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

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In this issue of *Haematologica*, 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 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) manufactured by Pfizer-BioNTech. The older woman (case 1) had a history of diabetes and connective tissue disease positive for antinuclear antibodies, whereas the younger (case 2) was negative regarding clinical history and laboratory markers of potential triggers of TTP such as autoimmune disorders, tumors and infections. Both women were promptly treated with glucocorticoids and daily sessions of plasma exchange, each followed by the nanobody caplacizumab. This state-of-the-art therapeutic approach based upon plasma therapy, immunomodulation and anti-von Willebrand factor medicines was successful in the younger woman, who had rapid normalization of a very low platelet count, even though plasma ADAMTS13 was still unmeasurable on days 14 and 30 after eight plasma exchanges and anti-ADAMTS13 were still present. The older woman with comorbidities had only a modest improvement of platelet count and she died suddenly after the second plasma exchange as the result of an ill-defined cardiac event, thus once again emphasizing that TTP is still associated with a significant mortality toll notwithstanding prompt and impeccable management.

The main interest of these two cases lies in the fact that new-onset autoimmune TTP occurred within 2 to 3 weeks after the first dose of a vaccine to protect against coronavirus disease 2019 (COVID-19). Administration of the vaccine within this short time window prior to the TTP episode as well as no evidence for other causes (at least in the younger woman) are consistent with causality according to the World Health Organization criteria for post-vaccination adverse events.[2] Until now, new-onset TTP had been reported as a single case after the Johnson & Johnson vaccine, which is based on a human adenovirus vector,[3] and a relapse of recurrent TTP which occurred 6 days after the second dose of the Pfizer-BioNTech vaccine.[4] The new-onset cases described 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) due to platelet autoantibodies occurring after either of the two mRNA-based vaccines 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 cerebral or 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 these cases from VITT is that they were not accompanied by serological positivity for autoantibodies directed against platelet factor 4. Table 1 summarizes the main clinical symptoms and laboratory findings in the different thrombocytopenias that did occur after vaccination against COVID-19.

What are the general messages that 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 vaccines, but also vaccines against polio, rabies, influenza

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

Disease (and acronym)	Severe thrombocytopenia ($<10x10^9$/L)	Mucocutaneous bleeding symptoms	Intracerebral hemorrhage	Associated thrombosis	Thrombosis sites	Laboratory diagnosis
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

GI: gastrointestinal; ADAMTS13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; PF4: platelet factor 4; ELISA: enzyme-linked immunosorbent assay.

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 have a particular 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 have occurred 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] Only VITT appears to be peculiar, because this complication has so far been described with convincing documentation only in patients receiving the vaccines based on adenoviral vectors, such as the AstraZeneca and the Johnson & 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 not yet fully understood why venous thrombi occur in unusual sites, and the source and composition of the polyanion are still unlcear. Moreover, it remains uncertain whether or not these rare post-vaccination disorders are more frequent than expected in the population at large, because epidemiologically-based studies evaluating their incidences in vaccinated *versus* non-vaccinated persons are scanty or absent. The reported prevalences in vaccinated people, usually affected by limited sample size, range from 1 in 50.000-100.000 for VITT depending on the age and gender of the vaccine recipients to a lower prevalence (1 in 1,000,000) 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, play a mechanistic role, because the currently licensed anti-COVID vaccines do not need nor contain typical adjuvants such as squalene and aluminum, because 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 have 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, which 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 individuals with multiple comorbid conditions, such as case 2. In addition, it appears that, albeit with the limited amount of available knowledge given the recent onset and short follow-up of these complications, responses to state-of-the-art therapies, as well as tendencies to recur or become chronic, are not overtly different from those of cases that occur irrespective of vaccination. By the same token, no prophylactic measure is warranted before or after vaccination, because useless and potentially dangerous.

Disclosures

No conflicts of interest to disclose.

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