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THROMBOSIS AND HEMOSTASIS

Comment on Schönborn et al, page 2305

VITT-like disorder HITs the headlines

Marie Scully | University College London Hospitals Biomedical Research Centre and National Institute for Health Research

Antibodies to platelet factor 4 (PF4) are central to the pathology of heparin-induced thrombocytopenia (HIT) and vaccine-induced thrombocytopenia and thrombosis (VITT). However, in this issue of *Blood*, Schönborn and colleagues present a new scenario, VITT-like disorder.[1]

HIT was first described in 1958[2] associated with heparin infusions; HIT is typically associated with a drop in platelet count at a median of 5 to 10 days after initiation of heparin (often unfractionated) and has a prothrombotic phenotype, mainly involving deep vein thrombosis but also arterial thrombosis.[3] Presentation is usually in hospital, and treatment requires use of an alternative nonheparin anticoagulant and avoidance of platelet transfusions despite the thrombocytopenia. Diagnosis is confirmed by assays involving PF4-heparin and immunoglobulin G (IgG) antibodies to this complex.

VITT was identified in 2021[3-5] related to adenoviral vaccines for COVID-19. VITT presents as an acute medical emergency and is associated with thrombocytopenia and thrombosis. It usually occurs 5 or more days (median 14 days) after vaccination, commonly following the first adenoviral COVID-19 vaccination. Thromboses are seen in atypical sites, including central venous sinus thrombosis (CVST) (often in multiple veins) and splanchnic thrombosis, with 20% arterial events (myocardial infarction, stroke, or arterial limb thrombosis) with associated mortality of 20%.[6] Diagnosis is based on very high D-dimer levels and positive anti-PF4 antibody enzyme-linked immunosorbent assay (ELISA). Many automated "fast HIT" assays were not positive in cases of VITT.

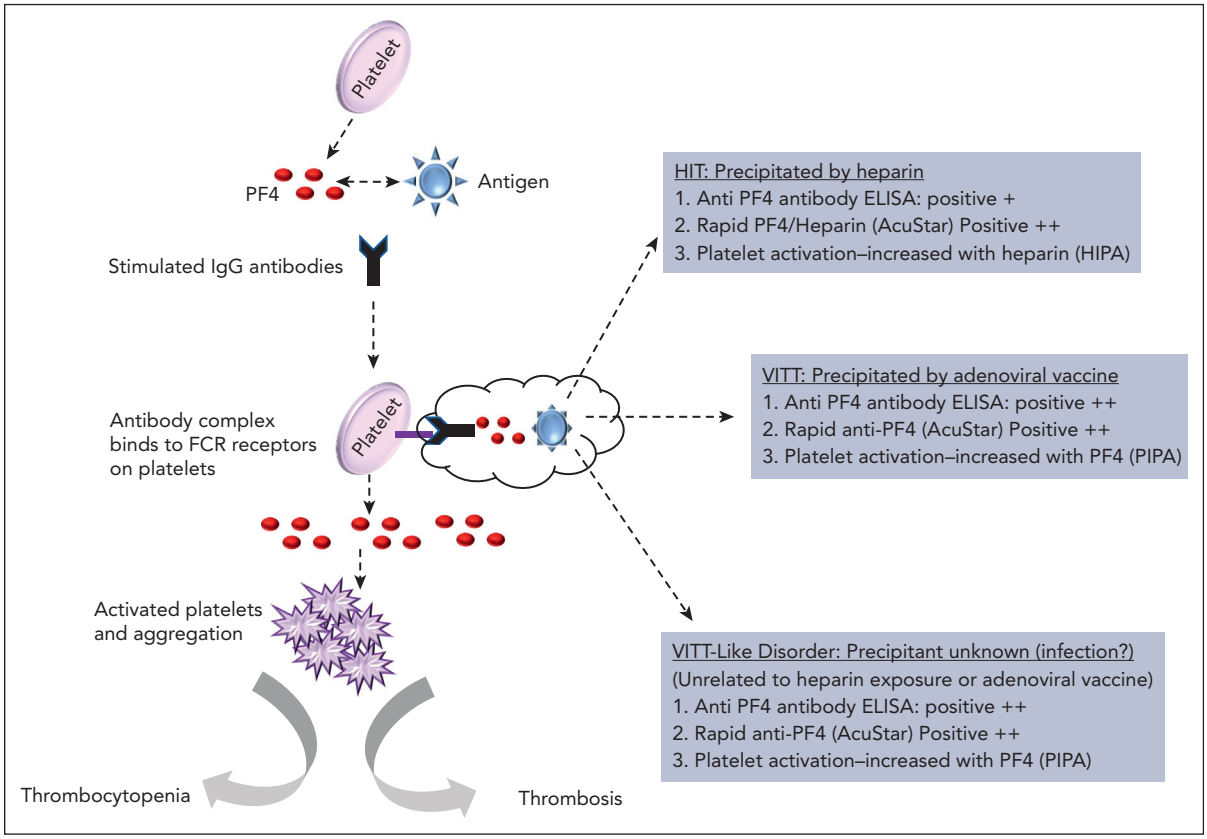
What of cases diagnosed as severe HIT, known as spontaneous or autoimmune HIT, that had not had previous heparin exposure? Are some cases presenting as strokes with thrombocytopenia positive for anti-PF4 antibodies, or are these antibodies prevalent in other conditions such as antiphospholipid syndrome?

In their study, Schönborn and colleagues investigated the specific laboratory findings in VITT compared with HIT to determine if a VITT-like disorder was evident before the COVID-19 pandemic. Three main anti-PF4 assays were used in this publication: first, rapid anti-PF4 antibody assays, using chemiluminescence technology (HemosIL AcuStar) (the standard assay is anti-PF4/heparin and a new rapid assay that detects anti-PF4 antibodies, as detected in VITT cases); second, anti-PF4 IgG antibodies detected by ELISA; third, platelet activation assays (only available in highly selective laboratories) demonstrating increased platelet activation with the addition of heparin (HIPA assays) as seen in HIT, compared with increased platelet activation with the addition of PF4 (PIPA assays) confirmed in VITT.

The authors reported a cohort of cases referred for HIT testing. However, their presentation was comparable to VITT, with a strongly positive anti-PF4 IgG antibody by ELISA and platelet activation positive to PF4 (PIPA) and not to heparin (HIPA), as seen in VITT. Furthermore, all samples were positive using the new rapid anti-PF4 antibody test. Clinically, there was no relation to heparin therapy, and the cases were pre-COVID-19 pandemic, therefore unrelated to either primary COVID-19 infection or COVID-19 vaccination. Thromboses were analogous to VITT with CVST and splanchnic bed thrombosis as well as arterial events, usually stroke. Associated thrombocytopenia and markedly raised D-dimer levels were evident. Although the cause of this new VITT-like disorder is not clear, there was confirmed infection in more than 50% of cases. Furthermore, 2 cases had recurrence of presentation a number of years after the first episode.

To aid confirmation of this new disorder and the distinction between the different assays for HIT and VITT-like disorders, a large cohort of normal, healthy controls were tested; these were anti-PF4 antibody negative, a similar finding for cases of stroke and thrombocytopenia and antiphospholipid syndrome. In VITT cases, 99% were positive to the new rapid anti-PF4 assay, although 15.5% were also positive to the rapid anti-PF4/heparin assay. But in platelet activation studies, a platelet stimulation was seen with PF4 but not with heparin. However, in confirmed cases of HIT, 96.9% were positive in the rapid anti-PF4/heparin assay, but 30.5% were also positive in the rapid anti-PF4 assay. Aside from increased platelet activation to heparin (HIPA), more than 50% also demonstrated a response in the presence of PF4 (PIPA).

Preceding the identification of this new condition, VITT-like disorder, which appears comparable to VITT (related to adenoviral vaccines), some HIT cases unrelated to heparin exposure now fulfill a diagnosis of VITT-like disorder.[7,8] Importantly, it is the presentation of life-threatening thrombosis that has implications for treatment. In VITT, we now know therapeutic heparin therapy is not contraindicated, but we have alternative non-heparin-based therapies that can be used. Furthermore, intravenous immunoglobulin was initiated promptly



HIT, VITT, and VITT-like disorder. A summary of the pathogenesis of development of anti-PF4 antibodies. The 3 conditions are summarized with regards to the precipitant: heparin in HIT, adenoviral vaccine in VITT, and unknown but possibly infection in VITT-like disorder. Included are the assays relevant to these 3 conditions to aid differentiation.

in many cases of VITT, but the improvement in mortality in severe cases of VITT was seen with plasma exchange and immunosuppressive therapies.

Therefore, in addition to HIT related to heparin therapy and VITT related to adenoviral vaccines, we now have a new condition to consider, VITT-like disorder, which has an acute presentation. This is a novel, severe clinical phenotype, associated with thrombocytopenia, arterial and venous thrombosis often in atypical vascular beds, and super high D-dimer levels. In many cases, there appears to be a possible relation to a recent infection. The use of rapid chemiluminescence assays for PF4 antibodies with or with out heparin, the latter being newly described and validated, will aid differentiation of the new condition from HIT (see figure).

VITT-like disorder doubtlessly will be rare. However, consideration is paramount, and future presentation of cohorts are important to understand therapy and outcomes. Concurrently, the use of more than 1 anti-PF4 assay is essential for diagnostic certainty and validation of this newly presented rapid anti-PF4 test in coagulation laboratories.

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