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CASE REPORT

Chronic cold agglutinin disease after a third COVID-19 mRNA vaccination

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Abstract

COVID-19 mRNA vaccines manufactured by Pfizer-BioNTech and Moderna have been approved in many countries, and have been administered since 2020. Recent reports of mRNA vaccination exacerbating autoimmune hematologic disorders, such as immune thrombocytopenia or autoimmune hemolytic anemia, have caught the attention of the general public, resulting in alarm over the risks of serious consequences. Meanwhile, in very rare cases, vaccination was reported to trigger new onset of hemolytic anemia. However, it remains unknown whether this was a transient reaction or a persistent event, because all cases reported to date were immediately treated with corticosteroids or rituximab. Here, we present a case of newly diagnosed cold agglutinin disease after a third COVID-19 mRNA vaccination. The patient was followed for 4 months without treatment and continued to exhibit high levels of cold agglutinin and aggregation of red blood cells. The present case indicates that the disease can become chronic, and provides insights into the pathogenesis and treatment strategies.

Keywords COVID-19 mRNA vaccine · Autoimmune hemolytic anemia · SARS-CoV-2 · Cold autoimmune hemolytic anemia · Cold agglutinin disease

Introduction

During the coronavirus disease-2019 (COVID-19) pandemic, there have been increasing reports of autoimmune diseases caused by infection with the causative virus or vaccination for its prevention. mRNA vaccines for COVID-19 have come under the spotlight as new technologies associated with the pandemic. Intolerance or adverse reactions to COVID-19 mRNA vaccines are usually transient and mild-to-moderate. While the safety of the vaccines has been well documented in clinical trials on healthy subjects, development or progression of pre-existing autoimmune hematologic diseases, such as immune thrombocytopenia (ITP) [17], paroxysmal nocturnal hemoglobinuria [16], or autoimmune hemolytic anemia (AIHA) [5, 8, 19], after COVID-19 infection or vaccination has been reported and warned about.

The most common immune cytopenia reported after vaccination is ITP, while AIHA has rarely been mentioned [13]. AIHA is characterized by increased destruction of red blood cells (RBCs) mediated by autoantibodies against RBC antigens. There are two types of AIHA: warm AIHA, and cold AIHA which is also known as cold agglutinin disease (CAD), constituting 80–90% and 10–20% of adult cases, respectively.

Approximately half of AIHA cases are idiopathic, while secondary cases are often associated with underlying autoimmune or lymphoproliferative diseases. Several infectious diseases are also known to be associated with AIHA, including human immunodeficiency virus, *Mycoplasma pneumoniae*, Epstein–Barr virus, and recently COVID-19 infections [13].

Here, we report the case of a female patient with newly diagnosed CAD after receiving a third mRNA vaccination.

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Case report

A healthy 51-year-old female presented to her primary clinic because of symptoms of severe generalized pain, finger joint pain, fatigue, and dark urine. The symptoms had developed 7 days after she received a third-dose vaccination with the Pfizer-BioNTech BNT16B2b2 mRNA vaccine (lot number: FK 8562). She had received the Moderna mRNA vaccine for the first and second doses (lot numbers: 3002540 and 3004220, respectively) approximately 6 months earlier, and had experienced intolerance reactions of mild fever and headache. The medical history was migraine and gallstone. There were no illnesses in the preceding 6 months. Her current medical treatment consisted of zolmitriptan and lomerizine hydrochloride, with no new drugs taken recently. Blood tests, showing reference range in parentheses, was performed after reheating at 37 ºC, since the blood sample was coagulated at room temperature, and revealed normocytic normochromic anemia with hemoglobin of 8.2 g/dL (11.3–15.2), hematocrit of 24.6% (33.4–44.9), and mean globular volume of 100.8 fL (79–100), but no other major morphological changes, and her leukogram and platelet counts were normal. Since finger joint pain was a chief complaint, the primary doctor suspected rheumatoid arthritis and examined rheumatoid factor, anti-cyclic citrullinated peptide antibodies, and other autoantibodies such as antinuclear antibody and so on, all of which were negative. Although anemia and abnormal blood coagulation was noted, Fe and ferritin levels were within the normal ranges, and no further testing was performed. She was diagnosed with a prolonged adverse reaction and prescribed analgesics, but her general symptoms persisted.

She subsequently visited a hematology outpatient clinic with concerns about anemia, and at that time 4 months had passed since the onset of symptoms. Laboratory examinations showed improvement of hemoglobin to 11.7 g/dL. We suspected hemolysis due to the presence of rapid anemia and dark urine suggestive of bilirubinuria soon after the symptoms appeared. Despite the improvement in the hemoglobin level, reticulocytosis, direct Coombs test positivity, and decreased haptoglobin were confirmed. LDH, total bilirubin and direct bilirubin were within normal range. At that time, the blood sample was coagulated, and she claimed that this had happened several times very recently. The cold agglutinin titer was 1:16,384 (normal value: 1:64). A peripheral blood film showed marked agglutination (Fig. 1) that was considered to be caused by CAD. Immunoglobulin level was within normal range that IgG 994 mg/dL (820–1740), IgA 217 mg/dL (90–400) and IgM 183 mg/dL (52–270). Complement test showed that C4 and CH50 were decreased but C3 was normal [C3 (β1C/β1A) 91 mg/dL (80–140), C4 (β1E) 4.1 mg/dL (11–34) and CH50 15 mg/dL (30–45)]. Serum protein electrophoresis revealed a protein band representing monoclonal IgM-κ which indicates cold agglutinin.

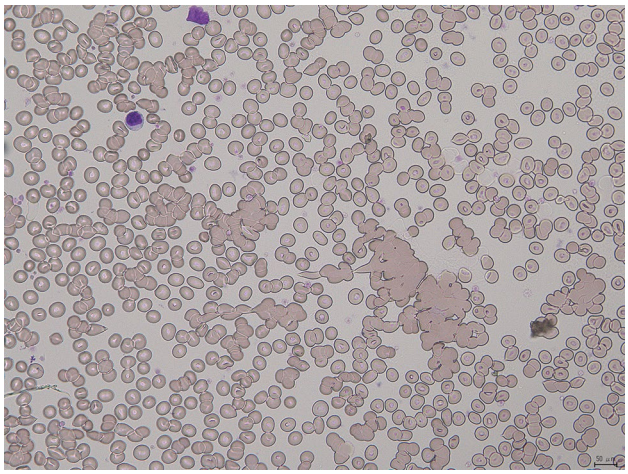

Fig. 1 Peripheral blood smear with red blood cell agglutination

Investigations for the underlying cause of CAD, including cytomegalovirus, Epstein–Barr virus, human immunodeficiency virus, parvovirus, mycoplasma, hepatitis B and C, and flow cytometric immunophenotyping were all negative. Bone marrow aspiration and biopsy revealed no evidence of lymphoproliferative disease. A computed tomography scan of the neck, chest, and abdomen and an upper gastrointestinal endoscopy were normal.

Although the anemia was mildly relieved without treatment, she complained of mild-to-moderate fatigue and her finger pain persisted. Because RBC agglutination was still observed, she currently remains under careful follow-up without treatment.

Discussion

There have been many cases reported in which COVID-19 infection itself contributed to exacerbation or development of AIHA, including CAD, and it is possible that episodes of disease activity can be triggered by the immune stimulation induced by COVID-19 infection [13]. Only a few cases of new-onset AIHA secondary to COVID-19 mRNA vaccination have been reported in healthy individuals [2, 4, 7, 10, 11, 14, 21, 22]. The onset of symptoms ranged from 2 days to 3 months after the first or second dose, and no cases have been reported after the third dose. Both the Pfizer-BioNTech and Moderna mRNA vaccines have been associated with reported cases. Most cases of warm AIHA were managed with blood transfusions along with typical

corticosteroids. One CAD case was treated with rituximab, an anti-CD20 monoclonal antibody.

Although the exact mechanism underlying the association between mRNA vaccines and AIHA remains to be fully characterized, there is a hypothesis that molecular mimicry between microbial epitopes and RBC epitopes. Because of the similarity between viral and erythrocyte proteins, antibodies targeting the spike protein may cross-react with erythrocytes, resulting in hemolysis [1]. If an immunoglobulin cross-reaction is the cause of the disease, it is necessary to test both COVID-19 neutralizing antibodies and cold agglutinin titer over time to clarify the interactions. Cases of AIHA after administration of vaccines are rare, and only two such cases have been reported to date for diphtheria-tetanus-pertussis [15] and influenza [20] vaccines. Several hypotheses including molecular mimicry of vaccine constituents or viral antigens have been discussed [1, 3, 6]. Meanwhile, immunologic hyperstimulation of B cells by vaccination may affect cellular characteristics and predispose patients to more severe hemolysis. Another possible hypothesis is that de novo disease is precipitated. Aggravation of presymptomatic autoimmune hematologic disease by the vaccination is not well understood and further study is needed.

It has remained unknown whether post-vaccination AIHA is a transient reaction or a persistent event, because all cases reported to date have immediately been treated. Notably, the present case is the first one of secondary CAD after a third-dose mRNA vaccine, as booster shot, and is also noteworthy for the 4 months chronic course since onset with high levels of cold agglutinin.

CAD is associated with not only hemolysis but also general symptoms such as fatigue, malaise, and pain in the extremities due to RBC agglutination during attacks. The present patient also complained about sustained these general symptoms after her anemia was improved. Regarding treatment, rituximab is also available but has the dilemma that its use markedly reduces neutralizing antibodies, thereby making patients vulnerable to COVID-19 infection [9, 12, 18]. In addition to conventional therapies, the novel drug sutimlimab, a monoclonal antibody that selectively targets the C1s protein, is considered a treatment option because it is effective for relief of the clinical symptoms including fatigue [23].

The present case indicates that it is possible for secondary CAD after mRNA vaccination to become chronic, and provides insights to the pathogenesis and treatment strategies.

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Data availability On reasonable request, derived data supporting the findings of this study are available from the correspondingauthor.

Declarations

Conflict of interest The authors declare no conflicts of interest.

Ethical approval Consent for publication of this case report was obtained from the patient.

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