Acquired Autoimmune Hemophilia Following SARS-CoV-2 Vaccines: Dual-Drug Effects on Blood Coagulation and the Scylla and Charybdis Phenomenon

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The global pandemic of coronavirus disease 2019 (COVID-19) from infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in high death rates and acute and chronic morbidity in all countries.[1,2] The development of vaccines against SARS-CoV-2 has dramatically reduced the transmission rate, the occurrence of COVID-19 by reducing the hospitalization rate, the severity of disease and incidence of mortality, and the transfection rate. The Food and Drug Administration and European Medicines Agency approved vaccines include two mRNA vaccines, the BNT162b2 from Pfizer-BioNTech and the Moderna vaccine, and two viral vector vaccines, the ChAdOx1 nCoV-19 (now called Vaxzevria) from AstraZeneca and the Johnson & Johnson/Janssen vaccine.[3–5]

Immunothrombosis after SARS-CoV-2 Vaccines

Vaccination against the SARS-CoV-2 may lead to immunologic reactions activating the hemostatic system and resulting in both venous and arterial thromboembolism, of differing severity.[6] In the present context, heparin-induced thrombocytopenia is the best known immunologic thrombotic complication caused by immunoglobulin G (IgG) antibodies against platelet factor 4 complexed with heparin, binding to the platelet FcRγIIA receptors, thereby causing platelet activation, microparticle formation, and thrombosis.[7] In 2021, rare thrombotic events in atypical locations (cerebral and/or splanchnic veins) associated with thrombocytopenia were reported 5 to 20 days after vaccination in young patients, mainly females, who were never exposed previously to heparin.[8,9] This syndrome, named vaccine-induced immune thrombotic thrombocytopenia (VITT), is associated with high fatality rate.[10] The U.S. Vaccine Adverse Event Reporting System and the U.K. Medicines and Healthcare products Regulatory Agency established coronavirus reporting systems and have made clear that the benefits of SARS-CoV-2 vaccination far outweigh the risk of VITT.[11]

Other Immunological Reactions to SARS-CoV-2 Vaccines

In addition to immunothrombosis, other immunological reactions to SARS-CoV-2 vaccines have been as well described. It is suggested that autoantibodies against the spike protein S1 of SARS-CoV-2 may be responsible for these complications as reported for immune thrombocytopenia,[12] vasculitis,[13] Schönlein-Henoch pupura,[14] autoimmune hepatitis,[15] and Guillain–Barré syndrome.[16] Additional case reports may increase the number of so far unknown immunological reactions to the available vaccines. Of note, some of the reactions were already described in the efficacy and safety studies of SARS-CoV-2 vaccines.[17]

Autoantibodies to Clotting Factor VIII after SARS-CoV-2 Vaccines

In mid-2021, the first cases of bleeding complications were reported 15 to 19 days (or later) after vaccination with adenoviral vector vaccine ChAdOx1.[18] Farley et al report on a case of acquired hemophilia with a large hematoma of his left posterior leg extending from his buttock to below his

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left knee, 19 days after the second dose of BNT162b2 Pfizer-BioNTech vaccine. Laboratory values revealed a two- to threefold prolongation of the activated partial thromboplastin time (aPTT), decrease of hemoglobin to 10 g/dL, factor VIII activity <1%, and 110 Bethesda Units/mL of factor VIII inhibitor. Platelet count, creatinine, and other laboratory parameters were in the normal range. The patient had no personal and family history of hemorrhagic diseases. The patient recovered without sequelae after adequate treatment.[19]

Other case reports also described the development of acquired hemophilia after SARS-CoV-2 vaccination.[20–22] These reports have as common the development of hemophilia with major bleeding following vaccination with one of the approved SARS-CoV-2 vaccines. All patients described so far presented with prolonged aPTT values, undetectable factor VIII levels, elevated factor VIII inhibitor concentrations, decreased platelet count, and reduced hemoglobin levels. After adequate treatment measures, they all recovered without sequelae and normalized coagulation values within a couple of weeks. One of these cases presented with negative polymerase chain reaction SARS-CoV-2 test and positive SARS-CoV-2 IgG antibodies, thus excluding with high probability that acquired hemophilia was an immunological reaction to virus.[22] Interestingly, the development of a factor VIIIIc inhibitor was already described in a patient with lichenoid dermatosis who had been vaccinated with BCG (Bacillus Calmette–Guérin) and a pool of various strains of live-attenuated corynebacteria and recovered without sequels after specific treatments.[23]

Anticoagulation and SARS-CoV-2 Vaccines

Thrombosis and hemorrhage may be a result of thromboinflammation due to viral infections, and the role of anticoagulation is important to consider.[24] Administration of anticoagulants is of huge importance for thrombotic disease prevention in COVID-19 patients, and heparins (unfractionated or low-molecular-weight heparins) are the currently recommended agents for hospitalized COVID-19 patients.[25,26] Nevertheless, excessive doses and/or an accumulative effect of heparins may favor bleeding, mainly in the hemorrhagic phase of the infectious disease when multiorgan failure also occurs. Therefore, from patients' point of view, anticoagulants and SARS-CoV-2 vaccines share their capacity to induce thrombosis as well as bleeding. Thus, clinicians are subjected to choosing between Scylla and Charybdis when they treat patients not only with anticoagulants but also with SARS-CoV-2 vaccines (►**Fig. 1**).

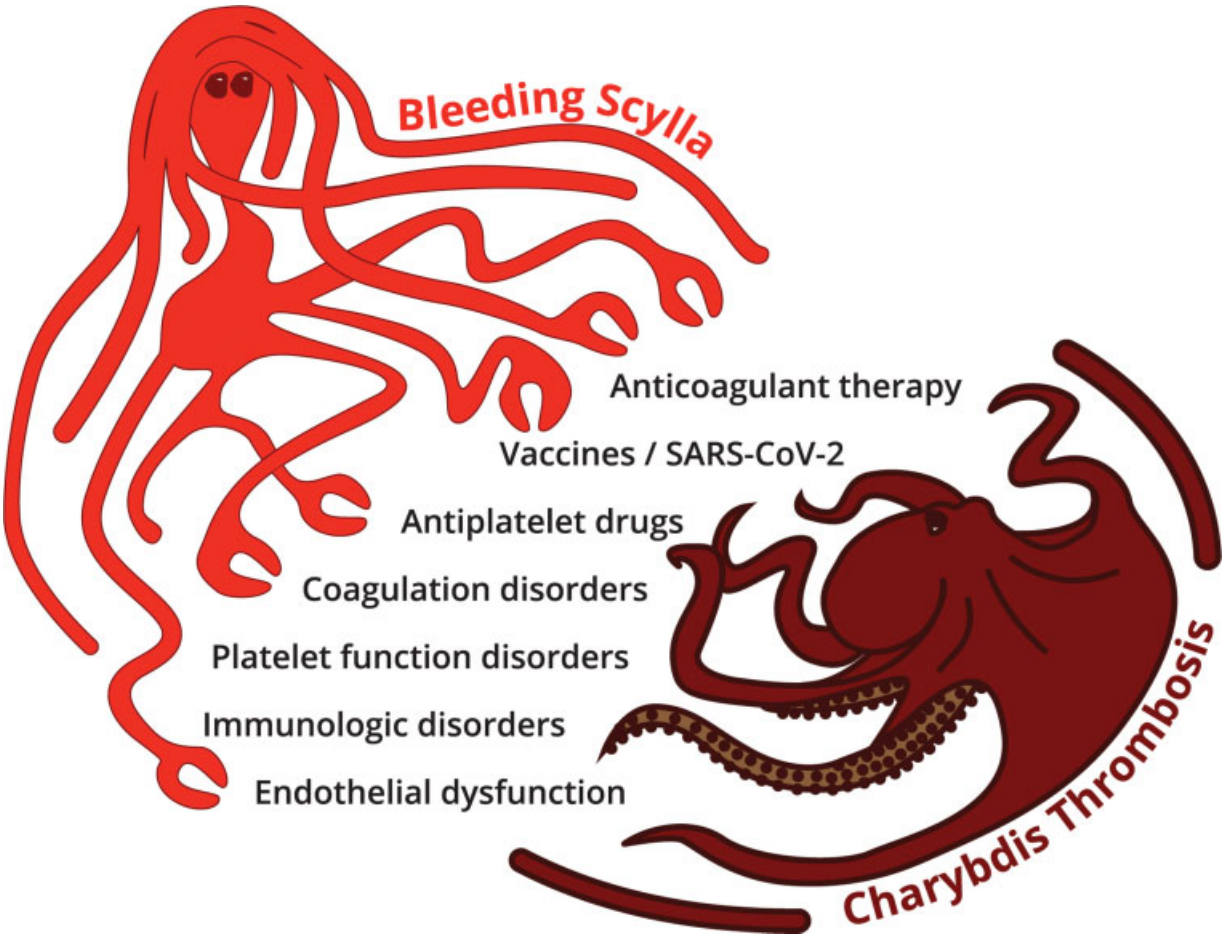

Fig. 1 Scylla and Charybdis phenomenon in hemostasis: similarities between anticoagulants, SARS-CoV-2 vaccines, and selected other pathways (Copyright.com.de; deposit number: DEP637698427981306749).

What the Future May Offer

Several aspects will guide in future due to immunological reactions to SARS-CoV-2 vaccines:

- Screening of patients for clinical symptoms of thrombosis and bleeding following vaccination may be regarded as an option.[27]
- Autoantibodies may be detected to other coagulation factors, proteins on platelet, and endothelium surface capable to induce bleeding and/or thrombotic events.
- Pan-sarbecovirus vaccines could seek to improve responses to this epitope by unmasking this and other cryptic broadly neutralizing epitopes[28] aiming to reduce immunologic blood coagulation effects.
- Careful analysis of coincidence and causality requires attention when reporting on acquired coagulation inhibitors regarding severity, treatments, duration, and statistical risk.[29]
- Careful documentation of case reports on immunological reaction to SARS-CoV-2 vaccines and of respective reactions from clinical studies in national and international registries.

Conflict of Interest
None declared.

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