



# Successful management of vaccine-induced immune thrombotic thrombocytopenia-related cerebral sinus venous thrombosis after ChAdOx1 nCov-19 vaccination

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Very recently, unusual thrombotic events in combination with severe thrombocytopenia have been reported 1–2 weeks following SARS-CoV-2 vaccination with ChAdOx1 nCov-19 (AstraZeneca). This condition, termed VITT (vaccine-induced immune thrombotic thrombocytopenia), has been related to high risk of fatal outcome with both ischaemic and haemorrhagic complications.<sup>1 2</sup> Optimal treatment strategies still need to be elucidated—especially in case of cerebral sinus venous thrombosis (CSVT) with associated brain haemorrhage as the underlying thrombotic event. We here report our clinical experience with two young women diagnosed with VITT-associated CSVT, treated with high-dose intravenous immunoglobulins (IVIGs), corticosteroids and argatroban in the hyperacute phase, followed by dabigatran resulting in excellent outcome.

## PATIENT 1

A 39-year-old woman with an unremarkable medical history was admitted with severe holocephalic headache since 2 days. Eight days earlier, she had received the first vaccination with ChAdOx1 nCov-19 (AstraZeneca). Physical and neurological examination was normal. Laboratory investigations revealed moderate thrombocytopenia ( $84 \times 10^9/L$ ) and significantly elevated D-dimer (14.2 mg/L; normal  $<0.5$  mg/L). Fibrinogen and other routine parameters were normal (table 1). Brain CT including venography was unremarkable as were CT pulmonary angiography and compression ultrasound of both legs. Coincidentally, the patient had contact with a COVID-19-positive person a few days after vaccination and SARS-CoV-2 reverse transcription PCR (RT-PCR) on admission was positive

with cycle threshold value 26 on a nasopharyngeal swab. Prophylactic treatment with danaparoid 750 IU two times per day subcutaneously and intravenous dexamethasone 40 mg were started. While the patient remained clinically stable, platelets further dropped ( $36 \times 10^9/L$ ) on day 4 after hospital admission, and fibrinogen depleted  $<150$  mg/dL (table 1). Remarkably, during the next night, she developed a new left-sided dull occipital headache and D-dimer again increased to 14.41 mg/dL (table 1). Brain MRI now showed left sigmoid/transverse sinus thrombosis without brain parenchymal involvement. Therefore, we initiated high-dose IVIG 1 g/kg bodyweight (for 2 days) and switched danaparoid to intravenous argatroban (starting with 2 µg/kg bodyweight/min with dose adjustments for target activated partial thromboplastin time (aPTT) 1.5× above baseline). From then on, her clinical condition improved; platelets and fibrinogen increased, while D-dimer levels markedly dropped (table 1). Four days later, anticoagulation was changed to oral dabigatran 150 mg two times per day. During the entire hospital stay, she did not develop any symptoms related to her COVID-19 infection. Moreover, COVID-19-specific laboratory markers (ferritin, C reactive protein or interleukin 6) remained normal. The patient was discharged 10 days after admission free of any symptoms. A follow-up examination 1 month after discharge was unremarkable. SARS-CoV-2 spike protein antibodies were 86.20 U/mL, while SARS-CoV-2 nucleocapsid antibodies were negative.

## PATIENT 2

A 24-year-old woman was admitted with a severe persisting headache in the past 4 days.

**Table 1** Laboratory parameters over the course of time in both patients

Variable (reference units)	d1*	d2*	d3*	d4*	d5*	d6*	d7*	d8*	d9*	d10*	d18†
Patient 1 (39 years, first ChAdOx1 nCov-19 vaccination 8 days before hospital admission)											
Platelets (140–440×10 <sup>9</sup> /L)	84	61	51	36	47	67	104	104	98	121	126
D-dimer (0.5 mg/L)	14.2	11.4	11.8	11.9	14.4	9.36	8.63	7.1	7.65	4.14	0.91
Fibrinogen (210–400 mg/dL)	236	234	173	143	83	62	64	90	201	292	285
Coagulation factor 13 (>70%)	119	117	–	94	77	67	–	68	65	–	99
CRP (<5.0 mg/L)	1.3	2.9	0.7	<0.6	<0.6	<0.6	<0.6	<0.6	–	6.2	–
Ferritin (9–140 ng/mL)	83	–	100	78	68	63	–	–	–	–	–
Interleukin 6 (0–7.0 pg/mL)	12	–	4	3.6	3.6	4.2	–	–	–	–	–
Patient 2 (24 years, first ChAdOx1 nCov-19 vaccination 12 days before hospital admission)											
Platelets (140–440×10 <sup>9</sup> /L)	29	41	78	135	166	188	258	304	337	254	183
D-dimer (0.5 mg/L)	>33	23.6	14.6	2.81	1.81	1.53	2.91	2.81	3.31	2.25	1.35
Fibrinogen (210–400 mg/dL)	95	55	<50	<50	<50	<50	152	169	208	232	254
Coagulation factor 13 (>70%)	–	25	–	36	22	–	–	–	46	58	98
CRP (<5.0 mg/L)	16.7	14.2	9.4	3.7	2.6	1.7	1.3	3.9	3.1	1.3	1.5
Ferritin (9–140 ng/mL)	80	–	–	61	47	–	–	–	–	–	–
Interleukin 6 (0–7.0 pg/mL)	11	–	–	2.7	2.5	–	–	–	–	–	–

\*Hospital treatment

†Follow-up visit 1 week after hospital discharge

CRP, C reactive protein; CSVT, cerebral sinus venous thrombosis (diagnosis); d, day.



Twelve days earlier, she had received the first vaccination with ChAdOx1 nCov-19 (AstraZeneca). She had an unremarkable medical history, and her physical as well as neurological examination was normal. Initial laboratory investigations revealed severe thrombocytopenia ( $29 \times 10^9/L$ ), massively elevated D-dimer ( $>33 \text{ mg/L}$ ) and fibrinogen depletion ( $95 \text{ mg/dL}$ ). SARS-CoV-2 RT-PCR on admission was negative. Brain MRI showed thrombosis of two cortical veins with related small frontal right juxtacortical haemorrhage. We immediately started IVIG 1 g/kg bodyweight, dexamethasone 40 mg and argatroban (target aPTT 1.5× baseline) intravenously. Apart from a short-lasting epileptic seizure on day 1, the patient remained clinically stable and her headache rapidly resolved. Thrombocytes increased and D-dimer dropped after treatment initiation (table 1). Fibrinogen initially decreased but recovered on day 7, and dabigatran 150 mg was started two times per day. The patient was discharged free of any symptoms and remained asymptomatic in a follow-up examination 2 weeks later. SARS-CoV-2 spike protein antibodies were 41.80 U/mL, while SARS-CoV-2 nucleocapsid antibodies were negative.

Notably, initial testing for platelet factor-4 antibodies was negative in a HemosIL HIT IgG test in both patients but they were later on tested positive in a confirmatory ELISA assay. Both patients had neither a positive prior or family history of thromboembolic events nor another genetic or acquired thrombophilia in extensive laboratory evaluations (eg, factor V Leiden or prothrombin mutation, protein C or S deficiency, antiphospholipid antibodies).

CSVT has been reported as one main thrombotic complication in VITT. Although it has also been associated with COVID-19 infection, such a link seems less likely in our SARS-CoV-2 PCR-positive patient 1 as she had no COVID-19-related symptoms or laboratory activity parameters, and a typical VITT laboratory profile. While patient 2 was admitted with an already established CSVT with haemorrhagic infarction, patient 1 developed CSVT during the course of VITT intrahospitally (on prophylactic anticoagulation with danaparoid). This gave us the unique opportunity to closely monitor clinical and laboratory changes associated with VITT. Interestingly, in parallel with a new onset headache type (left occipital pain pointing to the subsequently confirmed CSVT in the left lateral sinus system), we could observe a D-dimer increase attributable to the new thrombotic event immediately preceding diagnosis. This underlines that careful monitoring and prompt therapy initiation with full anticoagulation are indicated in patients with suspected VITT.

We propose prompt administration of IVIG, corticosteroids and anticoagulation with argatroban, and—despite low thrombocytes and fibrinogen—avoidance of platelet transfusions or other procoagulant medication as this might result in fatal thrombotic complications.<sup>3</sup> Instead,

anticoagulation with argatroban qualifies as a useful treatment option for VITT. First, it has a short half-life, which is beneficial in case of bleeding complications. Second, it has an additional platelet-inhibiting effect.<sup>4</sup> Third, as a thrombin inhibitor, it acts at the bottom of the coagulation cascade with a low interaction potential with other factors of the coagulation cascade. After stabilisation of the coagulation system (recovery of platelets), switching to the oral thrombin inhibitor dabigatran appears reasonable due to the availability of a specific antidote (ie, idarucizumab) and a recent positive randomised controlled trial in CSVT.<sup>5</sup> In accordance with common clinical practice in CSVT with a specific trigger factor, we planned anticoagulation with dabigatran for 3–6 months in both patients.

Although a platelet factor-4 antibody-related mechanism appears possible, the exact underlying pathophysiology still needs to be determined. We recommend rapid treatment initiation in suspected VITT based on clinical (history of ChAdOx1 vaccination, unusual thrombosis) and routine laboratory criteria (low thrombocytes, elevated D-dimer, low fibrinogen) without waiting for platelet factor-4 antibody test results to avoid severe complications reported in earlier cases.<sup>3</sup>

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#### REFERENCES

- Greinacher A, Thiele T, Warkentin TE. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. *N Engl J Med* 2021;9:NEJMoa2104840.
- Muster V, Gary T, Raggam RB, et al. Pulmonary embolism and thrombocytopenia following ChAdOx1 vaccination. *Lancet* 2021;397:1842.
- Schultz NH, Sørvoll IH, Michelsen AE, et al. Thrombosis and thrombocytopenia after ChAdOx1 nCov-19 vaccination. *N Engl J Med* 2021;384:2124–30.
- Lunven C, Gauffeny C, Lecoffre C, et al. Inhibition by Argatroban, a specific thrombin inhibitor, of platelet activation by fibrin clot-associated thrombin. *Thromb Haemost* 1996;75:154–69.
- Ferro JM, Coutinho JM, Dentali F, et al. Safety and efficacy of dabigatran etexilate vs Dose-Adjusted warfarin in patients with cerebral venous thrombosis: a randomized clinical trial. *JAMA Neurol* 2019;76:1457–65.