

Severe thrombocytopenia after Vaxzevria vaccination in a single patient: A case report

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Abstract

AstraZeneca vaccine became one of the four vaccines that encode different forms of the SARS-CoV-2 spike glycoprotein. We report the case of an 18-year-old medically free female with progressive bruising of the upper and lower extremities for 1 week, beginning 3 days after the first dose of AstraZeneca. Laboratory results showed severe thrombocytopenia of $4.3 \times 10^3/\mu\text{L}$ with a normal white blood cell count, renal profile, and hemolytic markers. She was treated conservatively with high-dose steroids and intravenous immunoglobulin, which resulted in a full recovery of her platelet count. In our case, the question was raised about the possibility of receiving a second dose of another vaccine product instead of not being vaccinated again, a subject for further research.

Keywords

Thrombocytopenia, side effect, COVID-19, vaccine, AstraZeneca, Saudi Arabia

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Introduction

The Severe Acute Respiratory Syndrome Coronavirus-2 (COVID-19) pandemic has prompted world scientists to develop and produce vaccines at the fastest pace, as vaccination is considered the most meaningful method to counter the ongoing pandemic.^{1–3} As a result, four vaccines the mRNA vaccines from BioNTech/Pfizer (BTN162b2/Comirnaty; EMA: 21.12.20) and Moderna (mRNA-1273/Spikevax; EMA: 6.1.21), as well as the adenoviral vector-based vaccines from AstraZeneca (AZD1222/ChAdOx1S/Vaxzevria; EMA: 29.1.21) and Janssen (Ad26.COV2.S; EMA: 11.3.21) have received conditional market authorizations by the regulatory bodies.³ All four vaccines encode different forms of the SARS-CoV-2 spike glycoprotein, which mediates virus binding to the host cell membrane and entry through angiotensin-converting enzyme 2 (ACE2) and transmembrane protease, serine 2 (TMPRSS2), respectively.^{3,4}

AstraZeneca was recommended to be administered in two doses with an interval of 4–12 weeks between both doses.⁵ However, as with any vaccine or drug, side effects of a COVID-19 vaccine such as AstraZeneca were also reported.^{1–3} Thus, starting in March 2021, 5–20 days after AstraZeneca vaccination, cerebral venous sinus thrombosis (CVST), internal vein thrombosis, and other unusual severe

thrombotic events associated with thrombocytopenia have been reported in healthy individuals.^{6–8} As of 4 April 2021, 169 cases of CVST have been reported, and 53 cases of internal vein thrombosis among approximately 34 million people vaccinated in the European Economic Area (EEA) and the United Kingdom.^{9,10} After the first CVST cases, immediately suspended the AZD1222/Vaxzevria vaccination campaign in Denmark, Thailand, Ireland, Germany, Italy, France, and Spain.^{6–8} In most of these cases, thrombocytopenia was associated with rare thromboembolism of the cerebral venous sinuses, which resulted in the death of one-third of the affected vaccinated persons in Germany. In addition, cases of CVST and some cases of internal vein

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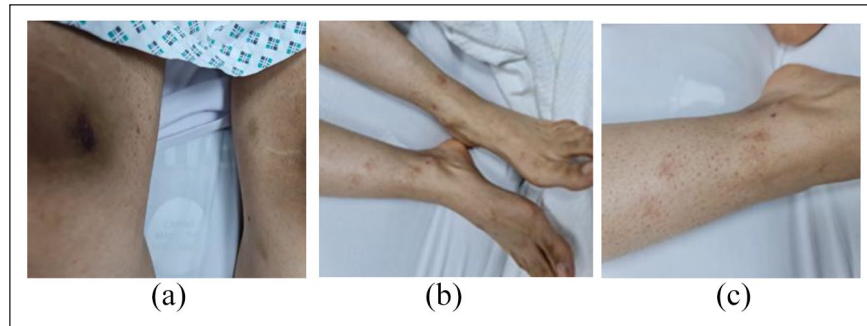


Figure 1. Examination of the skin of the patient: (a) a large blue-greenish bruise on the medial part of the left knee and two small bruises on the right knee, (b) bilateral distal side of the lower limb with multiple reddish bruises, and (c) three bruises are visible close up on the right lower limb.

thrombosis (superficial vein thrombosis (SVT)) have been reported in the EU drug safety database and the United Kingdom. However, the EMA considered the AstraZeneca vaccine to be effective as a preventive measure when the overall benefits of the vaccine outweigh the disadvantages. In addition, the German STIKO has suggested that the AstraZeneca vaccine should only be administered to people over 60 years of age since most cases in Germany affect women between the ages of 20 and 60 years.^{6–8}

Although there are numerous hypotheses and investigations on the mechanism of side effects caused by the AstraZeneca vaccine, including thrombocytopenia, this issue has become the subject of ongoing research due to controversial arguments such as errors in the concept and design of the spike protein antigen. This report from Saudi Arabia presents the case of a young female who developed severe thrombocytopenia after the first dose of the AstraZeneca vaccine.

Case report

An 18-year-old medically free female presented to the emergency department with progressive bruising on her upper and lower extremities lasting 1 week, which started 3 days after receiving her first dose of the COVID-19 vaccine (AstraZeneca). There was no active bleeding elsewhere, no history of similar condition, and no similar cases among family members, five of whom received the vaccine at the same time. There were no neurological symptoms, or any symptoms indicative of rheumatological or autoimmune disease, no history of using new medication herbal or illegal drugs. There was no palpable cervical, axillary, or inguinal lymphadenopathy. Respiratory, cardiovascular, and gastrointestinal examinations were normal. The musculoskeletal system and the central nervous system are also not changed.

Physical examination showed no pallor, jaundice, or respiratory distress. Vital signs were stable within normal limits, without fever, with a temperature of 37.0°C. Examination of the skin revealed multiple bruising and a petechial rash on the upper and lower extremities on both sides (Figure 1(a)–(c)).

Laboratory examinations showed that hemoglobin level was 12.2 g/dL, platelet $4.3 \times 10^3/\mu\text{L}$, white cell count of $10.5 \times 10^3/\mu\text{L}$. D-dimer $<0.19 \text{ mg/L}$ with normal prothrombin time (PT)/international normalized ratio (INR), partial thromboplastin time (PTT), and fibrinogen (1.02, 25.8 s, and 2.45 g/L, respectively). Renal and liver profiles were normal (Tables 1 and 2). The results of tests on hepatitis B virus surface antigen (HBV), anti-hepatitis C virus antibody (HCV), human immunodeficiency virus antibody (HIV), cytomegalovirus (CMV), and Epstein–Barr virus (EBV) were normal. Although a urea breath test was not performed, stool testing for *Helicobacter pylori* was negative. The Coombs' test and the reticulocyte count were also normal. The peripheral blood smear showed a reduced distribution of platelets with normal appearance, no clumping, normal appearance of red blood cells (RBCs) without fragmentation, no schistocytes, normal white blood cell (WBC) count with some neutrophils with toxic granules but no visible blasts.

For the treatment and follow-up, the patient was initially admitted to the intensive care unit with suspected vaccine-induced thrombocytopenia. Autoimmune markers were sent for research. She started high-dose steroids 1 mg/kg orally along with intravenous immunoglobulin (IVIG) 0.5 g/kg for a total of four doses (2 g/kg). There was an improvement in platelet count with levels normalizing within 5 days of starting this treatment plan (Tables 1 and 2). She was then discharged with a rapid taper of prednisolone. Six weeks later, at a follow-up outpatient clinic visit, she was completely free of bruising and bleeding, and had a platelet count of $411 \times 10^3/\mu\text{L}$. Further results of the examination, previously prescribed at admission, showed antinuclear antibodies (1:80) and anti-double-stranded DNA, lupus anticoagulant, rheumatoid factor (RF), and complements (C3 and C4) to be normal. However, the antibody analysis of PF4 was not carried out due to its absence in the center.

Discussion

Thrombocytopenia is a condition with a low blood platelet count, either due to impaired bone marrow formation or

Table 1. Hematology laboratory result before and after vaccination at the time of symptom onset.

Name	Reference range	Unit	Baseline investigation 6 months prior	After first dose COVID-19 vaccine	Poststeroid and IVIG at time of discharging home	Outpatient follow-up
PLT	140–450	$\times 10^3/\mu\text{L}$	400	4.23	180	411
MPV	7.2–11.1	fL	8.5	7.21	9.34	8.25
RBC	4.7–6.1	$\times 10^6/\mu\text{L}$	–	4.32	3.17	4.02
HCT	42–52	%	36	37.2	28.8	36.5
HGB	13–18	g/dL	12	13.1	9.75	12.7
Lymphocyte	1.0–5.0	$\times 10^3/\mu\text{L}$	2	2.73	1.73	3.48
MCH	27–32	pg	30.5	30.3	30.8	31.6
MCV	80–94	fL	88	86.1	91	90.8
WBC	4–11	$\times 10^3/\mu\text{L}$	10	8.43	5.15	10.6
Monocyte	0.2–0.8	$\times 10^3/\mu\text{L}$	0.5	0.642	0.354	0.607
Neutrophil	2.0–7.5	$\times 10^3/\mu\text{L}$	6.4	4.9	3.05	6.45
Eosinophil	0.0–0.8	$\times 10^3/\mu\text{L}$	0.001	0.072	0.001	0.042
Basophil	0–0.02	$\times 10^3/\mu\text{L}$	0.001	0.024	0.008	0

IVIG: intravenous immunoglobulin; WBC: white blood cell; HGB: hemoglobin; RBC: red blood cell; MPV: mean platelet volume; PLT: platelet; HCT: hematocrits; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; ESR: erythrocyte sedimentation rate.

Table 2. Biochemical laboratory results before and after vaccination at the time of symptom onset.

Name	Reference range	Unit	Baseline investigation 6 months prior	After first dose COVID-19 vaccine	Poststeroid and IVIG at time of discharging home
Albumin	34–50	g/L	30	39.4	24.5
Total protein	64–82	g/L	75	78	72
Alkaline phosphatase	50–136	U/L	72	79.2	57.9
ALT	16–36	U/L	14	16.2	14.6
AST	15–37	U/L	9	11.6	8.4
Bilirubin (conjugated)	0–3	$\mu\text{mol/L}$	1.4	1.91	<1.36
Bilirubin (total)	3–17	$\mu\text{mol/L}$	5	7.4	2.6
LDH	85–227	U/L	138	179	83
GGT	15–85	U/L	19	17	14
Creatinine	62–115	$\mu\text{mol/L}$	60	55	73
BUN	2.5–6.4	mmol/L	4.3	3.7	4.6

IVIG: intravenous immunoglobulin; LDH: lactic acid dehydrogenase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma glutamyl transferase; BUN: blood urea nitrogen.

increased peripheral destruction, which can be primary or secondary.^{11,12} Based on the platelet count, thrombocytopenia can also be classified into mild (platelet count $<150 \times 10^9/\text{L}$), moderate (platelet count $<100 \times 10^9/\text{L}$), and severe (platelet count $<50 \times 10^9/\text{L}$) categories. Acute secondary immune thrombocytopenia is defined as a drop in platelet count below normal levels within 3 months of exposure to a trigger such as a viral infection, vaccination, or certain medications.^{11,12}

Vaccines-induced thrombocytopenia could be explained by antigen-mediated response or due to the effects of the vaccine's formers like adjuvants, yeast proteins, and preservatives diluents.^{2,3,13} In the case of immune-mediated thrombocytopenia, an autoantibody against glycoproteins expressed on the platelet surface causes either opsonization, activation of the complements, or apoptotic effects. However, in the absence of the positive antiplatelet antibody, immune

thrombocytopenia cannot be excluded as there was a hypothesis of T-cell immune-mediated mechanism that typically induces thrombocytopenia by increased production of cytokines chemokines.^{2,3,13} The influence of age, gender, previous autoimmunity, and vaccine type on the development of vaccine-induced thrombocytopenia was also examined. Reports suggest a predominance of women under 60 years of age and a 12% overlap with other autoimmune diseases.^{13,14} Data available in the literature have shown that most vaccines can cause immune thrombocytopenia, such as influenza vaccine, pneumococcal vaccine, polio vaccine, hepatitis B virus vaccine, measles–mumps–rubella (MMR), diphtheria–tetanus–acellular pertussis (DTaP), and varicella vaccine.^{13,14}

In general, vaccine-induced thrombocytopenia is a rare but clinically serious and potentially life-threatening adverse event that has been observed with Pfizer BioNTech

BNT162b2 mRNA COVID-19 vaccine, Moderna mRNA-1273 SARS-CoV-2 vaccine as well as Oxford-AstraZeneca adenoviral (ChAdOx1) vector-based COVID-19 vaccine (AZD1222).^{7,10} However, the severity and frequency of thrombocytopenia were higher among those vaccinated with AstraZeneca than other types. Recent studies have demonstrated high levels of antibodies to platelet factor 4 (PF4) in affected individuals without prior exposure to heparin. As a result, immunoglobulin G (IgG) PF4 enzyme-linked immunosorbent assay (ELISA) has become central to the diagnostic algorithms of vaccine-induced immune thrombotic thrombocytopenia (VITT).^{15–17} It has been suggested that after vaccination, the immune system will stimulate the formation of antibodies against platelet antigens, which will cause immune-mediated destruction of platelets due to massive platelet activation against PF4 or due to a cross-reaction between the vaccine and platelets or PF4. However, the pathophysiology of VITT remains a subject of ongoing research.^{10,18,19}

Thus, this hypothesis contradicts the current case as there was no thrombosis on admission. Instead, there was bleeding and severe thrombocytopenia. In this case, the patient developed new immune thrombocytopenia after receiving her first dose of the AstraZeneca vaccine. In addition, her age at presentation was lower than in other studies. Therefore, a girl might benefit from other vaccines for the second dose, compared to no second dose at all. However, it was considered that in this case, other COVID-19 vaccines could also cause severe thrombocytopenia without a specific indicator of such a complication.

Still, using two different vaccines for the first two doses is the subject of ongoing discussions and research. As such, the Centers for Disease Control and Prevention (CDC), in its latest update on the matter (December 2021), recommended that products not be mixed for a two-dose primary vaccine series. However, mixing of COVID-19 vaccines has been allowed for people over the age of 18 years who will receive a third (booster) dose.²⁰

There are many studies on the effects of vaccines, including side effects; there is a lack of research on the benefits of switching the type of COVID-19 vaccine for specific complications such as severe thrombocytopenia. Although, in general, vaccine-induced prothrombotic immune thrombocytopenia (VIPIT) or thrombotic thrombocytopenia syndrome (TTS) has been widely reported as a serious side effect of the AstraZeneca vaccine, severe immune response thrombocytopenia is also critical and possibly occurs at the stage preceding thrombosis.

Conclusion

A number of hypotheses and studies have been developed to explore the side effects after the first dose of AstraZeneca vaccine, such as severe thrombocytopenia, may be either

immuno- or non-immune-induced and should be reported. In this clinical case, conservative treatment with steroids and IVIG was beneficial. However, questions remain about the feasibility of receiving a second dose of another vaccine product versus no vaccination at all.

Declaration of conflicting interests

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Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

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Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

Patient's consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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