haematologica
Journal of the Ferrata Storti Foundation

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"

by Flora Peyvandi

Received: December 10, 2024.
Accepted: January 22, 2025.

Citation: Flora Peyvandi. 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".
Haematologica. 2025 Jan 30. doi: 10.3324/haematol.2024.287163 [Epub ahead of print]

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"

Flora Peyvandi

1. Università degli Studi di Milano, Department of Pathophysiology and Transplantation, Milan, Italy
2. Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Milan, Italy

Correspondence

Flora Peyvandi, M.D., Ph.D., Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Via Pace 9, 20122 Milan, Italy.

Email: flora.peyvandi@unimi.it

Word counts:

Manuscript: 852

Reference Count: 15

Acknowledgments

This work was partially supported by the Italian Ministry of Health (Bando Ricerca Corrente). The Hemostasis & Thrombosis Unit of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico is member of the European Reference Network on

Rare Haematological Diseases EuroBloodNet-Project ID No 101157011. ERN-EuroBloodNet is partly co-funded by the European Union within the framework of the Fourth EU Health Programme. The author acknowledges the Italian Ministry of Education and Research - MUR ('Dipartimenti di Eccellenza' Programme 2023–27 - Department of Pathophysiology and Transplantation, Università degli Studi di Milano)

Conflict-of-interest disclosure: F.P. reports participation to educational meetings of Sanofi, Takeda and Spark, and to the advisory boards of Biomarin, CSL Behring, Pfizer, Roche, Sanofi and Sobi.

In the 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 (UL) VWF multimers in binding to Gp1b receptors on platelets. In the absence of ADAMTS13 (i.e., in TTP), UL VWF multimers accumulate in plasma, resulting in the widespread formation of von Willebrand factor- 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, that promote the clearance of ADAMTS13 from the circulation or inhibit its activity [5].

Mariotte E et al. [6] reported that TTP can also occur without anti-ADAMTS13 antibodies as an acquired form of unknown cause (uTTP) and unclear mechanism. The same group [7] reported that 20% of the cases in their national cohort were uTTP, 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 by ELISA 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 remind that anti-ADAMTS13 antibodies can circulate free or complexed with the ADAMTS13 enzyme. Lotta LA et al. [9] reported a group of iTTP patients (37% of all aTTP cases) in whom reduced ADAMTS13 activity was not associated with anti-ADAMTS13 autoantibodies, and showed that these patients had ADAMTS13-specific circulating immune complexes (CICs). Increasing levels of ADAMTS13-specific CICs were found clinically associated with a higher number of plasma exchange procedures required to achieve clinical remission. Moreover, Mancini et al. [10] reported an increased risk of recurrence in patients with CICs detected during the acute disease phase.

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 (HIV, 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 K et al. [12] reported a case of TTP caused by influenza A (H1N1) without anti-ADAMTS13 antibodies, that was successfully treated with plasma exchange. 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 I et al. [13] described in COVID-19 patients significant changes in the VWF-ADAMTS13 axis, including an elevated VWF:Ag to ADAMTS13 activity ratio that was strongly associated with disease severity. This imbalance enhances the hypercoagulable state of COVID-19 patients as well as their risk of microvascular thrombosis. In addition, it worsens significantly the clinical course of patients with iTTP and low ADAMTS13 activity affected by COVID19 [14].

The consensus guideline introduced by Scully M et al. in 2017 [11] 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 of our understanding of ADAMTS13 was introduced by Roose E et al [16] 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. All in all, despite major advances in recent years in the understanding the disease, many aspects of its pathophysiology still remain unclear. TTP remains primarily a clinical diagnosis, that must be confirmed by the presence of severely reduced ADAMTS13 activity (<10%) with or without the presence of anti-ADAMTS13 antibodies.

References

1. George JN. Thrombotic thrombocytopenic purpura: from 1972 to 2022 and beyond. Semin Thromb Hemost. 2022;48(8):926-936.
2. Tsai HM, Lian EC. Antibodies to Von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. N Engl J Med. 1998;339(22):1585-1594.
3. Furlan M, Robles R, Galbusera M, et al. Von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. N Engl J Med. 1998;339(22):1578-1584.
4. Levy GG, Nichols WC, Lian EC, et al. Mutations in a member of the ADAMTS gene family cause thrombotic thrombocytopenic purpura. Nature. 2001;413(6855):488-494.
5. Peyvandi F, Lavoretano S, Palla R, et al. ADAMTS13 and anti-ADAMTS13 antibodies as markers for recurrence of acquired thrombotic thrombocytopenic purpura during remission. Haematologica. 2008;93(2):232-239.
6. Mariotte E, Azoulay E, Galicier L, et al. Epidemiology and pathophysiology of adulthood onset thrombotic microangiopathy with severe ADAMTS13 deficiency (thrombotic thrombocytopenic purpura): a cross-sectional analysis of the French national registry for thrombotic microangiopathy. Lancet Haematol. 2016;3(5):237-245.
7. Simon D, Leclercq M, Joly B, Veyradier A, Coppo P, Benhamou Y. Acquired thrombotic thrombocytopenic purpura without detectable anti-ADAMTS13 antibodies: when should we consider an underlying autoimmune mechanism? Haematologica. 2024 Sep 26. [Epub ahead of print]
8. Paul Knöbl. The different faces of thrombotic thrombocytopenic purpura. Haematologica 2024 Nov 14. [Epub ahead of print]

9. Lotta LA, Valsecchi C, Pontiggia S, et al. Measurement and prevalence of circulating ADAMTS13-specific immune complexes in autoimmune thrombotic thrombocytopenic purpura. J Thromb Haemost. 2014;12(3):329-336.
10. Mancini I, Ferrari B, Valsecchi C, et al; Italian Group of TTP Investigators. ADAMTS13-specific circulating immune complexes as potential predictors of relapse in patients with acquired thrombotic thrombocytopenic purpura. Eur J Intern Med. 2017;39:79-83.
11. Scully M, Cataland S, Coppo P, et al, International Working Group for Thrombotic Thrombocytopenic P. Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and related thrombotic microangiopathies. J Thromb Haemost. 2017;15(2):312-322.
12. Kubo K, Abe T, Kawano N, Ochiai H. Acquired thrombotic thrombocytopenic purpura without anti-ADAMTS13 antibody caused by influenza A (H1N1) virus successfully treated by plasma exchange: a case report. Am J Case Rep. 2021;22:e932251.
13. Mancini I, Baronciani L, Artoni A, et al. The ADAMTS13-von Willebrand factor axis in COVID-19 patients. J Thromb Haemost. 2021;19(2):513-521.
14. Capecchi M, De Leo P, Abbattista M, et al. Risk of relapse after SARS-CoV-2 vaccine in the Milan cohort of thrombotic thrombocytopenic purpura patients. Haematologica. 2023;108(11):3152-3155.
15. Zheng XL, Vesely SK, Cataland SR, et al. ISTH guidelines for the diagnosis of thrombotic thrombocytopenic purpura. J Thromb Haemost. 2020;18(10):2486-2495.
16. Roose E, Schelpe AS, Tellier E, et al. Open ADAMTS13, induced by antibodies, is a biomarker for subclinical immune-mediated thrombotic thrombocytopenic purpura. Blood. 2020;136(3):353-361.