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Atypical hemolytic uremic syndrome (aHUS) is a subtype of thrombotic microangiopathy (TMA) characterized by a dysregulation of the alternative complement pathway. Here, we report a previously healthy 38-year-old woman in whom aHUS developed after a COVID-19 vaccine booster. One day after receipt of a booster dose of mRNA-1273 vaccine, she felt ill. Because of persistent headache, nausea, and general malaise, she went to her general practitioner, who referred her to the hospital after detecting hypertension and acute kidney injury. A diagnosis of TMA was made. Her treatment consisted of blood pressure control, hemodialysis, plasma exchange, and respiratory support. Kidney biopsy confirmed the diagnosis of acute TMA. The patient was referred for treatment with eculizumab, and kidney function improved after initiation of this therapy. Genetic analysis revealed a pathogenic C3 variant. SARS-CoV-2 infection as a trigger for complement activation and development of aHUS has been described previously. In addition, there is one reported case of aHUS occurring after receipt of the adenovirus-based COVID-19 vaccine ChAdOx1 nCoV-19, but, to our knowledge, this is the first case of aHUS occurring after a booster dose of an mRNA COVID-19 vaccine in a patient with an underlying pathogenic variant in complement C3. Given the time frame, we hypothesize that the vaccine probably was the trigger for development of aHUS in this patient.

Case Report

A 38-year-old woman received a booster dose (half dose) of the mRNA-1273 COVID-19 vaccine (Moderna) in January 2022. One day after the injection, she felt ill with headache and general malaise. On the following days, the headache persisted and she experienced nausea and loose stools for 2 days. On the sixth day after vaccination, she went to a general practitioner because of persistent headache and general malaise. She had no fever or respiratory symptoms.

Her primary vaccine series consisted of 2 doses of the mRNA COVID-19 vaccine BNT162b2 (Pfizer BioNTech) and was completed 5 months before the booster vaccination. After the first and second doses of the primary series, she had only minimal symptoms, with swelling and pain at the injection site. A routine blood test was done the day before the booster vaccination, at which time she had a creatinine concentration of 0.86 mg/dL (reference range, 0.5-0.9 mg/dL) and platelet count of 277 × 10^9/μL (reference range, 167-399 × 10^9/μL). She had been taking the same oral contraceptive agent (ethinylestradiol/dienogest; marketed as LOUISÉ [Mithra Pharmaceuticals]) for approximately 3 years. The examination by the general practitioner found severe new-onset arterial hypertension, and treatment with nebivolol was started. Laboratory testing showed acute kidney injury (AKI; creatinine level, 3.9 mg/dL), thrombocytopenia (platelet count, 57 × 10^9/μL), and anemia (hemoglobin level, 9.1 g/L). She was referred to the hospital.

Laboratory findings on admission 2 days after the testing performed by the general practitioner showed worsening AKI (creatinine level, 6.4 mg/dL), thrombocytopenia, and Coombs-negative hemolytic anemia with a low C-reactive protein value. Microscopic examination of the peripheral blood smear showed an excess of schistocytes (approximately 30 schistocytes per 1,000 red blood cells), confirming the diagnosis of TMA; samples were collected to assay ADAMTS-13 protease (von Willebrand factor protease) activity and complement factors, and plasma exchange and dialysis treatment were started after
Table 1. Complement Diagnostics

| Test               | Value | Reference Range |
|--------------------|-------|-----------------|
| CH50, U/mL         | 83    | 41-94           |
| Complement C3, mg/dL | 82    | 72-156          |
| Complement C3d, mg/dL | 1.3   | 1.2             |
| Complement C4, mg/dL | 25    | 10-46           |
| Factor B, mg/dL    | 9     | 11-22           |
| Factor Bb, mg/dL   | 0.5   | <0.15           |
| sC5b-9 complex, mg/dL | 1051  | <314            |
| Factor H antibodies, AU | <53  | <150            |
| Factor H, mg/dL    | 63    | 37-73           |
| Factor H activity  | 91%   | 79%-108%        |
| Factor I, mg/dL    | 17.3  | 7-10.7          |

Abbreviations: AU, arbitrary units; CH50, 50% hemolytic complement activity.

collection of the samples. Further treatment consisted of hypertension management with a need for intravenous antihypertensive medication. After administration of plasma during the plasma exchange, the patient experienced dyspnea, and a chest radiograph showed an infiltrate with a differential diagnosis of pulmonary edema and infection. Intravenous antibiotic agents were added. The required vaccines in preparation for treatment with eculizumab were administered. Following plasma exchange and antihypertensive treatment, the hematological parameters rapidly responded, but the patient continued to require dialysis. In total, she received 7 sessions of plasma-exchange therapy.

Further evaluation to detect a possible underlying disease was performed. There were negative results for viral screening, pneumococcal antigen detection, and immunological screening (for antinuclear factor, antineutrophil cytoplasmic antibodies, and anti–glomerular basement membrane antibodies). Because the patient had a history of frequent travel, testing for malaria was also performed, yielding negative results. Shiga toxin–producing Escherichia coli (STEC) hemolytic uremic syndrome was ruled out by polymerase chain reaction and antigen testing. No serological testing was performed, but the patient did not have diarrhea. Polymerase chain reaction testing for SARS-CoV-2 remained negative. Table 1 provides results of complement diagnostic tests. CH50 and C3 were within reference ranges, but there were increases in sC5b-9 complex, C3d, and factor Bb. There were no signs of chronic or malignant hypertension on eye examination and echocardiography.

A kidney biopsy performed on day 1 confirmed acute TMA involving glomeruli and arterioles, with ischemic wrinkling of the capillary tuft, mesangiolysis, endothelial cell swelling, and fibrin thrombi (Fig 1). Chronicity grading according to the method proposed by Sethi et al11 rendered a score of 0 of 10. After ADAMTS-13 activity was found to be within the reference range (87%), eculizumab was initiated, after which diuresis steadily improved and dialysis could be stopped 2 weeks later. Kidney function further recovered. At the time of writing, after 3 months of eculizumab, serum creatinine level has decreased to 1.04 mg/dL (corresponding to an estimated glomerular filtration rate of 68 mL/min/1.73 m²). Genetic analysis revealed a pathogenic (class V) variant in the C3 gene, a substitution of thymine for cytosine at nucleotide 481 of the coding sequence (c.481C>T). Risk haplotype evaluation showed that the patient was homozygous for the membrane cofactor protein risk haplotype MCP\textsubscript{GGAAC}. No other pathogenic variants were found.

**Discussion**

Here we describe what is, to our knowledge, the first case of aHUS developing after a booster dose of the mRNA-1273 COVID-19 vaccine in a patient with an underlying variant in the complement C3 gene who was also homozygous for the MCP risk haplotype.

aHUS is caused by a genetic or acquired dysregulation of the alternative pathway. In approximately 60%-70% of patients, an underlying variant can be found.1,2 The penetrance and disease severity for the pathogenic variant in complement C3 that was found in our patient is known to be modulated by inheritance of documented risk haplotypes.5 In addition to having this class V variant in C3, our patient was homozygous for the MCP\textsubscript{GGAAC} risk haplotype, further increasing the risk of disease.7

However, given the variable disease penetration, an additional trigger can usually be found at the time of acute clinical disease. The most common triggers described in the literature as being associated with aHUS are infections, immunization, transplant, pregnancy, drugs, and metabolic conditions. aHUS following vaccination, mainly for hepatitis B virus, has been reported in the literature, albeit rarely.8 COVID-19 has recently been identified as a trigger for acute illness or relapse of aHUS.14 Since the start of the pandemic, several cases of TMA after COVID-19 have been published, and in vivo and in vitro data provide evidence of activation of the complement system following SARS-CoV-2 infection. In particular, increased plasma levels of complement markers were found in patients with COVID-19, correlating with disease severity.9-13 In vitro data further corroborate these findings by demonstrating that SARS-COV-2 spike proteins activate complement.14 Thus, one might speculate that, because mRNA-based COVID-19 vaccines use the spike protein as an immunogenic target, vaccination might act as a trigger for complement activation. Indeed, Gerber et al reported a group of patients with paroxysmal nocturnal hemoglobinuria who had severe hemolysis after mRNA-based COVID-19 vaccination.15 Based on the absence of a direct effect of the SARS-CoV-2 spike protein on hemolysis by cell lysis testing, these authors postulated that strong complement amplification is responsible for the clinically observed hemolysis.15

It is noteworthy that our patient did not experience major side effects or health issues after the first 2 doses of BNT162b2. However, a recent report suggests that recipients of mRNA-1273 experienced more severe side effects but had a greater antibody response to COVID-19 vaccination.16 This is further corroborated by safety monitoring in the United
States that revealed that, in these surveillance data, among those who received BNT162b2 or Ad26.COV2.S (Janssen [Johnson & Johnson]) vaccine for the primary series, the odds of reporting a systemic reaction were greater among recipients of a heterologous mRNA-1273 vaccine booster than among recipients of a homologous booster. As part of a study of complement dysregulation in COVID-19, Yu et al analyzed complement activation in 5 healthy volunteers following BNT162b2 vaccination, and found that the 2 volunteers experiencing systemic side effects had an increase in serum Bb, a marker of complement activation. Therefore, it could be theorized that patients with known risk factors for aHUS should avoid heterologous vaccination, particularly with mRNA-1273.

TMA following COVID-19 vaccination is rarely described. Recently, a case of TMA following the first dose of ChAdOx1 nCoV-19 (Oxford-AstraZeneca), an adenovirus-based COVID-19 vaccine, in a patient with an underlying genetic variant was
reported, and a fatal case of rhabdomyolysis with TMA and positive for the lupus anticoagulant was reported after mRNA-1273 administration. These case reports underline the importance of reporting serious adverse events to provide more insight into a possible association or a higher risk in patients with an underlying complement abnormality.

In conclusion, we present a case of aHUS occurring 1 week after a booster dose of the mRNA-1273 COVID-19 vaccine. Although we cannot prove a causal relationship between vaccination and the subsequent occurrence of aHUS, we hypothesize that the vaccine was the trigger for disease development in this patient with an underlying complement variant. The hypothesis is further supported by the observation that the patient’s platelet count was within the reference range 1 day before vaccination. However, safety vigilance will continue and will provide further data on the occurrence of de novo or relapse of aHUS after mRNA COVID-19 vaccination.

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