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Kathleen J. Claes, MD, PhD, Inge Geerts, PharmD, Wim Lemahieu, MD, PhD, Alexander Wilmer, MD, PhD, Dirk RJ. Kuypers, MD, PhD, Priyanka Koshy, MD, Sara Ombelet, MD

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Atypical Hemolytic Uremic Syndrome Occurring After Receipt of mRNA-1273 COVID-19 Vaccine Booster: A Case Report

Kathleen J Claes MD, PhD[1,2]; Inge Geerts PharmD[3]; Wim Lemahieu MD, PhD[4]; Alexander Wilmer MD, PhD[5,6]; Dirk RJ Kuypers MD, PhD[1,2]; Priyanka Koshy MD[7]; Sara Ombelet MD[5]

[1] KU Leuven, Department of Microbiology, Immunology and Transplantation, Nephrology and Renal Transplantation Research Group, Leuven, Belgium

[2] UZ Leuven, Department of Nephrology and Renal Transplantation, Leuven, Belgium

[3] Imelda Hospital, Department of Laboratory Medicine, Bonheiden, Belgium

[4] Imelda Hospital, Department of Nephrology, Bonheiden, Belgium

[5] KU Leuven, Department of Microbiology, Immunology and Transplantation, Laboratory for Clinical Infectious and Inflammatory Disorders, Leuven, Belgium

[6] UZ Leuven, Department of General Internal Medicine, Medical Intensive Care Unit, Leuven, Belgium

[7] UZ Leuven, Department of Pathology, Leuven, Belgium

Correspondence to: K. Claes, MD, PhD
Department of Nephrology and Renal Transplantation
UZ Leuven
Herestraat 49
B-3000 Leuven
BELGIUM
E-Mail: kathleen.claes@uzleuven.be

Abstract:

Atypical hemolytic uremic syndrome (aHUS) is a subtype of thrombotic microangiopathy (TMA) characterized by a dysregulation of the alternative complement pathway. Here, we report on a 38-year old previously healthy woman who developed aHUS after injection of the booster Covid-19 vaccine. One day after this vaccine (mRNA-1273, Moderna,Spikevax®) she felt ill. Because of persistent headache, nausea and general malaise she went to the general practitioner who referred her to the hospital because of 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. Patient was referred for treatment with eculizumab. Renal function improved after initiation of this treatment. Genetic analysis revealed a pathogenic C3 variant. Covid-19 infection as a trigger for complement activation and development of aHUS has been described previously. While we describe the first case of aHUS occurring after a booster mRNA vaccine in a patient with an underlying pathogenic variant in complement C3, there is one reported case of aHUS occurring after CHADOx vaccine. Given the time frame, we hypothesize that the vaccine probably was the trigger for development of aHUS in this patient.

Keywords: aHUS; Covid-19; mRNA vaccine; mRNA-1273; complement; TMA; acute kidney injury; eculizumab; Spikevax; case report

Introduction:

Thrombotic microangiopathy (TMA) is a group of diseases defined by the triad: Coombs-negative hemolytic anemia, thrombocytopenia and organ damage[1]. Atypical hemolytic uremic syndrome (aHUS) is an ultra-rare disease classified in the group of TMAs and characterized by acquired or genetic dysregulation of the alternative complement pathway. This leads to endothelial dysfunction and thrombosis of the small vessels resulting in the typical clinical signs and symptoms. aHUS is a disease with a variable penetrance and the occurrence of the disease is, in addition to underlying pathogenic variants, dependent on the presence of high risk genetic polymorphism and a triggering event. Several triggers have been described previously most frequently infection, drugs, and pregnancy[2]. Covid-19 has recently been identified as one of the triggering viral agents that can activate complement and both patients with a first episode of aHUS as well as cases of relapse have been described[3,4]. aHUS occurring after vaccination is rare. Here we present a patient who developed aHUS after receiving the booster vaccination with mRNA-1273.

Case Report:

A 38-year old woman received the booster Covid-19 vaccine (mRNA-1273,Moderna, half dose) in January 2022. One day after the vaccine she felt ill with headache and general malaise. The following days the headache persisted and she experienced nausea and loose stools for 2 days. She went to the general practitioner (GP) because of persistent headache and general malaise. She had no fever or respiratory symptoms. Her initial vaccination scheme (1st and 2nd shot) consisted of BNT162b2 Pfizer BionTech and was completed 5 months before the booster vaccination. After the first and the second shot she only had minimal symptoms with swelling and pain at the injection site. A routine blood test was done the day before the booster vaccination which demonstrated a normal kidney function (creatinine 0,86 mg/dL normal values: 0,5-0,9 mg/dL) and normal value of blood platelets ($277*10^3$/µL normal value 167-$399*10^3$/µL). She took the same oral contraceptive (ethinylestradiol/diënogest - Louise®) since approximately 3 years. Clinical examination by the GP, 6 days after the injection, showed severe new onset arterial hypertension. Treatment with nebivolol was started. Blood sampling demonstrated an acute kidney injury (creatinine 3,9 mg/dL), thrombocytopenia ($57*10^3$/µL) and anaemia (Hb level 9,1 g/L). She was referred to the hospital. Laboratory findings on admission, two days after blood sampling by the GP, demonstrated progression of acute kidney injury (serum creatinine of 6.4 mg/dl), thrombocytopenia and Coombs negative hemolytic anemia with a low CRP value. Microscopic examination of the peripheral blood smear showed an excess of schistocytes (+/- 30 schistocytes/1000 red blood cells) confirming the diagnosis of TMA and after sampling for ADAMTS-13 and complement factors plasma exchange and dialysis treatment was started. Further treatment consisted of hypertension management with need for intravenous antihypertensive medication. After administration of plasma during the plasma exchange she developed dyspnea and chest X-ray demonstrated an infiltrate with a differential diagnosis of pulmonary oedema and infection. Intravenous antibiotics were added. The required vaccines in preparation for treatment with eculizumab were administered. After initiation of plasma exchange and antihypertensive treatment the hematological parameters rapidly responded but patient remained dialysis dependent. In total, she received 7 sessions of plasma exchange therapy. Further evaluation in order to detect a possible underlying disease was negative. There was a negative viral screening,

pneumococcal antigen detection and a negative immunological screening (ANF, ANCA, anti-GBM). STEC-HUS was ruled out by PCR and antigen testing. We did not perform serological testing but patient did not have diarrhea. Covid-19 PCR testing remained negative. Table 1 demonstrates the complement diagnostic tests. CH50 and C3 were normal but there was an increase in sCFB5-9 complex, C3d and Factor Bb. Because of frequent travelling, malaria was excluded as well. There were no signs of chronic or malignant hypertension on eye examination and echocardiography. A renal biopsy performed at day 1 confirmed acute thrombotic microangiopathy involving glomeruli and arterioles with ischemic wrinkling of the capillary tuft, mesangiolysis, endothelial cell swelling and fibrin thrombi. The chronicity grading according to Sethi[5] rendered a score of 0/10 (figure 1) . After ADAMTS13 came back normal (87%) patient was referred for initiation of eculizumab. After eculizumab initiation diuresis steadily improved and dialysis could be stopped two weeks later. Renal function further recovered. Currently, after 3 months of eculizumab, serum creatinine has decreased to 1.04 mg/dL (eGFR of 68 ml/min/1.73m²). Genetic analysis demonstrated a pathogenic (class V) variant in C3 gene: *c.481C>T*. Risk haplotype evaluation demonstrated that the patient was a homozygous carrier of the MCP_{GGAAC} risk haplotype. No other pathogenic variants were found.

Discussion:

Here we describe the first case of aHUS developing after a booster mRNA-1273 (Moderna) vaccine in a patient with an underlying variant in complement C3 gene and homozygous carrier of the MCP risk haplotype.

Atypical HUS 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 found in our patient is known to be modulated by inheritance of documented "risk" haplotypes[6]. Our patient carried, next to the class V variant in C3, homozygously the MCP_{GGAAC} risk haplotype further increasing the risk of disease [7].

However, given the variable disease penetrance, an additional trigger can usually be found at the time of acute clinical disease. The most common triggers described in literature associated with aHUS are infections, immunization, transplantation, pregnancy, drugs, and metabolic conditions. aHUS following vaccination, mainly hepatitis B, has been reported in literature, although rare[8].

Covid-19 infection has recently been identified as a trigger for acute illness or relapse of aHUS[3,4]. Since the start of the pandemic several cases have been published of TMA after COVID-19 infection. Both *in vivo* and *in vitro* data support the activation of the complement system following COVID-19 infection. Increased plasma levels of complement markers, were found in COVID-19 patients, 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 given the fact that mRNA COVID-19 vaccines use the SARS-COV-2 protein as an immunogenic target, vaccination might act as a trigger for

complement activation. Indeed, Gerber et al published a group of PNH patients with severe hemolysis after mRNA vaccination. Based on the absence of a direct effect of the SARS-CoV-2 spike protein on hemolysis by cell lysis testing, the authors postulated that strong complement amplification is responsible for the clinically observed hemolysis[15].

Peculiar in our case is the fact that our patient did not experience major side effects or health issues after the first two injections with BNT162b2 Pfizer BionTech. However, a recent report suggests that people injected with the Moderna vaccine experienced more severe side effects but had a greater antibody response[16]. This is further corroborated by safety monitoring in the United States which revealed that in registrants who received a Pfizer-BioNTech or Janssen primary series, the odds of reporting a systemic reaction were higher among those who received a heterologous Moderna vaccine booster than among those who received a homologous COVID-19 vaccine booster[17]. In a small study (n=5) complement activation was examined in healthy volunteers after mRNA vaccine. In the two volunteers experiencing systemic side effects an increase in serum Bb, a marker of complement activation was found[12]. Therefore, it could be theorized that patients with known risk factors for aHUS should avoid heterologous vaccination, particularly the Moderna vaccine.

TMA following COVID-19 vaccination is rarely described. Recently a case of TMA following first dose of CHadOx, an adenovirus based vaccine, in a patient with an underlying genetic variant was reported and a fatal case of rhabdomyolysis with TMA and positive lupus anticoagulant was reported after Spikevax®[18,19]. These case reports underline the importance of reporting serious adverse events, hence providing 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 one week after a booster injection with Spikevax®. Although we cannot fully prove causality between vaccination and the subsequent occurrence of aHUS, we hypothesize that the vaccine was the trigger for developing the disease in a patient with an underlying complement variant. The hypothesis is further supported by the fact that the patients platelet count was normal one 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 vaccination.

Article Information

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Patient Protections: The authors declare that they have obtained consent from the patient reported in this article for publication of the information about her that appears within this Case Report.

The ethics committee of the UZ Leuven has no objections against publication of this Case Report

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Table 1: Complement diagnostics

Test	Result (normal values)
Complement CH50	83 (41-94) U/ml
Complement C3	82 (72-156) mg/dl
Complement C3d	1.3 (<1.2) mg/dl
Complement C4	25 (10-46) mg/dl
Factor B	9 (11-22) mg/dl
Factor Bb	0.5(<0.15) mg/dl
sC5B-9 complex	1051 (<314) mg/dl
Factor H antibodies	<53 (<150) AU
Factor H	63(37-73) mg/dl
Factor H	91(79-108)%
Factor I	17.3(7-10.7) mg/dl

Figure 1: Microscopic findings of TMA on kidney biopsy

A: Silver stain (200X) – Fibrin thrombi present in glomeruli and arterioles (white arrows); 'tram track appearance' of glomerular capillary wall (yellow arrows). Presence of severe acute tubular injury

B: EM (1100X): Ultrastructural examination shows severe foot process effacement (red arrow), ischemic wrinkling of glomerular capillary wall (red arrow head), endothelial cell swelling with loss of endothelial fenestrations (yellow arrow)