mediated TTP.[5] A follow-up study initiated by the group of K. Vanhoorelbeke in Kortrijk showed that isolated IgG anti-ADAMTS13 autoantibodies purified from iTTP plasma samples were able to induce an open conformation of ADAMTS13 in normal plasma.[6] Furthermore, using a large multicenter cohort of patients with iTTP and plasma samples obtained during acute TTP episodes and during remission, a conformation index >0.5 was not only confirmed to be present in the acute disease phase but also in almost all iTTP samples in remission with an ADAMTS13 activity ≤50% and even in 38% of remission samples with normalized ADAMTS13 activity >50%.[6] Therefore, an open ADAMTS13 conformation was proposed as a specific biomarker for both manifest and subclinical iTTP.

In 2016, the French Reference Center for Thrombotic Microangiopathies reported a cross-sectional analysis of all 939 adult patients admitted with a first episode of acute thrombotic microangiopathy with severe ADAMTS13 deficiency between 1999 and 2013.[7] Of 772 patients for whom data and blood samples at admission were available, 378 (49%) had idiopathic TTP and 394 (51%) had non-idiopathic TTP, defined as TTP associated with various clinical conditions such as infections, autoimmune diseases, pregnancy, cancer, organ transplantation or drugs. Pathophysiologically, three distinct forms of TTP were delineated: 585 (75%) had iTTP (defined by the presence in plasma of free IgG anti-ADAMTS13 autoantibodies measured by a commercial assay), 21 (3%) had cTTP with biallelic *ADAMTS13* mutations, and 166 (22%) had acquired TTP of unknown cause (uTTP), defined by the absence of IgG anti-ADAMTS13 antibodies.[7] Of note, 345/378 (91%) of the cases of idiopathic TTP had iTTP whereas only 240/373 (64%) cases of non-idiopathic acquired TTP were classified as iTTP (displaying free anti-ADAMTS13 autoantibodies), and the remaining 133 non-idiopathic cases lacking autoantibodies were denoted as uTTP.

The letter by Joly *et al.*[1] now focuses on the ADAMTS13 conformation in acquired TTP of unknown pathophysiology, tentatively called uTTP. The authors selected a new cohort of 125 adult patients with a first episode of acute non-idiopathic TTP (ADAMTS13 activity <10% of normal) enrolled in the French Thrombotic Microangiopathy Registry between 2012 and 2016. Forty-nine of these 125 patients with non-idiopathic TTP had measurable anti-ADAMTS13 IgG antibodies and were classified as having iTTP whereas 76 did not have free anti-ADAMTS13 IgG and constituted the group of interest, i.e. the uTTP cases. Comparing the uTTP with the iTTP patients, the former were older, had a smaller proportion of females, more often had associated cancers and less often had accompanying autoimmune diseases. The clinical presentation in both groups was similar except for renal abnormalities being more prevalent in uTTP. Laboratory features showed less severe thrombocytopenia, higher creatinine values

and higher ADAMTS13 antigen levels in uTTP compared to iTTP cases.[1] The ADAMTS13 conformation index, measurable in 59/76 uTTP and in 30/49 iTTP patients with ADAMTS13 antigen levels of ≥0.03 µg/mL displayed an open conformation in 23/30 (76%) cases of iTTP but in only 8/59 (13.6%) uTTP patients.

The study by Mariotte *et al.*[7] and the letter by Joly *et al.*[1] suggesting the existence of a third pathophysiological form of TTP besides the well-established iTTP and cTTP, raise scientifically and practically important questions. What might the pathophysiology of uTTP be? And what is the most appropriate therapy for this provisional entity? Obviously, uTTP is associated with an acquired severe ADAMTS13 deficiency and several surviving patients may recover normal ADAMTS13 activity. In contrast to most iTTP cases displaying a conformation index >0.5, 51/59 (86.4%) uTTP patients of the present cohort showed a closed ADAMTS13 conformation. Could acquired alterations (deglycosylation, oxidation, proteolysis, high cytokine levels, other factors) during inflammatory reactions severely compromise ADAMTS13 activity? Or are IgM and/or IgA anti-ADAMTS13 autoantibodies,[8] not assessed by commercial IgG anti-ADAMTS13 tests, responsible for uTTP? Alternatively, could IgG anti-ADAMTS13 still be causative, but all bound within circulating IgG-ADAMTS13 complexes[9,10] leaving no detectable free antibodies?

It is clear that concerted, multicenter efforts would be ideal to clarify the nature of uTTP. Such exemplary country-wide collaborative cohorts as provided by the French Reference Center for Thrombotic Microangiopathies will be instrumental in unraveling the pathophysiology of uTTP and thereby establishing whether therapeutic plasma exchange with plasma replacement, corticosteroids, other immunosuppressant drugs and caplacizumab[2] are the optimal measures also in this form of TTP.

In brief, the research on TTP must go on!

Disclosures

BL is chairman of the data safety monitoring committees for the Baxalta 281102 and the TAK-755-3002 studies (both investigating recombinant ADAMTS13 in hereditary TTP) and for the Takeda SHP655-201 study (recombinant ADAMTS13 in immune-mediated TTP), all three now run by Takeda. He is a member of the advisory board of Ablynx, now part of Sanofi, for the development of caplacizumab; he received congress travel support and/or lecture fees from Baxter, Ablynx, Alexion, Siemens, Bayer, Roche and Sanofi.

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