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Case report

First Case of Atypic Hemolytic Uremic Syndrome after Pfizer-Biontech Vaccine

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Abstract

The SARS-COV-2 virus, which has become a part of our lives since December 2019, has caused severe viral pneumonia as well as severe disease in many cases due to organ damage secondary to endothelial damage. Due to the pandemic of the disease, vaccine studies have gained momentum and many different vaccines have been started to be applied. Although the common side effects of vaccines are mild, cases of thrombotic thrombocytopenia, thrombosis with thrombocytopenia syndrome, vaccine-induced prothrombotic immune thrombocytopenia syndrome, endothelial damage, which is a common feature of both vaccine and virus, and secondary organ damage to the resulting thrombotic process have begun to appear. Here, we present the first case of complement mediated hemolytic uremic syndrome (HUS) in a young woman without any known comorbid disease who presented to the emergency department with abdominal pain and hematochezia two days after the first dose of Pfizer-BioNTech BNT16B22 vaccination. Since the patient did not respond to intravenous immunoglobulin and steroid treatments, her disease was controlled with Eculizumab treatment.

Keywords: COVID-19, hematochezia, hemolytic uremic syndrome

Introduction

Coronavirus 2019 (Covid-19) is a global epidemic that causes high mortality and morbidity, affecting the whole world, especially China. In order to prevent this epidemic, vaccine studies were emphasized, and the mRNA vaccine, Pfizer-BioNTech BNT16B2b2 (Biontech), was included in the vaccination program in more than one country.

Microthrombus formations seen after Covid-19 infection were thought to be secondary to the interaction between inflammation and coagulation cascade. This is clinically seen as thrombosis formation in various organs [1]. There have been case reports of post-vaccine thrombocytopenia and organ damage secondary to thrombosis similar to the complement-mediated platelet activation caused by Covid-19 [2]. Venous and arterial thrombosis that is observed after Covid-19 vaccine is explained by different mechanisms. Arterial thrombosis develops as a result of platelet activation and venous thrombosis occurs as a result of excessive activation of the procoagulant system or insufficient anticoagulation [3].

Thrombocytopenia and thrombosis caused by Covid-19 vaccines are explained by different mechanisms. It is thought that vaccines acting through adenovirus vector cause vaccine-associated immune thrombocytopenia by acting on CD46 antibodies and platelet factor-4 antibodies. On the other hand, although it is thought to be more effective and safer in mRNA-based vaccines, it causes temporary expression of the SARS-CoV-2 spike protein and activates the alternative complement pathway on the cell surface and causes competitive inhibition with complement factor H binding to heparan sulfate. Thus, the SARS-CoV-2 spike protein in cells can convert the inactivator surface to the activetor surface and cause complement-mediated endothelial damage. The response to these two vaccines is generally mild, but increased complement amplification may theoretically cause an increase in the incidence of diseases such as paroxysmal nocturnal hemoglobinuria (PNH), thrombotic microangiopathies (TMAs) or present patients in remission with attacks [2-7].

Complement Factor H deficiency is seen as homozygous or heterozygous and causes complement-mediated HUS or membranoproliferative glomerulonephritis secondary to C3 convertase dysregulation. Here, we present a 24-year-old female patient who applied to the emergency service of our institution with severe segmental colitis findings after Biontech vaccination. She was diagnosed with complement-mediated HUS and was successfully treated.

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Case report

A 24-year-old female patient with no history of chronic disease was admitted to the emergency department with abdominal pain and hematochezia that started 48 hours after the first dose of Biontech vaccine. The patient, who had no history of additional disease or drug use, had a healthy normal birth history one year ago. The patient had no history of abortion or cesarean section, had no history of oral contraceptive use or gastrointestinal symptoms, and adverse reactions to childhood vaccines. There was no history of bleeding disorder, autoimmune disease, or inflammatory bowel disease in her family history.

The patient's body temperature was 37.5°C, blood pressure was 100/60 mm/Hg, pulse rate was 72 per minute and respiration rate was 12 breaths per minute. In the physical examination of the patient, no findings were observed except diffuse, mild tenderness in all quadrants of the abdomen on palpation and fresh blood smear on the rectal touche. Normal stomach contents came from the nasogastric tube. Blood tests showed that white blood cell count was 10.600/L (reference, <10.800), hemoglobin level was 12.7 gr/dL (reference, 14.0-18.0 gr/dL), platelet count was 203.000/L (reference, 180.000-400.000/L). Erythrocyte sedimentation rate was 12 mm/h (reference, <20 mm/h), high sensitivity C-reactive protein was 36.6 mg/L (reference, <5 mg/L). SARS-COV-2 PCR test was negative, other blood tests were normal, hepatitis and torch panel were negative.

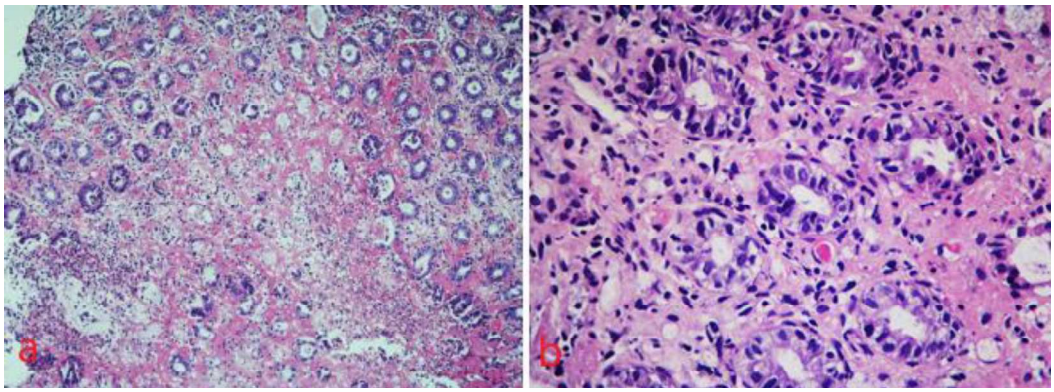

Fig. 1a, b. (a) Acute inflammatory exudate, mucosal necrosis and lamina propria hyalinization. (b) Fibrin thrombi in capillaries and reactive, degenerative atypia in crypt epithelium.

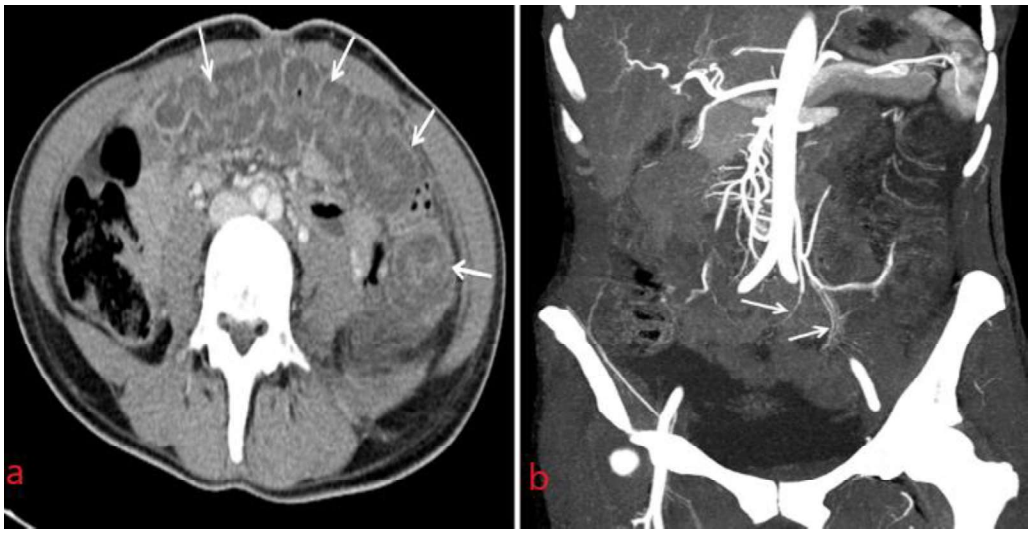

Fig. 2a, b. (a) Axial plane computed tomography image shows diffuse wall thickening of transverse colon and descending colon with low density which is consistent with ischemic colitis. (b) Coronal reformatted MIP image shows subtle enhancement of thinned and irregular distal branches of inferior mesenteric artery.

Severe segmental colitis findings were observed from the proximal to the transverse colon to the distal of the sigmoid colon has been observed during the colonoscopy of the patient. In the histopathology of biopsy samples taken from this area; acute inflammatory exudative changes, mucosal necrosis and hyalinization in the lamina propria, as well as fibrin thrombi in the capillaries were observed (Figure 1a, b). Inclusion bodies for infectious causes were found to be negative. The patient was presented with acute onset abdominal pain and

hematochezia had segmental colitis findings on colonoscopy she had been performed arterial and venous phase contrast-enhanced abdominal CT imaging for possible ischemic colitis. In addition to diffuse wall thickness increase from the proximal transverse colon to the distal sigmoid colon, irregularities that may be compatible with microthrombus were observed in the thinned and distal branches of the inferior mesenteric artery (Figure 2a, b). No pathology was observed in the stool culture and direct examinations of the patient for an infectious cause, including clostridium difficile. Tissue transglutaminase IGA and IGG, Anti-gliadin IGA and IGG, CMV-DNA, ANA, anti-dsDNA, anti-phospholipid antibody, MPO-ANCA, C-ANCA were negative. Echocardiography was normal. On the 3rd day of the patient's hospitalization, hemoglobin was 9.6 g/dL, platelet was 21 x 10^3/UL, total bilirubin was 3.55 mg/dL (reference, 0.3-1.2 mg/dL), direct bilirubin was 0.47 mg/dL (reference, <0.2 mg/dL).

In the peripheral smear of the patient who developed hyperbilirubinemia, anemia, and thrombocytopenia under indirect dominance, large platelets and 3-4% schistocytes were detected. ADAMTS-13 for non-immune hemolytic anemia in terms of TMAs and PNH in a patient with haptoglobulin 0.08 g/L (reference, 0.3-2 g/L), LDH level of 1119 U/L (reference, 0-247 U/L) and Coombs negative and the PNH panel was sent. ADAMTS13 level was 0.88 IU/mL (reference, 0.4-0.13). PNH was excluded in the patient without CD59 AND FLAER/ CD24 deficiency. No Factor V Leiden mutation was observed in the patient whose protein C, S and anti-thrombin III levels were normal.

Acute renal failure and massive proteinuria developed on the second day of 1 mg/kg/day steroid and 1 g/kg/day IVIG (Intravenous immunoglobulin) treatment for immune -thrombocytopenia (BUN 43.5 mg/dL, creatinine 2.07 mg/dL, protein in spot urine. 615.41 mg/dL, creatinine 48 mg/dL, 24-hour urine protein 12900.62 mg/day, creatinine 532 mg/day, kappa light chain 54.6 mg/L, lambda light chain 45.3 mg/L). Renal biopsy could not be performed in the patient because of severe thrombocytopenia. Hemodialysis treatment was started due to the progression in creatinine values (4.0 mg/dL) and metabolic acidosis on the eighth day of the follow-up of the patient, who did not have pathology in the Doppler USG of the renal artery and vein. Plasmapheresis treatment was started after hemodialysis due to continued decrease in hemoglobin values (5.3 g/dL), progression in LDH values (1293 U/L) and thrombocytopenia (15x10^3/UL) despite steroid and IVIG treatments. BUN (30 mg/dL), creatinine (1.9 mg/dL) and bilirubin values improved after plasmapheresis and hemodialysis treatments.

Eculizumab treatment was initiated as complement levels were found to be low. Before eculizumab treatment, prophylactic meningococcal vaccination was performed. Nine hundred mg was administered for the first 4 weeks, followed by 1200 mg at the 5th week. The patient achieved significant remission after eculizumab treatment. She was followed up via nephrology and hematology departments, and response to treatment was monitored. At the end of two months, significant improvement was observed in hemoglobin (13.9 g/dl), platelet (246 x10^3/UL), and creatinine (0.82 mg/dL) levels.

Discussion

Hemolytic uremic syndrome is one of the subgroups of microangiopathic hemolytic anemias and presents as Shiga-toxin-related or complement-mediated (atypical-HUS). In atypical HUS, complement system activation or complement regulatory proteins (factor I, H, thrombomodulin, membrane cofactor proteins) is explained by endothelial damage that develops as a result of impaired functions.

Although the importance of detecting complement proteins or complement gene mutations is still unclear, if the atypical hemolytic syndrome is evaluated as complement-mediated, plasma exchange or eculizumab therapy should be initiated as soon as possible to prevent irreversible renal damage. As a result, normal complement levels do not exclude the diagnosis of complement-mediated HUS.

SARS-COV-2 mRNA vaccine, which creates an immune response with a different mechanism than childhood vaccines, aims to give an adequate immune response in case of encountering the virus again, with the proliferation of the proteins of the virus and the development of the response to it. RNA vaccine not only creates an immune response, but also causes thrombotic events, similar to the endothelial damage caused by the disease, as a result of expressing the proteins of the virus. The development of a post-vaccine attack in young patients with immune thrombocytopenia or paroxysmal nocturnal hemoglobinuria in follow-up patients was evaluated as secondary to the thrombotic events caused by messenger RNA (mRNA) based vaccines that cause temporary expression of the SARS-CoV-2 spike protein [2]. High levels of sC5b-9 occur as a result of activation or dysregulation of the complement pathway in two-thirds of patients infected with SARS-COV-2 [10]. mRNA vaccines developed with a similar mechanism of action also produce the protein produced by the virus and provide an immune response. The adverse effects seen after the production of the SARS-COV-2 spike protein are explained in this way. It is thought that mRNA-based vaccines developed to prevent SARS-COV-2 and SARS-COV-2 transmission cause complement-mediated hemolytic uremic syndrome by causing complement-mediated endothelial damage.

It has been reported that TTP or ITP developed in individuals infected or vaccinated with the SARS-COV-2 virus during the pandemic [11-12]. A case of atypical HUS developed after ChAdOx1 nCoV-19 vaccine

was also observed in an individual with CFHR3/CFHR1 homozygous gene mutation [13].

Conclusion

In this case we have reported first atypical HUS caused by complement activation following the administration of Biontech vaccine. Considering the case as atypical HUS, starting plasma exchange therapy primarily ensured the clearance of factor H antibodies, then initiating C5 monoclonal antibody eculizumab treatment, which is recommended to be administered in the first 24-48 hours in atypical HUS, prevented the endothelial damage secondary to inflammation.

Conflict of interest statement. None declared.

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