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Is complement the culprit behind COVID-19 vaccine-related adverse reactions?

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The prothrombotic action of anti-PF4 antibodies likely involves antibody-mediated platelet activation through IgG-FcγR interactions and similar FcR-mediated engagement of immune effector cells such as monocytes/macrophages and neutrophils (Figure 1). Since VITT is a newly described syndrome, its clinical management mostly relies on its similarities with HIT and non-heparin-dependent autoimmune thrombotic thrombocytopenias. While nonheparin anticoagulants and intravenous immunoglobulin (IVIg) have been proposed as first-line treatments for patients with VITT, these approaches are not fail-safe and entail drawbacks that may curtail their effectiveness (e.g., risk of numerous FcR activation, acute anaphylaxis, or even thromboembolic events in the case of intravenous immunoglobulin) (4).

Several second-line therapies for HIT have also been suggested, including plasmapheresis, especially when nonheparin anticoagulation is contraindicated because of major bleeding events (5). Thus, more insight into the precise pathophysiology of VITT is needed to enable more personalized medicine approaches.

A proposed role for complement

Complement is a host innate immune sentinel comprising over 50 proteins that can be swiftly activated through any of three initiating pathways (classical, lectin, or alternative) that sense microbial invaders or other inflammatory cues, such as immune complexes. In fact, complement activation has been implicated as a perpetrator of immune complex-driven thromboinflammation in autoimmune pathologies such as the antiphospholipid syndrome, a systemic disorder that increases risk for blood clots (6). Prompted by the striking findings in patients who developed VITT after a single dose of adenoviral-associated vaccine, we posit here that the observed thrombotic complications may partly reflect immune complex-triggered complement activation through the classical pathway. PF4-containing immune complexes can be recognized by C1q, a soluble pattern recognition molecule of the classical pathway that binds to the Fc portion of IgG molecules. Anti-PF4 complex-driven classical pathway activation can lead to C3 activation, alternative pathway-mediated amplification of complement responses, and downstream generation of potent proinflammatory mediators and effectors (C3a, C5a and membrane attack complex) that can potentiate thromboinflammation (7).

In fact, the thrombogenic capacity of distinct complement activation fragments has been linked to a broad spectrum of immune-related mechanisms that underpin the immunothrombosis of severe COVID-19 (7, 8).

Considering that certain allelic combinations of complement gene polymorphisms within the population confer differential susceptibility to deregulated complement activity, it is tempting to speculate that these vaccinated individuals may represent cases where complement deregulation occurs due to genetic alterations that result in ineffective host regulatory control (9). Deregulated complement responses can perpetuate a vicious cycle of inflammatory tissue damage that renders the vascular endothelium and platelet/macrophage compartment more thrombogenic. In this regard, circulating anti-PF4 immune complexes may well serve as a first hit that ignites complement acti-
C3 activation may play a pivotal pathogenic role in this vaccine-induced immunothrombotic phenotype. C3-opsonized anti-PF4 immune complexes can enhance the phagocytic and inflammatory properties of monocytes and neutrophils through sulfation, in a way similar to complement-mediated thrombotic microangiopathies (10). The fact that a fraction of these anti-PF4 autoantibodies may recognize antigenic complexes between PF4 and polyanionic structures (such as GAGs or heparan sulfate) raises the possibility that these immune complexes may skew the binding of endogenous complement regulators to host polyanionic surfaces, thereby altering the capacity of these surfaces to withstand autologous complement attack.

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the synergistic engagement of FcγR and complement receptors, thereby increasing the thrombogenic milieu in the vasculature (Figure 1). C3 fragment deposition on the endothelium and on platelets/neutrophils can potentiate thromboinflammatory responses by promoting CR3-dependent platelet-neutrophil interactions that favor platelet adhesion and clotting (11). Also, C3αR signaling on platelets can further drive thrombotic responses (12). Of note, it has been shown that PF4-heparin complexes, a hallmark of HIT pathology, can potently activate C3 in the fluid phase and C3 inhibitors such as Cp40 can abrogate C3 activation triggered by HIT-associated PF4-heparin complexes (13). In line with this, the Cp40-based drug candidate AMY-101 has been shown to effectively decrease both neutrophils and neutrophil extracellular trap (NET) formation, two major drivers of HIT-associated thrombosis, in patients with COVID-19 (7, 14–16).

Potential treatment approaches

In an analogy to HIT, clinical-stage complement C3 inhibitors may represent a novel therapeutic strategy for ameliorating the thrombotic complications elicited in VITT. On one hand, C3 inhibition may quench anti-PF4 antibody production by reducing antigen uptake or processing in the lymphoid tissue. On the other hand, it can broadly suppress multiple pathways of immune complex–driven thromboinflammation in VITT (Figure 1). Moreover, C3 inhibition may offer broader therapeutic control of thromboembolic reactions mediated by pathogenic autoantibodies. In this regard, C3 activation, but not C5, was shown to be indispensable for antiphospholipid antibody-induced tissue factor (TF) activation and thrombosis in antiphospholipid syndrome (17). The recently reported resolution of vaccine-induced thrombotic microangiopathy in two patients following combined treatment with anticoagulants and the C5 inhibitor eculizumab further corroborates our hypothesis that therapeutic complement modulation may offer significant clinical benefits to patients with VITT (18). In this regard, C3 inhibitors may exert a broader therapeutic effect than anti-C5 agents by suppressing both terminal pathway activation and thrombogenic pathways operating upstream of C5 (14, 19).

Because this newly described immune syndrome is still poorly defined, it would be of great benefit to patients with VITT if the algorithm for VITT clinical management considered diagnostic monitoring of complement biomarkers as a means of validating the use of specific complement inhibitors. As a cautionary note, we should stress that plasma levels of complement proteins reflect both turnover and synthesis. Therefore, the accurate monitoring of complement activity should rely on markers of ongoing activation combined with corroborative functional assays that gauge the impact of complement activation on the tissue or cellular level.

mRNA vaccine reactions

In addition to these cases of VITT in individuals receiving adenovirus vectored vaccines, the rollout of COVID-19 mRNA vaccines has brought to the spotlight rare adverse events involving a maladaptive immune reaction to certain vaccine constituents. Rare cases of severe allergic reactions (anaphylaxis) were reported following the first dose of the Pfizer–BioNTech or Moderna SARS-CoV-2 mRNA vaccines (20). Such allergic reactions are likely triggered by the PEG or lipid moieties of these mRNA vaccines. They involve complement and mast cell activation in an IgE-independent manner and closely resemble the complement-mediated pseudo-allergy reaction (CARPA) that has been described in the case of liposomal carriers (21). Complement activation in this case may be initiated by IgG or IgM directed against the PEGylated lipids of these vaccine formulations.

Concluding remarks

Taken together, these paradigms of vaccine-related adverse reactions highlight the potential contribution of complement activation to vaccine-related pathology, raise the importance of incorporating complement diagnostic monitoring in the early clinical management of such patients, and endorse complement inhibitors as potential treatment options. In addition to the complement-activating capacity of anti-PF4 antibodies, we cannot rule out the possibility that complement activation in VITT may also be fueled by preformed (natural IgM) or induced IgG antibodies against adenoviral capsid antigens or direct inter-action of pattern recognition molecules with capsid elements (22). The relevance of these plausible mechanisms to VITT pathology warrants further investigation.

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