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EDITORIAL
Vascular medicine

Vaccination-induced thrombocytopenia and thrombosis (VITT) and pre-VITT: Do not miss (or misdiagnose) the new member of the thrombotic thrombocytopenias family

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This editorial refers to 'Early recognition and treatment of pre-VITT syndrome after vector-based SARS-Cov-2 vaccination may prevent from thrombotic complications: review of published cases and clinical pathway', by F. Salih *et al*. https://doi.org/10.1093/ehjopen/oeac036.

Vaccination-induced thrombocytopenia and thrombosis (VITT) can exceptionally occur after injection of COVID-19 adenovirus-based vaccines. Platelet activating antibodies to platelet factor 4 (PF4) are detected, related to but not identical with those characteristic of heparin-induced thrombocytopenia (HIT), another thrombotic thrombocytopenic syndrome, in particular the so-called autoimmune variant of the latter (see *Figure 1*).

The syndrome can be devastating, notably when thromboses are located in the cerebral sinuses and veins (CVT). In the article by Salih *et al*, published in European Heart Journal Open[1] the authors addressed the issue of early recognition of VITT, even before the occurrence of thrombosis detectable by cutting-edge imaging (hence coined as 'pre-VITT').[2]

What does their study tell us? Based on the literature search (as of 1 January 2022) and the careful analysis of 19 published cases (stressing the importance of case reports as long as they are sufficiently informative), the authors offer a clinical pathway how to diagnose patients at-risk of VITT, based on headache 4–42 days after vaccination (ChAdOx1 nCoV-19 first-dose; only one patient was reported after AD26.COV2.S vaccination), low platelet count—not very low though, not rarely just around 100×10^9/L—and high D-dimers plasma levels, with an ELISA positive for anti-PF4 antibodies; three laboratory features of VITT, but without evidence for established thrombosis.

The authors provide some evidence that early treatment (the one of VITT) in fact may prevent complications. There was, however, a substantial overlap of the latencies from onset of headache to treatment between those who progressed to VITT (seven) and those who did not (12): 2–5 days, moreover 18 patients survived, indicating that late treatment can be efficacious even if not preventing thrombosis. In addition they observed that the decline in platelet count after admission was significantly more pronounced in patients who progressed to VITT, whereas D-dimers did not differ between groups. Of note, already receiving anticoagulation for another reason does not rule out pre-VITT (one reported case—anticoagulation for atrial fibrillation). Moreover, no haemorrhagic complications occurred after initiation of non-heparin anticoagulation despite low platelet count.

Some words of caution are worthwhile here. Awareness of the side effects of COVID-19 adenovirus-based vaccination must be high but must also remain reasonable: high since VITT is a very serious complication, although fortunately exceptional, but the very exceptionality makes such an awareness difficult to maintain steady; reasonable since diagnostic suspicion of (pre)VITT is one among a multitude of settings that can correspond, or not, to life-threatening diseases, and not all persons presenting in the emergency departments can undergo complicated diagnostic workups. Thrombocytopenia if ascertained as real (pseudo-thrombocytopenia ruled out) and markedly elevated plasma levels of D-dimers should not escape the attention of a physician, how busy would she/he be.

Second, even though the authors of that study offer sound guidelines, advice from expert teams must always be sought for in emergency, because diagnosis and treatment can be far from straightforward.

Lastly, it is not fully established that (pre-)VITT cases are all due to anti-PF4 antibodies, and the full spectrum of pathogenesis is not elucidated. For instance, a clear explanation for the frequent of the otherwise unusual location of venous thrombosis is missing. The explanation for headaches in the absence of (detectable) CVT remains elusive, as thoroughly discussed by the authors.

We would like to take the opportunity of this comment to remind the readers that there are several thrombosis and thrombocytopenia syndromes, other than VITT. In this respect, we do not concur with

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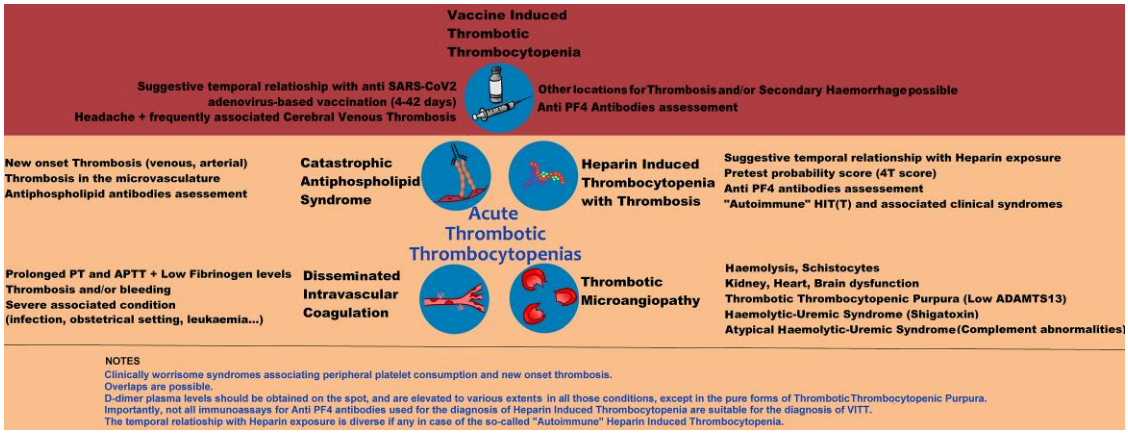

Figure 1 Summary diagram of main features of the Acute Thrombotic Thrombocytopenias 'family'.

the authors who seem to equate VITT and thrombosis with thrombosis and thrombocytopenia syndrome (TTS).

Thrombosis and thrombocytopenia syndrome encompass a range of pathogenic processes with some overlaps (see *Figure 1*). Regarding catastrophic antiphospholipid syndrome, coagulation testing should be scrutinized and immunoassays for the so-called antiphospholipid antibodies should be promptly performed, even in vaccinated persons (vaccination being a potential 'second hit'). In the absence of thrombosis, post-vaccinal immunothrombocytopaenia (ITP) belongs to the differential diagnosis. Of note, intracranial haemorrhage can result from profound thrombocytopenia seen in ITP patients; in that case the classical mucocutaneous haemorrhagic presentation can be a decisive clue, while purpura is much less frequent in (pre-)VITT. Of note as well, some clinical presentations of VITT, in the absence of neurological signs, should be suggestive as well, such as the association of Raynaud's phenomenon, chilblain-like lesions, and splinter haemorrhages,[3] or on the contrary more deceptive.[4]

What about the usefulness of such an expeditious though careful and insightful clinical research, while colleagues working in European countries are no longer be confronted with people vaccinated with COVID-19 adenovirus-based vaccines? First, all such COVID-19 vaccines are still in use elsewhere around the world. As rightly pointed out by the authors, the further global rollout of SARS-CoV-2 vaccines in low-to-middle-income countries will heavily rely on adenoviral vector-based vaccines, and a pragmatic approach to manage patients in areas with limited access to laboratory and imaging is welcome. In addition, it is likely that vaccines with an adenovirus platform directed at other viruses will be still developed. It is thus crucial to remain attentive to such complications in clinical practice and above all to fully understand what in such vaccines are responsible for them, and why some (very rare) persons are prone to them, something that has remained essentially elusive regarding HIT.

The take-home message: if you suspect a (pre-)thrombotic syndrome, whether or not the patient has recently been vaccinated, do not rely only on D-dimers testing in the laboratory, but look also carefully at the platelet count, and, if low, at the blood smear (schistocytes seen in thrombotic microangiopathies).

As the COVID-pandemic does not subside, we do concur with the authors that, as vaccination is the most effective approach to contain the pandemic, efficient management of complications should help to maintain and even increase the acceptance for vaccinations worldwide.

Conflict of interest: None declared.

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