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Letter to the Editor-in-Chief

Association between SARS-CoV-2 infection or vaccination and acquired hemophilia A: A case report and literature update

Dear Editor,

Acquired hemophilia A (AHA) is a rare, but often life-threatening, bleeding disorder due to the development of autoantibodies which neutralize the activity of coagulation factor VIII (FVIII) and/or accelerate its clearance [1]. The incidence of AHA has been estimated about 1.5 cases per million/year, showing an increase with age and being significantly more frequent in people over 65 years old, without gender difference [2–4]. It is likely, however, that the true incidence of AHA is underestimated, given the difficulty in making the correct diagnosis, which is based on the laboratory demonstration of a prolonged activated partial thromboplastin time (aPTT), reduced plasma clotting FVIII levels and the detection of anti-FVIII autoantibodies [2]. Approximately half of the cases do not have any recognized cause associated with the development of anti-FVIII inhibitors and are, therefore, considered idiopathic AHA. According to the largest published series from studies or registries, the most common secondary forms are those associated with solid cancers and hematological malignancies, autoimmune diseases, particularly rheumatoid arthritis and systemic lupus erythematosus, pregnancy, infections, skin disorders and drugs, especially antibiotics and interferon [5]. Recently AHA has been diagnosed in patients with coronavirus 2-associated disease 2019 (COVID-19) or after anti-COVID-19 vaccination [6]. These findings are quite interesting although not surprising, considering the already known immune dysregulation following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [7] and the association between AHA and vaccinations, especially against influenza and tuberculosis [8,9]. Possible pathophysiological mechanisms of vaccine-triggered autoimmunity lie in the activation of quiescent autoreactive T and B cells, as well as molecular mimicry. This latter pathomechanism could be also involved in AHA associated with SARS-CoV-2 infection [10]. In this paper, we describe a recent case regarding the association between vaccination against SARS-CoV-2 and AHA. We also revise the current literature about the link between SARS-CoV-2 infection or vaccination and AHA onset or relapse.

A 67-year-old man presented on May 18, 2021 at the emergency room of the Mantua city hospital with spontaneous cutaneous and muscle bleeding at the trunk and limbs. His hemorrhagic history was positive for two previous episodes of AHA (idiopathic in 2011 and associated with SARS-CoV-2 infection in 2020), in both cases successfully treated with steroids and cyclophosphamide. His medical history revealed a diagnosis of pulmonary sarcoidosis in 1996, of rheumatoid arthritis in 2020 (treated with steroids and methotrexate), of steroid diabetes (under insulin therapy) and a depressive state (under alprazolam therapy). Twenty-two days before the symptom onset, the patient had received the first dose of anti-COVID-19 mRNA vaccine (Spikevax, Moderna). Blood tests revealed mild normocytic anemia (hemoglobin 9.7 g/dL) with normal white cell and platelet count and a prolonged

aPTT (ratio 1.86, normal range 0.82–1.18) with normal prothrombin time. A mixing study resulted in failure of aPTT correction, suggesting the presence of an inhibitor that was successively identified as directed against FVIII (FVIII activity <2.5 %, inhibitor titer 4 Bethesda units [BU]). The diagnosis of AHA was again made. Patient's bleeding was successfully treated with rFVIIa (90 µg/kg every 3 h until bleeding stopped). Inhibitor eradication was started with rituximab (four doses of 375 mg/m² administered intravenously one week apart; steroid use was contraindicated due to diabetes and depression). Before starting rituximab, the patient underwent a biopsy of a retroperitoneal mass detected during an abdominal ultrasound check. The diagnosis was of differentiated liposarcoma. Effective hemostasis during the invasive procedure was obtained using 6 doses of rFVIIa administered intravenously over 24 h at bolus injection intervals of 2 to 6 h using an automated bolus infusion pump (Perfusor Space, B. Braun, Milan, Italy). The response to rituximab was slow: the autoantibody started to decrease and FVIII to increase one week after the fourth dose of the monoclonal antibody (FVIII inhibitor: 2 BU; FVIII: 11.9 %) with progressive disappearance of hematoma. Complete remission (FVIII inhibitor: negative; FVIII: 74 %) was reached 5 weeks after the last rituximab dose. On 11 December 2021 the patient underwent surgical removal of the retroperitoneal mass, but unfortunately he died on December 31, 2021 secondary to post-operative complications (intestinal perforation and pancreatitis) while it was still in complete remission from AHA.

Although we cannot rule out an association between AHA onset and cancer diagnosis, the case reported here is exceptional because describes for the first time a possible double relapse of AHA following Coronavirus Disease 2019 (COVID-19) first (see case description in Table 1) and then after vaccination against SARS-CoV-2. A recent review on this topic by Jacobs and colleagues [6] showed 58 cases of FVIII inhibitors associated with SARS-CoV-2 vaccination from the US Center for Disease Control and Prevention's Vaccine Adverse Event Reporting System (CDC's VAERS) database, suggesting a rate of 1.2 cases per 10 million doses. Although this incidence appeared to be similar to that in the general population, this type of analysis suffers from some limitations that might affect accuracy of reporting (e.g., passive reporting, which may result in inaccurate risk estimates; absence of investigation for causality).

We performed a systematic review, analyzing the medical literature for published articles on the association between AHA and SARS-CoV-2 infection or vaccination. A literature search of the MEDLINE (through PUBMED), EMBASE, SCOPUS, OVID, and Cochrane Library electronic databases was carried out from September 2020 to September 2022, using English language as a restriction. Only articles published following a peer reviewing process were included in the final analysis. The Medical Subject Heading (MeSH) and key words used were: ("COVID-19" OR "SARS-CoV-2" OR "coronavirus disease 2019") AND ("vaccine" OR

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Table 1
SARS-CoV-2 vaccine/infection-associated acquired hemophilia A: cases from literature review.

Author	Age [y], gender	Comorbidities	Vaccine	Days between SARS-CoV-2 vaccine (dose)/ infection and AHA	FVIII inhibitor titer (BU) ^a	Symptoms	Treatment			Outcome ^b	Reference
							AHA		SARS-CoV2		
							Bleeding	Inhibitor eradication			
Ai Vuen	80, M	Diabetes, hypertension, CKD, BPH, IS	BNT162b2 (Pfizer/ BioNTech)	14 days (1)	High	Multiple-site hematoma	rFVIIa, TA	STD, AZT	–	CR	Ai Vuen L, Aun Su-Yin E, Naila Kori A, Shah TM. Case of acquired hemophilia a in Southeast Asia following COVID-19 vaccine. BMJ Case Rep 2022;15(3): e246922.
Al Hennawi	75, M	Hypertension, dyslipidemia, CAD, BPH	BNT162b2 (Pfizer/ BioNTech)	90 days (2)	High	Multiple-site hematoma	rFVIIa	STD, RTX, CPH, CSP	–	FVIII 20 % with no evidence of active bleeding	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:e21909.
Cittone	85, M	Hypertension, CAD, PAD	mRNA-1273 (Moderna)	7 days (1)	Low	Multiple-site hematoma, joint bleeding	rFVIIa, APCC	STD, RTX	–	Death due to hemorrhagic complications CR	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):2360–2.
	86, F	AVS	mRNA-1273 (Moderna)	21 days (2)	Low	Hemothorax following injury	rFVIIa, APCC	STD	–		
	72, F	CAD	mRNA-1273 (Moderna)	14 days (1)	High	Multiple-site hematoma	rFVIIa, TA	STD, RTX	–	FVIII 5 %, FVIII inhibitor 5.6 BU with improvement of bleeding tendency	
Farley	67, M	Hypertension, pulmonary sarcoidosis	BNT162b2 (Pfizer/ BioNTech)	19 days (2)	High	Multiple-site hematoma	APCC	STD, RTX	–	CR	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(12):1674–6.
Franchini	66, M	Previous AHA successfully treated 9 years before (CR)	Severe SARS- CoV-2 infection	Concomitant	High	Extensive trunk hematoma	rFVIIA	STD, CPH	LR, NIMV	CR	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: E197–8.
Fu	77, M	NR	mRNA-1273 (Moderna)	21 days (2)	High	Diffuse ecchymoses	rFVIIa	STD, CPH	–	FVIII 9 %, FVIII inhibitor 49 BU with improvement of bleeding tendency	Fu PA, Chen CW, Hsu YT, Wei KC, Lin PC, Chen TY. A case of acquired hemophilia A and bullous pemphigoid following SARS-CoV-2 mRNA vaccination. J Formos Med Assoc 2022;121(9):1872–6.
Gonzalez	43, F	None	BNT162b2 (Pfizer/ BioNTech)	21 days (2)	High	Hematoma with swelling	NR	RTX, STD	–	NR	Gonzalez R, Gutierrez-Nunez J, Ferrer VF, et al. “Dark skin” acquired hemophilia A after Pfizer -COVID-19 vaccine. Chest 2021;160:A1384.
Ghafouri	89, M	Hypertensin, prostate cancer, diabetes, LAC	Severe SARS- CoV-2 infection	Concomitant	High	Hematuria	rFVIIa	None	Tocilizumab	Death due to cardiopulmonary failure	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;21:e926728.
Guerra	74, F	Hypertension, fibromyalgia	Mild SARS-CoV- 2 infection	30 days	High	Hematuria	rFVIIa	STD, CPH, RTX	None	CR	Guerra JD, Gowarty J, Buess J, Mason J, Halka K. A Case of Acquired Hemophilia A in a Patient with Exposure to COVID-

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Table 1 (continued)

Author	Age [y], gender	Comorbidities	Vaccine	Days between SARS-CoV-2 vaccine (dose)/infection and AHA	FVIII inhibitor titer (BU) ^a	Symptoms	Treatment		SARS-CoV2	Outcome ^b	Reference
							AHA	Inhibitor eradication			
Hafzah	73, M	CKD, benign prostatic hypertrophy, dyslipidemia	Severe SARS-CoV-2 infection	120 days	High	Spontaneous ecchymoses	None	STD, CPH	Heparin – APX for COVID-19 associated pulmonary emboli	CR	19. Case Rep Hematol 2022;2022:9494249. Hafzah H, McGuire C, Hamad A. A Case of Acquired Hemophilia A Following SARS-CoV-2 Infection. Cureus. 2021 Jul 23;13(7):e16579.
Lemoine	70, M	Rheumatic polymyalgia	mRNA-1273 (Moderna)	8 days (1)	High	Multiple-site hematoma	APCC	STD, CPH	–	FVIII 7 %, FVIII inhibitor 11.4 BU with no evidence of active bleeding	Lemoine C, Giacobbe AG, Bonifacino E, et al. A case of acquired hemophilia A in a 70-year-old post COVID-19 vaccine. Hemophilia 2022;28(1):e15-e17.
Leone	86, M	Rheumatic polymyalgia	BNT162b2 (Pfizer/BioNTech)	14 days (2)	Low	Multiple-site hematoma	None	STD	–	CR	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;211:60–2.
	73, F	Rheumatoid arthritis, Sjogren syndrome	BNT162b2 (Pfizer/BioNTech)	14 days (1)	Low	Multiple-site hematoma	None	STD	–	CR	
	67, M	None	BNT162b2 (Pfizer/BioNTech)	49 days (2)	Low	Multiple-site hematoma	rFVIIa	STD	–	CR	
	77, M	Bladder cancer	BNT162b2 (Pfizer/BioNTech)	52 days (2)	High	Multiple-site hematoma, hematuria	rFVIIa	STD, RTX	–	CR, death for infectious complications	
Melmed	61, F	Rheumatoid arthritis	mRNA-1273 (Moderna)	15 (2)	NR	Diffuse ecchymoses, gastrointestinal bleeding	rFVIIa	STD, RTX	–	CR	Melmed A, Kovoov A, Flippo K. Acquired hemophilia A after vaccination against SARS-CoV-2 with the mRNA-1273 (Moderna) vaccine. Proc (Bayl Univ Med Cent). 2022;35(5):683–5
Murali	95, F	Dementia, hypertension, CHF	BNT162b2 (Pfizer/BioNTech)	7 days (1)	High	Multiple-site hematoma	rFVIII, TA	STD, RTX	–	CR	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;10781552221075545.
Nardella	53, F	None	Mild SARS-CoV-2 infection	A few weeks	High	Multiple-site hematoma	rpFVIII, rFVIIa	STD, CPH, RTX	None	CR	Nardella J, Comitangelo D, Marino R, et al. Acquired Hemophilia A After SARS-CoV-2 Infection: A Case Report. J Med Cases 2022;13(5):197–201.
Nikolina	73, M	Diabetes, hypertension, prostatic hypertrophy	Severe SARS-CoV-2 infection	7 days	NR	Multiple-site hematoma	APCC	STD, CPH	LMWH, STD	CR	Nikolina B, Marija M, Marija B, Maja M, Dubravka P. Acquired hemophilia A secondary to SARS-CoV-2 pneumonia: a case report. Biochem Med (Zagreb) 2022;32(3):030801.
Olsen	83, F	None	Mild SARS-CoV-2 infection	7 days	High	Extensive ecchymoses, iliac muscle hematoma	None	STD, RTX	None	FVIII 17.5 %, FVIII inhibitor 8 BU with no evidence of active bleeding	Olsen GM, Rinder HM, Tormey CA. De novo acquired hemophilia as an immune dysregulation phenomenon following SARS-CoV-2 infection. Transfusion 2021;61(3):989–91.

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Table 1 (continued)

Author	Age [y], gender	Comorbidities	Vaccine	Days between SARS-CoV-2 vaccine (dose)/infection and AHA	FVIII inhibitor titer (BU) ^a	Symptoms	Treatment			Outcome ^b	Reference
							AHA	SARS-CoV2			
							Bleeding	Inhibitor eradication			
O'Shea	72, M	Prostate cancer, hypertension, diabetes	BNT162b2 (Pfizer/BioNTech)	7 days (1)	High	Extended bruising	APCC	STD	–	CR	O'Shea E, Daly O, Duggan C, Crowley M. Haemostatic Disarray Following COVID-19 Vaccine - a Case of Acquired Haemophilia A. Clin Appl Thromb Hemost 2022;28:10760296221077981.
Plüß	72, M	BPH	BNT162b2 (Pfizer/BioNTech)	9 days (3)	High	Diffuse ecchymoses	rFVIIa	STD, CPH, RTX	–	FVIII 8 %, FVIII inhibitor 20.6 BU with no evidence of active bleeding	Plüß M, Mitteldorf C, Szusziess CJ, Tampe B. Case Report: Acquired Hemophilia A Following mRNA-1273 Booster Vaccination Against SARS-CoV-2 With Concurrent Diagnosis of Pleomorphic Dermal Sarcoma. Front Immunol 2022;13:868133.
Portuguese	76, F	Asthma, Raynaud's phenomenon	mRNA-1273 (Moderna)	4 days (2)	High	Multiple-site hematoma, melanotic stool	VWF/FVIII replacement therapy	STD, IVIG	–	CR	Portuguese AJ, Sunga C, Kruse-Jarres R, et al. Autoimmune- and complement-mediated hematologic condition recrudescence following SARS-CoV-2 vaccination. Blood Adv 2021;5 (13):2794–8.
Radwi	69, M	Diabetes, hypertension, prostate cancer	BNT162b2 (Pfizer/BioNTech)	9 days (1)	High	Multiple-site hematoma	None	STD	–	FVIII 5 %, FVIII inhibitor 2 BU with no evidence of major bleeding	Radwi M, Farsi S. A case report of acquired hemophilia following COVID-19 vaccine. J Thromb Haemost 2021;19 (6):1515–8.
Rashid	75, M	Diabetes	BNT162b2 (Pfizer/BioNTech)	6 days (3)	NR	Multiple-site hematoma	rFVIIa	STD, CPH	–	CR	Rashid A, Khan Z, Alam J. Acquired hemophilia A with SARS-CoV-2 mRNA vaccine: first case from Pakistan. Scand J Clin Lab Invest 2022;1–3.
Soliman	39, F	None	BNT162b2 (Pfizer/BioNTech)	10 days (1)	High	Hematuria, abdominal pain	None	None	–	CR (spontaneous resolution)	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;13:1–4.
Wang	65, M	CHF, COPD, Hashimoto thyroiditis	Asymptomatic SARS-CoV-2 infection	NR	High	Multiple-site hematomas	rFVIIa, massive transfusion (RBC, FFP, PLTS)	STD, RTX, CPH	None	CR	Wang KY, Shah P, Roarke DT, Shakil SA. Severe acquired hemophilia associated with asymptomatic SARS-CoV-2 infection. BMJ Case Rep 2021;14(7): e242884.

Abbreviations: M, male; F, female; BU, Bethesda units; rFVIIa, recombinant activated factor VII; STD, steroids; RTX, rituximab; CPH, cyclophosphamide; CSP, cyclosporine; HCV, hepatitis C virus; CAD, coronary artery disease; BPH, benign prostatic hyperplasia; APCC, activate prothrombin complex concentrate; CR: complete remission; VWF, von Willebrand factor; IVIG, intravenous immunoglobulin; PAD, peripheral artery disease; TA, tranexamic acid; AVS, aortic valve stenosis; CHF, congestive heart failure; rFVIII, recombinant factor VIII; CKD, chronic kidney disease; IS, ischemic stroke; AZT, azathioprine; NR, not reported; AHA, acquired hemophilia A; LR, lopinavir/ritonavir; NIMV, non-invasive mechanical ventilation with oxygen; LAC, lupus anticoagulant; APX, apixaban; COPD, chronic obstructive pulmonary disease; RBC, red blood cells; FFP, fresh frozen plasma; PLTS, platelet concentrates; rFVIII, recombinant porcine FVIII; LMWH, low molecular weight heparin.

^a High titer: ≥ 5 BU; Low titer: <5 BU.

^b Complete remission: persistently normal FVIII levels (>70 %) with undetectable FVIII inhibitor.

“vaccination”) AND (“acquired hemophilia” OR “factor VIII autoantibodies” OR “factor VIII inhibitors”). We also screened the reference lists of the most relevant review articles for additional studies not captured in our initial literature search. Our search identified 29 cases from 24 articles (see Table 1 for details). Of them, the majority (21/29, 72.4 %) regarded AHA associated with SARS-CoV-2 vaccine (in all cases mRNA vaccine), while the remaining (8/29, 27.6 %) occurred after SARS-CoV-2 infection. The median age at presentation was 73 years (range 39–95 years) with a male/female ratio of 2.5 (28 males and 11 females). The median days between SARS-CoV-2 vaccination or infection and AHA onset were 14 days (range 4–90 days) and 7 days (range 1–120 days), respectively. In approximately half of the cases (10/21), AHA arose following the second dose of vaccine. In most cases (21/26, 80.8 %) FVIII autoantibody was at high titer (i.e., >5 Bethesda units), accounting for undetectable FVIII levels and a frequent severe clinical bleeding (mostly multiple-site hematomas) often requiring treatment with bypassing agents (21/27 cases, 77.8 %). Regarding inhibitor eradication, it was performed in 27/29 (93.1 %) cases and included steroids associated with immunosuppressive agents cyclophosphamide and/or rituximab. Complete remission (i.e., persistently normal FVIII levels [>70 %] with undetectable FVIII inhibitor) was reached in 17/28 (60.7 %) cases, with a mortality rate of 10.3 % (3/29), in line with data from international registries [2].

In conclusion, the analysis of the literature data documented an increasing number over time of case reports of AHA associated with SARS-CoV-2 infection and, in particular, vaccination. Clinicians should be aware of this rare but potentially severe adverse event and hemostasis should be investigated, as previously reported, in all patients with COVID-19 and vaccinated individuals in the case of an otherwise unexplained onset of a hemorrhagic picture. Due to the particularly complex management, once diagnosed these AHA patients should be referred to specialized hemophilia centers.

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Declaration of competing interest

The authors declare that they have no conflicts of interest.

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