

Cold agglutinin disease and COVID-19 requiring therapeutic plasma exchange

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SUMMARY

A 70-year-old man with known cold autoimmune haemolytic anaemia was referred to the emergency department with increased shortness of breath on exertion. He had been confirmed positive for non-variant COVID-19 infection 1 week earlier based on nasopharyngeal swab PCR assay. CT thorax demonstrated diffuse patchy bilateral ground glass opacities, consistent with COVID-19 pneumonia. Bloodwork demonstrated severe cold agglutinin mediated haemolytic anaemia. To help stabilise the patient, he was transferred to a tertiary care hospital for urgent therapeutic plasma exchange. Key supportive therapy included folic acid supplementation, ensuring the patient was kept warm and warmed infusions including transfusions via the apheresis machine. The patient made a good recovery following plasma exchange, and his haemoglobin levels remained stable by discharge.

BACKGROUND

COVID-19 had rapidly spread across the globe, resulting in over 147 million cases worldwide as of April 2021.¹ COVID-19 has also been associated with exacerbation of underlying autoimmune diseases due to dysregulated immune responses following infection.² Here, we describe a patient with an exacerbation of cold autoimmune haemolytic anaemia (cAIHA) after COVID-19 infection. This case discusses treatment modalities for patients with cold agglutinin disease (CAD) exacerbation while infected with COVID-19.

CASE PRESENTATION

A 70-year-old man with underlying CAD, gout and chronic viral hepatitis B without cirrhosis, presented to the emergency department with progressively increasing dyspnoea on exertion and haemoglobinuria. In the emergency department, the patient was afebrile, tachycardic and tachypneic with no hypoxaemia (table 1). Clinical examination revealed no evidence of any acute bleed. The patient was diagnosed with rapid haemolysis with a precipitous decline in his haemoglobin of 34 g/L within 12 hours. CAD was confirmed by positive haemolytic markers, blood film demonstrating agglutination (figure 1), and a direct antiglobulin test positive for C3d. Further testing confirmed a high thermal amplitude of 34°C.

TREATMENT

Given positive clinical, microbiological and radiological symptoms of COVID-19 pneumonia, the patient was monitored closely. Although there were

no episodes of hypoxia, he was started on dexamethasone 6 mg orally daily in the intensive care unit (ICU) due to concern for possible rapid clinical deterioration.³ The patient's haemoglobin levels were closely monitored given his history of cold agglutinin haemolytic anaemia. Progressive haemolysis required transfusion of two units of cross-matched compatible packed red blood cells (pRBC) through a blood warmer. The transfused pRBCs were phenotypically matched for RhD, C, E and K antigens. For urgent treatment of the cAIHA, the patient was transferred to our centre and received therapeutic plasma exchange (TPE), allowing rapid removal of pathogenic cold agglutinins. Rituximab could not be used acutely due to concerns for worsening underlying COVID-19 pneumonia. He also received folic acid supplementation and was kept warm. This was achieved by ensuring that the room temperature was above the thermal amplitude of the cold antibody (34°C), by covering the patient with hats, gloves, socks and blankets, and by warming all infusions throughout his stay, including the pRBC transfusions, via an apheresis machine.

OUTCOME AND FOLLOW-UP

The patient responded well to cAIHA treatment. With treatment, his haemoglobin and haemolytic parameters rapidly improved. He remained in the ICU for 4 days and his haemoglobin levels gradually increased to 90 g/L before he was discharged to his home hospital for further monitoring. From a COVID-19 perspective, he remained stable and he did not require oxygen during his hospital stay. The follow-up plan included evaluation for either rituximab and bendamustine versus enrolment in a complement inhibitor clinical trial once he recovered from COVID-19.

DISCUSSION

Cold agglutinins are autoantibodies targeting red blood cell antigens. In primary CAD, there is evidence of a low-grade expansion of B cells producing monoclonal IgM or rarely IgA antibodies that cause complement-mediated haemolysis by binding the I antigen on the red cell surface.⁴ Clinically relevant pathological cold autoantibodies can cause complement-mediated haemolysis close to room temperature or higher.^{5 6} This leads to haemolysis in individuals at temperatures experienced in their day-to-day lives.

Cold agglutinin syndrome (CAS) is a secondary process, due to an underlying infection (eg, Epstein-Barr virus (EBV) or mycoplasma), autoimmune disorder (eg, anti-IH) or lymphoid malignancy.⁷ It



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Table 1 Findings and lab results

Variable	Reference range (units)	Value
Vital signs		
Heart rate	60–100 bpm	140 bpm
Blood pressure	90/60–130/90 mm Hg	135/69 mm Hg
Respiratory rate	12–18 breaths/min	27 breaths/min
Oxygen saturation	>92% on room air	97% on room air
Temperature	36°C–37.5°C	37°C
Investigations		
Haemoglobin	125–170 g/L	Baseline 140 g/L 80 g/L initial 56 g/L after rapid haemolysis within 12 hours
Mean corpuscular volume (MCV)	80–98 fl	123 fl
Reticulocyte count	30–110×10 ⁹ /L	99×10 ⁹ /L initial 329×10 ⁹ /L after rapid haemolysis within 24 hours
Blood film		
		Significant for red cell agglutination which dispersed when heated to 37°C, nucleated red cells, polychromasia and spherocytes (figure 1)
Platelets	150–400×10 ⁹ /L	229×10 ⁹ /L
Coagulation factors		
	International Normalized Ratio (INR) 0.9–1.1	INR 1.1
	Prothrombin time (PT) 9.4–12.4 s	PT 11.1 s
	Partial Thromboplastin Time (PTT) 21–29 s	PTT 17 s
Liver enzymes		
	Aspartate aminotransferase (AST) 15–37 IU/L	AST 203 IU/L initial; repeat 47 IU/L
	Alanine aminotransferase (ALT) 17–63 IU/L	ALT 33 IU/L
	Alkaline phosphatase (ALP) 50–136 IU/L	ALP 169 IU/L initial; repeat 107 IU/L
Serum albumin	34–50 g/L	33 g/L
Bilirubin		
	Total 2–20 µmol/L	Total 66 µmol/L
	Direct <5 µmol/L	Direct 9 µmol/L
Lactate dehydrogenase (LDH)	50–150 U/L	2362 U/L At discharge: 430 U/L (near baseline)
Haptoglobin	0.3–2.0 g/L	<0.08 g/L
D-Dimer	<0.5 ng/mL	>4400 ng/mL
IgM level	0.45–2.81 g/L	Preplasma exchange: 18.9 g/L Postplasma exchange: 2.67 g/L
Direct antiglobulin test		Positive; C3d 1+
Thermal amplitude		34°C
Cold agglutination titre		
		1:256 at 30°C 1:1024 at 22°C
Bacterial blood culture x2	Incubated for 5 days	No growth
Urine culture		No growth
COVID-19 PCR from Nasopharyngeal swab		Detected (2 March 2021)
COVID-19 variants of concern Gene mutation, NAA+probe		Not detected
Imaging		
Thorax CT scan with pulmonary angiogram contrast		No evidence of pulmonary embolism. Diffuse patchy peripherally predominant bilateral ground glass opacities in keeping with known COVID-19 infection/pneumonia.
Echocardiogram		Normal left ventricular size, borderline concentric left ventricular hypertrophy (LVH), ejection fraction of 60%. No obvious regional wall motion abnormalities. Normal right ventricular (RV) size with borderline RV dysfunction.

is usually due to pathologic IgM, and rarely IgG. When associated with an infection or autoimmune disorder, the implicated immunoglobulins are polyclonal, while lymphoid malignancies produce monoclonal immunoglobulins.

Treatment with rituximab as either monotherapy or in combination with bendamustine is the first-line pharmacological approach to CAD.⁸ Corticosteroids are not an effective cAIHA treatment.⁸ In the context of COVID-19, however, B-cell depletion can impair development of neutralising anti-SARS-CoV-2

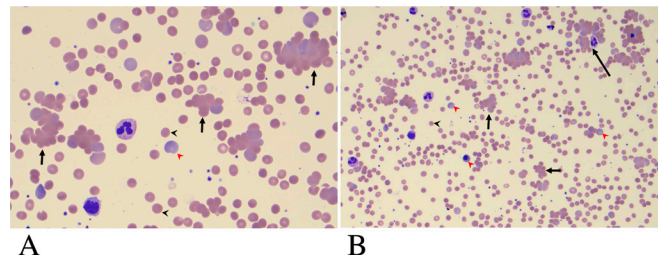


Figure 1 Peripheral blood smear (A: ×20, B: ×40) showing multiple areas of red blood cell agglutination (arrows), spherocytes (black arrowhead), polychromasia (red arrowhead) including nucleated red cells suggesting cold autoimmune haemolysis.

antibodies, increasing the risk of infection and impaired vaccine efficacy.⁹ In patients with inflammatory/rheumatological diseases, exposure to rituximab has been correlated with higher severity of COVID-19 illness.¹⁰ Nonetheless, the evidence is unclear whether this higher severity is due to the inflammatory disease itself versus rituximab treatment. The evidence regarding the safety of rituximab in active COVID-19 is incompletely understood, and there remains concern for potential harm. We therefore avoided rituximab in acute treatment of decompensated cAIHA to prevent worsening of COVID-19 due to safety concerns including delay in therapeutic activity.

There have been a few case reports published on CAD exacerbation and CAS development in conjunction with COVID-19 infection.^{11–16} Six of eight (75%) described patients improved, while two (25%) perished. Those who improved were primarily treated with rituximab or disease-modifying antirheumatic drugs (DMARDs) in addition to transfusion support.^{11–16} Those who perished were primarily treated with red cell transfusions alone. It remains unclear which of these additional treatments may be most effective. Interestingly, there has been one case report of new-onset CAD in the context of COVID-19 where rituximab was used and the patient’s haemoglobin stabilised, however, the acuity of the patient’s haemolysis was unclear.¹¹ None of these patients were treated with TPE.

TPE has traditionally been used for CAD patients in fulminant haemolytic anaemia when other pharmacological therapies and supportive transfusions are insufficient.^{12–17} The majority of IgM antibodies are in the intravascular compartment. Hence, TPE is able to effectively remove these circulating pathologic IgM auto-antibodies. TPE is a temporary solution, with patients subsequently requiring combination immunosuppressive therapy.¹⁸ In this patient, TPE was used as a temporising treatment, allowing time for recovery from COVID-19 and further assessment for

Learning points

- ▶ Cold agglutinin disease can be exacerbated by an acute viral infection like COVID-19.
- ▶ Cold agglutinin disease can result in rapid autoimmune haemolysis causing morbidity without appropriate emergent therapy.
- ▶ Rituximab-based therapy, the first-line treatment of cold autoimmune haemolytic anaemia, is relatively contraindicated in acute COVID-19 illness.
- ▶ Therapeutic plasma exchange is a rapid temporary solution for fulminant cold autoimmune haemolysis and can stabilise a patient.

either rituximab-based therapy or consideration of enrollment in a complement inhibitor clinical trial.¹⁹

Glucocorticoid treatment, specifically dexamethasone, has been shown to reduce mortality in patients with COVID-19 who are receiving respiratory support.²⁰ However, this patient did not have severe pneumonia, nor acutely required supplemental oxygen. Glucocorticoids are an important treatment option in warm autoimmune haemolytic anaemia. However, in cAIHA, glucocorticoids are not effective and can delay appropriate therapy. It is likely that the guideline dexamethasone treatment in this patient was not indicated at the time, but may have been helpful in mitigating further clinical worsening due to COVID-19.

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