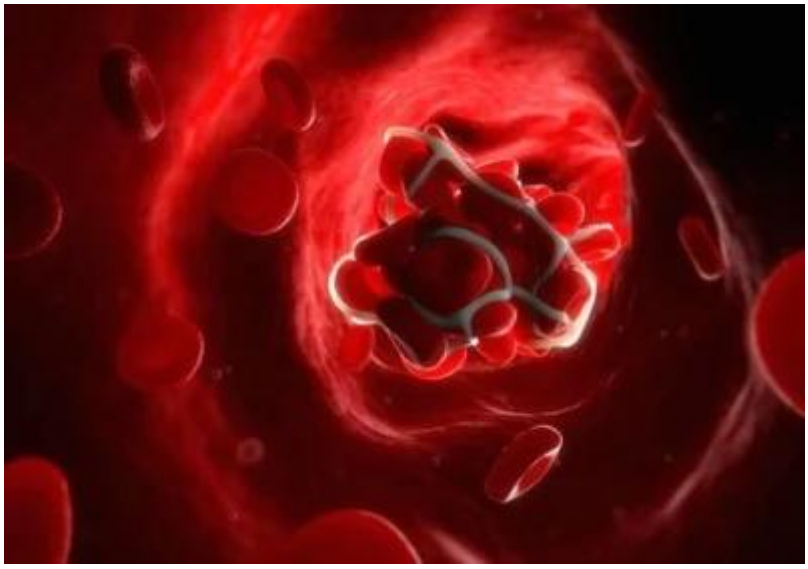
Vaccine-induced immune thrombotic thrombocytopenia (VITT) is characterized by thrombosis at unusual locations such as the cerebral venous sinuses, thrombocytopenia, and increased titers of antibodies against platelet factor-4 (PF-4). Thrombocytopenia and major thrombotic events have been reported after the administration of adenoviral vector-based COVID-19 vaccines (ChAdOX1-nCoV-19, AstraZeneca/Oxford or Ad26.COV2 Janssen/Johnson&Johnson). These adverse effects usually occur between 5 and 20 days after the vaccination and often have a severe outcome. In this study, French authors performed an immunohistological analysis of cerebral thrombi obtained from three fatal cases of cerebral venous thrombosis (CVT) related to vaccine-induced immune thrombotic thrombocytopenia (VITT).



About the Study and Results

The authors performed an immunohistological analysis of clots from three people who died from CVT related to VITT after receiving a single dose of ChAdOX1-nCoV-19, AstraZeneca/Oxford vaccines. In all three patients, the *premortem* blood analysis confirmed the presence of anti-PF4 IgG antibodies.

In all three cases of VITT, the autopsy demonstrated extensive thrombosis of cerebral venous sinuses. Importantly, the organization of cerebral thrombi was similar in all cases despite differences in treatment and time from admission to death.

Cerebral thrombi from patients who died of VITT had a remarkable architecture and specific progression of thrombus growth. The clot organization showed a high density of neutrophils,

intermingled platelets, and nucleated cells in the thrombus core. The SARS-CoV-2 spike (S) protein was detected within neutrophils in the thrombus. The thrombus tail was rich in fibrin and red blood cells, with a low density of neutrophils. The processes, such as neutrophil extracellular trap and complement activation, which are both highly thrombogenic, were present at the border and within the thrombi.

The CVT was also associated with injuries to vessel walls. Even at a distance from the thrombi, the walls of the superior sagittal sinus were inflamed and hemorrhagic. The CD34 staining showed that the endothelial cells adjacent to the thrombus were largely destroyed. The SARS-CoV-2 spike (S) protein was found in the wall of the superior sagittal sinus adjacent to the thrombus, particularly in CD45-positive cells.

According to the authors, immune complexes that contain SARS-CoV-2 S protein and anti-S protein IgG antibodies can induce thrombi formation mediated by platelets. The subsequent release of PF4 further enhances the production of anti-PF4 antibodies, massive activation of platelets, and the formation of neutrophil extracellular traps.

Conclusion

This *postmortem* analysis demonstrated extensive thrombosis of cerebral venous sinuses and similar organization of cerebral thrombi in all three patients who died of VITT. These findings provided strong evidence of immunothrombosis related to vaccine-induced immune thrombotic thrombocytopenia.

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