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Case report

Sutimlimab suppresses SARS-CoV-2 mRNA vaccine-induced hemolytic crisis in a patient with cold agglutinin disease

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Cold agglutinin disease (CAD) is a rare form of acquired autoimmune hemolytic anemia driven mainly by antibodies that activate the classical complement pathway. Several patients with CAD experience its development or exacerbation of hemolysis after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or after receiving the SARS-CoV-2 mRNA vaccine. Therefore, these patients cannot receive an additional SARS-CoV-2 mRNA vaccination and have a higher risk of severe SARS-CoV-2 infection. Sutimlimab is a monoclonal antibody that inhibits the classical complement pathway of the C1s protein and shows rapid and sustained inhibition of hemolysis in patients with CAD. However, whether sutimlimab could also inhibit hemolysis caused by SARS-CoV-2 mRNA vaccination is uncertain. Here, we present the case of a 70-year-old man with CAD who repeatedly experienced a hemolytic crisis after receiving SARS-CoV-2 mRNA vaccines. The patient eventually underwent SARS-CoV-2 mRNA vaccination safely, without hemolytic attack, under classical pathway inhibition therapy with sutimlimab. This report suggests that appropriate sutimlimab administration can suppress SARS-CoV-2 mRNA vaccination-induced CAD exacerbation, and that it could be a preventive strategy to minimize hemolytic attacks in susceptible populations.

Keywords: cold agglutinin disease, severe acute respiratory syndrome coronavirus 2, sutimlimab

INTRODUCTION

Cold agglutinin disease (CAD) is a rare form of acquired autoimmune hemolytic anemia (AIHA) caused by antibodies that activate the classical complement pathway.[1] Cold agglutinin is usually an immunoglobulin M (IgM) autoantibody that binds to surface antigens of red blood cells, and monoclonal IgM is detected in most cases.[1] Patients with CAD have a very indolent B-cell lymphoproliferative disorder without clinical or radiological malignant manifestations.[1,2] Moreover, they often experience chronic hemolysis with anemia, jaundice, splenomegaly, and acute hemolytic crises. These patients also experience agglutination-mediated ischemic symptoms in the acral area, including acrocyanosis and Raynaud's phenomenon. Furthermore, hemolytic anemia increases the risk of venous thromboembolism, particularly when active intravascular hemolysis occurs.[1,3] Therefore, the prevention of hemolytic crisis in patients with AIHA or paroxysmal nocturnal hemoglobinuria (PNH) is important.

During the coronavirus disease-2019 (COVID-19) pandemic, many people received severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccinations to prevent severe COVID-19 infection. Although many clinical studies confirmed the safety of SARS-CoV-2 mRNA vaccines,[4,5] a few patients experienced the development or exacerbation of autoimmune hematologic disease after receiving them.[6–8] Therefore, these patients could not undergo additional SARS-CoV-2 mRNA vaccination and had a higher risk of severe COVID-19 infection. However, the exact mechanism underpinning the relationship between SARS-CoV-2 mRNA vaccination and the exacerbation of AIHA remained

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unclear.

Sutimlimab is a monoclonal antibody that inhibits the classical complement pathway of the C1s protein. In the CARDINAL and CADENZA studies, sutimlimab showed rapid and sustained inhibition of hemolysis and improved fatigue in patients with CAD.[9,10] However, it was uncertain whether sutimlimab could also inhibit the hemolysis caused by other factors, including SARS-CoV-2 mRNA vaccination. This case report describes a patient with CAD who experienced a hemolytic crisis caused by SARS-CoV-2 mRNA vaccination. Although he had repeatedly experienced hemolytic crisis owing to the vaccine, he safely received an additional SARS-CoV-2 mRNA vaccination without hemolysis exacerbation under classical pathway inhibition therapy with sutimlimab.

CASE PRESENTATION

A 70-year-old Japanese man was diagnosed with CAD by a primary care physician a few years before admission to our hospital. He had experienced Raynaud's phenomenon under cold exposure. Although his anemia had gradually worsened since diagnosis, especially in winter, he did not experience any anemia-related symptoms. He received the first and second shot of the Pfizer-BioNTech BNT162b2 monovalent SARS-CoV-2 mRNA vaccine 7 months before admission to our hospital, without adverse events. However, he experienced shortness of breath and general malaise after receiving the third Pfizer-BioNTech BNT162b2 monovalent SARS-CoV-2 mRNA vaccination. The patient was referred to our hospital because laboratory data from a primary care clinic revealed exacerbated anemia.

Physical examination on admission revealed conjunctival icterus and pallor, indicating a hemolytic crisis. Notably, peripheral lymphadenopathy was not observed. Furthermore, laboratory findings showed severe anemia (hemoglobin, 6.8 g/dL; normal range, 13.7–16.8 g/dL) with reticulocytosis (absolute reticulocyte count, 237,000/μL), elevated lactate dehydrogenase (827 IU/L; normal range, 124–222 IU/L) and bilirubin levels (total bilirubin, 3.9 mg/dL; normal range, 0.4–1.5 mg/dL), and decreased haptoglobin level (<2 mg/dL; normal range, 93–147 mg/dL). Moreover, the direct Coombs test result was positive for complement protein C3d and negative for IgG. The serum C3 and C4 levels were 66 mg/dL (normal range, 88–160 mg/dL) and less than 1 mg/dL (normal range, 17–45 mg/dL), respectively. A peripheral blood smear showed red blood cell agglutination (Fig. 1A), and cold agglutinin was identified at a titer of 512, which was compatible with the diagnosis of CAD. The serum IgM level of the patient was slightly increased (187 mg/dL; normal range, 33–183 mg/dL), and serum immunofixation electrophoresis revealed an IgM Kappa protein band. Computed tomography demonstrated mild splenomegaly without significant lymphadenopathy. Bone marrow aspiration showed increased erythroblasts with no evidence of lymphoproliferative disorder (Fig. 1B). Histopathological findings demonstrated an increase in erythroblast cells without lymphocyte clustering (Fig. 1C). Immunohistochemistry staining indicated the absence of CD20-positive or CD3-positive cell infiltration in the bone marrow (Fig. 1D and E), and no evidence of monoclonal IgM production was observed (Fig. 1F). Flow cytometric analysis confirmed the absence of immunoglobulin light-chain restriction in the B cell population (Fig. 1G). SARS-CoV-2 polymerase chain reaction (PCR) test results were negative.

The patient received a red blood cell transfusion and was treated with 35 mg of prednisolone daily to avoid an immune response. His hemolytic parameters gradually improved, and prednisolone was tapered off; however, his hemoglobin level did not reach the normal range (Fig. 2).

As we assumed that his hemolysis would worsen in winter, we planned to administer sutimlimab in autumn. The patient received a pneumococcal and meningococcal vaccine prior to sutimlimab infusion without any adverse effects. Three days after the fourth Pfizer-BioNTech BNT162b2 bivalent SARS-CoV-2 mRNA vaccination, the patient presented with fatigue and dark urine at our hospital. Physical examination revealed conjunctival icterus, and laboratory findings revealed a hemoglobin level of 8.6 g/dL, high reticulocyte count, and elevated bilirubin levels, consistent with the exacerbation of hemolytic anemia (Fig. 2). Notably, SARS-CoV-2 PCR test results were negative. His anemia gradually resolved without corticosteroid therapy; however, his hemoglobin levels did not reach the normal range. Thus, the patient started receiving sutimlimab treatment one month after the hemolytic attack. Sutimlimab infusion stabilized his blood counts, improving hemoglobin levels (Fig. 2), while Raynaud's phenomenon was still present.

Based on the patient's clinical course, the exacerbation of hemolytic anemia induced by the SARS-CoV-2 mRNA vaccine was reproducible. However, he wanted to receive a fifth vaccine. Therefore, we planned for him to receive the Pfizer-BioNTech bivalent SARS-CoV-2 mRNA vaccine a few hours after the completion of sutimlimab administration. Notably, he had no complaints of fatigue after the fifth vaccination, and laboratory findings showed no evidence of hemolysis (Fig. 2).

DISCUSSION

Several studies have shown that COVID-19 exacerbates or leads to the development of AIHA, including CAD.[8,11,12] Therefore, it is important that patients with AIHA undergo SARS-CoV-2 vaccination to prevent severe COVID-19 infection. However, the SARS-CoV-2 mRNA vaccine itself also triggers hemolytic attacks in a few patients.[7,8] Notably, before initiating sutimlimab therapy, our patient had received pneumococcal and meningococcal vaccines, which did not cause hemolytic attacks. Indeed, unlike conventional vaccines, SARS-CoV-2 mRNA vaccines are associated with a risk of hemolysis in patients with CAD. Specifically, the SARS-CoV-2 spike glycoprotein has an epitope identical to that of ankyrin-1, which is an important erythrocyte membrane protein.[11] As SARS-CoV-2 mRNA vaccines encode

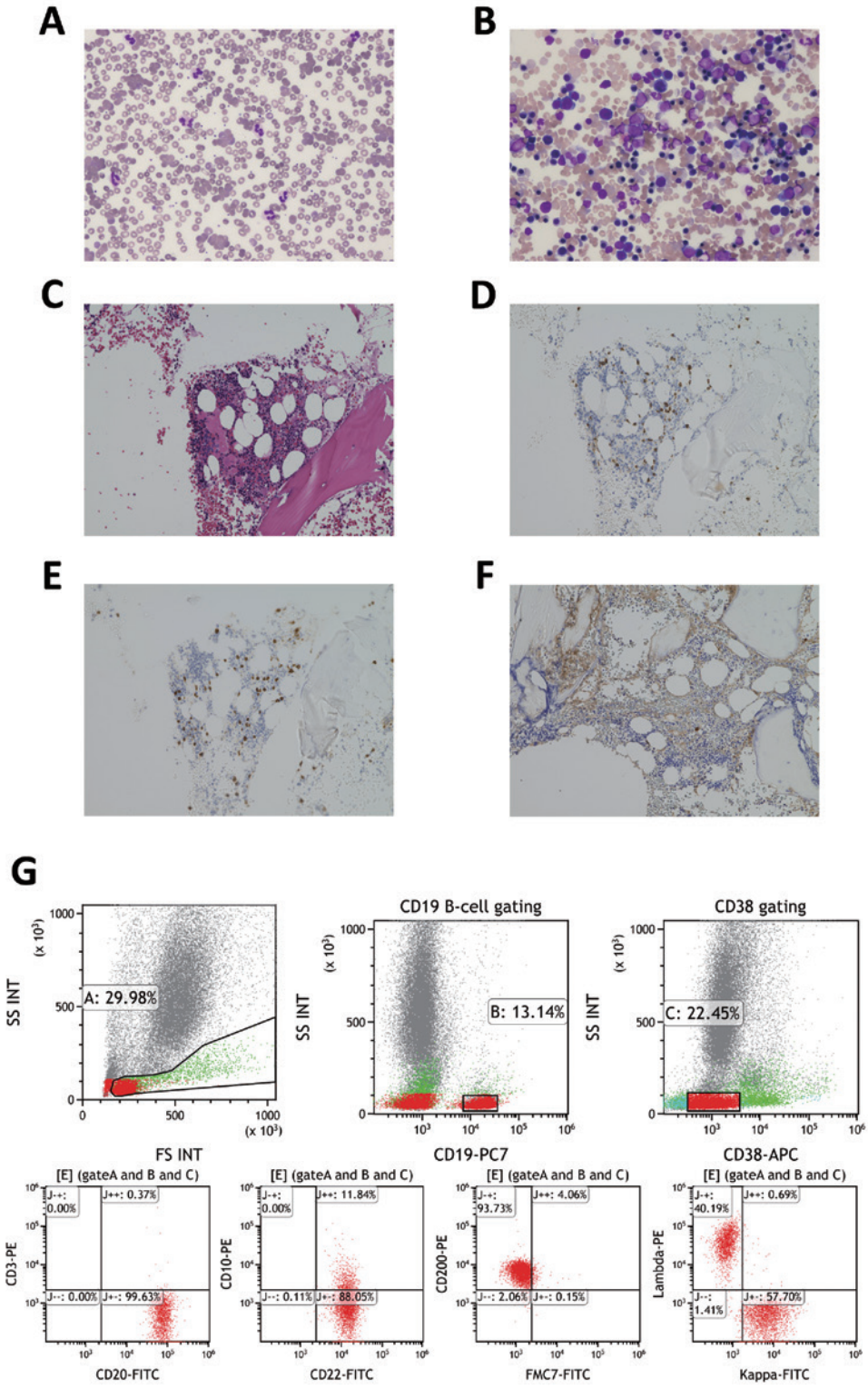

Fig. 1.
Peripheral blood smear on admission shows red blood cell agglutination (***A***, May Giemsa staining; magnification ×200). Bone marrow smear on admission shows a high number of erythroblasts and red blood cell agglutination (***B***, May Giemsa staining; magnification ×200). Histopathological examination reveals an elevated erythroblast count and absence of lymphoid cell infiltration (***C***, Hematoxylin and Eosin staining; magnification ×200). Immunohistochemical staining reveals the absence of distinct clusters of CD20-positive cells (***D***, magnification ×200) or CD3-positive cells (***E***, magnification ×200). Immunohistochemical staining for IgM indicates few lymphocytes positive for IgM (***F***, magnification ×200). Flow cytometric evaluation of the bone marrow reveals that a B-cell population did not harbor immunoglobulin light-chain restriction (***G***).

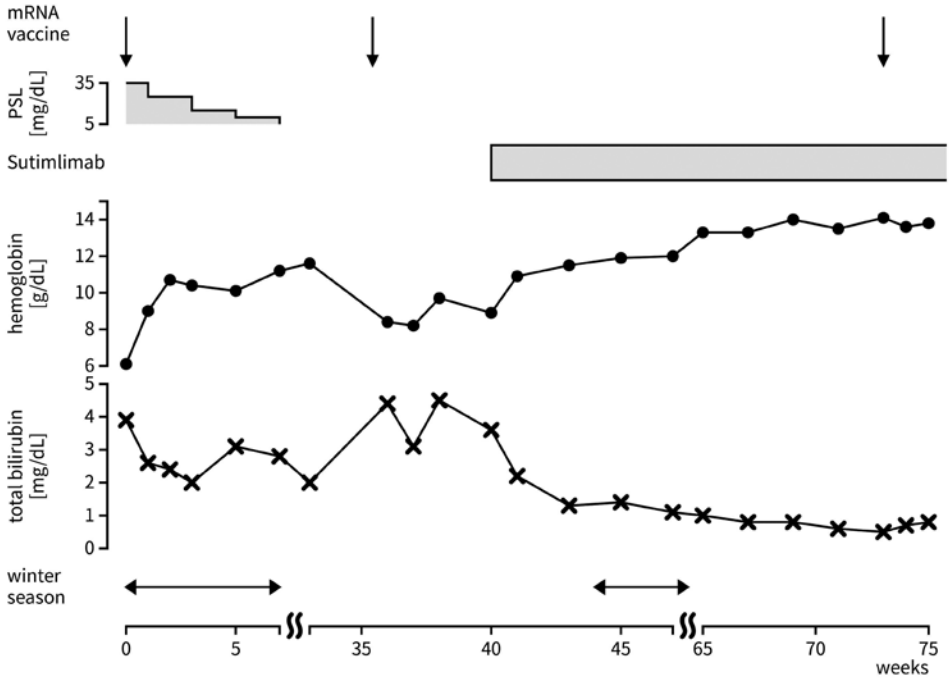

Fig. 2.
Clinical course and laboratory findings after admission. Arrows indicate times of SARS-CoV-2 mRNA vaccination. PSL: prednisolone.

the spike glycoprotein,[4,5] the antibodies generated by the vaccine can bind to erythrocytes via cross-reactivity.[7] An alternative hypothesis is that the inflammatory response after vaccination causes an immunological hyperreaction in B cells, leading to severe hemolysis.[6] A previous report has shown that sutimlimab suppresses the activation and proliferation of primary human B cells *in vitro*.[13] Thus, the inhibition of SARS-CoV-2 mRNA vaccine-induced hemolytic attack under sutimlimab administration in our patient may be related to B-cell inactivation.

Furthermore, our patient was treated with sutimlimab to prevent hemolysis during winter, which increased his hemoglobin levels, indicating effective inhibition of hemolysis. Corticosteroids were frequently used in the treatment of CAD in Japan.[14] However, corticosteroids have limited efficacy in CAD, with a response rate of only 14%.[15] Notably, rituximab monotherapy is recommended in many countries and has shown an approximately 50% response rate in prospective studies.[16] However, the effect of rituximab monotherapy was not sustained,[16] impairing the response to SARS-CoV-2 vaccination,[17] which could cause severe COVID-19 infection in these patients. In contrast, sutimlimab provided a rapid and sustained clinical response in the CARDINAL and CADENZA studies,[9,10] and did not influence the response to SARS-CoV-2 vaccination.[18] Based on these outcomes, we chose sutimlimab monotherapy for our patient.

Our patient received the SARS-CoV-2 mRNA vaccine without severe hemolysis under complement inhibition therapy with sutimlimab. According to a report of a sutimlimab phase 1 trial, peak sutimlimab concentrations were observed at the end of infusion after doses of 60 and 100 mg/kg.[19,20] Furthermore, classical pathway activity was suppressed by over 95% within one hour of infusion initiation at doses of 30 and 60 mg/kg.[19,20] Based on these findings, we hypothesized that sutimlimab blood levels would peak immediately after administration, strongly suppressing classical pathway activity. Thus, we planned for our patient to receive the SARS-CoV-2 mRNA vaccine a few hours after receiving sutimlimab.

This case indicates that SARS-CoV-2 mRNA vaccination can cause hemolytic crisis in patients with CAD and that appropriate sutimlimab administration can suppress the SARS-CoV-2 mRNA vaccination-induced exacerbation of CAD. Furthermore, our report suggests an effective preventive strategy to avoid or minimize hemolytic attacks induced by the SARS-CoV-2 mRNA vaccine in susceptible populations.

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AUTHOR CONTRIBUTIONS

H.K. and T.O. performed conceptualization, patient care, data collection, and writing of the manuscript. W.K. performed conceptualization and writing of the manuscript.

S.A., T.Y., H.T., and Y.T. performed patient care, review, and editing. T.Y. performed pathological experiments and reviews. Y.M. supervised, reviewed, and edited the manuscript.

CONFLICT OF INTEREST

H.K. and W.K. received honoraria from Sanofi. The other authors declare that they have no conflict of interest.

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