Cold agglutinin hemolytic anemia in a patient with COVID-19 infection– a case report

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ABSTRACT

Background: Autoimmune hemolytic anemia (AIHA) is a rare but increasingly recognized complication of COVID-19. We present a unique case of severe cold autoimmune hemolytic anemia (cAIHA) in the setting of concurrent COVID-19 infection that exhibited a relapsing course requiring rescue therapy.

Case Presentation: A 73-year-old male with chronic obstructive pulmonary disease who presented with worsening cough and dyspnea was found to have acute COVID-19 infection. Laboratory investigations revealed severe anemia, elevated lactate dehydrogenase, low haptoglobin, reticulocytosis, and positive direct antiglobulin test (DAT) with cold agglutinin titers, consistent with cAIHA. Extensive infectious, autoimmune, and malignancy workup was unremarkable. He was initially managed with corticosteroids, folic acid, and weekly rituximab. While symptoms improved temporarily, he experienced hemolytic relapse, necessitating plasmapheresis and transfusion support. Hematologic parameters stabilized, and he was asymptomatic with no evidence of hemolysis at three-month follow-up.

Conclusion: COVID-19 may trigger cold AIHA through immune dysregulation and complement activation. Diagnosing cAIHA in COVID-19 is complex due to overlapping features and high DAT positivity rates without active hemolysis. This case underscores the importance of individualized management, balancing immunosuppression and supportive care. Further research is needed to understand the pathogenesis and optimal treatment strategies for COVID-19-associated cAIHA.

Keywords: Hemolytic anemia, COVID-19, cold agglutinins, immune-mediated hemolysis, plasma exchange, case report.

Type of Article: CASE REPORT **Specialty:** Hematology

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Background

Several autoimmune phenomena have been reported in the setting of COVID-19 infection, including autoimmune hemolytic anemia (AIHA), multisystemic inflammatory syndromes, Guillain-Barre syndrome, and thrombotic thrombocytopenic purpura [1]. cold autoimmune hemolytic anemia (cAIHA) is primarily mediated by IgM autoantibodies that bind to red blood cells (RBCs) at low temperatures, leading to complement activation and hemolysis. COVID-19 exacerbates this condition through speculated mechanisms of cytokine storm and direct complement activation via auto-antibodies. Prompt recognition enables the initiation of immunosuppressive therapy against complement-mediated hemolysis and counters the elevated thromboembolic risk, all of which may alleviate disease severity and improve patient outcomes. In the following report, we describe a rare case of cAIHA in a patient with severe acute COVID-19 infection, highlighting diagnostic and therapeutic challenges.

Case Presentation

A 73-year-old gentleman presented to our center with worsening shortness of breath and cough for 10 days. He denied fever, chest pain, orthopnea, palpitations, hematemesis, melena, or hematuria. Past medical history was notable for chronic obstructive pulmonary disease, well-controlled hypertension, and non-insulin-dependent diabetes mellitus. He was a previously reformed smoker with a history of 40 pack-years of smoking. He worked as a car mechanic and had not traveled out of the country remotely or recently. At presentation, he was afebrile and found to have tachycardia (pulse rate 110/minute), blood pressure of 128/74 mm Hg, respiratory rate of 20/minute, and oxygen saturation of 82% on room air, which increased to 95% with supplemental oxygen of 2-3 l/minute via nasal cannula. Marked conjunctival pallor was seen, while the rest of the systemic examination was unremarkable.

Investigations and Differential Diagnoses

Laboratory investigations revealed leukocytosis, severe anemia with macrocytosis, unconjugated hyperbilirubinemia, and elevated liver enzymes (Table 1). A respiratory BioFire panel of the nasopharyngeal swab was positive for severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). The chest radiograph was unremarkable, while computed tomography of the chest showed a right basal pulmonary nodule measuring 1.4 cm. Ferritin was slightly elevated; serum B12 and folate were within normal limits. Further workup was significant for high lactate dehydrogenase (nearly 10 times the upper limit of normal), elevated corrected reticulocyte count, and undetectable haptoglobin; the overall picture suggested ongoing hemolysis. Peripheral blood film showed marked anisocytosis, poikilocytosis, polychromasia, and RBC clumping without significant schistocytes. A direct antiglobulin test (DAT) and cold agglutinin antibody screen were strongly positive, confirming the diagnosis of cold AIHA. Serum complements (C3, C4) were low. An extensive infectious and autoimmune workup was performed to delineate the underlying cause. Viral serologies, blood and urine cultures, blood quantitative Epstein-barr virus, anti-nuclear antigens, ds-DNA, anti-cardiolipin antibody, anti-ribonucleoprotein, anti-Smith, and anti-Anti-Sjögren's-syndrome-related Antigen A/Anti-Sjögren's-syndrome-related Antigen B antibodies were negative. Serum and urine electrophoresis did not reveal any evidence of monoclonal gammopathy. We attributed the acute cAIHA to the underlying COVID-19 infection as the trigger.

Table 1. *Lab parameters and investigations at admission.*

LAB PARAMETER	RESULT	REFERENCE RANGE
Total leukocyte count	21.95 × 10^3/µl	4.5-11 × 10^3/µl
Hemoglobin	6.7 g/dl	12.0-16.0 g/dl
Hematocrit	19.5 %	38.0%-47.0 %
Mean corpuscular volume	99 fl	82.0-98.0 fl
Mean corpuscular hemoglobin concentration	34.9 g/dl	31.0-36.9 g/dl
Platelet count	155 × 10^3/µl	150-450 × 10^3/µl
Prothrombin time	16.1 seconds	11.8-14.8 seconds
International normalized ratio	1.3	0.9-1.2
Fibrinogen level	344	234-500
Reticulocyte count	12.2%	0.5%-1.5%
Serum blood urea nitrogen	21 mg/dl	9-21 mg/dl
Serum creatinine	1 mg/dl	0.66-1.25 mg/dl
Serum calcium	7.6 mg/dl	8.4-10.2 mg/dl
Serum phosphorus	3.8 mg/dl	2.5-3.5 mg/dl
Serum albumin	2.9 g/dl	3.5-5.0 g/dl
Serum protein	5.4 g/dl	6.3-8.2 g/dl
Serum total bilirubin	5.0 mg/dl	0.2-1.3 mg/dl
Serum direct bilirubin	0.8 mg/dl	0-0.3 mg/dl
Serum vitamin B12	725 pg/ml	239-931 pg/ml
Serum folate	14.9 ng/ml	2.76-20.0 ng/ml
Serum iron	218 mcg/dl	49-181 mcg/dl
Serum transferrin	153 mg/dl	206-381 mg/dl
Serum Total iron-binding capacity	269 mcg/dl	261-462 mcg/dl
Aspartate aminotransferase	134 IU/l	17-59 IU/l
Alanine transaminase	74 IU/l	0-50 IU/l
Alkaline phosphatase	59 IU/l	38-126 IU/l
Serum lactate dehydrogenase	2256 IU/l	120-246 IU/l
Serum ferritin	1390 ng/ml	17.9-464 ng/ml

Treatment, Outcomes, and Follow-Up

Remdesivir, oral antibiotics, and supportive treatment with inhaled bronchodilators were started for COVID-19-related hypoxemic respiratory failure. Daily prednisone (1.5 mg/kg) with folic acid was added empirically for presumptive acute AIHA pending definite diagnosis. The patient also required transfusion support with two units of packed RBCs. Given the complement-mediated nature of hemolysis in cAIHA and the limited response to steroids, early initiation of rituximab was deemed appropriate due to the severity of anemia, the likelihood of steroid resistance, and the need to minimize transfusion burden. Blood parameters improved by day seven of admission, with hemoglobin increasing to nearly 8 g/dl with marked amelioration of symptoms. He was discharged on steroids and rituximab (375 mg/m^2, once weekly) to provide sustained immunological control of hemolysis. However, he was readmitted 6 days later due to worsening fatigue and a progressive decline in hemoglobin levels, accompanied by evidence of ongoing hemolysis (elevated lactate dehydrogenase) on follow-up investigations. Rescue plasmapheresis was initiated in conjunction with transfusion support due to the persistence of marked hemolysis despite initial immunosuppressive therapy with corticosteroids and rituximab. Following three sessions, hematologic parameters stabilized (hemoglobin levels improved to 8.4 g/dl), and the patient was transfusion-independent. Glucocorticoids were gradually tapered off with the completion of four cycles of rituximab. At the 3-month follow-up, he was clinically asymptomatic and doing well without evidence of anemia or hemolysis on blood investigations (Figure 1).

Discussion

This case describes an uncommon presentation of cold AIHA in a patient with acute COVID-19 infection,

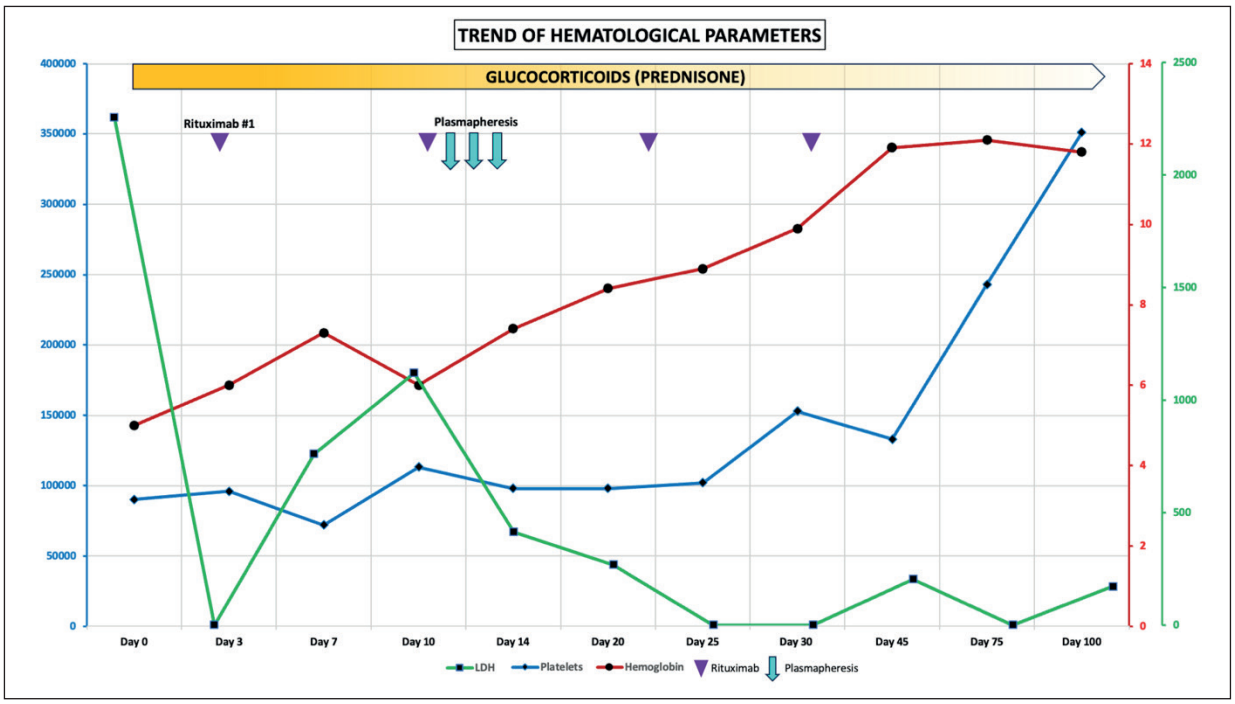

Figure 1. *Trend of hematological parameters over the course of treatment.*

highlighting the diagnostic and therapeutic challenges encountered. Cold AIHA can be primary or secondary, with cold agglutinin disease, a lymphoproliferative disorder more common than secondary cold agglutinin syndrome associated with autoimmune diseases, infections (e.g., COVID-19), or malignancies. Although a systematic review of 50 patients linked COVID-19 infection and vaccination to cAIHA (n = 18), warm AIHA (n = 14), mixed-type AIHA (n = 3), DAT-negative AIHA (n = 1), DAT-negative Evans syndrome (n = 1), Evans syndrome (n = 3), and unspecified AIHA subtypes (n = 10), the true incidence and prevalence of COVID-19-associated cAIHA remain uncertain [2]. The median onset of AIHA in COVID-19 is 9 days (range 4-13 days) [3].

Proposed mechanisms linking COVID-19 and autoimmune disorders include epitope spreading, bystander activation, cross-reaction or molecular mimicry, and the presentation of cryptic antigens [4]. SARS-CoV-2 can induce autoantibodies or directly damage erythrocytes via interactions with receptors like CD147 and Band-3 protein [4,5]. cAIHA is precipitated by IgM kappa light chain autoantibodies binding to the erythrocyte I antigen at temperatures below 37°C, resulting in RBC agglutination and complement activation. Low levels of C3 and C4 in this patient likely represent ongoing complement pathway activation and consumption in the setting of immune-mediated hemolysis. However, the exact pathogenesis of cAIHA in the context of SARS-CoV-2 infection remains unclear.

Cold AIHA is diagnosed with the help of cold-induced symptoms exacerbation, positive DAT for C3d, elevated cold agglutinin titers, and blood markers suggestive of hemolysis [6]. However, diagnosing cAIHA in the context of acute COVID-19 infection is challenging. Compared to non-COVID-19 patients, a higher prevalence of DAT positivity is seen in hospitalized COVID-19 patients [7,8]. Mechanisms proposed include RBC membrane alteration exposing cryptic antigens, antigenic mimicry between the ankyrin-1 protein and the SARS-CoV-2 spike protein, and subsequent hyperinflammation cascade [8,9]. Critically ill COVID-19 patients often have a higher prevalence of low hemoglobin (37%) attributed to altered iron metabolism, hepcidin mimicry by the spike protein, ferroportin blockage, and RBC membrane disruption [8,10,11]. These patients typically show higher haptoglobin levels than non-COVID patients, likely due to an acute phase response. Up to 50% of acute COVID-19 infections exhibit positive DAT, emphasizing the role of careful interpretation in conjunction with clinical symptoms and other hemolytic markers to inform treatment decisions [12].

Treatment protocols align closely with standard cAIHA management and are warranted in cases of moderate-to-severe anemia or acral symptoms. Supportive care in COVID-19-associated cAIHA, such as avoiding cold exposure and administering warm blood transfusions, mirrors the approach in patients without COVID-19. Corticosteroids are rapid-acting first-line immunosuppressive therapy to stabilize hemolysis in AIHA, particularly when a specific subtype (warm *vs.* cold) may not be immediately delineated. Monotherapy with rituximab is recommended for patients with unstable patients with comorbidities, while rituximab-based combination

regimens (e.g., with fludarabine and bendamustine) are preferred for otherwise fit patients [13]. B-cell depletion therapy, effective in AIHA, carries the risk of prolonged viral shedding and severe COVID-19 infection [14]. Therefore, rituximab-based regimens in COVID-19-associated cAIHA may require concurrent antivirals (e.g., remdesivir in our patient) to mitigate COVID-19 severity, though evidence on their efficacy is limited. For patients who fail initial therapies or experience relapses, second-line options include complement inhibitors, bortezomib, and ibrutinib [13]. Plasmapheresis, a temporizing intervention with the potential to rapidly reduce pathogenic IgM levels and subsequent complement activation in severe refractory cases while awaiting the delayed onset of action from biologicals, was effectively employed in our case due to persistent hemolysis and transfusion dependence. Similar to several published case reports, our patient presented with severe anemia in the setting of COVID-19 infection, with laboratory findings consistent with cAIHA. Unlike previously reported cases where hemolysis emerged in the context of severe systemic illness or multiorgan dysfunction, this patient's hematologic manifestation was a distinct clinical concern, complicating early recognition. In terms of management, our case stands out for the early addition of rituximab and the eventual need for rescue plasmapheresis, serving as a distinguished example of a refractory disease course that required treatment escalation beyond conventional immunosuppression modalities.

Conclusion

AIHA in COVID-19 is associated with increased length of stay, mortality, and poor prognosis [2,15]. Hospitalized patients with COVID-19 infection have a higher prevalence of positive DAT without acute hemolysis, warranting interpretation with supplementary laboratory data and clinical symptoms to determine appropriate treatment. Management involves balancing the immunosuppression to control hemolysis with the risk of exacerbating viral infection and severity. The impact of these immunosuppressive therapies on COVID-19 infection needs further research.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Consent for publication

Written informed consent was obtained from the patient for their anonymized information to be published in this article.

Ethics approval

Ethical approval is not required at our institution to publish an anonymous case report.

What's new

This case highlights cold agglutinin hemolytic anemia (cAIHA) as a rare autoimmune complication of COVID-19, requiring prompt diagnosis and tailored immunosuppressive management. Further research is needed to understand the pathogenesis of COVID-19-associated cAIHA.

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Summary of case

1	Patient (gender, age)	73 years, male
2	Final diagnosis	COVID-19 related cold autoimmune hemolytic anemia
3	Symptoms	Shortness of breath
4	Medications	Rituximab, steroids
5	Clinical procedure	Immunosuppressive therapy, plasma exchange
6	Specialty	Hematology