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Letter to the Editors-in-Chief

Four cases of acquired hemophilia A following immunization with mRNA BNT162b2 SARS-CoV-2 vaccine

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ABSTRACT

Acquired hemophilia A (AHA) is a rare autoimmune disease caused by neutralizing autoantibodies against coagulation Factor VIII. Immunomodulatory effects of SARS-CoV-2 vaccination are still poorly understood, with reports of immune-mediated conditions developing after immunization. In the province of Reggio Emilia, Northern Italy, we observed four cases of AHA following SARS-CoV-2 immunization with mRNA BNT162b2 vaccine (produced by Pfizer-BioNTech) during the first eight months from the beginning of SARS-CoV-2 vaccination campaign. During this time frame, 235,597 people received at least one dose of BNT162b2 vaccine. The total population of Reggio Emilia province is 526,349. The unusual observation of four cases of AHA in our province could be of interest and could sensitize healthcare personnel toward a possible complication of SARS-Cov-2 immunization. Nonetheless, vaccination benefits exceed potential side effects and play a central role in individual and public health to effectively protect people from COVID-19 and to stop the pandemic.

1. Introduction

Acquired hemophilia A (AHA) is a rare autoimmune disease caused by neutralizing autoantibodies against coagulation Factor VIII. Estimates of its incidence vary, with roughly 1.4 cases every one million people per year [1]. AHA is mainly associated with malignancy, autoimmune diseases, the postpartum period or some medications; nonetheless, almost half of the cases remain idiopathic [1]. Sporadic AHA cases have been reported in association with infectious diseases or vaccinations [2].

Up to August 2021, more than 200 million cases of COVID-19 have been confirmed worldwide, with more than 4 billion doses of vaccines administered totally (World Health Organization, https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports). SARS-CoV-2 infection has been associated with severe impairment of the immune system, and inflammatory and autoimmune manifestations have been described during the clinical course of COVID-19 [3]. Immunomodulatory effects of SARS-CoV-2 vaccination are still poorly understood, with reports of immune-mediated conditions developing after immunization [4]. Since the beginning of COVID-19 pandemic, rare cases of AHA have been reported in association with SARS-CoV-2 infection [5] and vaccination [6,7]. In the province of Reggio Emilia, Northern Italy, we observed four cases of AHA following SARS-CoV-2 immunization with BNT162b2 mRNA vaccine (produced by Pfizer-BioNTech) during the first eight months since the beginning of the vaccination campaign (Table 1).

2. Case 1

On April 2, 2021, a 86 year-old man, affected by rheumatic polymyalgia under low dose steroid therapy was admitted to our Hospital for spontaneous disseminated hematomas, with severe anemia (hemoglobin concentration 66 g/L) and increased activated partial thromboplastin time (APTT) ratio (1.91; reference interval: 0.8–1.2), persisting after mixing study. No personal or family history of coagulopathy was recorded. The measured FVIII procoagulant activity (FVIII:C) was 0.06 IU/mL (reference interval: 0.5–1.5 IU/mL) with detectable inhibitor (2.1 Bethesda Units/mL). APTT was measured with Siemens Actin (Siemens Healthineers, Erlangen, Germany) on a Sysmex CS-5100 automated coagulometer (Sysmex corporation, Kobe, Japan). FVIII:C was measured with HemosIL one-stage assay on a ACL TOP 750 (Werfen, Barcelona, Spain). Anti-FVIII activity was measured with a Nijmegen-Bethesda assay. He had been injected with the second dose of BNT162b2 on the 19th of March. He was discharged after treatment with red cell transfusions and methylprednisolone therapy (1 mg/kg/day), with stable hemoglobin concentrations, FVIII:C within the reference range and undetectable inhibitor. At a follow-up visit seven months after discharge, clinical and laboratory remission persisted.

3. Case 2

On May 29, 2021, a 73 year-old woman with a remote diagnosis of rheumatoid arthritis and Sjogren syndrome was admitted to our Hospital for spontaneous tongue, jaw and right knee hematomas. She had been injected with BNT162b2 on May 3 (2nd dose). She noticed a first haematoma on the tongue 14 days after the first dose and knee and jaw hematomas few days after the second dose. At admission, hemoglobin concentration was 97 g/L, APTT ratio was increased (2.1) and not corrected by a mixing study. FVIII:C was 0.05 IU/mL, with anti-FVIII activity (0.8 Bethesda Units/mL). Methylprednisolone therapy was started (1 mg/kg/die). At discharge, hemoglobin values were stable and FVIII:C was within the reference range, with undetectable anti-FVIII. At a follow-up visit five months after discharge, clinical and laboratory remission persisted.

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Table 1
Four acquired hemophilia A cases observed following immunization with BNT162b2.

	Case 1	Case 2	Case 3	Case 4
Sex, age	Male, 86 y-o	Female, 73 y-o	Male, 67 y-o	Male, 77 y-o
Clinical presentation	Spontaneous disseminated hematomas with severe anemia. APTT ratio 1.91; FVIII:C: 0.06 IU/mL; anti-FVIII: 2.1 Bethesda Units/mL	Tongue, jaw and right knee hematomas. APTT ratio 2.1; FVIII:C: 0.05 IU/mL; anti-FVIII: 0.8 Bethesda Units/mL.	Hematoma of the tongue extending in the cervical region. APTT ratio 2.55; FVIII:C: 0.06 IU/mL; anti-FVIII 2.5 Bethesda Units/mL.	Hematuria. APTT ratio 3.61; FVIII:C: 0.02 IU/mL; anti-FVIII 6.9 Bethesda Units/mL.
Time from last dose of vaccine	14 days	26 days	49 days	52 days
Comorbidities	Rheumatic polymyalgia (remission)	Rheumatoid arthritis, Sjogren syndrome (remission)	Unremarkable	Bladder cancer
Clinical course	Hematomas resolved after steroid therapy. At seven month follow-up (steroid tapering): no bleeding events, FVIII:C 0.82 IU/mL, undetactable inhibitor.	Hematomas reabsorbed after steroid therapy. At five months follow-up FVIII:C 1.63 IU/mL; undetectable inhibitor.	Appearence of a hematoma in the upper left arm and drop in hemoglobin. Therapy with rFVIIa and immunosuppressants. Six days after discharge: FVIII:C 1.21 IU/mL, undetectable inhibitor.	Improvement of laboratory and clinical parameters (FVIII:C 0.96 IU/mL; undetectable inhibitor) after methylprednisolone, rituximab and rFVIIa. Developed a severe sepsis and died from its respiratory complications.

APTT: activated partial thromboplastin time (ratio reference interval: 0.8–1.2); Factor VIII:C: factor VIII procoagulant activity (reference interval: 0.5–1.5 IU/mL); rFVIIa: recombinant activated Factor VII.

4. Case 3

On August 4, 2021, a 67 year-old man was admitted to the Emergency Room for urgent otolaryngological assessment due to a large hematoma of the tongue, extending in the cervical region. His medical history was unremarkable. He received the second dose of BNT162b2 on June 16. Hemoglobin concentration was 125 g/L, the APTT ratio was 2.55, FVIII:C was 0.06 IU/mL with detectable anti-FVIII activity (2.5 Bethesda Units/mL). Due to appearance of a hematoma in the upper left arm and a concomitant drop in hemoglobin concentrations, recombinant activated clotting Factor VII was administered (90 mg/kg every 6 h during active bleeding) and immunosuppressive therapy with prednisone and cyclophosphamide (both 1 mg/kg per os) was initiated. At discharge, hemoglobin values were stable and FVIII:C was within reference range, with undetectable inhibitor. Three months after discharge, no bleeding events nor alterations in laboratory results were recorded.

5. Case 4

On August 19, 2021, a 77 year-old man with relapsed bladder carcinoma was admitted to the Emergency Room for hematuria. No personal or family history of hemorragic disorders was reported. On June 28, he received the second dose of BNT162b2. Hemoglobin concentration was 66 g/L, APTT was increased (3.61 ratio) and FVIII:C was 0.02 IU/mL with detectable inhibitor (6.9 Bethesda Units/mL). Immunosuppressive therapy with high dose methylprednisolone was initiated without clinical and laboratory resolution. He was then treated with recombinant activated clotting Factor VII for severe anemia (90 mg/kg every 6 h during active bleeding) and the appearance of widespread cutaneous hematomas. Rituximab was added with improvement in laboratory and clinical parameters, leading to undetectable anti-FVIII activity. However, during hospital stay the patient developed sepsis and died from its respiratory complications seven weeks after admission.

The total population of Reggio Emilia province is 526,349 (Italian National Institute of Statistics, http://dati.istat.it/Index.aspx?QueryId=18560). During the last five years (from January 2016 to December 2020), we observed 0–2 cases per year for a total of 5 cases of AHA (1.9 cases per million people/year), in line with the estimated incidence of the disease. During the first eight months since the beginning of the vaccination campaign against SARS-CoV-2, in our province 235,597 people received at least one dose of BNT162b2. During this time frame, we observed four cases of AHA following the administration of BNT162b2. Two more cases have been diagnosed in patients not vaccinated nor affected by COVID-19. The same mRNA vaccine was reported in association with other immune complications [8] and in particular with AHA by other authors [6,7]. Mucocutaneous bleeding occurred 2–7 weeks after the administration of the second dose. Interestingly, also the other two cases described following injection of BNT162b2 presented after the second dose [6,7]: if this could simply be the result of a latency period between the first dose and the occurrence of signs and symptoms or instead the second dose is pathophysiologically relevant is currently unknown. However, one of the cases described by other authors reported mild bruises already after the first dose, even if they aggraveted requiring medical attention only at the second injection [6]; similarly, our Case 2 reported a first haematoma after the first dose. In three cases, patient history revealed at least one common clinical association of AHA [1]: since co-occurence of autoimmune diseases or immune derangement in the oncological patient are both well-known phenomena, these associations could reflect susceptibility to autoimmunity potentially triggered by vaccination. Case 4 died due to complications from sepsis after being treated with steroid and rituximab, whereas the first three cases underwent clinical and laboratory remission after immunosuppressive therapy and no relapse has been observed during follow-up, as in the other 2 cases reported [6,7]: this could suggest a more favorable prognosis in respect to other nonvaccine-associated cases [1], but longer-term data are definitely needed.

In conclusion, the overall number of cases observed does not allow to draw any definitive conclusion over a possible causal relationship between SARS-CoV-2 vaccination and AHA, which would need more epidemiological and pharmacovigilance data about suspected vaccine-related adverse events [9]. Nonetheless, we think the unusual observation of four cases of a rare disease during the first months of the vaccination campaign in our province could be of interest and could sensitize healthcare personnel toward a possible complication of SARS-Cov-2 immunization. Finally, it should nonetheless be underlined that vaccination benefits exceed potential side effects and play a central role in individual and public health to effectively protect people from COVID-19 and to stop the pandemic [10].

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Maria Cristina Leone[a], Simone Canovi[b,*], Annalisa Pilia[b], Annamaria Casali[a], Luca Depietri[a], Tommaso Fasano[b], Rossana Colla[b], Angelo Ghirarduzzi[a]

[a] *Medicina Cardiovascolare e Centro Emostasi e Trombosi, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy*

[b] *Laboratorio Analisi Chimico-Cliniche e di Endocrinologia, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy*

[*] Corresponding author at: Laboratorio Analisi Chimico-Cliniche e di Endocrinologia, Azienda USL-IRCCS di Reggio Emilia, viale Risorgimento, 80, 42123 Reggio Emilia, Italy.
E-mail address: Simone.Canovi@ausl.re.it (S. Canovi).