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A Possible Case of Acquired Hemophilia Following COVID-19 Vaccination

Kanak Parmar[1]*, Shivam Singh[2], Robert Horn[3] and Udit Verma[3]

[1]Department of Internal Medicine, Texas Tech University Health Sciences Center, 3601 4th St, Lubbock, TX, 79430-0002, USA
[2]King George's Medical University, Lucknow, India
[3]Department of Hematology Oncology, Texas Tech University Health Sciences Center, Lubbock, TX, USA

Abstract

COVID-19 vaccination has been very efficient in preventing severe illness and death from SARS CoV-2. These vaccines are usually reported to have mild and transient side effects. We report a case of a 59-year-old woman with an acquired hemophilia A following the administration of her second dose of mRNA 1273 vaccine. The patient presented with worsening swelling and bruising of her left arm three days after vaccination. She had a history of COVID-19 infection 3 months ago. Laboratory workup showed elevated partial thromboplastin time (PTT) and mixing study showed possible inhibitor. Factor VIII level (%) was <5% and the inhibitor panel confirmed presence of inhibitor. The patient was treated with high dose steroids and cyclophosphamide. Currently the patient is on slow taper steroids and hematoma has improved.

Keywords: COVID-19 • Vaccination • Hemophilia

Introduction

The COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS CoV-2), has affected lives globally. According to the World Health Organization (WHO), till date 6.3 million COVID-19 associated deaths have occurred [1]. COVID-19 vaccination has been very effective in protecting against serious illness, hospitalization, and death from COVID-19. Eleven vaccines have been granted emergency use authorization (EUA) by the WHO [2]. These include two m-RNA vaccines developed by Pfizer/BioNTech (Comirnaty) and Moderna (Spikevax), 3 adenovirus-vectored vaccines developed by AstraZeneca/Oxford (Vaxzevria), Jansen/Johnson & Johnson (Ad26.COV2.S) and CanSino (Convidecia), 2 protein subunit vaccine developed by Serum institute of India (CovoVax) and NovoVax (Nuvaxovid) and 3 inactivated vaccines: Bharat Biotech (Covaxin), Sinovac (CORONAVAC), Sinopharm (Covilo) [2].

Adverse Events Following Immunization (AEFI) is reported in 53.7 per 100,000 COVID-19 vaccine doses administered [3, 4]. The most common adverse events associated with the COVID-19 vaccine to date are allergic skin reactions and pain/redness/swelling at the injection site. Serious AEFI was reported in 2.8 per 100,000 doses of COVID-19 vaccine administered. Serious side effects reported so far from COVID-19 vaccines include myopericarditis, vaccine induced immune thrombocytopenia, anaphylaxis, pulmonary embolism, stroke, acute myocardial infarction, Bell palsy, cerebral venous sinus thrombosis, and Guillain-Barre syndrome, acute disseminated encephalomyelitis [5-7]. The major safety concerns are few and there is a stronger indication for universal vaccination and pharmacovigilance. Acquired Hemophilia A (AHA) is another very rare adverse effect of COVID-19 vaccination [8,9]. AHA is a rare disorder with an incidence of 1.48 per million per year [10]. AHA occurs due to development of autoantibody against factor VIII and distinct comorbidities such as autoimmune diseases and cancers are commonly associated. We report a case of AHA following the second dose of Moderna vaccination.

Case Presentation

A 59-year-old Hispanic female presented to the hospital on with worsening swelling and ecchymosis of her left arm. She received her second dose of the Moderna vaccine on the right arm 3 days ago. Following her vaccination three days later she noticed a bruise in her right arm which progressed to involve her left upper extremity (Figure 1). Her past medical history was remarkable for obesity, mild COVID infection 3 months ago, and sciatica. The patient had no allergies, no history of immune deficiency, no recent infections or fevers, and no personal or family history of any bleeding disorders. Vitals were normal. Labs on admission showed macrocytic hyper-proliferative anemia with hemoglobin 7.2 g/dl (Table 1). Peripheral blood smear showed macrocytic anemia, leukoerythroblastosis and neutrophilic leukocytosis. Serum Total

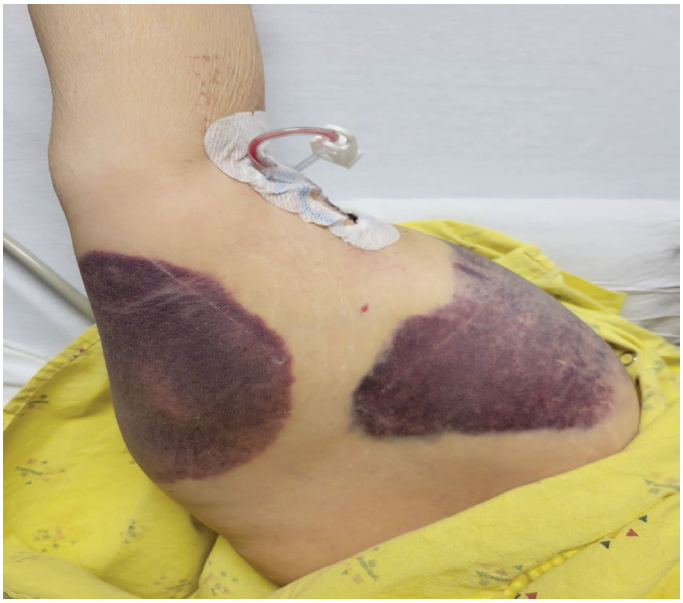

Figure 1. Bruise in the patient's right arm.

***Address for Correspondence:** Kanak Parmar, Department of Internal Medicine, Texas Tech University Health Sciences Center, 3601 4th St, Lubbock, TX, 79430-0002, USA, Tel: +1(832) 449-9758; E-mail: kanak.parmar@ttuhsc.edu*

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Table 1. Laboratory tests.

Laboratory Tests					
Variable	**Values on admission**	**Labs on second admission**	**Labs on first follow up (4/7/22)**	**Labs on second follow up (4/19/22)**	**Reference value**
CBC					
WBC (K/uL)	14.69	13.32	15.55	10.6	4.5-11
RBC (million/mm^3)	2.91	3.52	3.87	3.97	3.5-5.5
Hemoglobin (g/dl)	9.2	11.5	12.5	13	13-16
MCV (fl)	97.9	100.6	100.3	97.7	78-98
RDW - SD (fl)	55.6	60	54.7	51.7	39-46
Platelet (K/uL)	267	242	217	201	150-400
Erythrocyte sedimentation rate (mm/hr)	1	NA	NA	NA	<20
Iron (mcg/dl)	79	-	-	-	37-145
TIBC (mcg/dl)	193	-	-	-	250-450
Ferritin (ng/ml)	226	-	-	-	13-150
Vitamin B12 (pg/ml)	171	-	-	-	232-1245
Total Bilirubin (mg/dl)	2.1	-	-	-	0-1
Direct Bilirubin(mg/dl)	0.5	-	-	-	0-0.2
LDH (U/L)	280	-	-	-	135-225
Haptoglobin	149	-	-	-	43-212
CRP	<0.3	-	-	-	0-0.5
D Dimer	6277	-	-	-	<500
Differential					
Automated segmented neutrophils (%)	80	93.7	76.8	80.6	40-60
Automated lymphocytes (%)	8.6	2.1	10.2	9.5	20-40
Automated monocytes (%)	9.9	2.9	11.8	8.3	04-Aug
Automated Eosinophils (%)	0	0	0.1	0.3	01-Mar
Automated absolute IGAB	NA	0.14	0.15	0.12	
Automated immature granulocytes (%)	NA	1.1	1	1.1	<1
Coagulation					
PT (sec)	11	11.2	10.1	10.2	9.4-12.5
INR	0.96	0.98	0.89	0.89	<1.1
PTT (sec)	92.8	89.1	60	39.5	25.1-36.5
Fibrinogen level (mg/dl)	168	NA	NA	NA	200-400
Factor VII level (%)	75	NA	NA	NA	50-200
Factor VIII level (%)	<5	NA	<5	42	50-150
Factor IX level (units/dl)	135	NA	NA	NA	50-150
Factor XI level (units/dl)	66	NA	NA	NA	60-70
Factor XII level (%)	42	NA	NA	NA	50-200
Thrombin time (sec)	15.8	NA	NA	NA	14-19
Normal plasma PTT (sec)	33.6	NA	NA	NA	25-35
Ristocetin Cofactor (%)	248	NA	NA	NA	60-180
Factor VIII Inhibitor Screen	Positive	Positive	Positive	NA	NA
Factor VIII activity	<1	<1	<1	NA	50-180
Nijmegen assay	52.8	41.1	25.7	NA	<0.6
Factor VIII AG	NA	NA	0.5	NA	0.6-1.95
Vwf activity	273	-	-	-	40-163
Vwf Ag	248	-	-	-	42-176

Abbreviations: NA,Not available; TIBC,Total iron binding capacity; PT,Prothrombin time; PTT,Partial thromboplastin time; INR,International normalized ratio; MCV, Mean corpuscular volume; RDW-SD,Red cell distribution width standard deviation; Vwf,Von Willebrand factor

bilirubin and Lactate Dehydrogenase (LDH) were elevated but haptoglobin was normal. Iron panel showed high ferritin and low Total iron binding capacity (TIBC). Vitamin B12 levels were low. Comprehensive metabolic panel was normal. D dimer was 6277ng/ml. Coagulation panel showed elevated partial thromboplastin time (PTT) of 92 seconds. Differential coagulation diagnostics showed normal factor activities except Factor VIII level (%) was <5%, Factor VII was 75% and factor XII was 42%. Von Willebrand factor (vwF) levels were high. Mixing study initially corrected to 43.5 seconds at 0 seconds but prolonged to 85 seconds at 60 seconds indicating a possible inhibitor. Antinuclear antibody and extensive antibody screen were negative. Ultrasound of abdomen was normal. Computed Tomography (CT) Scan of Chest was normal except a 3 mm pulmonary nodule. Factor VIII inhibitor panel showed positive inhibitor which was 52.8 on admission. After this work up a case acquired hemophilia A (AHA) was diagnosed.

On Day 2 prednisone was started and patient received one dose of four factor prothrombin concentrate (Kcentra) on day 3. Cyclosporine was started on day 5 at a dose of 250 mg BID. Patient's hematoma improved and PTT was 87.8 on day 10 and she was discharged on steroid taper. She was readmitted on day 14, PTT was 89 seconds. Cyclosporine 250 mg BID and prednisone 120mg daily were continued. Factor VIII inhibitor panel was sent which continued to show positive inhibitor with 41.1 Bethesda units (BU) and <5% factor VIII level. Cyclosporine trough was within the expected therapeutic

range. She continued to have stable hematoma size and was discharged same medications on day 20 with close follow up appointment on day 23. On follow-up her hematoma was stable in the clinic and coagulation panel showed improving PTT from 80 to 60 seconds and inhibitor level was 25.7 Bethesda units (BU). Factor VIII inhibitors are still present, and factor 8 levels are undetectable. Cyclosporine was stopped and the patient was started on cyclophosphamide 150 mg daily. Patient was started on daily prophylaxis for Pneumocystis jirovecii. On follow-up on day 36, PTT was trending down, and factor VIII level increased to 42. On subsequent follow ups patient is doing well and left arm hematoma has completely disappeared, and the right arm bruise is 3 x 3 cm.

Results and Discussion

The most common autoantibodies that affect clotting factor activity and lead to a bleeding disorder are directed against, and interfere with, the activity of factor VIII, a condition also called acquired hemophilia A (AHA) [11,12]. The reasons for the production of factor VIII autoantibodies in a particular individual are not clear but may involve the presence of certain gene polymorphisms (eg, HLA, CTLA4) and/or autoreactive CD4+ T lymphocytes [13]. Recent findings have documented the presence of immunoglobulin G (IgG) with proteolytic activity against FVIII and factor IX in patients with AHA [13]. This condition is most associated with malignancy, postpartum status, autoimmune disorders, and various drugs [13]. Bleeding is often severe, constituting a medical emergency [14]. Vaccines have long been implicated in generating autoantibodies. 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 [15]. One case of AHA has also been reported following development of Factor IX [16]. Interesting our patient also had COVID-19 infection in the past and it has been reported that failure of regulatory T-cell activation by the infection might play a crucial role in FVIII inhibitor synthesis [17].

Hematological adverse effects reported following Covid vaccination include thrombocytopenia, anemia, leucopenia, and neutropenia [18]. A nested case-control study conducted by Sing, et al., reported that the incidence of hematological abnormalities after COVID-19 vaccination was rare with only 0.2-2.5 cases per 10 000 vaccine doses [18]. The observed AHA incidence in the vaccinated >65-years-old population was 4.1 per million, which is a 4-fold increase compared to the historical overall incidence of 1.5 per million but is exactly what can be expected when calculating with an overall AHA incidence of 6 per million. As SARS-CoV-2 infection and vaccine are both capable of triggering autoimmunity, a shared element such as the spike protein is perhaps a necessary pathogenic component.

Studies have also reported the occurrence of AHA following influenza vaccination [18]. According to our review of literature, we found 18 cases of AHA following SARS Co-V2 vaccination and 3 cases of AHA following influenza vaccination, which were summarized in a systemic review [19].

We present a case of AHA following the second dose of Moderna vaccine. Our patient had a history of mild COVID-19 infection and whether it played a role in the immunological process of this phenomenon remains unknown.

The primary initial diagnostic test for a factor VIII inhibitor (after documenting a prolonged aPTT) is the mixing test or inhibitor screen [20]. The next step is adding a source of phospholipid to the mixed plasma. Correction of the aPTT suggests the presence of antiphospholipid antibodies. If the aPTT does not correct, the Bethesda assay is performed. The Bethesda assay both establishes the diagnosis of a factor VIII inhibitor and quantifies the antibody titer [20]. In our Nimegen assay was used for quantification of factor VIII inhibitor [21]. Our patient had high PTT and low Factor VII level which improved after cyclophosphamide treatment on day 36.

The initial management of AHA can be broken down into two parts: obtaining and maintaining hemostasis and re-establishing FVIII immune tolerance by eradicating the inhibitor [22]. Treatment strategies to control active bleeding include the use of desmopressin (DDAVP), factor VIII concentrates, activated prothrombin complex concentrates (aPCCs; eg, factor eight inhibitor bypassing activity [FEIBA]), recombinant human factor VIIa [22]. More recent clinical trial data showed recombinant porcine factor VIII (rpFVIII) had efficacy in AHA. A case by Cives TL, et al used rpFVIII in the treatment of refractory AHA after COVID-19 infection [23].

For the elimination of inhibitor various immunosuppressive agents such as glucocorticoids, cyclophosphamide, cyclosporine, and rituximab can be used to eliminate the inhibitor [23]. Immunosuppressive agents may work by either direct cytotoxicity to the hematopoietic cells in case of cyclophosphamide or by inhibition of calcineurin-dependent gene transcription caused by cyclosporine [24]. Recent studies have shown that combination treatment with steroids have a better complete response rate than monotherapy but was associated with higher infection rate [25].

Spontaneous remission may occur or in some cases with the treatment of the underlying condition (eg. malignancy) [26]. A better understanding into the mechanisms is warranted along with a clinical suspicion of any sign/symptoms of hematological abnormality after vaccination.

Conclusion

This case report is not conclusive that COVID-19 vaccination was the cause of AHA, as we could not completely exclude spontaneous hemophilia from other causes in these patients. The authors and the medical community continue to advocate for universal COVID-19 vaccination in society. Overall, further research and monitoring for adverse events will lead to best treatment practices related to COVID-19 vaccination.

Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Author Contributions

1. Drafting of the manuscript: KP, SS.
2. Tables and formatting: KP, SS.
3. Concept and design: KP.
4. Acquisition, analysis, or interpretation of data: KP, SS.
5. Critical revision of the manuscript for important intellectual content: RH.
6. Supervision: RH, UV.

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