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Case Report

Safety Warning for ChAdOx1 nCov-19 Vaccine in Patients with Sickle Cell Disease

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Abstract. Vaccines against acute respiratory syndrome Coronavirus 2(SARS-CoV2) are critical weapons to control the spread of the deadly Coronavirus 2019(COVId-19) virus worldwide. Although these vaccines are generally safe, their widespread use has produced reports of rare complications, including vaccine-induced immune thrombotic thrombocytopenia (VIITT), particularly in connection with ChAdOx1 nCov-19. We have identified three cases of sickle cell disease (SCD) experiencing a severe vaso-occlusive crisis (VOC) shortly after the vaccine. Despite being stable for a long time, they had fever with tachycardia, along with a significant rise in WBC, liver enzymes, particularly alkaline phosphate, with a remarkable drop in hemoglobin, and platelets and one of them had probably a fatal TTP like syndrome. Given these findings, physicians and patients should exercise caution when taking this type of vaccine and be aware of these safety concerns.

Keywords: SARS-CoV2, ChAdOx1 nCov-19 vaccine, Sickle cell disease, Vaso-occlusive crisis, Vaccine-induced immune thrombotic thrombocytopenia.

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Introduction. Introduction of vaccines against acute respiratory syndrome Coronavirus 2 (SARS-CoV2) is a critical weapon to control the spread of the deadly Coronavirus 2019 (COVId-19) virus worldwide. More than 3.35 billion vaccine doses have been administered worldwide, equal to 44 doses for every 100 people, as of the beginning of July 2021.[1] Vaccines approved by licensing authorities generally encode spike protein of SARS-CoV-2, which encodes spike glycoprotein of SARS-CoV-2. Investigators used a recombinant adenoviral vector that encodes spike glycoprotein, as produced by Astra-Zeneca (ChAdOx1 nCov-19) and AD26.COV2.S produced by Johnson & Johnson. Additionally, platforms using m-RNA based technology are also in use [(BNT162b2 of Pfizer-BioNTech), and (mRNA-1273 of Moderna)]. Although these vaccines are generally safe, their widespread use worldwide has produced reports of unusual complications. They include rare cases associated with thrombocytopenia (thrombotic thrombocytopenic purpura-like), particularly in connection with ChAdOx1 nCov-19.[2-3] Sickle cell disease (SCD) is a systemic disease is characterized by repetitive episodes of Vaso-occlusive crisis (VOC), with a predisposition to infection and a higher risk of thromboembolic disease.[4] We report here three cases of SCD experiencing severe VOC and a fatal TTP-like syndrome with thromboembolic complications following the ChAdOx1 nCov-19 vaccine.

Case 1. A twenty-nine-year-old man with S/B^0

thalassemia presented with shoulder and back pain six days after receiving his COVID-19 vaccine (AstraZeneca). He had no admissions over the past two years (21 months) before this. At the time of entry, he had right shoulder tenderness, with no other important findings. Past medical history was significant for splenectomy, cholecystectomy, and bilateral avascular necrosis (AVN) and received stem cell injection locally at the AVN site previously. While in hospital, he developed fever, with no further localizing signs. Blood work showed significant abnormal liver enzymes and raised C-reactive protein (CRP) **Table 1**. He was given pain management and IV antibiotics, made a good recovery, and was discharged after eight days.

Case 2. A thirty-four-year-old man with S/B^0 thalassemia was admitted five days following the AstraZeneca vaccine with lower back pain, chest pain, and shoulder pain. He was on Hydroxyurea and had a history of splenic sequestration, tuberculosis of the spine, and cholecystectomy. He had no recent admission for over three years (39 months). While in hospital, he developed fever, tachycardia, and dropped saturation, with right-sided crepitations and chest X-rays showing

Table 1. Demographic, clinical and laboratory features.

Parameter	Case1	Case2	Case3	Mean ±SD	P Value*
Age (Yrs)	29	35	28	30.7 ± 3.8	
Sex	M	M	M		
Genotype	S/B^0	S/B^0	S/B^0		
Period from last admission (months)	21	39	6	22 ± 16.5	
Onset of symptoms after vaccine (days)	6	5	4	5±1	
PMH	Bilateral avascular necrosis of shoulders, splenectomy & cholecystectomy, and acute chest syndrome	Cholecystectomy, TB of spine	Splenectomy, acute chest syndrome		
Presenting symptoms	Back and shoulder pain, fever		Severe back pain		
Length of stay (days)	8	6	3	5.7±2.5	
SARS-Cov-2 RNA PCR	Not detected	Not detected	Not detected		
Complications	VOC with fever	Acute chest syndrome and splenic sequestration	Massive Pulmonary embolism		
Baseline Hb g/dl	10.2	8.2	12	10.1±1.9	P=0.25
Nadir at admission	8.8	4.5	9.47	7.6±2.7	
Baseline WBC x 10^9/l	8.4	5.4	11.5	8.4±3.1	P=0.59
WBC at admission x 10^9/l	13.5	10.3	6.28	10.0±3.6	
Baseline platelets x 10^9/l	425	192	474	363±150	P=0.19
Platelets at admission x 10^9/l	357	60	67	161±169	
Baseline Bilirubin µmol/l	36	36	26	32**±5.8**	P=0.16
Bilirubin at admission	61	95	34	63±30.6	
AST baseline U/l	46	16	21	27.7± 16.	P=0.02
AST at admission U/l	157	89	218	157±64	
ALT baseline U/l	37	12	23	24±16	P=0.09
ALT at admission U/l	182	42	121	115±70.2	
ALP baseline U/l	70	61	182	104 ± 67.4	P=0.03
ALP at admission U/l	247	333	494	358 ±125	
LDH baseline U/l	462	298	258	339 ± 08	NA
LDH at admission U/l	476	NA	NA		
CRP at admission mg/l	153	213	258	208 ± 52	NA
Outcome	Resolved with antibiotics.	Recovered with Red cell transfusions & antibiotics.	died		

Key: * Students paired t-test; M: male, PMH-past medical history, Hb: hemoglobin, WBC-white blood cells, AST-aspartate aminotransferase, ALT-alanine transaminase, ALP-alkaline phosphatase, LDH-lactate dehydrogenase. NA-Not available.

right-sided infiltrates. He was also noted to have significant anemia at 4.5 g/dl, thrombocytopenia at 60 x 10^9/l, hyponatremia at 127, and a substantial rise in CRP, bilirubin, and other liver enzymes as outlined in **Table 1**. SARS-COVID-19 testing by PCR was negative. He received blood transfusions antibiotics and recovered gradually and was discharged home six days later.

Case 3. A 28-year-old man with S/B^0 thalassemia post-splenectomy and cholecystectomy presented with significant back pain to the local hospital three days after receiving the COVID-19 vaccine (AstraZeneca). He was started on pain analgesia, noted to have tachycardia and tachypnea, and saturation dropped to 93% on room air. Lung examination did not show any significant findings, and Chest X-ray did not show any abnormalities. He was started on Oxygen supplementation, and a chest CT scan with contrast confirmed right-sided filling defects with mild bilateral pleural effusions. Repeat blood tests showed a significant drop in hemoglobin to 9.47 g/dl from baseline of 12 g/dl and platelets to 67 x 10^9/l from baseline of >400 x 10^9/l. D-Dimers were elevated at >80mg/l (Normal 0.1-0.5), and he had a high CRP at 258 (0-5). He was also noted to have raised liver enzymes, in particular alkaline phosphatase, and other transaminases. He was started on therapeutic low molecular weight heparin and exchange transfusions. Although he was stable on oxygen via facemask, he suddenly developed bradycardia, was resuscitated but became hypotensive. It was then decided to proceed with thrombolysis; however, he deteriorated, became severely hypotensive with bradycardia, and died three days after admission.

Discussion. We describe three young patients with SCD who presented with a significant VOC after a long period of steady state. It was characterized by severe back pain, a significant drop in hemoglobin, platelets, and a statistically significant rise in liver enzymes, in particular, ALP in all the three cases (P-value < 0.05), denoting possibly significant bone infarction (most likely spinal, given the persistent back pain). One patient had a massive pulmonary embolism. Although we do not have the definitive laboratory confirmation, it resembles the recently described vaccine-induced immune thrombotic thrombocytopenia (VIITT) with a TTP-like syndrome. As all three patients are young, it is plausible that the vaccine, through intensive immune medicated antibody reaction or antibodies formation against platelet PF4, led to platelets activation and consumption and initiating thrombosis. As reported in the literature, the antibody reaction could also have precipitated severe pain with a VOC in patients with sickle cell disease.[2-3] Subsequent guidelines suggested avoiding heparin preparation for therapy, using immunoglobulin (to block FC receptor of the binding antibodies), and alternative anticoagulation agents for thrombosis such as rivaroxaban and fondaparinux.[5] Recent data suggest that young patients are at increased risk of the Astra Zeneca COVID-19 vaccine.[6] It is also interesting to note that all three patients had S/B^0 thalassemia, and it is not clear if this has contributed to the development of these complications. In light of these findings, we have asked our patients to exercise caution when taking this type of vaccine. We have 12 patients who have taken two doses and nine who have taken one dose of the BNT162b2 Pfizer-BioNTech vaccine without significant complications. It is also important to note that although mortality in patients with SCD who had COVID-19 was slightly higher than that of the general population, our own experience with COVID-19 related illness in SCD was generally of a mild to moderate in severity.[7]

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