Received: 8 April 2021 | Accepted: 14 April 2021

DOI: 10.1111/jth.15347

CASE REPORT

Thrombocytopenia with acute ischemic stroke and bleeding in a patient newly vaccinated with an adenoviral vector-based COVID-19 vaccine

Rolf Ankerlund Blauenfeldt[1,2] | Søren Risom Kristensen[3,4] | Siw Leiknes Ernstsen[5] | Claudia Christina Hilt Kristensen[1,4] | Claus Ziegler Simonsen[2,6] | Anne-Mette Hvas[7]

[1]Department of Neurology, Aalborg University Hospital, Aalborg, Denmark

[2]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

[3]Department of Clinical Biochemistry, Aalborg University Hospital, Aalborg, Denmark

[4]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

[5]Norwegian National Unit of platelet immunology, University Hospital of North Norway, Tromsø, Norway

[6]Department of Neurology & Danish Stroke Center, Aarhus University Hospital, Aarhus, Denmark

[7]Department of Clinical Biochemistry, Aarhus University Hospital, Aarhus, Denmark

Correspondence
Rolf Ankerlund Blauenfeldt, Department of Neurology, Aalborg University Hospital, DK-9000, Aalborg, Denmark.
Email: rolfblau@rm.dk

Abstract

We describe the first Danish case of presumed inflammatory and thrombotic response to vaccination with an adenoviral (ChAdOx1) vector-based COVID-19 vaccine (AZD1222). The case describes a 60-year-old woman who was admitted with intractable abdominal pain 7 days after receiving the vaccine. Computed tomography of the abdomen revealed bilateral adrenal hemorrhages. On the following day, she developed a massive right-sided ischemic stroke and magnetic resonance imaging angiography showed occlusion of the right internal carotid artery. The ischemic area was deemed too large to offer reperfusion therapy. During admission, blood tests showed a remarkable drop in platelet counts from 118,000 to 5000 per μl and a substantial increase in D-dimer. The patient died on the sixth day of hospitalization. Blood tests revealed platelet factor 4 reactive antibodies, imitating what is seen in heparin-induced thrombocytopenia. This may be a novel immune-mediated response to the vaccine.

KEYWORDS
hemorrhage, platelet factor, stroke, thrombocytopenia, vaccines

1 | INTRODUCTION

The COVID-19 virus has caused increased morbidity and mortality worldwide. To meet this extraordinary challenge, new vaccines have been developed with a speed never seen before in medical history.[1-4] The safe implementation of these vaccines is of major importance to avoid more deaths because of COVID-19 and for the restoration of normal social life. There have been media reports and a preliminary research report (Greinacher A, et al. Research square. April 7, 2021) of unusual thrombotic and/or hemorrhagic events following the ChAdOx1 nCoV-19 vaccine, and the possibility of specific immune-mediated thrombocytopenia have been raised by Austrian and Norwegian researchers.[5,6]

Here, we describe the first Danish case, in which a 60-year-old woman developed bilateral adrenal hemorrhages and a massive ischemic stroke, and laboratory results revealed a rapid decline in platelet counts and substantial increase in D-dimer. The patient was later found positive for platelet factor-4 (PF-4) antibodies.

2 | CASE REPORT

Denmark began vaccinating against the COVID-19 infection with the messenger RNA (mRNA)-based vaccine BNT162b2 (Pfizer/

Manuscript handled by: David Lillicrap

Final decision: David Lillicrap, 14 April 2021

Essentials

- We describe the first-ever case of presumed immune mediated thrombocytopenia, hemorrhage, and ischemic stroke after vaccination with an adenoviral (ChAdOx1) vector based COVID-19 vaccine (AZD1222).
- Thrombocytopenia with thrombosis and bleeding may be a novel immune-mediated response to an adenoviral vector-based COVID-19 vaccine, resembling heparin-induced thrombocytopenia.
- The presence of platelet factor 4 antibodies was confirmed.

BioNTech) on December 27, 2020. This was later followed by the mRNA-1273 vaccine from Moderna. The AZD1222 (AstraZeneca) vaccine was approved by the European Medicines Agency and vaccination was commenced on February 5, 2021, in Denmark.

The present case describes a 60-year-old woman who had a medical history significant of Hashimoto thyroiditis and hypertension. She was on losartan 50 mg daily, simvastatin 40 mg, and levothyroxine 50/100 µg on alternating days. She received the first dose of vaccine (AZD1222) and had, according to relatives, a light headache the following days.

The patient was admitted on the seventh postvaccination day with strong, persistent abdominal pain. Urine analysis was positive for blood. A computed tomography (CT) scan of the abdomen was performed, showing bilateral adrenal hemorrhages and a subcapsular renal hematoma.

On the second day of admission, she was last seen well in the afternoon and found 1 hour later with left-sided weakness and eye deviation to the right. A magnetic resonance imaging scan performed 2 hours after she was last seen well showed diffusion restriction and hence completed infarction in the entire area supplied by the right middle cerebral artery (Figure S1). Because of the size of the infarct, it was deemed that reperfusion therapy could not be offered. A CT scan of the aorta excluded dissection. Treatment by hydrocortisone 100 mg three times daily as substitution therapy and cefuroxime was initiated. Platelet inhibitor treatment was deferred because of the possibility of malignant media infarction with subsequent surgery.

On the third hospital day, her Glasgow Coma Scale score dropped from 12 to 5. CT of the cerebrum showed a malignant media infarction with a midline shift of 12 mm (Figure S1).

Blood tests (Table 1) showed a drop in platelet counts and the patient received three pools of platelet concentrates before hemicraniectomy. During admission, she received a total of seven pools of platelet concentrates. Hemicraniectomy was performed, but the patient did not regain consciousness. Postoperative dalteparin 5000 IU daily was started. On the fourth hospital day, the first through third fingers of the left hand were discolored dark/blue. The skin of the left foot was mottled with decreased capillary response. Follow-up CT scan of the cerebrum showed edema of the right hemisphere and no new ischemic or hemorrhagic lesions, but an unresolved midline shift. The patient was transferred to palliative care, in agreement with the family, and died on the sixth hospital day.

3 | DISCUSSION

A vaccine activates the immune system, and unwanted side effects are often seen. Common side effects may include pain at the injection site, headache, muscle and joint pain, and general feeling of being unwell. Rarely, autoimmune diseases may be elicited such as Guillain-Barré syndrome.[7] Anaphylactic shock with vasodilation and hypotension is the most feared side effect, and rapid identification and treatment can be life-saving.

The syndrome suffered by the patient in this case, has to our knowledge, not previously been described in the medical literature as a potential postvaccination reaction. It is a highly unique and a rarely seen reaction with a temporal relation to vaccination. Therefore, an association between vaccination and the clinical syndrome is suspected.

Several differential diagnoses were considered. Infectious and noninfectious endocarditis was unlikely, given normal blood cultures and a normal transthoracic echocardiography. Septicemia and in particular Waterhouse-Friedrichsen syndrome with adrenal hemorrhages caused by meningococcal disease was also unlikely, given normal blood culture and negative *Neisseria meningitidis* antibody. Aortic dissection was ruled out by a CT scan of the aorta. Thrombotic thrombocytopenic purpura was ruled out by a normal blood smear and a normal a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 level. Catastrophic antiphospholipid syndrome was considered, but tests for lupus anticoagulant, and beta2-glycoprotein1 and cardiolipin antibodies were all negative. The picture could resemble disseminated intravascular coagulation, but the biochemical panel was not compatible with this because changes in activated partial thromboplastin time, fibrinogen, and antithrombin were unremarkable.

The clinical picture mirrors what is seen in heparin-induced thrombocytopenia (HIT). However, the patient had not received heparin during her admission. She had received dalteparin, but this was administered on the third hospital day and after the onset of stroke and thrombocytopenia.

Blood samples were sent to the Norwegian National Unit of platelet immunology at the University Hospital of North-Norway, Tromsø, Norway. Here, anti-PF-4 immunoglobulin G antibodies were detected with high optical density PF-4/polyvinylsulfonate complex enzyme-linked immunosorbent assay. PF-4 antibodies may be found positive randomly,[8] but suspicion of a causative link was heightened

TABLE 1 Blood tests during the admission of a 60-year-old woman with ischemic stroke and immune-mediated thrombocytopenia following vaccination

	Day 1	Day 2[a]	Day 3	Day 6	Reference range
C-reactive protein (mg/L)	2.6	188	235	67	<8.0
Pro-calcitonin (μg/L)			0.33	0.17	<0.5
White-cell count (per μl)	11,100	8500	6700	5800	3500–10,000
Neutrophil count (per μl)	9500	6220	4940	3960	2000–7000
Lymphocyte count (per μl)	860	1560	1130	900	1300–3500
Monocyte count (per μl)	630	600	470	680	200–700
Eosinophil count (per μl)	10	110	100	0	<500
Hemoglobin (g/dl)	14.0	13.7	13.5	8.4	11.8–15.3
Haptoglobin (mg/dl)			160		50–210
Sodium (mmol/L)	138	133	135	159	137–145
Potassium (mmol/L)	3.1	3.5	3.7	4	3.5–4.6
Lactic acid (mg/dl)	18.02	5.40	5.40	6.31	4.5–22.5
Creatinine (mg/dl)	0.77	1.14	1.0	1.04	0.51–1.02
INR	1.0	1.1	1.2	1.1	<1.2
APTT (s)		28	32	27	22–38
Platelet count (per μl)	118,000	50,000	24,000	5000	165,000–400,000
D-dimer (ng FEU/ml)		41,800	97,800	106,200	<500
Factor V Leiden mutation			Heterozygous		
Antithrombin (IU/ml)		0.70	0.67	0.9	0.80–1.20
Fibrinogen (mg/dl)		374	269	231	170–374
Thromboelastometry (ROTEM)					
EXTEM CT (sec)[b]			84		<74
EXTEM A10 (mm)[b]			46		>48
FIBTEM A10 (mm)[b]			14		>8
INTEM CT (sec)[b]			144		<121
Protein C activity (IU/ml)			0.70		0.70–1.40
Protein S, free antigen			0.68		0.55–1.20
Antiphospholipid antibodies[c]			Negative		
Blood smear description			No definite schistocytes		
Immunoglobulins IgA/IgM/IgG				Normal	
Complement C3c/C4				Normal	
Cryoglobulins				Not present	
Antineutrophilic antibodies			0		<1
ADAMTS13				Normal	
Platelet antibodies[d]				Not present	

To convert values for hemoglobin to millimoles per liter multiply by 0.6202, lactic acid to millimoles per liter multiply by 0.1110, creatinine to micromoles per liter multiply by 88.4, and fibrinogen to micromoles per liter multiply by 0.0294.

Abbreviations: ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; APTT, activated partial thromboplastin time; FEU, fibrinogen-equivalent units; INR, international normalized ratio; ROTEM, rotational thromboelastometry.

[a]The blood sample on day 2 was sampled 1–2 h after stroke onset, and additional tests (D-dimer, fibrinogen, antithrombin) 7 h after the first sample. Platelet count 8 h before stroke onset was 55,000 per μl.

[b]EXTEM CT: extrinsic pathway (tissue factor) clotting time. EXTEM A10: amplitude of formed clot 10 min after formation. FIBTEM A10: fibrin-dependent clot formation, amplitude of the formed clot at 10 min. INTEM CT: intrinsic pathway clotting time.

[c]Lupus anticoagulant, and beta-2-glycoprotein 1 and cardiolipin antibodies.

[d]Antibodies against GP-IIb/IIIa, GP-Ia/IIa, GP-Ib/IX, and GP-IV.

because serum from the patient also caused platelet aggregation of donor platelets in heparin-induced multiple electrode aggregometry.

Antibodies against PF-4 are typically seen in HIT. HIT is a complication of heparin treatment in which heparin binds to PF-4 present in platelet granules.[9] PF-4 is part of the immunological system and can bind to, for example, bacteria, and by that contribute to their removal. During treatment with heparin the positively charged PF-4 can bind to the negatively charged heparin and this complex may in some patients induce formation of antibodies against PF-4/heparin complexes. The heparin/PF-4/antibody immune complex activates platelets by interacting with FcγRIIa on the platelet surface. This leads to release of procoagulant factors, extensive clot formation in both veins and arteries, and at the same time platelet degradation.[10,11]

HIT is a devastating syndrome, often emerging 5 to 10 days after initiation of heparin therapy, with a high morbidity and mortality. The PF-4 antibodies can persist for months, but the present patient had not been exposed to unfractionated heparin or low molecular weight heparin previously. During the past decade, some patients have developed autoimmune HIT without having received heparin, and thus, other factors are able to induce the formation of these antibodies leading to HIT.[9] Interestingly, HIT has recently been identified in a high proportion of hospitalized patients with severe COVID-19 exposed to heparins.[12] Early identification and shift of anticoagulant treatment from heparins to direct thrombin inhibitors is the mainstay of HIT treatment, but treatment with immunoglobulins may have a role as well.[9]

4 | CONCLUSION

We present a case of thrombocytopenia, hemorrhage, and ischemic stroke after vaccination with an adenoviral vector-based vaccine. The clinical picture resembles HIT, and the presence of IgG PF-4 antibodies was confirmed. Awareness of this possible immune reaction is important for clinicians worldwide to ensure rapid identification, diagnostics, and treatment. Larger investigations are warranted to confirm these findings and to improve understanding of the pathophysiology.

ACKNOWLEDGMENTS

After writing this case report, two papers have been published. The condition described in this article has been coined vaccine-induced immune thrombotic thrombocytopenia (VITT): Schultz NH, Sørvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Ahlen MT, Wiedmann M, Aamodt A-H, Skattør TH, Tjønnfjord GE, Holme PÅ. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. N Engl J Med 2021. April 9; https://doi.org/10.1056/NEJMoa2104882; and Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic thrombocytopenia after ChAdOx1 nCoV-19 vaccination. N Engl J Med 2021. April 9; https://doi.org/10.1056/NEJMoa2104840) We note that the thromboses in the published papers were mainly venous thromboses. This case demonstrates that a primary arterial thrombosis also may be a complication.

CONFLICT OF INTEREST

Dr. Blauenfeldt reports grants from the National Institutes of Health and TrygFonden and a speaker's fee from Bayer, outside the submitted work. Dr. Simonsen reports grants from Novo Nordisk Foundation and Health Research Foundation of Central Denmark Region, outside the submitted work. Dr. Hvas reports grants from CSL Behring, and speaker's fees from CSL Behring, Boehringer-Ingelheim, Bayer, and Astellas, outside the submitted work. Dr. Ernstsen, Dr. Hilt Kristensen, and Dr. Søren Kristensen have nothing to disclose.

AUTHOR CONTRIBUTIONS

Anne-Mette Hvas, Søren Risom Kristensen, Siw Leiknes Ernstsen, Claudia Christina Hilt Kristensen, and Rolf Ankerlund Blauenfeldt were involved in the clinical problem-solving process. Literature review were performed by Anne-Mette Hvas, Søren Risom Kristensen, Siw Leiknes Ernstsen, and Rolf Ankerlund Blauenfeldt. Biochemical analysis was performed and interpreted by Siw Leiknes Ernstsen. First draft was made by Claus Ziegler Simonsen and Rolf Ankerlund Blauenfeldt. All authors have critically revised the manuscript and approved the final version.

ORCID

Rolf Ankerlund Blauenfeldt https://orcid.org/0000-0002-4846-9516
Søren Risom Kristensen https://orcid.org/0000-0002-2649-506X
Claudia Christina Hilt Kristensen https://orcid.org/0000-0002-8720-8810
Claus Ziegler Simonsen https://orcid.org/0000-0003-1363-0266
Anne-Mette Hvas https://orcid.org/0000-0002-7136-7534

REFERENCES

1. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med*. 2020;383:2603-2615.
2. Baden L, El Sahly H, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384:403-416.
3. Ramasamy M, Minassian A, Ewer K, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. *Lancet*. 2020;396:1979-1993.
4. Voysey M, Clemens S, Madhi S, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet*. 2021;397:99-111.
5. Sciencenorway.no. Norwegian doctors are investigating if blood clots could be linked to the AstraZeneca-vaccine. March 16, 2021. Available from: https://sciencenorway.no/covid19-vaccines/norwegian-doctors-are-investigating-if-blood-clots-could-be-linked-to-the-astrazeneca-vaccine-heres-what-theyre-looking-for/1829070
6. Informationsdienst Wissenschaft. Researchers from Greifswald Germany report breakthrough in SARS-CoV2 vaccination related thrombotic complications. March 21, 2021. Available from: https://idw-online.de/en/news765335

7. Haber P, DeStefano F, Angulo F, et al. Guillain-Barré syndrome following influenza vaccination. *J Am Med Assoc*. 2004;292:2478-2481.
8. Warkentin TE, Sheppard J. Testing for heparin-induced thrombocytopenia antibodies. *Transfus Med Rev*. 2006;20:259-272.
9. Greinacher A, Selleng K, Warkentin TE. Autoimmune heparin-induced thrombocytopenia. *J Thromb Haemost*. 2017;15:2099-2114.
10. Jaax ME, Greinacher A. Management of heparin-induced thrombocytopenia. *Expert Opin Pharmacother*. 2012;13:987-1006.
11. Perdomo J, Leung H, Ahmadi Z, et al. Neutrophil activation and NETosis are the major drivers of thrombosis in heparin-induced thrombocytopenia. *Nat Commun*. 2019;10(1):1–14.
12. Daviet F, Guervilly C, Baldesi O, et al. Heparin-induced thrombocytopenia in severe COVID-19. *Circulation*. 2020;142:1875-1877.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Blauenfeldt RA, Kristensen SR, Ernstsen SL, Kristensen CC, Simonsen CZ, Hvas A-M. Thrombocytopenia with acute ischemic stroke and bleeding in a patient newly vaccinated with an adenoviral vector-based COVID-19 vaccine. *J Thromb Haemost*. 2021;19:1771–1775. https://doi.org/10.1111/jth.15347