Commentary
COVID vaccine-induced immune thrombotic thrombocytopenia: Rare but relevant
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Marietta, Coluccio, and Luppi present a comprehensive review of the current understanding and hypotheses on the mechanisms of vaccine-induced immune thrombotic thrombocytopenia (VITT) [1]. Although the title of the review implicates a somewhat broader discussion, the authors focus on patients with VITT among the several entities leading to thrombocytopenia and/or thrombotic complications after the vaccination against coronavirus disease 2019 (COVID-19). The term VITT is restricted to cases in whom high titer anti-PF4 antibodies are present in the typical time window of 5–30 days after the COVID-19 vaccination, together with a reduced platelet count, high D-dimer levels and very often new thrombosis [2,3]. Beside VITT, also other mechanisms may underlie some forms of vaccine-induced thrombosis, but they are not very well understood yet. For this reason, the term thrombosis and thrombocytopenia syndrome (TTS) is used by the World Health Organization (WHO), unless high titer PF4 antibodies have been demonstrated [4].

Over the last 18 months, several laboratories performing diagnostic assays for VITT have observed patients with thrombocytopenia and thrombosis in whom no anti-PF4 antibodies could be detected. This is not an issue of reduced sensitivity of individual anti-PF4 antibody assays, as typically these sera tested negative with a wide variety of different assays (personal experience of the author and discussion with other laboratories specialized in the diagnosis of anti-PF4 antibodies). However, these PF4 antibody independent cases of TTS seem to be even more rare than VITT.

The review provides a good balance between emphasizing the severity of VITT, but also its rarity. Without any doubt, COVID-19 vaccination prevented morbidity and mortality by far outweighing the small risk of VITT. This is also true, if only adenovirus vector-based vaccines are considered. Accordingly, the WHO and all responsible medical agencies around the world strongly recommended to continue the vaccination campaign, even if a medical system can only afford adenovirus vector-based vaccines.

While this recommendation was absolutely correct in hindsight, major uncertainty was present in regard to frequency and mechanisms of VITT after the first cases of VITT had been observed in March 2021. At that time it was highly important to rapidly understand the underlying mechanisms and to define, how VITT can be diagnosed by clinical and laboratory means, and to provide treatment recommendations for affected patients. The scientific community faced three major tasks related to VITT in March 2021.

1. To identify and to effectively treat affected patients. In the first reports of VITT, mortality was about 50% [5–7]. The lower numbers of about 15 to 20%, currently reported in reviews, are a composite of very high numbers in the first patient series and lower numbers after introduction of appropriate measures for diagnosis and treatment. Australia started the vaccination campaign a few weeks after Europe. With the vaccination campaign they launched an educational program informing the public and especially physicians about symptoms of VITT and appropriate treatment. This resulted in an overall mortality of 5 to 6% of VITT in Australia [8]. Recognition of pre-VITT with headaches as warning symptom for an increased risk to develop cerebral vein sinus thrombosis which requires immediate start of anticoagulation and intravenous immunoglobulins is one very obvious example [9].

2. To reduce fear and irrational prejudices related to COVID-19 vaccination. The general public is well aware that medical interventions have potential side effects. Even the package inserts of over-the-counter painkillers and anti-inflammatory drugs list rare but severe and even fatal adverse effects. However, the informed patient expects that the treating physician can recognize and treat adverse effects. Therefore, scientific data were urgently needed on VITT to counterbalance irrational statements increasingly used by populist anti-vaccination movement protagonists.

3. To exclude that VITT is a general effect of all COVID-19 vaccines. When the first patients with VITT had been observed, it was unclear whether the spike protein itself (and therefore all COVID-19 vaccines) could be the trigger for anti-PF4 antibodies, e.g. by molecular mimicry. It was a strong relief for the vaccination campaign when it
became clear that the spike protein is not the trigger of the anti-PF4 antibodies and that mRNA-based vaccines (and later inactivated virus-based vaccines) very unlikely cause VITT.

Rapid acceleration of data on diagnosis, treatment and mechanisms of VITT was probably the most important contribution of physicians and scientists of different groups all over the world. Within days the scientific community provided the public with urgently needed information. This was instrumental to address VITT in the public by a rational rather than populist discussion.

Eighteen months after the first patients have been recognized, research on VITT is still ongoing and the genomes of several hundred VITT patients are currently sequenced to potentially identify genetic predisposition. However, given the rarity of VITT, it is very unlikely that a single genetic factor will predispose for this adverse immune mediated effect. It might very well be that the coincidence of three, four, or even more events in one individual triggers VITT. A recent genome wide study enrolling several thousand patients with the rather similar syndrome of heparin-induced thrombocytopenia did not reveal a common genetic risk factor, and “only” showed that blood group 0 is associated with an increased risk for anti-PF4 antibodies with platelet activating capacity [10,11].

In the opinion of the author it is much more relevant to clarify which constituent(s) of the vaccine trigger VITT than to identify individual risk factors. Especially in countries with limited resources it will be impossible to screen an entire population for risk factors to prevent adverse effects of vaccination in a very small number of individuals.

The factor triggering immunization against PF4 is unlikely a protein derived from the cell culture in which the virus has been propagated, because there is barely any overlap in this proteins between the AstraZeneca vaccine and the Johnson & Johnson vaccine [12]. The factor can also not be simply the presence of negatively charged molecules. Also mRNA in the mRNA vaccines is negatively charged and RNA perfectly forms complexes with PF4 [13]. Although it cannot be excluded for certain that mRNA vaccines induce an anti-PF4 response, such events are extremely rare. In fact, as mentioned by the authors of the review, it is still unresolved whether the few VITT cases after an mRNA vaccine are simply reflecting the background of natural occurrence of autoimmune HIT [14].

Adenovirus vector-based vaccines can be produced and distributed rather cost-effectively and are one of the few currently available vaccine platforms that can be made available for the populations of the majority of low and middle income countries. The “One Health” discussion in times of globalization [15] makes it rather clear that prevention of disease spreading is highly important. Either we work together to provide global vaccination for existing and emerging pathogens, or we will inevitably face endemic and pandemic spreading of other pathogens beside SARS-CoV-2. Based on the current level of vaccination technology, adenovirus vector-based vaccines will be key in achieving world-wide vaccination campaigns. Identification of the molecular mechanisms that trigger the anti-PF4 immune response leading to VITT is absolutely key for rational approaches to make adenoviral vector-based vaccines safer by reducing the risk to induce an anti-PF4 immune response.

A few aspects of VITT have not been addressed in the comprehensive review of Marietta et al. Adenovirus vector-based vaccines also induce anti-platelet antibodies. About 25% of all VITT patients show free anti-platelet antibodies in their serum [16]. These antibodies have the same characteristics as antibodies identified in patients with autoimmune thrombocytopenia (ITP). This was a highly unexpected finding. The sensitivity of current assays to detect free anti-platelet antibodies is only 10%, which compares to a sensitivity of about 60% to identify platelet bound antibodies. Nicolai et al. [16], showed that platelets bind the adenovirus of the vaccine, which is then transported into the spleen, interacting there with marginal zone B cells. It is very likely that co-presentation of viral epitopes and platelet proteins breaks tolerance against platelets. These findings may also help to better understand ITP after viral infections. Especially ITP in childhood typically manifests about two weeks after an acute viral infection.

VITT may probably even guide us to better understand mechanisms of recurrent thrombotic complications. We are currently working up a patient who developed (several years before the pandemic) thrombocytopenia, cerebral vein sinus thrombosis, and high titer anti-PF4 antibodies about two weeks after an upper respiratory tract infection. Also, patients with monoclonal gammopathy can develop a VITT like picture. One of such patients with recurrent venous and arterial thrombosis has been investigated in detail [17]. Before 2021, we tested her at several occasions in the typical heparin-dependent functional HIT test. This assay was always (false) negative. After understanding VITT, we tested her for PF4 dependent, platelet activating antibodies, for which she tested strongly positive. Functional assays for PF4 dependent antibodies are the domain of specialized laboratories and can barely be automated. To better understand whether PF4-dependent platelet activating antibodies may be an important cause of recurrent thromboses in some patients requires availability of a widely applicable standardized laboratory assay, which can differentiate between HIT-like and VITT-like antibodies. Careful prospective studies will show whether anti-PF4 antibodies should be added to the immune mediated prothrombotic disorders, beside heparin-induced thrombocytopenia (HIT), thrombotic-thrombocytopenic purpura (TTP) and the antiphospholipid syndrome (APS).

Declaration of Competing Interest

AG has no COI to declare related to this commentary

References


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