

# Thrombotic thrombocytopenic purpura and other immune mediated blood disorders following SARS-CoV-2 vaccination

by Pier Mannuccio Mannucci

*Received: July 29, 2021.*

*Accepted: August 2, 2021.*

*Citation: Pier Mannuccio Mannucci. Thrombotic thrombocytopenic purpura and other immune mediated blood disorders following SARS-CoV-2 vaccination.*

*Haematologica. 2021 Aug 12. doi: 10.3324/haematol.2021.279649. [Epub ahead of print]*

## *Publisher's Disclaimer.*

*E-publishing ahead of print is increasingly important for the rapid dissemination of science. Haematologica is, therefore, E-publishing PDF files of an early version of manuscripts that have completed a regular peer review and have been accepted for publication. E-publishing of this PDF file has been approved by the authors. After having E-published Ahead of Print, manuscripts will then undergo technical and English editing, typesetting, proof correction and be presented for the authors' final approval; the final version of the manuscript will then appear in a regular issue of the journal. All legal disclaimers that apply to the journal also pertain to this production process.*

## Editorial

### **Thrombotic thrombocytopenic purpura and other immune mediated blood disorders following SARS-CoV-2 Vaccination**

Pier Mannuccio Mannucci

Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi  
Hemophilia and Thrombosis Center, Milan, Italy

Running title: vaccine induced blood disorders

Keywords: immune thrombocytopenic purpura, autoimmune hemophilia, vaccine-induced immune thrombotic thrombocytopenia, COVID-19 vaccine, acquired bleeding disorders

Correspondence to: P.M. Mannucci

Via Pace 9, 20122 Milano, Italy

Phone +39 0255035421

Email: [piermannuccio.mannucci@policlinico.mi.it](mailto:piermannuccio.mannucci@policlinico.mi.it)

Giuffrida et al (1) report two cases of new-onset, immune-mediated thrombotic thrombocytopenic purpura (TTP) in 81-year-old and 30-year-old women diagnosed with this very rare disease 14 and 18 days after the first dose of the mRNA-based vaccine against SARS-CoV-2 manufactured by Pfizer-BioNTech. The oldest woman (case 1) had a history of diabetes and connective tissue disease positive for antinuclear antibodies, whereas the youngest case 2 had was negative regarding clinical history and laboratory markers of potential triggers of TTP such as autoimmune, tumoral and infectious diseases. Both cases were promptly treated with glucocorticoids and daily sessions of plasma exchange (PEX) each followed by the nanobody caplacizumab. This state-of-the-art therapeutic approach based upon plasma therapy, immunomodulation and anti-VWF medicines was successful in the younger woman, with a rapid normalization of the very low platelet count, even though plasma ADAMTS13 was still unmeasurable on days 14 and 30 after 8 PEX and anti-ADAMTS 13 were still present. In the oldest woman with comorbidities, there was only a modest improvement of the platelet count and she died suddenly after the second PEX owing to an ill defined cardiac event, thus witnessing once again that notwithstanding a prompt and impeccable management TTP is still associated with a significant mortality toll.

The main interest of these two cases stays with the fact that autoimmune TTP occurred afresh within two-three weeks from the first dose of an anti-COVID-19 vaccine. Its administration within this short time window as well as no evidence for other causes (at least in the youngest woman) are consistent for causality according to the WHO criteria for post-vaccination adverse events (2). Until now, new-onset TTP was reported as a single case after the Johnson and Johnson vaccine based upon a human adenovirus vector (3) and a relapse of recurrent TTP occurred 6 days after the second dose of the Pfizer-BioNTech

vaccine (4). The new-onset cases described herewith by Giuffrida et al (1) of such a rare immune mediated blood disease associated with a bleeding tendency follow the report of a mRNA-vaccine (Pfizer-BioNTech)-associated case of autoimmune hemophilia due to anti-factor VIII antibodies (5) and multiple cases of immune thrombocytopenic purpura (ITP) owing to platelet autoantibodies occurring after either mRNA-based vaccine produced by Pfizer and Moderna (6). Common features of these cases are that the majority of them occurred in women, at young but also at older ages, thus reproducing the two typical age peaks of occurrence of autoimmune diseases. At variance with the recent reports of vaccine-induced immune thrombotic thrombocytopenia (VITT) (7), these cases were not associated with thrombosis in the cerebral and abdominal veins but only with hemorrhagic symptoms compatible with the degree of thrombocytopenia in ITP and TTP and of factor VIII deficiency in autoimmune acquired hemophilia. Another feature that distinguishes from VITT these cases is that they were not accompanied by serological positivity for autoantibodies directed towards platelet factor 4. Table 1 summarizes the main clinical symptoms and laboratory findings in the different thrombocytopenias that did occur post-COVID vaccination.

Which general messages may be drawn from these reports of immune-mediated hematological diseases associated with a bleeding tendency in persons recently vaccinated to prevent COVID-19? It is well established that a number of diseases due to the formation of autoantibodies against autologous cells and/or proteins may occur after vaccination against various infectious agents (8-10): common examples are measles-mumps-rubella and diphtheria-tetanus-pertussis, but also polio, rabies, influenza and bacterial pneumonia, especially in children but also in adults. There is no evidence that the innovative technologies recently developed for anti-COVID vaccine production had a

peculiar role in the dysregulation of the immune system that led to the production of antibodies other than those towards the spike SARS-CoV-2 protein, because autoimmune diseases did occur after all types of vaccines, spanning from those traditionally based upon inactivated virions to those newly employing viral DNA vectors or mRNA technology (8-10). Among them, only VITT appears to be peculiar, because this complication was so far described with convincing documentation only in patients receiving the vaccines based upon adenoviral vectors, such as the AstraZeneca and the Johnson- and Johnson products. In VITT the very rare but catastrophic thrombohemorrhagic complications are due to the formation of highly pathogenic autoantibodies against a complex between platelet factor 4 and a still poorly defined polyanion that triggers platelet activation, consumptive thrombocytopenia and a hypercoagulable state perhaps amplified by antibody induced NETosis (7). However, it is as yet not fully understood why venous thrombi occur in unusual sites, nor is definitely known the source and composition of the polyanion. Moreover, it is still uncertain whether or not these rare post-vaccination diseases are more frequent than expected in the population at large, because epidemiologically-based studies evaluating their incidence in vaccinated versus non-vaccinated persons are scanty or absent. The reported prevalences in vaccinated persons, usually affected by limited sample size, range from 1 in 50.000-100.000 for VITT depending on the age and gender of vaccine recipients to a lower prevalence (one in one million) for ITP (6,11,12).

An array of innate or adaptive immunological mechanisms may be responsible for these adverse events, but vaccine-induced danger signals accompanied by inflammation, as well as antigenic mimicry with activation of quiescent autoreacting B and T cells, are the most plausible (8,10). It is unlikely that adjuvants, frequently employed in some vaccines in

order to boost antibody production towards the target antigen, played a pathogenic role, because the currently licensed anti-COVID vaccines do not need nor contain such typical adjuvants as squalene and aluminum, owing to the fact that their RNA and DNA components offer intrinsic adjuvanticity.

On the whole, these exceptional cases of immune mediated hematological diseases associated with bleeding and/or thrombosis that occurred in the current frame of global vaccination of more than 400 million people should not put in doubt nor jeopardize, in general and in the specific instance of COVID-19, the effectiveness of vaccines, that are the only weapon currently available to control this pandemic. The majority of ITP and TTP cases seem to be less severe than VITT and are usually not life-threatening, except in older multimorbid persons such as case 2. In addition, it appears that within the limited amount of available knowledge owing to recent onset and short follow-up of these complications, responses to state-of-the-art therapies, as well as tendency to recur or become chronic, are not overtly different from the cases that occur irrespective of vaccination. By the same token, no prophylactic measure is warranted before nor after vaccination, because useless and potential dangerous.

## References

1. Giuffrida G, Condorelli A, Di Giorgio MA, et al. Immune-mediated thrombotic thrombocytopenic purpura following Pfizer-BioNTech COVID-19 vaccine. *Haematologica*. 2021 XXX.
2. World Health Organization. Global manual on surveillance of adverse effect following immunization. 2015 Update. World Health Organization. 2014.

3. Yocum A, Simon EL. Thrombotic thrombocytopenic purpura after Ad26.COVS-2 vaccination. *Am J Emerg Med.* 2021 May 4. [Online ahead of print]
4. Sissa C, Al-Khaffaf A, Frattini F, et al. Relapse of thrombotic thrombocytopenic purpura after COVID-19 vaccine. *Transfus Apher Sci.* 2021 Apr 16. [Online ahead of print]
5. Radwi M, Farsi S. A case report of acquired hemophilia following COVID-19 vaccine. *J Thromb Haemost.* 2021;19(6):1515-1518.
6. Lee EJ, Cines DB, Gernsheimer T, et al. Thrombocytopenia following Pfizer and Moderna SARS-CoV-2 vaccination. *Am J Hematol.* 2021;96(5):534-537.
7. Cines DB, Bussell JB. SARS-CoV-2 Vaccine-induced immune thrombotic thrombocytopenia. *N Engl J Med.* 2021;384(23):2254-2256.
8. Guimarães LE, Baker B, Perricone C, Shoenfeld Y. Vaccines, adjuvants and autoimmunity. *Pharmacol Res.* 2015;100:190-209.
9. Perricone C, Ceccarelli F, Neshet G, et al. Immune thrombocytopenic purpura (ITP) associated with vaccinations: a review of reported cases. *Immunol Res.* 2014;60(2-3):226-35.
10. Watad A, De Marco G, Mahajna H, et al. Immune-mediated disease flares or new-onset disease in 27 subjects following mRNA/DNA SARS-CoV-2 Vaccination. *Vaccines (Basel).* 2021;9(5):435.
11. Simpson CR, Shi T, Vasileiou E, et al. First-dose ChAdOx1 and BNT162b2 COVID-19 vaccines and thrombocytopenic, thromboembolic and hemorrhagic events in Scotland. *Nat Med.* 2021;27(7):1290-1297.
12. Pottegård A, Lund LC, Karlstad Ø, et al. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study. *BMJ.* 2021;373:n1114.

**Table 1:** Main features of vaccine-induced, immune mediated thrombocytopenias

<b>Disease (and acronym)</b>	<b>Severe thrombocytopenia (<math>\leq 10 \times 10^9/L</math>)</b>	<b>Mucocutaneous bleeding symptoms</b>	<b>Intracerebral hemorrhage</b>	<b>Associated thrombosis</b>	<b>Thrombosis sites</b>	<b>Laboratory diagnosis</b>
Immune thrombocytopenic purpura (ITP)	Frequent	Frequent	Rare	Rare	-	Anti-platelet antibodies
Thrombotic thrombocytopenic purpura (TTP)	Frequent	Rare	Rare	Frequent, microvascular	Microcirculation of heart, brain and GI tract	ADAMTS-13 deficiency and ADAMTS-13 antibody
Vaccine-induced immune thrombotic thrombocytopenia (VITT)	Frequent	Rare	Frequent	Frequent, macrovascular	Cerebral and abdominal veins	Anti-PF4 ELISA positivity