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CASE REPORT

Acquired hemophilia following COVID-19 vaccination: Case report and review of literature

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Abstract

Background: Acquired hemophilia A (AHA) is a rare bleeding disorder that can lead to spontaneous hemorrhage or bleeding induced by invasive procedures or trauma. We describe a patient who presented with multiple hematomas and a relapse of bullous pemphigoid shortly after his first dose of Vaxzevria ChAdOx1-S COVID-19 vaccination. We reviewed literature for cases of AHA following COVID-19 vaccination.

Key Clinical Question: Can COVID-19 vaccines induce (a recurrence of) AHA?

Clinical Approach and Conclusions: The diagnosis of AHA with a relapse of bullous pemphigoid was made. The patient was treated with recombinant activated factor VII, emicizumab, rituximab, and methylprednisolone. There were no further bleeding events. However, the patient deteriorated because of sepsis and died on the fifteenth day of admission.

Conclusion: Vaccines may trigger autoimmune events such as AHA. However, proof of causality is not possible and in this case the relapse of bullous pemphigoid before vaccination challenges this even more.

KEYWORDS
acquired hemophilia A, case report, COVID-19, emicizumab, vaccination

Essentials

- Acquired hemophilia A (AHA) is a rare autoimmune disease.
- Vaccinations and infections can trigger immunological events.
- Isolated prolongation in activated partial thromboplastin time (aPTT) may herald AHA.
- Emicizumab shows promise for hemostatic management of AHA.

1 | INTRODUCTION

Acquired hemophilia A (AHA) is a rare autoimmune disease in which patients develop autoantibodies directed against clotting factor VIII. This often results in spontaneous and severe hemorrhage in patients without personal or family history of bleeding. Bleeding is most commonly subcutaneous, muscular, or mucosal. AHA is associated with autoimmune disease, cancer, and pregnancy; however, most cases are idiopathic.[1,2] Mortality is high and most commonly because of fatal bleeding, infection, underlying disease, or complications of the immunosuppressive therapy. There are reports of AHA, following vaccination[3–6] or COVID-19 infection.[7–10] We report

a case of AHA, diagnosed shortly after an Vaxzevria ChAdOx1-S SARS-CoV-2 vaccination (AstraZeneca) and reviewed literature to evaluate if there could be an association between COVID-19 vaccination and (a recurrence of) AHA.

2 | CASE DESCRIPTION

A 75-year-old Caucasian man was referred to our hospital with multiple hematomas, hemorrhagic bullous pemphigoid, and a gastrointestinal ulcer. The patient's medical history included chronic kidney disease stage 3b, arterial hypertension, and insulin-dependent diabetes mellitus, complicated with polyneuropathy and a chronic foot ulcer.

In April 2020, he was hospitalized with a COVID-19 pneumonia. During that admission, as part of ward-based care, he received amoxicillin and clavulanic acid and Anakinra 100 mg daily (Kineret, as part of the COVAID study). In June 2020, bullous pemphigoid was diagnosed. Treatment consisting of methylprednisolone, nicotinamide, and doxycycline was subsequently initiated.

In June 2021, he presented to the emergency department with dyspnea, anorexia, hematomas on the right arm and left buttock, and hemorrhagic bullae. Ten days prior, he received his first dose of the Vaxzevria ChAdOx1-S Sars-CoV-2 vaccination (AstraZeneca). He additionally mentioned a one-time intake of nonsteroidal anti-inflammatory drug. No personal or family history of any bleeding disorders were recorded. Blood examination reference ranges laboratory values in parentheses showed a hemoglobin level of 5.6 g/dl (14.3–17.6) or 3.48 mmol/L (8.5–11), normal thrombocytes 289×10^3/µl (132–299), elevated white blood cell count of 12.0×10^3/µl (4.0–7.6) of which 9.5×10^3/µl (2.5–7.0) neutrophils, no signs of hemolysis, a normal prothrombin time of 89% (>70%) or 12.4 s (9.4–12.5) or international normalized ratio 1.1, a prolonged activated partial thromboplastin time (APTT) of 73.3 s (22.6–35.0) or an APTT ratio of 2.1, normal electrolytes, a stable serum creatinine of 1.75 mg/dl (0.67–1.17), and a C-reactive protein level of 60 mg/L (<5). There was no correction of the APTT following mixing with normal plasma (APTT mixing study: 72.4 s). The diagnosis of acquired hemophilia was therefore suspected. Gastroscopy demonstrated one duodenal lesion, which was treated endoscopically. The anemia was corrected with blood transfusions. While assessments of factor VIII activity and factor VIII-inhibitor were pending, the patient was referred to the University Hospital of Leuven. Upon admission, physical examination revealed large ecchymosis on his right arm and left buttock, with multiple new bullae. The remainder of the physical examination was unremarkable. Ultrasound confirmed multiple subcutaneous hematomas and a left iliopsoas hematoma. There was no detectable factor VIII activity in the presence of a factor VIII inhibitor (135 Bethesda units/ml).

The diagnosis of AHA with a relapse of bullous pemphigoid was made. Treatment with recombinant activated factor VII (Eptacog alfa activated, NovoSeven), emicizumab 270 mg weekly (Hemlibra, 3 mg/kg, 2 gifts), rituximab 375 mg/m^2 weekly (2 doses), and methylprednisolone 64 mg daily was initiated. During hospitalization, there were no further bleeding events. One week after treatment initiation, the factor VIII inhibitor decreased to 75 BU/ml and factor VIII activity using chromogenic assay was 13%.[11] However, the patient did develop new atrial fibrillation, acute kidney injury, and methicillin-sensitive *Staphylococcus aureus* sepsis and his clinical condition further deteriorated. Following consultation with the patient and his family, it was decided that escalation of care (i.e., intubation, mechanical ventilation, and vasopressor therapy) was not appropriate or in his best interests. Palliative and supportive measures were therefore prioritized. The patient died on the fifteenth day of admission at the university hospital.

3 | DISCUSSION

Acquired hemophilia A is a rare autoimmune disease in which patients develop autoantibodies (inhibitors) against clotting factor VIII. AHA should be considered in patients who present with spontaneous or severe bleeding, especially in the elderly, pre- or postpartum women, and in patients with cancer or autoimmune disease.[1] In many cases, there is an association with an immunological event like infection or inflammation. Our literature research revealed 16 cases of (recurrence of) AHA following COVID-19 vaccination (Table 1). Most among them are older patients and all cases occurred after mRNA vaccination. We report a case of AHA, shortly after a viral vector COVID-19 vaccine (AstraZeneca), in an older man with known autoimmune disease (bullous pemphigoid).

An unexplainable and isolated prolongation in APTT is suggestive of AHA and should prompt further investigations. After exclusion of interference by therapeutic anticoagulants, factor VIII activity and antibodies should be determined. Management consists of prevention of bleeding, supportive measures including transfusions in the event of bleeding, eradication of the inhibiting antibodies using immunosuppressive therapy, and if applicable, treatment of the underlying disease. Recombinant factor VIII is not useful as replacement therapy due to inhibiting antibodies. Bypassing agents, such as activated recombinant factor VII (NovoSeven) can be used to obtain initial hemostatic control. A recent case series of 12 cases suggests that off-label use of emicizumab (Hemlibra), a bispecific antibody that binds to factor IX and factor X, thereby mimicking the cofactor action of factor VIII, shows promising results in the acute management of AHA.[12] It has the advantages of subcutaneous therapy, good hemostatic efficacy, early discharge, and reduction of immunosuppression and adverse events. Initial hemostatic response is determined clinically. There are no standardized laboratory tests.

Both infections and vaccines may trigger an immune reaction that can result in the exacerbation of or new autoimmune events.[13] It is not possible to confirm whether AHA in this patient was directly triggered by COVID-19 vaccination. No specific test is available to establish causality. Until now, only a few cases of AHA following any type of COVID-19 vaccinations have been reported,[5,6,12,14–23] despite billions of administered doses of COVID-19 vaccines and a

TABLE 1 Overview of reported cases of AHA, following COVID-19 vaccination

Author	Vaccine (brand)	Age and sex	First symptoms (days post-vaccination)	Presentatation	APTT (s)	Inhibitor-titer at presentation (BU)	Treatment	Outcome
Happaerts and Vanassche	Viral vector (AstraZeneca, first dose)	75, M	10	Hemorrhagic bullae, muscular and cutaneous hematoma	73.3	135	Corticosteroids and rituximab	Dead
Radwi and Farsi[5]	mRNA (Pfizer, 1st dose)	69, M	9	Muscular and cutaneous hematoma	115.2	80	Corticosteroids	Remission
Portuguese et al.[6]	mRNA (Moderna, second dose)	76, F	4	Cutaneous hematoma	122	11.2	Corticosteroids and IVIG	Remission
Al Hennawi et al.[17]	mRNA (Pfizer, second dose)	75, M	±90	Muscular and subcutaneous hematomas	89.2	318	Corticosteroids, rituximab, cyclophosphamide, and cyclosporine	Remission
Cittone et al.[16]	mRNA (Moderna, first dose)	85, M	±7	Hemarthrosis, muscular and cutaneous hematoma	49	2.2	Corticosteroids and rituximab	Dead
	mRNA (Moderna, second dose)	86, F	±21	Hemothorax	Not stated (prolonged)	1.01	Corticosteroids	Remission
	mRNA (Moderna, first dose)	72, F	±14	Cutaneous hematoma	184	12.4	Corticosteroids and rituximab	Remission
Soliman et al.[18]	mRNA (Pfizer, first dose)	39, F	±7	Hematuria	65–72.2	17.2	Corticosteroids and rituximab	Remission
Leone et al.[19]	mRNA (Pfizer, second dose)	86, M	14	Cutaneous hematoma	ratio 1.91	2.1	Corticosteroids	Remission
	mRNA (Pfizer, second dose)	73, F	26	Hemarthrosis, mucosal and cutaneous hematoma	ratio 2,1	0.8	Corticosteroids	Remission
	mRNA (Pfizer, second dose)	67, M	49	Mucosal and cutaneous hematoma	ratio 2.55	2.5	Corticosteroids and cyclophosphamide	Remission
	mRNA (Pfizer, second dose)	77, M	52	Hematuria (comorbidity: bladder cancer)	ratio 3.61	6.9	Corticosteroids and rituximab	Dead
Murali et al.[19]	mRNA (Pfizer, first dose)	95, F	±7	Cutaneous hematoma	83	5.4	Corticosteroids and rituximab	Remission
Farley et al.[15]	mRNA (Pfizer, second dose)	67, M	19	Cutaneous and muscular hematoma	72	110	Corticosteroids and rituximab	Remission
Vuen et al.[21]	mRNA (Pfizer, first dose)	80s, M	±14	Cutaneous and muscular hematoma	90	7.5	Corticosteroids and azathioprine	Remission
Lemoine et al.[22]	mRNA (Moderna, first dose)	70, M	8	Cutaneous hematoma	57.5	39.9	Corticosteroids and cyclophosphamide	Remission
Gutierrez-Nunez et al.[23]	mRNA (Pfizer, second dose)	43, F	±21	Cutaneous hematoma	86.1	78.4	Corticosteroids and rituximab	Not stated

high level of public and health care alertness to possible vaccine-related adverse events. During an extensive worldwide vaccination campaign, it is likely that the onset of a rare disease will temporarily coincide with vaccination.[16] In our patient, there was also a relapse of bullous pemphigoid the week before the diagnosis of AHA. It has been postulated that there may be a relation between these two autoimmune diseases.[24]

Further surveillance and comparative epidemiological studies should be done before drawing conclusions about causative relationships. However, this will be difficult because of the low incidence of AHA and the potential risk of reporting bias. Vaccine-related risks should also be weighed against the benefit of risk reduction of severe illness or death from a vaccine-preventable disease.

AUTHOR CONTRIBUTIONS

Michiel Happaerts wrote the manuscript, performed the literature review, and created the figures for the report in consultation with Thomas Vanassche.

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RELATIONSHIP DISCLOSURE

The authors declare no conflict of interest.

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REFERENCES

1. Kruse-Jarres R, Kempton CL, Baudo F, et al. Acquired hemophilia A: updated review of evidence and treatment guidance. *Am J Hematol*. 2017;92(7):695-705.
2. Knoebl P, Marco P, Baudo F, et al. Demographic and clinical data in acquired hemophilia A: results from the European Acquired Hemophilia (EACH2) registry. *J Thromb Haemost*. 2012;10:622-631.
3. Moulis G, Pugnet G, Bagheri H, et al. Acquired factor VIII haemophilia following influenza vaccination. *Eur J Clin Pharmacol*. 2010;66(10):1069-1070.
4. Li Z, Chen Z, Cheng X, et al. A previously treated severe haemophilia A patient developed high-titre inhibitor after vaccinations. *Int J Immunopathol Pharmacol*. 2020;34:2058738420934618.
5. Radwi M, Farsi S. A case report of acquired hemophilia following COVID-19 vaccine. *J Thromb Haemost*. 2021;19(6):1515-1518.
6. Portuguese AJ, Sunga C, Kruse-Jarres R, Gernsheimer T, Abkowitz J. Autoimmune- and complement-mediated hematologic condition recrudescence following SARS-CoV-2 vaccination. *Blood Adv*. 2021;5(13):2794-2798.
7. Franchini M, Glingani C, De Donno G, et al. The first case of acquired hemophilia A associated with SARS-CoV-2 infection. *Am J Hematol*. 2020;95(8):E197-e198.
8. Wang KY, Shah P, Roarke DT, Shakil SA. Severe acquired haemophilia associated with asymptomatic SARS-CoV-2 infection. *BMJ Case Rep*. 2021;14(7):e242884.
9. Ghafouri S, Rettig M, Kahlon KS. An 89-year-old man with COVID-19-associated coagulopathy presenting with a prolonged partial thromboplastin time, lupus anticoagulant, and a high titer of factor VIII inhibitor. *Am J Case Rep*. 2020;30(21):e926728.
10. Olsen GM, Rinder HM, Tormey CA. De novo acquired hemophilia as an immune dysregulation phenomenon following SARS-CoV-2 infection. *Transfusion*. 2020;61(3):989-991.
11. Miller CH, Boylan B, Payne AB, Driggers J, Bean CJ. Validation of the chromogenic Bethesda assay for factor VIII inhibitors in hemophilia A patients receiving Emicizumab. *Int J Lab Hematol*. 2021;43(2):e84-e86.
12. Knoebl P, Thaler J, Jilma P, Quehenberger P, Gleixner K, Sperr WR. Emicizumab for the treatment of acquired hemophilia A. *Blood*. 2021;137(3):410-419. doi:10.1182/blood.2020006315
13. Wraith DC, Goldman M, Lambert PH. Vaccination and autoimmune disease: what is the evidence? *Lancet*. 2003;362(9396):1659-1666.
14. Hafzah H, McGuire C, Hamad A. A case of acquired hemophilia A following SARS-CoV-2 infection. *Cureus*. 2021;13(7):e16579. doi:10.7759/cureus.16579
15. Farley S, Ousley R, Van Wagoner N, Bril F. Autoimmunity after coronavirus disease 2019 (COVID-19) vaccine: a case of acquired hemophilia A. *Thromb Haemost*. 2021;121:1674-1676. doi:10.1055/a-1579-5396
16. Cittone MG, Battegay R, Condoluci A, et al. The statistical risk of diagnosing coincidental acquired hemophilia A following anti-SARS-CoV-2 vaccination. *J Thromb Haemost*. 2021;19(9):2360-2362.
17. Al Hennawi H, Al Masri MK, Bakir M, et al. Acquired hemophilia A post-COVID-19 vaccination: a case report and review. *Cureus*. 2022;14(2):e21909. doi:10.7759/cureus.21909
18. Soliman DS, Al Battah A, Al Faridi D, Ibrahim F. Acquired hemophilia A developed post COVID-19 vaccine: an extremely rare complication. *J Med Cases*. 2022;13(1):1-4. doi:10.14740/jmc3827
19. Leone MC, Canovi S, Pilia A, et al. Four cases of acquired hemophilia A following immunization with mRNA BNT162b2 SARS-CoV-2 vaccine. *Thromb Res*. 2022;211:60-62. doi:10.1016/j.thromres.2022.01.017
20. Murali A, Wong P, Gilbar PJ, Mangos HM. Acquired hemophilia A following Pfizer-BioNTech SARS CoV-2 mRNA vaccine, successfully treated with prednisolone and rituximab. *J Oncol Pharm Pract*. 2022;28:10781552221075545. doi:10.1177/10781552221075545
21. Ai Vuen L, Aun Su-Yin E, Naila Kori A, Shah TM. Case of acquired haemophilia A in Southeast Asia following COVID-19 vaccine. *BMJ Case Rep*. 2022;15(3):e246922. doi:10.1136/bcr-2021-246922
22. Lemoine C, Giacobbe AG, Bonifacino E, Karapetyan L, Seaman C. A case of acquired haemophilia A in a 70-year-old post COVID-19 vaccine. *Haemophilia*. 2022;28(1):e15-e17. doi:10.1111/hae.14442
23. Gutierrez-Nunez J, Torres G. "Dark skin"-acquired hemophilia A after Pfizer-Biontech COVID-19 vaccine. *Chest*. 2021;160:A1384.
24. Abdul-Halim NA, Ng HJ. Bullous pemphigoid is a common associated disorder with acquired haemophilia A. *Int J Hematol*. 2021;113(1):58-62.

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