Hemolytic Uremic Syndrome: A Covid-19 Vaccine Reaction Case Report

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Abstract

Hemolytic uremic syndrome (HUS) is associated with microthrombi, mainly in the kidneys. It may be classified as typical HUS or atypical HUS (aHUS). Majority of HUS occur in children (usually at 6 months of age), as a sequela of shigella infection. 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. Consequently, there is formation of obstructive thrombi in the vessel lumina and shearing of red blood cells, creating schistiocytes, that results in the triad of Coombs negative hemolytic anemia, renal impairment, and thrombocytopenia. We report a rare case of a 43-year-old black male who reacted to the 2nd booster dose (some 7 months after the 1st) of Astra Zeneca Covid-19 vaccine with aHUS. He had ophthalmoplegia, occipital headaches and suicidal ideation which all resolved on high dose oral prednisolone. The Astra Zeneca vaccine which uses a chimpanzee platform is the only one reported to have similar reactions and this is important to note and manage such potentially life threatening rare adverse event.

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). Majority of HUS patients are children (mostly 6 months of age), diagnosed with typical HUS as a sequela 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 formation of obstructive thrombi in the vessel lumina and shearing of red blood cells, creating schistiocytes, that 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. And renal impairment symptoms include elevated creatinine, 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 of 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 University teacher from Sub Saharan Africa which started 4 days after he received a second booster dose of ChAdOx1 nCoV-19. 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, with no chronic medical condition 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) on 2nd September, 2021. The symptoms started some 2 hours after the injection.

He developed a cola-like urine on the 3rd day which turned “black” the 4th day when he presented to the hospital. 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 litres of intravenous fluids. Parenteral artesunate was continued until he could tolerate orals and the urine color was now amber. Oral artemether/lumefantrine course for malaria was completed.

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 were intact in both eyes. The Red blood cell count decreased from 3.61 X 10^6/µL on day 4 of admission to 3.94 x10^12/L on day 16th of admission indicative of hemolysis .There was a corresponding anaemia ,of 10.7 g/dl and 10.9 g/dl on similar admission days. Hemolytic anaemia is a triad of aHUS. The other triad of HUS ,thrombocytopenia ,manifested on the 1st and 4th day of admission revealing a platelets count of 140 x 10^9/L and 134 x 10^9/L 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 16 of admission and urea of 7.3mmol/L. These values are as captured in Table 1.

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 for 5 days which resolved headaches and diplopia. The patient was discharged after 16 days of admission and he resumed work a week later.

Laboratory investigations done are presented below in Table 1.
| TYPE OF TEST ADMISSION DAYS | 1      | 4      | 6      |
|-----------------------------|--------|--------|--------|
| **RDT for Malaria**         | +      | +      | +      |
| **Urine Chemistry**         |        |        |        |
| Urobilinogen                | Not detected | ++ | normal |
| Protein in urine            | + +    | -      | not detected |
| Blood                       | + + +  | -      | not detected |
| **Urine Macroscopy**        |        |        |        |
| Appearance                  | Cloudy | Clear  | Clear  |
| Colour                      | Dark red | Light amber | Straw  |
| **Urine Microscopy**        |        |        |        |
| RBC Casts                   | Not seen | Not seen | not observed |
| **Full Blood Count**        |        |        |        |
| Hb                          | 14.2   | 10.7   | 10.9   |
| (12-18g/dl)                 |        |        |        |
| RBC (4.5-6.5 x 10^{12/L})   | 5.96 x 10^{12/L} | 3.61 x 10^{6/uL} | 3.94 x 10^{12/L} |
| Platelets                   | 140 x 10^{9/L} | 134 x 10^{9/L} | 298 x 10^{9/L} |
| (150-450 x 10^{9/L})        |        |        |        |
| WBC(with Diff)              |        |        |        |
| Gran %                      | 73.5 x 10^{9/L} | not done | not done |
| ESR                         | not done | not done | 66mm/hr |
| (1-30mm/hr)                 |        |        |        |
| Hematocrit                  | 0.518  | not done | 0.34 |
| (0.4-0.54)                  |        |        |        |
| WBC(only)                   | 3.1 x 10^{9/L} | 5.6 x 10^{9/L} | 10.8 x 10^{9/L} |
| (4-12 x 10^{9/L})           |        |        |        |
| **Biochemistry**            |        |        |        |
| TYPE OF TEST ADMISSION DAYS |
|-----------------------------|
| Renal                       |
| S-Urea (2.1-7.1 mmol/L)     | Not done | 6.17 mmol/L | 7.3 mmol/L |
| S-Creatinine (62-106 µmol/L)| not done | 124.6 µmol/L | 121 µmol/L |
| LFTS                        |
| S-Bilirubin (Total) (3.42-20.5) | Not done | 19.85 µmol/L | 22 µmol/L |
| S-Bilirubin (Conjugated) (1-5 µmol/L) | Not done | 15.97 µmol/L | 7 µmol/L |
| S-AST(GOT) (1-40 IU)        | not done | 70 IU/L | 30 IU/L |
| S-ALT(GPT) (1-41 IU/L)      | not done | 55.2 IU/L | 29 IU/L |
| S-GGT (1-55IU/L)            | not done | 61.66 IU/L | 56 IU/L |

**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 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 and thrombocytopenia with acute renal dysfunction which made us suspect aHUS. Infections and drugs are among the triggers of aHUS. He had falciparum malaria and this could have triggered this, however it is unlikely because Sub-Saharan Africa is a malaria endemic region and they 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 [14]. The clinical picture depicts a likely vaccine related aHUS as the only event close to disease presentation was the administration of 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 in the event that other similar trends are captured in the medical community, a link or association could be made.

With regards to available information to us, this is the first report of aHUS associated with COVID-19 vaccination in a black male, namely, with a chimpanzee adenovirus-vectored vaccine. There is a case of a 54-year-old Caucasian female, with a past medical history relevant for pulmonary tuberculosis and due to her antecedents of pulmonary disease, this patient was vaccinated with ChAdOx1 nCoV-19 (Batch No. ABV3025) at the beginning of March 2021 [13]. Soon after vaccine administration, she complained of “flu-like” symptoms that resolved with paracetamol. Five days later, she was admitted to the emergency department with general malaise, abdominal pain, myalgia, vomits, and low urine output; there were no complaints of respiratory symptoms or diarrhea.

Conclusion

Considering ongoing global mass vaccination, further observations should be reported to confirm this risk, with vaccination acting as a trigger for abnormal complement activation. Despite the importance of capturing these singular cases to the medical community, we should not be oblivious of inexistence of an effective treatment of SARS-CoV-2, the only known therapy to avert the pandemic is mass worldwide vaccination and hopefully the world can return to normal.

Declarations

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Statement of Ethics
This is a case report. Ethical approval not is required, however informed consent was obtained from the patient reported in this case and he consented to the submission of the case report to the journal. A copy of the written consent form is available for review by the Editor-in-Chief

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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**Author Contributions**

Mrs. Thelma M Alalbila Aku contributed to the conceptualization, writing out, data curation, analysis and reviewing of the manuscript. Dr. Eugene K Dordoye contributed to the conceptualization, writing and reviewing of the manuscript and data, Dr. Peter Yamoah contributed to data analysis and review of the manuscript. Drs. Adwoa Gyamera and Theodore Apraku contributed to the management of the patient, data analysis and review of the manuscript.

**Data Availability Statement**

Data and material and code availability is not applicable.

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