Nigerian Medical Journal
NIGERIA MEDICAL ASSOCIATION
Print ISSN 0300-1652, E-ISSN 2229-774X

Case Report

Hemolytic Uremic Syndrome: A COVID-19 Vaccine Reaction Case Report.

***Thelma Alalbila Aku[1], Eugene Kobla Dordoye[2], Theodore Ofori Apraku[3], Adwoa Ansomaa Gyamera[4], Peter Yamoah,[1]Patrick Adjei[5]**

[1]Pharmacy Practice Department, School of Pharmacy, University of Health and Allied Sciences, Ghana. [2]Psychological Medicine Department, School of Medicine, University of Health and Allied Sciences, Ghana. [3]Ho Teaching Hospital, Volta Region, Ghana. [4]Cape Coast Teaching Hospital, Ghana. [5]University of Ghana Medical School, Ghana.

DOI : https://doi.org/10.60787/nmj-64-6-343

Abstract

The World Health Organization declared the Coronavirus disease of 2019 (COVID-19) a public health emergency of international concern on 30 January 2020, and a pandemic on 11 March 2020. Vaccines have proven to be vital in the effort to control and possibly eventually eradicate this viral infection. There have been reports of thromboembolic events associated with the use of vaccine but from available information, no reported case of atypical Hemolytic Uremic syndrome (HUS) in a black male has been described. We report a case of a 43-year-old black male Sub-Saharan African who presented with chills, fever, and generalized body aches of 3 days duration after receiving the second booster dose of the COVID-19 vaccine. He developed thrombocytopenia, hemolytic anaemia, and acute kidney injury on admission, and an initial diagnosis of malaria was made. He was managed with parenteral artesunate and then oral artemether/lumefantrine. His hemolytic anaemia was thought to be from malaria-associated hemolysis. This diagnosis was however later re-evaluated to hemolytic uremic syndrome and managed with 50mg daily oral prednisolone which resolved, and he resumed work a week later. Although mass vaccination is a key strategy to control the spread of COVID-19, critical observations should be made to confirm the risk of trigger for abnormal complement activation. Further observations should be made especially if it is a chimpanzee adenovirus-vectored vaccine.

Keywords: AstraZeneca; Chimpanzee Platform; Hemolytic Anaemia; Thrombocytopenia; Acute Kidney Injury; Vaccine Reaction; Case Report.

***Correspondence**: Thelma Alalbila Aku, University of Health and Allied Sciences, School of Pharmacy, Pharmacy Practice Department PMB 31, Ho, Volta Region, Ghana.
https://orcid.org/0000-0002-3769-9367, talalbila@uhas.edu.gh, tmalalbila@gmail.com

How to cite: Aku TA, Dordoye EK, Apraku TO, Gyamera AA, Yamoah P, Adjei P. Hemolytic Uremic Syndrome: A COVID-19 Vaccine Reaction Case Report. Niger Med J 2023; 64 (6):846 - 850

Quick Response Code:

Introduction

Hemolytic uremic syndrome (HUS) is a group of simultaneous features comprising a triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. It usually occurs after a prodromal illness of acute gastroenteritis in children.[1] Hemolytic uremic syndrome (HUS) can be classified into typical HUS and atypical HUS (aHUS). The majority of HUS patients are children (mostly 6 months of age), diagnosed with typical HUS as a sequel a of an infection with Shiga-toxin.[2]]In aHUS, a genetic or sporadic insult causes dysfunction in the complement cascade leading to complement deposition on endothelial cells, thickening of arterioles and capillaries, and endothelial swelling and detachment.[3] Consequently, there is the formation of obstructive thrombi in the vessel lumina and shearing of red blood cells, creating schistocytes, which results in the triad of Coombs-negative hemolytic anemia, renal impairment, and thrombocytopenia. [4] Central nervous symptoms include irritability, drowsiness, convulsions, encephalopathy, diplopia, cortical blindness, hemiparesis, hemiplegia, stupor, and/or coma. Renal impairment symptoms include elevated creatinine, a fall in estimated Glomerular Filtration Rate (eGFR) , high blood pressure, and abnormal urinalysis.[5]The evolving knowledge of complement cascade has been determinant in elucidating the pathophysiology of aHUS and in the advent of new and targeted therapies for the disorder. However, for a complement-mediated aHUS to manifest, in addition to a mutation in a complement gene and an "at-risk" haplotype, a second trigger is often necessary. [6]This second trigger is often related to infections, pregnancies, other intercurrent illnesses, or drug induced. We report a rare case of aHUS in a 43-year-old black male from Sub-Saharan Africa which started 4 days after he received a second booster dose of ChAdOx1 nCoV-19, AstraZeneca vaccine. The second dose of the chimpanzee adenovirus-vectored vaccine was taken seven months after the first dose.

Case

A 43-year-old black male Sub-Saharan African university teacher, DP, presented with chills, fever, and generalized body aches of 3 days duration after receiving the second booster dose of ChAdOx1 nCoV-19, a chimpanzee adenovirus-vectored vaccine (Batch number PV46704). The symptoms started some 2 hours after the injection. He developed a cola-like urine on the 3rd day which turned "black" on the 4th day when he presented to the hospital. Physical examination revealed a pale middle-aged man with a tinge of jaundice fever and lethargy. With malaria being a common cause of intravascular hemolysis in this region, a positive rapid diagnostic test for malaria got him started on intravenous artesunate and rapid hydration with crystalloids. The black urine started clearing and became cola-like on the 2nd day of admission after receiving 7 liters of intravenous fluids. Parenteral artesunate 180mg was administered at 0hrs,12hrs,24hrs, and then daily for two days until he could tolerate orals and the urine colour was now amber following a positive rapid diagnostic test for malaria. Oral artemether/lumefantrine 80/480mgadministered at 0hrs, 8hrs, and then every 12hours for two days also for the malaria.

He developed diplopia, a central nervous symptom of aHUS, for far objects on the 3rd day of admission when the initial presenting symptoms were resolving. This was also associated with occipital headaches even though visual acuity was intact in both eyes. The Red blood cell count decreased from 5.96x 10^{12}/µL on day 1 of admission to 3.61 x10^{12}/µL on day 4 of admission indicative of haemolysis. There was a corresponding anaemia, of 10.7 g/dl on day 4 of admission. Hemolytic anaemia is a triad of aHUS. The other triad of HUS, thrombocytopenia, manifested on the 1st and 4th day of admission revealing platelets count of 140 x 10^9/L and 134 x 10^9/L respectively. There is an inversely proportional association between platelet count and percentage schistocyte, where the lower count between 100 to 200, the higher the % schistocyte between 2.5 to 6.5. Lactate dehydrogenase was 500 and 600 on days 6 and 16

respectively. The last but equally life-threatening triad is acute kidney injury, evident in creatinine 124.6µmol/L and 121µmol/L on days 4 and 6 of admission and urea measurement of 7.3mmol/L.
He had severe general body weakness and became suicidal. A diagnosis of ophthalmoplegia and atypical hemolytic uremic syndrome secondary to vaccine reaction was made after a neurologist among other internists examined him. This was treated with oral prednisolone 50 mg daily from the fifth day of admission for 5 days which resolved headaches and diplopia. There were no available resources to afford eculizumab at the time of treatment. The patient was discharged after 16 days of admission based on improved outcomes as assessed by the attending physician and he resumed work a week later.

Discussion

Following the genetic sequencing of the SARS-CoV-2 in January 2020, several vaccine developers channeled efforts towards the rapid development of a vaccine for the prevention of COVID-19.[7]By March 10, 2021, 5 million people had received this vaccine in Europe. Among them, 30 cases of thromboembolic events were reported.[8]Similar to other vaccines, the most common adverse effects were local injection site pain, tenderness, erythema and swelling, nausea and vomiting, fever with chills, muscle ache, headache, and malaise which were predominantly seen on day 1 after vaccination. However, there were other rare Serious Adverse Events (SAE) such as neutropenia, hemolytic anemia, and transverse myelitis that were associated with the use of the AstraZeneca (ChAdOx1 nCoV-19) vaccine, a chimpanzee adenovirus-vectored vaccine.[9, 10]There have been two reports of serious adverse events related to the administration of the ChAdOx1 nCoV-19 vaccine in Austria, Germany, and Norway, that were recently published.[11, 12] These serious reactions to this vaccine consisted of thromboembolic episodes, mainly in young women, associated with thrombocytopenia and the production of Platelet Factor 4 (PF4)-heparin antibodies, similar to what happens in heparin-induced thrombocytopenia a condition called by the authors as vaccine-induced immune thrombotic thrombocytopenia.[13]It is not very clear whether these thromboembolic events and the rare SAE are linked to the chimpanzee adenovirus-vectored Platform used to manufacture the vaccine or not, but these reports are so far only associated with this platform.

In our patient, the evidence of hemolysis was largely clear since hospital admission due to the association of nonimmune hemolytic anaemia due to disseminated intravascular coagulation and thrombocytopenia with acute renal dysfunction which made us suspect aHUS. Infections and drugs are among the triggers of aHUS. Serum ADAMTS13 is an enzyme that cleaves von Willebrand factor, a large protein involved in blood clotting. Its activity is often <10% in thrombotic thrombocytopenic purpura (TTP), and can be used to distinguish between typical and atypical HUS; notably, atypical HUS often exhibits a high level of serum ADAMTS13.[14]Although aHUS typically responds to C5-complement inhibitors, there have been rare instances where aHUS has responded to steroids.[15]Percentage Schistocyte is not routinely done in this part of our world, however, there is an inversely proportional association between platelet count and percentage schistocyte, where the lower count between the range of 100 to 200,the higher the % schistocyte which is between 2.5 to 6.5. [16].

He had falciparum malaria, and this could have triggered this, however, it is unlikely because Sub-Saharan Africa is a malaria endemic region and there would been a myriad of reports of aHUS and the patient has had episodes of malaria in his lifetime. Although the rapid diagnostic test showed positive falciparum malaria throughout the admission, this is most likely due to a false positive result because he had taken parenteral antimalarial and completed a 3-day same oral course. Buffer solution substitution in malaria rapid diagnostic tests causes false-positive tests and could be the explanation for the positive results throughout his admission.[17]The clinical picture depicts a likely vaccine-related aHUS as the only

event close to disease presentation was the administration of the ChAdOx1 nCoV vaccine, we think this could have been the trigger. Even though there is no evidence available linking the hiatus between the first dose and the second dose of the vaccine, it is important to note it so that if other similar trends are captured in the medical community, a link or association could be made.

This case report is an aHUS associated with COVID-19 vaccination in a black male with a chimpanzee adenovirus-vectored vaccine. There is also a case of a 54-year-old Caucasian female, with a past medical history relevant for pulmonary tuberculosis due to her antecedents of pulmonary disease, this patient was vaccinated with ChAdOx1 nCoV-19 (Batch No. ABV3025) at the beginning of March 2021, and was later diagnosed with aHUS.[13]

Conclusions

Considering ongoing global mass vaccination, further observations should be reported to confirm this risk; with vaccination acting as a trigger for abnormal complement activation. This therefore means that there is a need to observe closely persons receiving especially COVID-19 vaccines that are chimpanzee adenovirus-vectored.

References

1. Lynn RM, O'Brien SJ, Taylor CM, Adak GK, Chart H, Cheasty T, Coia JE, Gillespie IA, Locking ME, Reilly WJ, Smith HR, Waters A, Willshaw GA. Childhood hemolytic uremic syndrome, United Kingdom and Ireland. Emerg Infect Dis. 2005;11(4):590-6. doi: 10.3201/eid1104.040833.
2. Ishihara T, Ozawa H. Hemolytic uremic syndrome and encephalopathy from Shiga toxin-producing Escherichia coli. CMAJ. 2019 Jul 22;191(29):E81. doi: 10.1503/cmaj.190155
3. Stühlinger W, Kourilsky O, Kanfer A, Sraer JD. Letter: Haemolytic-uraemic syndrome: evidence for intravascular C3 activation. Lancet. 1974;2(7883):788-9.
4. Ruggenenti P, Noris M, Remuzzi G. Thrombotic microangiopathy, hemolytic uremic syndrome, and thrombotic thrombocytopenic purpura. Kidney Int. 2001;60(3):831-46.
5. Loirat C, Frémeaux-Bacchi V. Atypical hemolytic uremic syndrome. Orphanet J Rare Dis. 2011;6:60. doi: 10.1186/1750-1172-6-60.
6. NorisM, Remuzzi G.*Atypical hemolytic–uremic syndrome.* New England Journal of Medicine, 2009. 361(17): 1676-1687.
7. World Health Organisation (WHO).*Draft landscape of COVID-19 candidate vaccines. 2020.* WHO https://www. who. int/publications/m/item/dr aft-landscape-of-covid-19-candidatevaccines, 2020.
8. WHO, *Interim recommendations for use of the ChAdOx1-S [recombinant] vaccine against COVID-19(AstraZeneca COVID-19 vaccine AZD1222 Vaxzevria™, SII COVISHIELD™.*https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-AZD1222GRADE-ETR-2021.1 2021.
9. Alexander JL, Moran GW, Gaya DR, Raine T, Hart A, Kennedy NA, Lindsay JO, MacDonald J, Segal JP, Sebastian S, Selinger CP, Parkes M, Smith PJ, Dhar A, Subramanian S, Arasaradnam R, Lamb CA, Ahmad T, Lees CW, Dobson L, Wakeman R, Iqbal TH, Arnott I, Powell N; Inflammatory Bowel Disease section of the British Society of Gastroenterology and the the Inflammatory Bowel Disease Clinical Research Group. SARS-CoV-2 vaccination for patients with inflammatory bowel disease: a British Society of Gastroenterology Inflammatory Bowel Disease section and IBD Clinical Research Group position statement. Lancet Gastroenterol Hepatol. 2021 Mar;6(3):218-224. doi: 10.1016/S2468-1253(21)00024-8.

10. AstraZeneca, *UK and EU regulatory agencies confirm COVID-19 Vaccine AstraZeneca is safe and effective.* 2021.
11. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. N Engl J Med. 2021 Jun 3;384(22):2092-2101.
12. Schultz NH, Sørvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Ahlen MT, Wiedmann M, Aamodt AH, Skattør TH, Tjønnfjord GE, Holme PA. Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination. N Engl J Med. 2021 Jun 3;384(22):2124-2130.
13. Ferrer F, Roldão M, Figueiredo C, Lopes K. Atypical Hemolytic Uremic Syndrome after ChAdOx1 nCoV-19 Vaccination in a Patient with Homozygous CFHR3/CFHR1 Gene Deletion. Nephron. 2022;146(2):185-189..
14. Lin IH, Chen YJ, Chang PY, Hsiao PW, Weng TH, Chang YH. Bilateral proliferative retinopathy and ischemic optic neuropathy in a patient with atypical hemolytic-uremic syndrome: A case report. Medicine (Baltimore). 2019 Sep;98(39):e17232. doi: 10.1097/MD.0000000000017232.
15. Mittal N, Hartemayer R, Jandeska S, Giordano L. Steroid Responsive Atypical Hemolytic Uremic Syndrome Triggered by Influenza B Infection. J Pediatr Hematol Oncol. 2019 Jan;41(1):e63-e67.
16. Lesesve JF, Salignac S, Alla F, Defente M, Benbih M, Bordigoni P, Lecompte T. Comparative evaluation of schistocyte counting by an automated method and by microscopic determination. Am J Clin Pathol. 2004 May;121(5):739-45.
17. Gillet P, Mori M, Van den Ende J, Jacobs J. Buffer substitution in malaria rapid diagnostic tests causes false-positive results. Malar J. 2010 Jul 22;9:215. doi: 10.1186/1475-2875-9-215.