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CASE REPORT

# A case report of acquired hemophilia following COVID-19 vaccine

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## Abstract

Acquires hemophilia A (AHA) is rare bleeding condition commonly associated with malignancy, autoimmune disease, or pregnancy. We report a case of a 69-year-old gentleman who developed bleeding symptoms after receiving COVID-19 vaccine. Laboratory testing showed isolated prolongation of the activated partial thromboplastin time, and normal von Willebrand factor. Further testing confirmed the presence of factor VIII inhibitor. To date, no cases of AHA have been reported after exposure to COVID-19 vaccine. There have been two cases of AHA following seasonal flu and H1N1 vaccination, as well as two cases of AHA following COVID-19 infection. We present a summary of these cases and review of literature of autoimmune reactions following vaccination.

## KEY WORDS

hemophilia A, hemorrhage, immunosuppression, glucocorticoids, immune system

## 1 | INTRODUCTION

Acquired hemophilia A (AHA) is a bleeding condition in which patients develop autoantibodies directed against clotting factor VIII (FVIII).<sup>1</sup> AHA is a rare disorder, with an incidence of around 1 per million.<sup>2</sup> Patients with AHA are often elderly, except for female patients who tend to be young and are either pregnant or postpartum. Comorbidities such as autoimmune disease and cancers are commonly associated with AHA.<sup>3</sup> Bleeding in AHA most commonly involves the skin. Deep tissue bleeding (e.g., joints) is not as common compared to congenital hemophilia A.<sup>3</sup> Few cases have reported infection or vaccination as a possible trigger for AHA.<sup>4-6</sup> We report on a case of AHA following a Pfizer-BioNTech SARS-CoV-2 mRNA vaccine.

## 2 | CASE REPORT

A 69-year-old gentleman presented with a history of mild bruising on his left wrist, 9 days after receiving the first dose of

COVID-19 vaccine. He gave no personal or family history of any bleeding disorders. Following the second dose of COVID-19, he noticed several new bruises appearing on his arms and legs. All the bruises were spontaneous except for a significant bruise associated with swelling on his right thigh following minor trauma, which continued to expand over the next 2 days. He also received an intramuscular injection in his thigh, which resulted in localized swelling associated with pain upon walking. His comorbidities included diabetes, hypertension, and a history of adenocarcinoma of the prostate, now in remission. He underwent prostatectomy in 2017 followed by radiation. His latest computed tomography and positron emission tomography scans 6 months prior to COVID-19 vaccination were unremarkable, and his last prostate-specific antigen was 0.05 ng/ml (normal range = 0–4 ng/ml). His physical exam revealed large ecchymosis on his left forearm and elbow, as well as his right thigh (Figure 1). He also had swelling on his left anterior mid-thigh with no discoloration suggestive of intramuscular hematoma. The rest of the physical exam was unremarkable, with no palpable lymph nodes. His complete blood count showed mild anemia (hemoglobin 11.6 g/dl [normal range = 13–18 g/dl] and platelets of  $237 \times 10^9/L$  [normal range  $150–500 \times 10^9/L$ ]).

Manuscript handled by: David Lillicrap

Final decision: David Lillicrap, 07 March 2021

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His coagulation profile revealed a normal prothrombin time at 10.8 s (normal range = 9.4–12.5 s) and a severely prolonged activated partial thromboplastin time (APTT) at 115.2 s (normal range = 25.1–36.5 s). Magnetic resonance imaging of his thigh showed a large heterogeneous well-defined lobulated mass within the right rectus femoris muscle measuring 7.5 × 4.5 cm, consistent with intramuscular hematoma. The mixing study showed immediate near correction of APTT, 45 s, and prolongation of APTT upon incubation, 76.5 s, suggesting the presence of an inhibitor. Further testing revealed elevated von Willebrand antigen/function, FVIII level at 1% using APTT-based assay, and FVIII inhibitor titer at 80 Bethesda units, which were consistent with the diagnosis of AHA. He did not require FVIII inhibitor bypassing activity (FEIBA) or recombinant activated factor VII (FVIIa) and was started on a high dose of prednisone orally (1 mg/kg). He experienced no further major bleeding episodes after the start of treatment. After 4 weeks of treatment with corticosteroids, FVIII level increased to 5% and FVIII inhibitor titer decreased to 2 Bethesda units.

### 3 | DISCUSSION

This is the first case of AHA possibly triggered by COVID-19 vaccination. Our literature search found two cases of AHA associated with COVID-19 infection.<sup>4,7</sup> The first case involved an 83-year-old woman who presented with bruising symptoms 1 week after recovering from mild COVID-19 infection. The second case involved a 66-year-old man who was diagnosed with AHA in 2011 and went into remission with treatment. He was admitted with COVID-19 and extensive ecchymosis on the trunk in 2019. Both cases revealed prolonged APTT, low FVIII, and presence of FVIII inhibitors. Treatment in the first case involved administration of prednisone and rituximab, while in the second case immunosuppressive treatment was given in addition to antiviral medication (lopinavir-ritonavir). Both patients responded to treatment and went into remission.

In addition, we found two cases of AHA associated with vaccination. The first case involved a 72-year-old woman who experienced bruising 8 days after receiving a seasonal influenza vaccine. The second case involved a 66-year-old woman who developed ecchymoses 20 days post H1N1 vaccination. Both cases revealed low FVIII and presence of FVIII inhibitors. Both patients were treated with steroids; however, in the first case, due to non-responsiveness, rituximab was added to achieve remission.

The pathophysiology of AHA is unclear, although it is thought that T-lymphocytes and certain genetic polymorphisms may play a role.<sup>8</sup> Vaccines have long been implicated in generating auto-antibodies. It has been suggested that vaccination may trigger an autoimmune response due to antigenic mimicry as well as due to activation of quiescent auto-reactive T and B cells.<sup>9,10</sup> Other forms of autoimmune diseases have been reported post-vaccination. For example, the swine-flu vaccine had been associated with an outbreak of Guillain-Barre syndrome in 1976 and a causal relationship

#### Essentials

- Acquired hemophilia (AHA) is commonly associated with malignancy, autoimmune disease, and pregnancy. Few cases have reported development of AHA after vaccination.
- We report a case of AHA after administration of COVID-19 vaccine. We did a literature search for similar cases and examined any link between COVID-19 infection and vaccination in general with development of AHA.
- We found two cases of AHA that have occurred after vaccination (not related to COVID-19 vaccination), and similar number of cases that have occurred after COVID-19 infection.
- Increase in vigilance regarding extremely rare side effects associated with COVID-19 vaccination is needed.

has been suggested between oral polio and transverse myelitis as well as the two combination vaccines of diphtheria--tetanus--pertussis and measles--mumps--rubella with occurrence of thrombocytopenic purpura.<sup>11-13</sup> Moreover, there is growing evidence associating COVID-19 infection with hematological and non-hematological autoimmune disease, for example, cold agglutinin autoimmune hemolytic anemia,<sup>14</sup> thrombotic thrombocytopenic purpura,<sup>15</sup> Guillain-Barre syndrome,<sup>16</sup> and immune thrombocytopenic purpura.<sup>17</sup>

### 4 | CONCLUSION

There have been more than 200 million COVID-19 vaccine doses administered and 43.6 million individuals are deemed fully vaccinated worldwide.<sup>18</sup> The most common side effects reported with COVID-19 vaccine are pain at injection site, fever, chills, arthralgia, myalgia, and headache.<sup>19</sup> Anaphylaxis, the most serious side effect reported with vaccines, is extremely rare (11.1 cases per million doses).<sup>20</sup> We, the authors, acknowledge that it is difficult to confirm a definitive link between COVID-19 vaccine and AHA, and the emergence of FVIII inhibitors post vaccination is most likely be a coincidence; however, it is plausible that a link may exist and is supported by: (1) the fact that the patient did not have usual diseases commonly associated with AHA, for example, presence of active solid malignancy or autoimmune disease and (2) several case reports have suggested that COVID-19 infection and vaccines in general may trigger an autoimmune reaction.

It is important to emphasize that clinical trials involving COVID-19 vaccines will fail to detect rare reactions.<sup>21</sup> The purpose of this case report is to raise awareness among health-care workers about a possible rare side effect that may be associated



**FIGURE 1** In order, ecchymosis involving left thigh, right forearm (posterior), right elbow, and right forearm (anterior) [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

with COVID-19 vaccine and to highlight the need for further vigilance and surveillance worldwide in order to better understand the relationship between autoimmune reactions and COVID-19 vaccination.

#### CONFLICTS OF INTEREST

All authors declare absence of any real or potential conflicts of interest related to this case.

#### AUTHOR CONTRIBUTIONS

S.F was responsible for conceiving the idea and wrote the manuscript. M.R. was responsible for critical revision of the manuscript. Both authors contributed to literature search and in the approval of final manuscript.

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**How to cite this article:** Radwi M, Farsi S. A case report of acquired hemophilia following COVID-19 vaccine. *J Thromb Haemost*. 2021;19:1515-1518. <https://doi.org/10.1111/jth.15291>