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1. Introduction

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.

2. Case 1

On April 2, 2021, a 86 year-old man, affected by rheumatic polyarthritis and Sjogren syndrome was admitted to our Hospital for spontaneous tongue, jaw and right knee hematomas. She 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.
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 hemorrhagic 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 undetectable 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.

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 aggravated 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: since co-occurrence 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 pharmacoepidemiology 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 public health to effectively protect people from COVID-19 and to stop the pandemic [10].

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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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