Is the heparin-induced thrombocytopenia-like syndrome associated with ChAdOx vaccine related to the vaccine itself or to an autoimmune reaction to severe acute respiratory syndrome 2 coronavirus: insights and implications from previous reports in infected cases?

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Abstract

Prothrombotic states, similar to heparin-induced thrombocytopenia (HIT) in recipients of the ChAdOx vaccine, sounded alarm bells internationally. Equivalent episodes of HIT were detailed in several case reports of coronavirus disease 2019. This suggests a common pathogenesis and warrants a shift in the management of implicated cases.

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Background

Over 150 coronavirus vaccines are currently under development. In an attempt to stop the ongoing pandemic, numerous countries have issued emergency use authorization for a number of those vaccines [1]. This hectic vaccine rollout means that not enough is known about their short-term and long-term consequences. In March 2021, reports appeared of strokes and prothrombotic states in recipients of the ChAdOx vaccine (AZD1222, AstraZeneca, Cambridge, UK). The vaccine was temporarily suspended in several European countries [2].

The European Medicines Agency stated concern for the safety of the ChAdOx vaccine. However, Greinacher et al. revealed (in a preprint) the serological profile of patients who developed this unusual set of symptoms after the ChAdOx vaccine [3]. They concluded that the prothrombotic state in these patients is similar to heparin-induced thrombocytopenia (HIT). All nine patients showed positive anti-platelet factor 4 antibodies (anti-PF4), frequently seen in recipients of heparin. None of these patients were on heparin before vaccination. This implies that the ChAdOx vaccine can potentially induce such autoantibodies [3]. EMA temporarily suspended the use of ChadOx vaccine then confirmed that its benefits outweighs the prevalence of the observed complication.

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TABLE 1. Summary of COVID-19-related cases of heparin-induced thrombocytopenia

Authors	Country of authors	Age in years	Sex	Type of prothrombotic state
Madala *et al.* [4]	USA	65	Female	Lacunar infarct in basal ganglia and right-sided hemiplegia
Kewan *et al.* [5]	USA	56	Male	DVT
Lingamaneni *et al.* [6]	USA	63	Male	DVT
Sartori *et al.* [7]	Italy	78	Male	DVT
Bidar *et al.* [8]	France	62	Female	Pulmonary embolism
		38	Male	Deteriorating oxygenation
Ogawa *et al.* [9]	Japan	37	Male	DVT, massive pulmonary thromboembolism
Daviet *et al.* [10]	France	46	Male	DVT
		50	Male	Intracardiac thrombosis
		43	Female	DVT
		63	Male	Stroke
		59	Male	DVT
		57	Male	None
		69	Male	
Phan *et al.* [12]	Vietnam	43	Male	DVT/Pulmonary micro-thrombi, deteriorating oxygenation
Lozano and Franco [11]	Spain	45	Male	None
		71	Male	
		90	Male	
Summary		Maximum age: 90 years Minimum age: 37 years Median age: 58 years Sex distribution: male: 84%, female: 16% Total of 18 cases		13 presented with thrombotic events (72%) DVT/pulmonary embolism: commonest prothrombotic event (9 cases/61%)

Abbreviations: COVID-19, coronavirus disease 2019; DVT, deep venous thrombosis.

Is this an old, misinterpreted feature of Coronaviridae or is it a brand new feature?

Some cases of HIT were reported before the current vaccine rollout; these are reviewed and summarized in Table 1 [4–12]. All the reports incriminated heparin in the development of the observed prothrombotic state. These patients received heparin for one of three reasons: (a) initial presentation with thrombosis; (b) increased risk of thrombo-embolism development due to an underlying medical condition, e.g. atrial fibrillation; (c) extracorporeal membrane oxygenation.

The commonest type of thrombosis observed was venous thrombosis, mimicking the pattern of thrombosis observed in recipients of ChAdOx vaccination, men were affected more than women (84% versus 16%), and median age was 58 years.

A rise in equivalent reports following ChAdOx vaccination indicates that heparin might not be the cause of this HIT-like syndrome after all. Instead, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) could induce an autoantibody profile just like that of HIT (see Fig. 1).

Why is the prothrombotic thrombocytopenic disorder observed mainly with ChAdOx vaccine and not with other vaccines?

It remains unclear why the HIT-like syndrome is observed mainly with the ChAdOx vaccine and not with other coronavirus disease 2019 (COVID-19) vaccines. A possible explanation was given by Othman *et al.* [13], who confirmed the occurrence of persistent unexplained thrombocytopenia and platelet dysfunction with vaccines that use adenoviruses as viral vectors. This might signify that adenoviruses can synergize with SARS-CoV-2 antigens in inducing the autoantibodies causing such prothrombotic thrombocytopenic disorders. This indicates that all other COVID-19 vaccines using the same technology may cause the same complication. This is yet to be determined.

Diagnostic and therapeutic implications

These findings necessitate updating laboratory testing and treatment of individuals with COVID-19 presenting with thrombosis, through the following protocol.

Routine anti-PF4 testing

The high prevalence of anti-PF4 in individuals with COVID-19 previously diagnosed with HIT (as mentioned in Table 1) warrants screening of this antibody profile in individuals presenting with thrombotic events, both COVID-19 patients and individuals after ChAdOx vaccination.

Alternative anti-coagulants

Three non-heparin anticoagulants, namely danaparoid, lepirudin and argatroban, are used in HIT as alternative anticoagulants because they do not cross-react with HIT antibodies. Similarly, low-molecular-weight heparin should not be used in individuals with COVID-19 and in ChAdOx-vaccinated individuals because

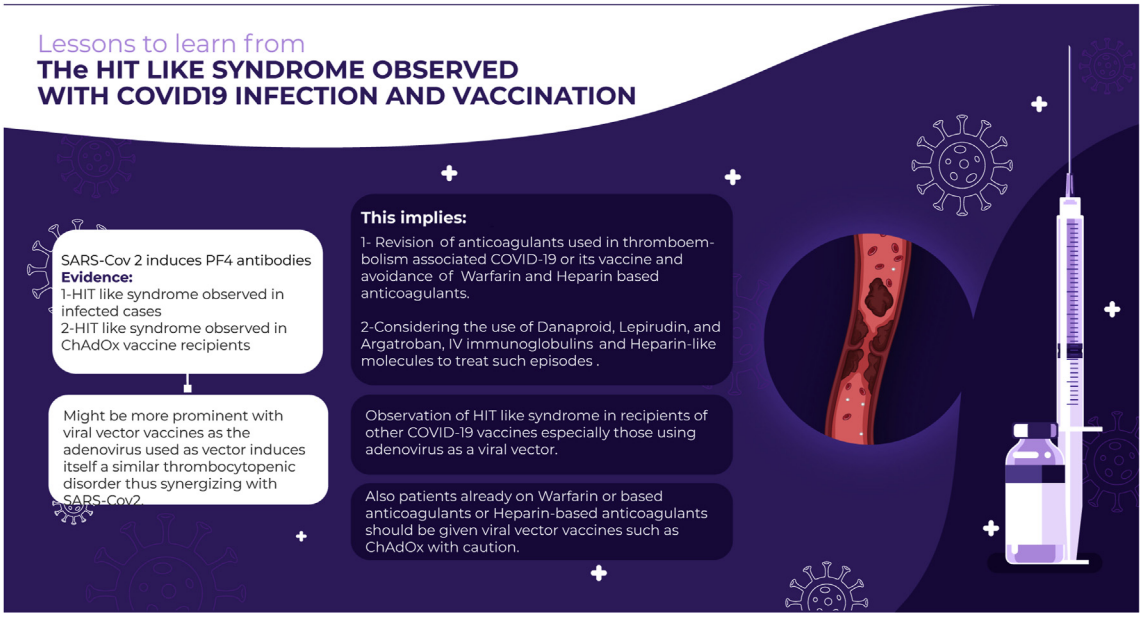

FIG. 1. Lessons to learn from the HIT-like syndrome observed in SARS-CoV-2 infection and vaccination. Abbreviations: COVID-19, coronavirus disease 2019; HIT, heparin-induced thrombocytopenia; PF-4, platelet factor 4; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

of its cross-reactivity with PF4 autoantibodies. Warfarin is also discouraged in HIT because of a paradoxical increase in the thrombotic tendency.

On the other hand, high-dose intravenous immunoglobulins are one of the best-established therapies for HIT.

A final therapeutic approach of importance is using heparin-like molecules to disrupt the PF4–glycosaminoglycan complexes. This is considered in the treatment of HIT and could be regarded as a treatment for the prothrombotic state in individuals with COVID-19 and in ChAdOx-vaccinated individuals [14].

Vaccination of recipients of warfarin and heparin-based anticoagulants

A final aspect learnt from the observed prothrombotic syndrome is the choice of a suitable COVID-19 vaccine in those receiving heparin-based anticoagulants or warfarin. Caution should be exercised on administering adenovirus-mediated viral vector vaccines, such as ChAdOx, because of the ability of those medications to induce the same autoimmune complication.

Conclusion

Increasing evidence suggests that SARS-CoV-2 is an independent risk factor for PF4 autoantibody development, regardless of previous heparin therapy. The reports encountered following ChAdOx vaccination and SARS-CoV-2 infection advocate for this hypothesis. This information warrants clinicians to screen for specific autoantibodies in any individual with COVID-19 and in ChAdOx-vaccinated individuals presenting with a thrombotic event. It may also lead to advances in the anti-coagulant regimens and treatments used in these patients; such as avoidance of heparin-based anticoagulants and the use of immunoglobulins and Hep-like molecules that can disrupt PF4–glycosaminoglycan complexes. Finally, yet importantly, the autoimmune reaction observed with ChAdOx vaccine, might not only be mediated by SARS-CoV-2 antigens but also by the adenovirus used as a vector for this vaccine. Recipients of similar vaccines using the same technology should therefore be followed up for similar thombotic thrombocytopenic events.

Conflict of interest

The authors declare that they have no financial links with any of the suppliers of the suggested alternative anticoagulants.

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