

[CASE REPORT]

Severe Anemia Due to Cold Agglutinin Syndrome in a COVID-19 Patient with IgM Monoclonal Gammopathy of Undetermined Significance Successfully Treated with Corticosteroids

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Abstract:

Secondary cold agglutinin syndrome (CAS) is autoimmune hemolytic anemia secondary to infections and lymphoid disorder. We here report the first Asian case of CAS secondary to novel coronavirus disease 2019 (COVID-19). A 72-year-old Japanese woman presented with a 2-week history of dyspnea and cough, and laboratory data revealed severe hemolytic anemia with a hemoglobin level of 4.7 g/dL. She was diagnosed with COVID-19, CAS, and monoclonal gammopathy of undetermined significance (MGUS). The anemia responded to corticosteroids administered for COVID-19 and required maintenance therapy. Although corticosteroids are not a standard therapy for CAS, they might be effective for CAS secondary to COVID-19 complicated with MGUS.

Key words: COVID-19, cold agglutinin syndrome, autoimmune hemolytic anemia, monoclonal gammopathy of undetermined significance, corticosteroid

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Introduction

Since the novel coronavirus disease 2019 (COVID-19) pandemic emerged, we have been rapidly accumulating clinical experiences of treating this new disease. Autoimmune hemolytic anemia (AIHA) has also been recognized as an uncommon complication of COVID-19, and cold agglutinin syndrome (CAS) is a rarer comorbidity (1-6). CAS/cold agglutinin disease (CAD) is a cold antibody-mediated type of AIHA.

CAS develops secondary to infection, such as Epstein-Barr virus (EBV) and *Mycoplasma pneumoniae*, autoimmune disorder and lymphoid disorder, and, generally, corticosteroids are not recommended in CAS related to infection (7). Several case reports and case series of CAS with

COVID-19 have been published, but the optimal treatment has not been established (1-6).

We herein report the first Asian case of a patient with CAS associated with COVID-19 in whom anemia persisted even after blood transfusion and COVID-19 recovery, with the re-administration of corticosteroids required.

Case Report

A 72-year-old Japanese woman with a history of hypertension visited a local clinic with a 2-week course of cough and gradually progressive dyspnea on exertion. She denied a fever before admission. It was May in Japan at that time, when the temperature is around 20°C. She was diagnosed with severe anemia and referred to the previous hospital for a gastroscopic examination. However, a saliva-based reverse

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transcriptase-polymerase chain reaction, conducted as a screening test prior to gastroscopic examination, revealed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection with a viral load of 743 copies (76 copies on day 6). Based on the patient's history and the low viral load, the onset of COVID-19 was thought to be about 2 weeks before her admission.

Her height and weight were 154 cm and 55 kg, respectively. Vital signs were remarkable for tachypnea at 24 breaths per minute, oxygen saturation 98% on 1 L per minute supplemental oxygen with a nasal cannula, and a fever of 38.6°C. Laboratory data were notable for hemoglobin 4.7 g/dL, hematocrit 13.5%, total bilirubin 2.8 mg/dL, indirect bilirubin 1.8 mg/dL, lactate dehydrogenase (LDH) 505 U/L (reference 124-222 U/L), haptoglobin 2.7 mg/dL (ref. 19-170 mg/dL) and total hemolytic complement (CH50) <14.0/mL (ref. 30-46/mL). The white blood cell count was 2,800/ μ L (neutrophils 52%, lymphocytes 40%), and the platelet count was 235,000/ μ L. The reticulocyte percentage was 3.65% with a reticulocyte index of 0.4, which suggested a relatively inadequate bone marrow response. Other data related to COVID-19 were ferritin 3,097 ng/mL, D dimer 2.1 μ g/mL, and C reactive protein 3.56 mg/dL. Total protein and albumin were 6.4 g/dL and 3.5 g/dL, respectively. Further evaluations revealed a high titer of cold agglutinin antibody (titer 1:524,288) and a positive direct Coombs test for C3b and C3d. We confirmed the diagnosis of CAS.

We investigated the underlying causes of CAS. Antinuclear antibody (ANA) was positive for coarse speckles and centromere with a 1:80 titer, but the patient did not have any significant symptoms or signs consistent with collagenous diseases. Negative results were obtained for anti-*Mycoplasma pneumoniae* antibody, Epstein-Barr virus (EBV) anti-viral capsid antigen (VCA) immunoglobulin (Ig) M antibody, human immunodeficiency virus (HIV) antigen/antibody, hepatitis B virus surface antigen, hepatitis C virus antibody, anti-Ro/SSA antibody, anti-La/SSB antibody and antiphospholipid antibodies. The patient's immunoglobulin levels showed increased IgM; IgG was 1,113 mg/dL (ref. 861-1,747 mg/dL), IgA was 169 mg/dL (ref. 93-393 mg/dL), and IgM was 714 mg/dL (ref. 50-269 mg/dL). Serum protein electrophoresis showed M band, IgM- κ type, and a urine test detected Bence Jones protein, light chain of the κ type, which indicates the existence of monoclonal IgM. The serum κ chain value was 73.1 mg/dL (ref. 3.3-19.4 mg/L), with the λ chain of 19.4 mg/dL (ref. 5.7-26.3 mg/L) and κ/λ ratio of 3.77 (ref. 0.26-1.65).

A bone marrow biopsy showed slight hypercellularity and increased erythroblasts but did not demonstrate plasma cells or lymphoplasmacytic cell infiltration. *MYD88* mutation was negative. Computed tomography (CT) of the chest, abdomen, and pelvis showed no considerable findings except for mild ground-glass opacity and a reticular pattern peripherally in both lungs and mild hepatosplenomegaly but was negative for lymphadenopathy. These findings indicated that the potential etiologies for the patient's CAS were COVID-

19 and IgM monoclonal gammopathy of undetermined significance (MGUS).

The patient received a 2-unit red blood cell (RBC) transfusion on the day of admission (day 1), and treatment was initiated with oral dexamethasone 6 mg daily for 11 days, with remdesivir 200 mg on day 1 and then 100 mg daily for 4 more days intravenously. Deep vein thrombosis prophylaxis was performed using heparin. The patient's respiratory condition, hemolysis, and hemoglobin improved gradually, and she did not need supplemental oxygen on day 7. Dexamethasone was discontinued on day 11 because we considered both the COVID-19 and the CAS to be resolved. We concluded that COVID-19 was the main cause of the patient's CAS at that time point and that the CAS would improve spontaneously following the resolution of COVID-19. However, the patient's anemia worsened (7.1 g/dL on day 11, 5.8 g/dL on day 14) after the dexamethasone was discontinued, and indirect bilirubin was also elevated from 1.0 mg/dL (day 11) to 1.2 mg/dL (day 14), although LDH was not changed. We found no other causes of anemia and considered the anemia to likely be due to CAS. Therefore, we administered oral 30 mg prednisolone daily; the hemoglobin level then increased again. The patient was discharged 18 days after admission and was advised to avoid cold environments. Her prednisolone treatment was tapered during the outpatient period, without relapse (Figure).

At the follow-up on day 84, the patient's immunoglobulin levels were IgG at 886 mg/dL, IgA at 75 mg/dL, and IgM at 188 mg/dL. Protein electrophoresis showed a weakly positive M band in the serum and Bence Jones protein in the urine. The serum κ chain value was 22.7 mg/dL, with the λ chain at 15.9 mg/dL and the κ/λ ratio of 1.43.

Discussion

We encountered an adult COVID-19 patient with underlying MGUS who was admitted with severe hemolytic anemia due to CAS, which persisted and required the re-administration of corticosteroids for treatment. AIHAs are usually classified as either the warm antibody- or cold antibody-mediated type depending on the temperature optimal to their binding to RBCs. Warm antibody-mediated AIHA is usually due to the binding of polyclonal IgG immunoglobulin to less-abundant RBC antigens, such as Rh proteins or glycophorins A-D, whereas cold antibody-mediated AIHA, such as CAD, is caused by a clonal or oligoclonal IgM antibody to abundant RBC antigens, such as polymers of aminyl-lactose disaccharides. Primary CAD is defined as chronic hemolysis with the absence of underlying clinical diseases. If the patient has an associated condition, such as an infection, autoimmune disorder, B-cell lymphoma, or other malignancy, the condition is called CAS (7). CAS secondary to an infection usually shows polyclonal proteins, but in our case, we detected monoclonal IgM, suggesting MGUS as a potential cause.

One report described the incidence of CAD as around

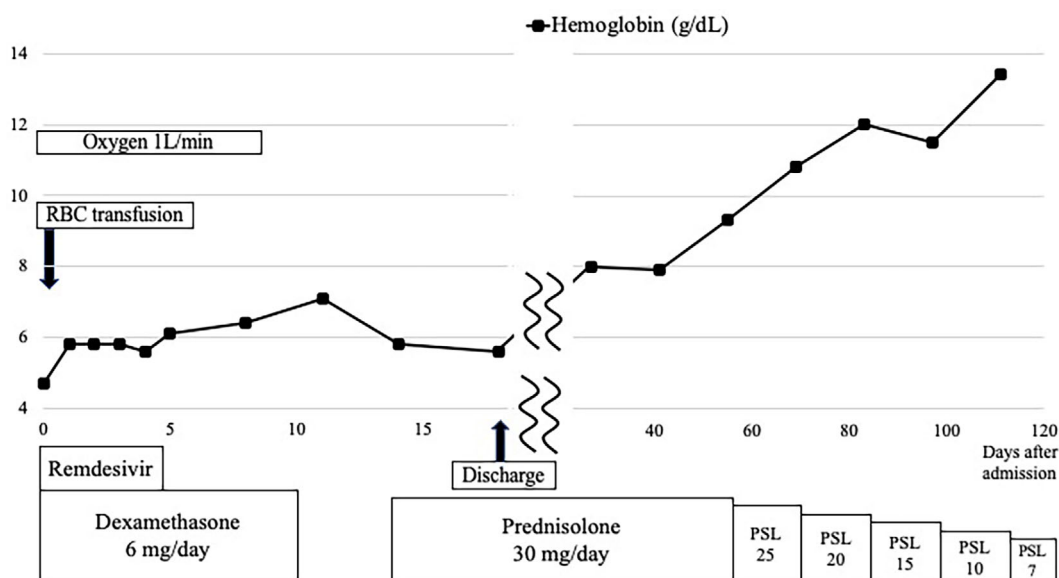


Figure. The patient's clinical course. RBC: red blood cell, PSL: prednisolone (mg/day)

0.18 per 100,000 person-years in Denmark (8). No epidemiological data are available concerning the incidence of CAS in the Japanese population, but given the warmer climate in Japan, there may be fewer CAS patients than in Denmark.

There have been six published reports describing COVID-19 cases associated with either CAS or CAD, including the current case (1-5), and to our knowledge, this is the first case report of CAS associated with COVID-19 in Asia. The main features of the reported patients are summarized in Table. Six patients required blood transfusion, and one died. Regarding the possible underlying conditions causing CAS, at least in three cases (including our patient), a hematologic disorder, such as marginal zone B-cell lymphoma or MGUS, was diagnosed in addition to COVID-19. Steroid-containing treatment was documented as the initial treatment for COVID-19 in five cases.

For the treatment of warm AIHA in adults, corticosteroids have been established as the first-line treatment strategy for patients with severe anemia (7, 9). In contrast, CAS secondary to infections, such as EBV and *Mycoplasma pneumoniae*, usually improves spontaneously, and the treatment of underlying infection (e.g., with antibiotics and antiviral drugs) is important; corticosteroids are thus not used in most patients with CAS caused by infections, especially in patients with predominantly IgM cold agglutinin (7, 9, 10). In our patient's case, the symptoms were likely to have been caused by IgM cold agglutinins, as she had monoclonal IgM proteins.

We initially treated the patient with both remdesivir and dexamethasone as treatment for COVID-19. Her COVID-19 symptoms subsided and the viral load decreased, but her anemia rapidly worsened when the dexamethasone was suspended. Given that the patient's anemia responded to the initial steroid treatment, we restarted prednisolone, and the anemia eventually resolved. This clinical course suggests that corticosteroids were an effective treatment in this pa-

tient's case.

Several hypotheses about the relationship between autoimmune diseases, such as systemic lupus erythematosus and Guillain-Barré syndrome, and COVID-19 have been reported (11). SARS-CoV-2 infection can induce autoimmunity through molecular similarity and break immune tolerance (12). Increased levels of autoantibodies [e.g., antinuclear antibody (ANA), antineutrophil cytoplasmic antibodies (ANCA), anti-Ro/SSA antibodies, and anti-ganglioside GD1b antibody] have been observed in COVID-19 patients. Berzuini et al. reported that the prevalence of direct Coombs test positivity among COVID-19 transfusion candidates was about one-half, whereas hemolysis was very rare (13). It is plausible that the production of pre-existing cold agglutinins and autoantibodies against RBCs is enhanced by COVID-19.

Anti-I antibodies, anti-i antibodies, anti-Ii antibodies, and Sialo agglutinins are potential causes of hemagglutination and immune-mediated hemolysis. In patients with infectious mononucleosis and *Mycoplasma pneumoniae*, an increase in V_{H4-34} antibody was observed in most cases. Those antibodies binding to RBCs were related to circulating V_{H4-34} antibody concentrations. Therefore, the antibody titer can increase under such infectious disease conditions, which may lead to hemolysis. In addition, cross-reactivity and molecular mimicry may cause a rise in cold agglutinins after infection (14). As such, SARS-CoV-2 may have similarity to *Mycoplasma pneumoniae*, making this one possible explanation for the existence of COVID-19-related CAS. In addition, one report stated that the erythrocyte membrane protein Ankyrin 1 was completely identical to the SARS-CoV-2 surface glycoprotein, i.e. the spike protein (15).

During our patient's admission, she was diagnosed with IgM MGUS, which is the most common premalignant clonal plasma cell disorder. The potential significance of MGUS during COVID-19 has been discussed (16, 17). Previous authors have suggested that MGUS might increase the

Table. CAS Patients' Features Associated with COVID-19.

No.	Age	Gender	Underlying disease(s) Etiologies potentially related to CAS are underlined	Disease severity of COVID-19	Lowest hemoglobin level (g/dL) [Days after onset]	Direct antiglobulin test	Cold agglutinin titer	Treatment	Transfusion	Outcome of COVID-19	Outcome of CAS	Ref.
1	62	Woman	Hypertension, cirrhosis, <u>marginal zone lymphoma</u>	Severe in CT scan	10.8 [Not described]	C3d (+) IgG (-)	Positive (not available)	Steroids, rituximab	Not described	Improved	Partial response	1
2	69	Woman	Obesity, <u>marginal zone lymphoma</u>	Moderate in CT scan	3.8 [Not described]	C3d (+) IgG (+)	Positive (not available)	Steroids	Not described	Improved	Partial response	1
3	61	Man	Hypertension, diabetes, chronic renal failure, hypercholesterolemia, <u>prostate cancer</u>	Mild in CT scan	7.2 [Not described]	C3d (+) IgG (-)	Positive (not available)	Not available	Yes	Improved	Not described	1
4	43	Woman	Multiple sclerosis	Needed oxygen support	6.1 [16]	Positive	Positive (not available)	Ceftriaxone, azithromycin, tazocillin	Yes	Improved	Improved	2
5	63	Man	Hypertension	Severe respiratory failure, admitted in ICU	8.2 [20]	C3d (+) IgG (+)	Positive (not available)	Not available	Not described	Improved	Improved	2
6	51	Woman	<u>Breast cancer</u> , VTE	Severe due to pulmonary embolism	5.1 [Not described]	C3d (+) IgG (-)	Positive (1:80)	mPSL, hydroxychloroquine	Yes	Improved	Improved	3
7	48	Man	IDDM, obesity, ESRD on peritoneal dialysis	Severe due to clotting	4.5 [7]	Positive	Positive (not available)	Not available	Yes	Death	Death	4
8	54	Man	None	Moderate	6.5 [Not described]	C3d (+) IgG (-)	Not available	mPSL, hydroxychloroquine, tocilizumab, PE	PE	Improved	Improved	5
9	72	Woman	Hypertension, <u>IgM MGUS</u> appendectomy,	Moderate	4.7 [14]	C3d (+) IgG (-)	Positive (1:524,288)	Dexamethasone, prednisolone, remdesivir	Yes	Improved	Improved	Current case

CT: computed tomography, ESRD: end-stage renal disease, IDDM: insulin-dependent diabetes mellitus, IgM: immunoglobulin M, ITP: immune thrombocytopenic purpura, MGUS: monoclonal gammopathy of undetermined significance, mPSL: methylprednisolone, PE: plasma exchange, VTE: venous thromboembolism

susceptibility and severity of COVID-19 and that MGUS patients may have increased susceptibility to bacterial and viral infections and coagulation abnormalities. MGUS is known to be a cause of CAS (10), and we believe that the cytokine disturbance, such as increased interleukin (IL)-1 β , IL-2, IL-6, IL-17, IL-1, tumor necrosis factor (TNF) and C-C motif chemokine ligand 2 (CCL2), induced by SARS-CoV-2 infection might trigger patients with MGUS to produce a high titer of monoclonal IgM, resulting in CAS (18).

Our patient reported that she had not experienced any episodes of dyspnea or anemia even in the cold winter, and that her blood test conducted 18 months prior to this admission showed a normal hemoglobin level of 13.1 g/dL. Her hypergammaglobulinemia, M band, and Bence Jones protein levels declined together with the improvement of hemolysis during follow-up. We do not know when the MGUS started to develop in her case. A relationship among infection, autoimmunity, and MGUS has been described (19), and SARS-CoV-2 may be an etiology of MGUS. In the present case, these episodes and findings suggested that the patient's CAS was likely to have been caused by immunological abnormalities associated with MGUS, which were exacerbated by or possibly occurred in tandem with COVID-19, rather than autoantibodies directly induced by COVID-19. The association between SARS-CoV-2 and autoimmunity is a possible reason why corticosteroids were effective in this situation.

Conclusion

COVID-19 can cause AIHA, including CAS. Corticosteroids are a potential treatment of persistent cases of CAS related to COVID-19 complicated with MGUS. Further prospective studies with larger numbers of patients are needed to assess both the beneficial effect of corticosteroids in this setting and the relationship between COVID-19 and MGUS.

The authors state that they have no Conflict of Interest (COI).

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