

# Thrombosis with Thrombocytopenia after First Dose of ChAdOx1 nCoV-19 Vaccine: A Case Report

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**Summary.** More than 5 billion vaccine doses against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been administered worldwide. In Lithuania, more than 1.72 million people have been vaccinated with at least one vaccine dose. Vaccines against SARS-CoV-2 are considered to be safe and effective measures to cope with COVID-19 pandemic. However, several cases of acute thrombotic events with thrombocytopenia after receiving ChAdOx1 nCoV-19 (AstraZeneca (Vaxzevria)) vaccine have been published. We report findings in one patient who presented with cerebral venous sinus thrombosis, intracerebral hemorrhage, and thrombocytopenia which occurred 12 days after receiving the first dose of ChAdOx1 nCoV-19 vaccine. The patient complained of headache and pain in the right eye, nausea, vomiting, and subfebrile fever. After deterioration of the state of consciousness, CT scan of the head showed a massive intracerebral hemorrhage, and laboratory tests revealed severe thrombocytopenia, high D-dimer level, and a low fibrinogen concentration. On the basis of clinical, laboratory and radiological findings, as well as the presence of antibodies to platelet factor 4 (PF4), the vaccine-induced immune thrombotic thrombocytopenia (VITT) was confirmed. After surgery and therapy with high doses of intravenous immunoglobulin, methylprednisolone and non-heparin anticoagulants, the patient's clinical condition and laboratory parameters improved.

**Keywords:** COVID-19, vaccination, thrombocytopenia, thrombosis, intracerebral hemorrhage, vaccine-induced immune thrombotic thrombocytopenia, antibodies to platelet factor 4.

## INTRODUCTION

Vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are considered to be effective and safe measures in coping with COVID-19 pandemic [1]. The European Medicines Agency has authorized 4 vaccines against COVID-19 to this date: 2 mRNA vaccines (Pfizer–BioNTech and Moderna (Spikevax)) and

2 adeno-viral vector-based vaccines (AstraZeneca (Vaxzevria) and Johnson & Johnson (Janssen)) [2]. The rate of human vaccination against COVID-19 is increasing and more than 5 billion vaccine doses have been administered worldwide [3]. In Lithuania, more than 1.72 million people have been vaccinated with at least one vaccine dose [4]. However, since March 2021, several cases of acute thrombotic events with thrombocytopenia have been reported following administration of ChAdOx1 nCoV-19 (AstraZeneca (Vaxzevria)) vaccine [5–7]. All of these events occurred after receiving the first vaccine dose [5–8] of the two doses regimen. These unusual thrombosis with thrombocytopenia cases have led to further studies of post-vaccine adverse reactions (ADRs) and their mechanisms [5] and to increased concern about their diagnosis

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and treatment strategy. According to research comparing mRNA-based vaccines and adenoviral vector-based vaccines, the latter are more likely to cause thrombosis and thrombocytopenia syndrome [7], which can also be termed vaccine-induced thrombotic thrombocytopenia (VITT). Although the exact incidence of VITT is still unknown, it appears to be extremely rare (1 in 100,000) [9].

Here we report a clinical case of cerebral venous sinus thrombosis and thrombocytopenia that occurred after administration of ChAdOx1 nCoV-19 vaccine.

## CASE PRESENTATION

A 30-year-old woman received the first dose of ChAdOx1 nCoV-19 vaccine against COVID-19 on April 10, 2021; no immediate ADRs were reported. However, on day 6 after vaccination, she had fever (37.8 °C) and complained of severe headache, nausea, vomiting, and pain in the right eye. On day 7, she felt pain in her face, head and jaw (non-steroidal anti-inflammatory drugs (NSAIDs) were ineffective), after which she lost consciousness. The next day, she was admitted to the Kaunas hospital where her head CT scan showed no pathology, and blood test showed thrombocytopenia ( $51 \times 10^9/L$ ). NSAIDs were prescribed, and the patient was discharged for outpatient treatment. On day 11 after vaccination, she was found at home with altered consciousness and was admitted to the Emergency Department (ER) of the Hospital of Lithuanian University of Health Sciences Kauno klinikos (April 21, 2021).

The patient's previous medical history revealed migraine and oral contraceptives use. On physical examination, she had a Glasgow Coma Scale (GCS) score of 11 (E-3, V-3, M-5), her SpO<sub>2</sub> was 99% without supplemental oxygen, respiratory rate 18 breaths per minute, arterial blood pressure 152/68 mmHg, heart rate 50/min. Brain CT scan showed a massive intracerebral hemorrhage (ICH) in the left frontal lobe (3.5×3.4 cm) with a breakthrough into the ventricular system and subdural space, while CT angiography raised suspicion of cerebral venous thrombosis and showed a possible active bleeding site (Fig. 1). Laboratory tests revealed severe thrombocytopenia ( $7 \times 10^9/L$ ), high D-dimer level (20 mg/L), prolonged activated partial thromboplastin time (aPTT) 48.3 s, fibrinogen 0.71 g/L. SARS-CoV-2 RNA polymerase chain reaction (PCR) assay of nasopharyngeal swab was negative. Treatment according to ICH protocol was initiated and 4 units of platelet concentrate were administered. The neurosurgeon prioritized conservative treatment of ICH and intracranial hypertension over intervention.

One and a half hours after admission to the ER, the patient's condition deteriorated to GCS 9 (E-3, V-1, M-5). Rapid sequence induction was performed with intravenous fentanyl, propofol, and rocuronium. The patient was intubated, mechanically ventilated, and transferred to the general intensive care unit (ICU) until her SARS-CoV-2 RNA PCR was confirmed negative, after which she was



Fig. 1. Massive intracerebral hemorrhage (ICH) in the left frontal lobe (3.5×3.4 cm) with a breakthrough into the ventricular system and subdural space. The midline structures are dislocated to the right ~0.63 cm.

transferred to the neurosurgical intensive care unit (Neuro-ICU).

Subsequently, treatment of ICH was continued, and according to the multidisciplinary team consensus, treatment with methylprednisolone and intravenous immunoglobulin was initiated. 6 hours after admission, the control head CT scan showed negative changes: hematoma in the left frontal lobe remained of similar size, the amount of hemorrhagic content in the ventricles increased, perifocal edema was present, and subarachnoid hemorrhage (SAH) in the right fronto-temporo-parietal region appeared (Fig. 2). Unfortunately, maximal efforts to treat intracranial hypertension had no effect as transcranial Doppler ultrasound showed intracranial hypertension (PI 2.0–2.2) and ultrasound of optic nerve sheath diameter (ONSD) showed edema (right 0.7 cm, left 0.66 cm). Decompressive craniectomy was indicated for the treatment of intracranial hypertension, but due to the high risk of bleeding during surgery, it was delayed until thrombocytopenia and coagulopathy were corrected. In addition, thromboelastometry (ROTEM) was performed which showed a prolonged clot formation and reaction time, decreased maximum clot firmness. In order to normalize abnormal blood test results and minimize the risk of intraoperative bleeding, a massive transfusion of 43 units of blood products (platelet concentrate 5 units, packed red blood cells 4 units, fresh frozen plasma 4 units, cryoprecipitate 30 units) was performed. 14 hours after admission to the hospital, head CT scan showed negative dynamics: the dislocation of midline structures increased, new ischemic foci appeared on the right frontal lobe



**Fig. 2.** Hematoma in the left frontal lobe is of similar size (3.5×3.4 cm), the amount of hemorrhagic content in the ventricles increased, perifocal edema is present, and subarachnoid hemorrhage (SAH) in the right fronto-temporo-parietal region appeared. The midline structures are dislocated to the right ~1.0 cm.



**Fig. 3.** Hematoma in the left frontal lobe is of similar size, the dislocation of midline structures to the right increased to ~1.1 cm. In the right anterior part of the frontal lobe, a hypodense zone emerged cortically-subcortically, resembling acute ischemic changes.

(Fig. 3). The patient underwent emergency unilateral decompressive craniotomy which confirmed cerebral infarction due to cerebral venous thrombosis with hemorrhagic ischemic stroke transformation on the left frontal lobe. After the operation, the patient was transferred to the Neuro-ICU; 6 hours after surgery, head CT scan showed no major postoperative changes, transcranial Doppler ultrasound showed no signs of intracranial hypertension.

After surgery, treatment according to ICH protocol was continued and differential diagnosis of possible causes was performed. Laboratory test results denied infective (septic), endocrine, and partially autoimmune origin of thrombosis and thrombocytopenia.

Unfortunately, there was no positive effect from the administration of methylprednisolone, intravenous immunoglobulin, and blood product transfusion: platelet count and fibrinogen concentration continued to decrease. Taking into account the anamnesis of vaccination, and suspecting a condition similar to VITT, the multidisciplinary team decided to refrain from further blood product transfusions, eliminate exposure to heparin-based anticoagulation agents, and administer factor Xa inhibitor, apixaban, to prevent thrombosis. Positive effects were soon noted: the patient's condition improved clinically (GCS increased from 5 to 10), platelet count and fibrinogen concentration increased, coagulopathy regressed. Nevertheless, positive antibodies against platelet-factor 4 (anti-PF4 antibodies)

were detected and the diagnosis of vaccine-induced thrombotic thrombocytopenia (VITT) was confirmed. According to the guidelines, intravenous administration of methylprednisolone was continued [10]. On day 13 after admission to the Neuro-ICU, due to the need for prolonged mechanical ventilation and airways support due to impaired state of consciousness, the patient underwent a tracheostomy. This allowed the patient to be weaned from mechanical ventilation. On day 20, with stable vital signs, the patient was discharged to Neurosurgery department.

## DISCUSSION

We present a case of severe cerebral venous sinus thrombosis with intracranial hemorrhage and severe thrombocytopenia which occurred 12 days after vaccination against COVID-19 with the first dose of ChAdOx1 nCoV-19 vaccine. In most published cases, symptoms of venous thrombosis accompanied by thrombocytopenia appeared 5–24 days after administration of ChAdOx1 nCoV-19 vaccine. Although potential risk factors for VITT are still unclear, the majority of patients with reported thrombotic events and thrombocytopenia were women younger than 50 years old taking oral contraceptives or receiving estrogen replacement therapy [5–7, 9]. Our patient's case is similar to those described above.

Typically, VITT presents with clinical features such as thrombocytopenia, thrombosis (frequently, cerebral venous thrombosis), and coagulation abnormalities, especially disseminated intravascular coagulation (DIC) (thrombocytopenia, elevated D-dimer levels >10 mg/L, hypofibrinogenemia, normal or mildly increased aPTT, INR, PT, or bleeding) [11]. However, VITT is a very rare condition which clinically resembles spontaneous autoimmune heparin-induced thrombocytopenia. However, patients with VITT do not receive heparin therapy and do not have any autoimmune disorders. Thus, the suspicion and diagnosis of VITT is challenging, but clinicians should be aware of it given the increasing use of adenoviral COVID-19 vaccines.

Clinical examinations and treatment of our patient were complex and performed simultaneously. First of all, due to the presence of thrombosis with thrombocytopenia, an autoimmune disorder, DIC, sepsis, and complications of oral contraceptives were suspected (thrombosis, low platelet count, high D-dimer levels, prolonged aPTT, hypofibrinogenemia). There was also an assumption of VITT. Initially, treatment with 1 g/kg intravenous immunoglobulin was started and continued for two days (in VITT, intravenous immunoglobulin is administered to stop platelet activation caused by VITT antibodies). Furthermore, suspecting autoimmune origin of low platelet count, intravenous methylprednisolone was administered. However, these treatment measures were not successful as the platelet count did not increase.

On the one hand, due to coagulopathy and the risk of expanding intracerebral hemorrhage, anticoagulation was not initiated right after surgery. However, recommendations suggest, that therapeutic anticoagulation is the primary treatment for VITT [12], as further activation of thrombocytes leads to an increased risk of thrombosis. After 2 days, we started anticoagulation with low-molecular-weight heparin to prevent serious thrombotic events, but it was noted that platelet count was still decreasing. According to the literature, although evidence is sparse, anticoagulation with heparin is thought to exacerbate a critically ill condition. More data are needed, and it is suggested to consider anticoagulation with non-heparin anticoagulants [7]. Therefore, all heparin-based anticoagulants were discontinued, further exposure to heparin was prevented (intravenous catheters were flushed with normal saline), and a factor Xa inhibitor apixaban was prescribed.

Furthermore, our patient was treated with massive transfusions of blood products until the diagnosis of VITT was considered the most likely, even without having anti-PF4 antibodies count. According to Scully et al [7], platelet transfusions should be avoided because such treatment can lead to further process of antibody-mediated activation of platelets and further coagulopathy. Therefore, further transfusions of platelet concentrates and cryoprecipitates were discontinued.

An important priority was to make a correct diagnosis. Thrombocytopenia and bleeding of unknown cause were differentiated between autoimmune thrombocytopenia, thrombotic thrombocytopenic purpura, VITT, and DIC. The diagnosis of VITT was confirmed only after the detec-

tion of anti-PF4 antibodies, which due to technical barriers was received on April 30, 2021. Looking back, this condition could have been suspected during the initial headache, when the patient underwent the first CT scan at the Kaunas hospital and had thrombocytopenia.

However, chronologically, at the time this happened, knowledge of VITT after vaccination with the ChAdOx1 nCoV-19 vaccine was not yet available, with only few cases reported worldwide, and the mechanism of this rare ADR has not yet been elucidated, and regulatory authorities had no opinion on whether this should be considered ADR.

## CONCLUSIONS

In conclusion, this case report highlights the importance of detecting a thrombotic event with thrombocytopenia and positive antibodies against PF4 after vaccination with ChAdOx1 nCoV-19 (AstraZeneca (Vaxzevria)) for timely diagnosis of VITT. This case also stresses the importance of timely and accurate reporting of ADRs in order to increase clinicians' awareness of this condition so that it can be properly treated in the future, which will benefit public health.

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**TROMBOZĖ IR TROMBOCITOPENIJA PO PIRMOS ChAdOx1 nCoV-19 VAKCINOS DOZĖS: KLINIKINIS ATVEJIS**

**Santrauka**

Vakcinacija yra pripažinta efektyvia priemone, kovojant su COVID-19 pandemija. Naujausiais duomenimis, Lietuvoje

bent viena vakcinu nuo sunkaus ūminio respiracinio sindromo koronaviruso 2 (SARS-CoV-2) doze yra paskiepyta daugiau nei 1,72 milijono, o pasaulyje – daugiau nei 3,3 milijardo žmonių. Šiame straipsnyje pristatome vieną pirmųjų ir sunkiausių vakcinu sukeltos imuninės trombozinės trombotocitopenijos su intracerebrine kraujosruva atvejų Lietuvoje, kuris pacientei pasireiškė praėjus 12 dienų po pirmos ChAdOx1 nCoV-19 vakcinu dozės. Pirmieji simptomai buvo nespecifiniai: stiprus galvos ir dešinės akies skausmas, pykinimas, vėmimas, subfebrilus karščiavimas. Atsiradus sąmonės sutrikimui, pacientei buvo atlikta galvos kompiuterinė tomografija, kurioje nustatyta intracerebrinė kraujosruva. Laboratoriniuose kraujo tyrimuose stebėta didelė trombotocitopenija, didelė D-dimerų ir maža fibrinogeno koncentracijos. Remiantis paciente klinikiniais, laboratoriniais ir radiologiniais tyrimais bei nustatytais antikūnais prieš trombotocitų 4 faktorių (*platelet factor 4* (PF4)), jai buvo diagnozuota vakcinu sukelta imuninė trombozinė trombotocitopenija (*vaccine-induced immune thrombotic thrombocytopenia*, VITT). Po atliktos neurochirurginės operacijos ir gydymo didelėmis intraveninio imunoglobulino, metilprednizolono ir tiesiogiai veikiančių antikoagulantų dozėmis paciente klinikinė būklė pagerėjo, o laboratoriniai kraujo rodikliai normalizavosi.

**Raktažodžiai:** COVID-19, vakcinacija, trombotocitopenija, trombozė, intracerebrinė kraujosruva, vakcinu sukelta imuninė trombozinė trombotocitopenija, antikūnai prieš trombotocitų 4 faktorių.

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