Using Nonheparin Anticoagulant to Treat a Near-Fatal Case With Multiple Venous Thrombotic Lesions During ChAdOx1 nCoV-19 Vaccination-Related Vaccine-Induced Immune Thrombotic Thrombocytopenia

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OBJECTIVES: To describe the successful recovery from multiple and life-threatening venous thrombosis after ChAdOx1 nCoV-19 vaccination.

DESIGN: Case report.

SETTING: University Hospital.

PATIENT: Few days after the first dose of the ChAdOx1 nCoV-19 vaccine, a 21-year-old woman experienced massive thrombosis in the deep and superficial cerebral veins together with seizures, neurologic focal deficit, and thrombocytopenia. In the neurointensive care unit, her condition worsened despite early decompressive craniectomy. She developed bilateral segmental pulmonary embolism, left hepatic, and left external iliac venous thrombosis.

INTERVENTION: Argatroban (0.5–2.2 µg/kg/min) and high-dose IV immunoglobulin (1 g/kg/d for 2 consecutive days) were initiated on day 6 after admission. With these therapies, there was a gradual resolution of multiple sites of venous thrombosis, and platelet count returned to normal. The patient left the ICU with full consciousness, expressive aphasia, and right hemiparesis.

CONCLUSIONS: This case of vaccine-induced immune thrombotic thrombocytopenia shows that a good outcome can be obtained even with multiple and life-threatening venous thrombotic lesions. Argatroban and high-dose IV immunoglobulin along with management of severe cerebral venous thrombosis played a major role in this epilogue.

KEY WORDS: argatroban; cerebral venous thrombosis; ChAdOx1 nCoV-19 vaccine; hepatic venous thrombosis; immunoglobulin; thrombocytopenia

Control of the coronavirus disease 2019 pandemic requires vaccination of the population. Besides its efficacy, the ChAdOx1 nCoV-19 vaccine (AstraZeneca, Oxford, United Kingdom) has raised recent concerns due to its association with serious thrombosis in young patients (1–3). Within few days after the first dose of the ChAdOx1 nCoV-19 vaccine, it was reported the development of a prothrombotic disorder with acute atypical thrombosis, in particular cerebral, hepatic and splanchnic vein thrombosis, and thrombocytopenia. Some patients had fatal outcome despite the use of several therapeutic options (1–3). This syndrome has been named vaccine-induced immune thrombotic thrombocytopenia (VITT). We report the case of young woman with multiple and life-threatening thrombotic lesions, including extensive cerebral and hepatic vein thrombosis. She showed good recovery once the decision was taken to initiate nonheparin anticoagulant and immunoglobulin. Written informed consent was obtained from her relatives.

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CASE PRESENTATION

A 21-year-old woman (47 kg; 1.62 m) with a history of migraine, smoking, and oral contraception received a first dose of the ChAdOx1 nCoV-19 vaccine on March 12, 2021. She developed unusual headaches 9 days after vaccination, then a focal seizure leading to a fall with dislocation of her right knee on March 26. At presentation to the emergency department, the patient had a Glasgow Coma Scale score of 14, a right-sided hemiplegia, expressive aphasia, and no pupillary abnormalities. CT of the head showed massive thrombosis in the deep and superficial cerebral veins (**Fig. 1**), thrombosis of the left jugular vein, and left frontoparietal venous hemorrhagic infarction. The platelet count was 61,000 per cubic millimeter. D-dimer measurements were not done.

In the absence of VITT description at that time, the patient received an IV treatment with unfractionated heparin (UFH, 85 UI/kg bolus, then 18 UI/kg/hr continuous infusion) once transferred to the neuro-ICU. Twelve hours later, she had a generalized tonic-clonic seizure and a persistent drowsiness that required tracheal intubation, mechanical ventilation, and sedation. A new brain CT scan showed growth of cerebral venous infarction with a midline shift of 9 mm, leading to a decompressive craniectomy after heparin reversal on March 27 (**Fig. 2**). During the operation, the patient had hemorrhagic shock due to a lesion of a branch of the right popliteal artery secondary to her initial knee trauma: a selective arterial embolization was performed immediately after decompressive craniectomy. Orthopedic surgery was not required.

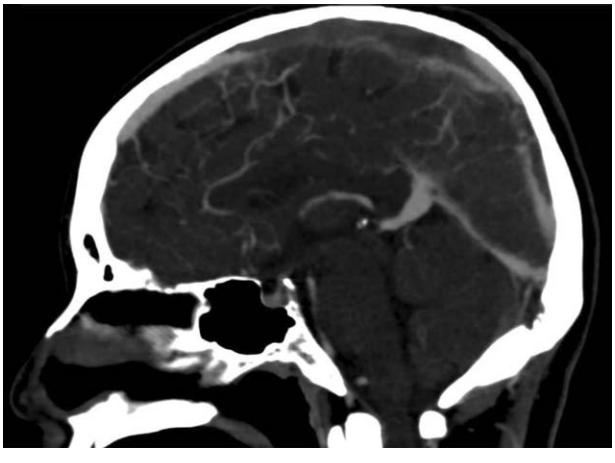

Figure 1. Brain CT scan showing the cerebral vein thrombosis extended to the upper longitudinal sinus and cortical veins.

The postoperative progression of cerebral vein thrombosis to the left transverse and sigmoid sinuses prompted physicians to resume UFH treatment on March 28. The effectiveness of UFH therapy was monitored from coagulation tests (**Supplemental Table 1**, http://links.lww.com/CCM/G520). However, thrombocytopenia was still persisting, and other sites of venous thrombosis were found on body CT: bilateral segmental pulmonary embolism, left hepatic, and left external iliac venous thrombosis. Because of this extensive prothrombotic disorder along with variable enzyme-linked immunosorbent assay tests for antiplatelet factor 4 (PF4) antibodies (Asserachrom heparin platelet-induced antibodies immunoglobulin G; Diagnostica Stago, Asnieres, France) (Supplemental Table 1, http://links.lww.com/CCM/G520), two therapeutic decisions were taken on March 31, that is, on day 6 from admission: switching UFH to nonheparin therapy with argatroban (0.5 µg/kg/min initial dose to 2.2 µg/kg/min maximum dose) and initiating high-dose IV immunoglobulin (IVIG) treatment (1 g/kg/d for 2 consecutive days). No steroid treatment was administered. The 24 hours a day monitoring of serum concentrations of argatroban (Hemoclot Thrombin Inhibitors; Hyphen Biomed, Neuville-sur-Oise, France) allowed targeting the concentration of argatroban between 0.5 and 1.2 µg/mL for several days.

Meanwhile, the patient was kept deeply sedated with optimization of hemodynamics, respiratory, and metabolic variables until the progressive resolution of cerebral venous infarction. She developed no intracranial hypertension, compromised cerebral blood flow, or new parenchymal hematoma. With these therapies, cortical veins were visualized with partial resolution of deep cerebral vein thrombosis, complete resolution of hepatic vein thrombosis, and a gradual return of platelet count to normal (Supplemental Table 1, http://links.lww.com/CCM/G520). On April 13, sedation was tapered to allow weaning from the ventilator. Neurologic examination found a patient with full consciousness, expressive aphasia, and right hemiparesis. Her anticoagulation treatment was subsequently changed from argatroban to fondaparinux. On April 19, the patient was transferred from the neuro-ICU to a neurologic rehabilitation unit. Cranioplasty is scheduled by the end of May 2021. The sensitized serotonin release assay was retrospectively positive and confirmed the diagnosis of VITT.

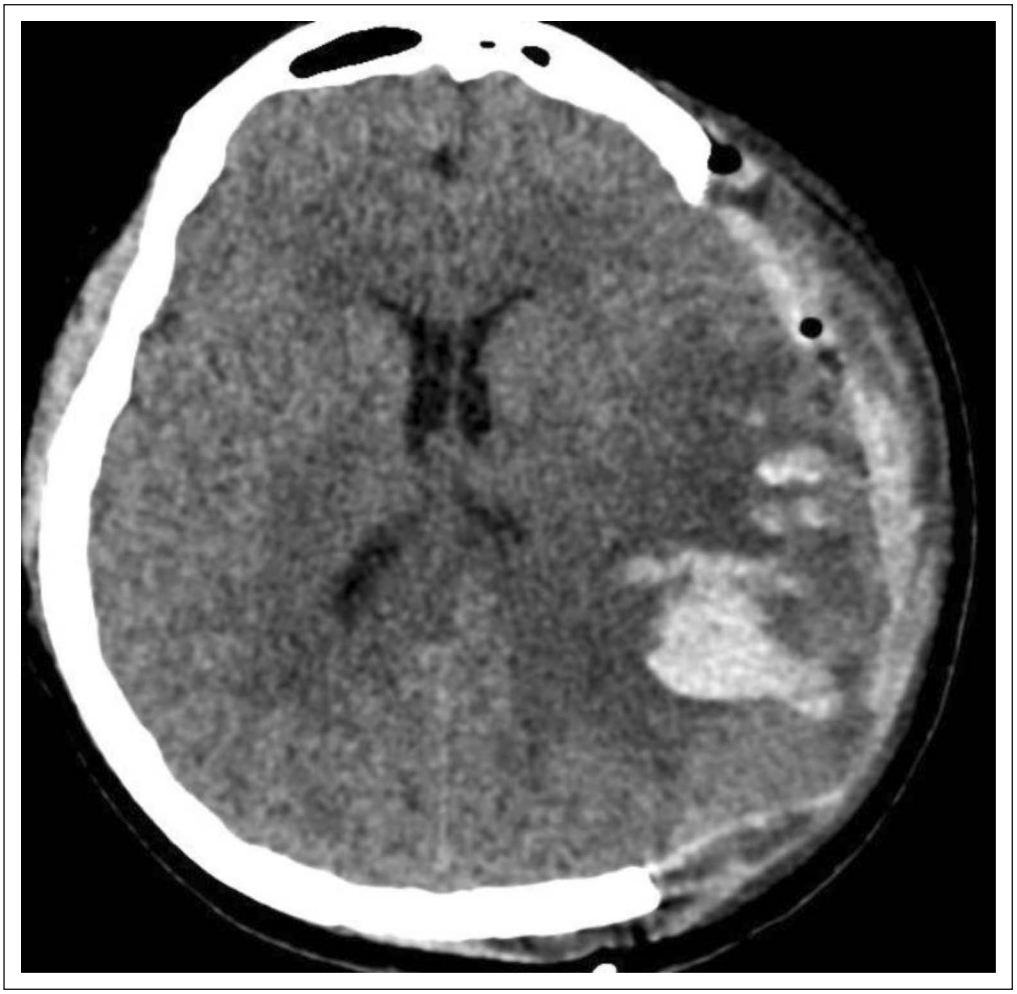

Figure 2. Brain CT scan after decompressive craniectomy.

DISCUSSION

The clinical picture of our patient with severe thrombocytopenia and life-threatening thrombotic lesions beginning 9 days after the first dose of ChAdOx1 nCoV-19 vaccine is in line with other case series (1–3). This serious situation was however reversed using nonheparin anticoagulant and IVIG. Three lessons could be learned from this case.

First, this prothrombotic disorder mimics heparin-induced thrombocytopenia (HIT) as previously noted (2). HIT is classically due to platelet-activated antibodies that recognize molecular complexes between cationic PF4 and anionic heparin (4). Other causes of HIT unrelated to heparin exposure have been described, including polyanionic drugs, infections, or knee replacement surgery, leading to the denomination of autoimmune HIT (5). Our patient had received no heparin at the time she was diagnosed with cerebral vein thrombosis. Whether a vaccine using a recombinant adenoviral vector encoding the spike protein antigen of severe acute respiratory syndrome coronavirus 2 can directly trigger the formation of antigen-antibody complexes on the endothelial cell surface is still unknown. Positive PF4/heparin antigen tests were found in several patients with VITT (1–3). However, the tests for PF4 antibodies have a slow turnaround time, and results may depend on laboratory techniques. Our patient had a weak positive then negative response to PF4/heparin tests (Supplemental Table 1, http://links.lww.com/CCM/G520), and the current situation did not allow us to timely refer to another technique. In clinical practice, the decision to use nonheparin therapy must be taken on platelet count less than 150 per cubic millimeter and the development of thrombosis imaging within 4–28 days after this vaccination, according to the most recent International Society on Thrombosis and Hemostasis interim guidance (https://www.isth.org/news/561406/The-ISTH-Releases-Interim-Guidance-on-Vaccine-Induced-Immune-Thrombotic-Thrombocytopenia-VITT-.htm). Argatroban is administered through IV route, and its short half-life (45 min) makes this drug suitable in the context of critical care and possible invasive procedures. In the present case, the monitoring of serum concentrations of argatroban was undoubtedly helpful to administer higher doses than those predicted with measurements of activated partial thromboplastin time (Supplemental Table 1, http://links.lww.com/CCM/G520).

Second, we used high-dose IVIG together with argatroban to possibly interrupt as fast as possible this

vaccine-induced platelet activation. Indeed, high-dose IVIG has been recognized as an emerging treatment of persisting thrombocytopenia in the setting of autoimmune HIT (6, 7). Although the exact mechanism of action remains unknown, IVIG could inhibit platelet activation, preferentially secondary to heparin-independent process (6). Interestingly, in vitro studies from serum of patients with VITT showed inhibition of the platelet-activating properties by high-dose IVIG (2). Whether the combination of argatroban and IVIG therapies was synergistic to treat VITT in our patient is unknown.

Third, acute cerebral venous thrombosis is a therapeutic emergency because timely decisions can provide remarkable outcome for these patients (8). Large cerebral venous infarctions or parenchymal hemorrhages with mass effect are the major causes of death in this disorder. High-dose UFH is necessary to block clot propagation and obtain vein recanalization and is not contraindicated in the presence of intracranial bleeding (9). To our knowledge, the use of argatroban to treat severe cerebral venous thrombosis related to HIT-type physiology has been reported in one case only (10). Considering the nature of her prothrombotic condition, our patient was not eligible for endovascular therapies such as in situ thrombolysis or thromboaspiration. Early decompressive craniectomy might have facilitated the dissemination of IV infused anticoagulant to cerebral blood clots through lowering venous pressure. Finally, the prolonged duration of deep sedation, in a patient with full anticoagulation and brain herniation, was required to prevent variation of intracranial pressure and to give time for the resolution of cerebral venous infarction.

In conclusion, a severe presentation of VITT with multiple and life-threatening venous thrombotic lesions can have a good outcome. Argatroban and high-dose IV immunoglobulin along with management of severe cerebral venous thrombosis played a major role in this epilogue.

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