American Journal of Medical Case Reports, 2021, Vol. 9, No. 6, 328-330
Available online at http://pubs.sciepub.com/ajmcr/9/6/6
Published by Science and Education Publishing
DOI:10.12691/ajmcr-9-6-6

Cold Agglutinin Hemolytic Anemia Induced by COVID-19

Amandeep S. Saini, Kevin Shayani, Jacob Schwartz*

Lenox Hill Hospital, Department of Internal Medicine New York, NY, 10075
*Corresponding author: Jschwartz5@northwell.edu

Received February 03, 2021; Revised March 09, 2021; Accepted March 18, 2021

Abstract Autoimmune hemolytic anemia (AIHA) is an acquired autoimmune disorder characterized by the production of antibodies against red blood cell (RBC) antigens causing reduced circulation time. Diagnosis is based on clinical and laboratory signs of hemolysis and a positive direct antiglobulin test (DAT) after excluding alternative causes for those findings. AIHA is sub-classified according to auto-antibody, cold versus warm, and whether primary or secondary in nature. Warm AIHA is associated with the IgG antibody type and generally causes extravascular hemolysis in the spleen. Cold AIHA is less common, associated with the IgM antibody type, and leads to intravascular hemolysis after activating the classical complement pathway. Throughout the COVID-19 pandemic, it has been noted that hospitalized patients are in a pro-inflammatory state (e.g. elevated D-dimer, ferritin, C-reactive protein) that predisposes them to hematological complications such as venous thromboembolisms (VTE). Although the exact pathophysiology remains unclear, evidence points towards fatal cytokine release. Moreover, there have been case reports of AIHA in a subset of COVID-19 patients and researchers postulate molecular mimicry amongst the epitopes of Ankyrin 1 and viral spike protein as a potential culprit. This case report discusses an elderly patient with multiple co-morbidities who was admitted for acute hypoxemic respiratory failure from COVID-19 and found to have cold agglutinin hemolytic anemia. We are looking to contribute to the current understanding of AIHA as a complication of COVID-19 infection.

Keywords: *coronavirus, COVID-19, AIHA, anemia, hemolysis, DAT, Coombs test*

Cite This Article: Amandeep S. Saini, Kevin Shayani, and Jacob Schwartz, "Cold Agglutinin Hemolytic Anemia Induced by COVID-19." *American Journal of Medical Case Reports*, vol. 9, no. 6 (2021): 328-330. doi: 10.12691/ajmcr-9-6-6.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) is the strain that causes coronavirus disease 2019 (COVID-19). While recent Emergency Use Authorization allows for phased vaccine rollouts, to date there are approximately 92 million global cases with 2 million deaths and growing concerns regarding virulent strain mutations [1]. Most patients with COVID-19 have mild disease, however, individuals with comorbid medical conditions can succumb to severe complications such as encephalopathy, acute respiratory distress syndrome, renal failure and death. Noted for its pro-inflammatory state, COVID-19 commonly presents with elevated D-dimer, ferritin, and C-reactive protein along with increased risk for VTE and strokes. Hospital protocols incorporate aggressive anticoagulation and imaging modalities in order to reduce unfavorable thrombotic complications. Interestingly, there have been case reports of AIHA in patients with COVID-19 [2-7]. The relationship between COVID-19 and AIHA has not been well investigated. Hemolytic anemia typically presents with anemia, decreased haptoglobin, and increased lactate dehydrogenase and bilirubin levels. Here we report a case of a 94-year-old female with a past medical history of atrial fibrillation, CKD, anemia, heart failure with preserved ejection fraction (HFpEF) who presented after being hypoxemic at home, found to be positive for COVID-19 along with positive direct antiglobulin test suggestive of cold AIHA.

2. Case Presentation

A 94-year-old female with a past medical history of atrial fibrillation, chronic kidney disease, anemia (baseline hemoglobin 8.1), and HFpEF presented to the emergency department (ED) after being hypoxemic at home. The patient was in her usual state of health when she developed progressively worsening nausea three days prior with non-bloody non-biliary emesis that resolved after one day. She subsequently developed headaches along with decreased appetite. Her son, who was present at bedside, reported that the patient looked unwell on the day of ED visit. He checked her vitals and noted she was tachycardic, hypotensive, and hypoxemic to 89% on room air. On arrival to the ED the vitals were noted to be 102°F, heart rate 91-106, blood pressure 107-139/56-77,

respiratory rate (RR) 28 breaths per minute, and saturating 88% (SpO2) on room air. She was placed on 4 L nasal cannula (NC) with SpO2 98-100% and RR 20. On physical exam, the patient was in no acute distress and without accessory muscle use. The lungs were notable for left sided crackles throughout along with a grade 2/6 systolic murmur in the aortic region. Her abdominal exam was remarkable for moderate distention and tympanic to percussion. The lower extremities had trace bilateral edema with notable skin changes consistent with venous stasis dermatitis. Shown in Table 1 are her pertinent admission labs. Her venous blood gas (VBG) on 4 L NC was unremarkable with a pH of 7.41 and pCO2 of 43.

The urinalysis was positive for leukocyte esterase, nitrates, and many white blood cells. A decision was made not to consider urinary tract infection given that epithelial cells were noted and patient did not complain of dysuria, flank pain, and polyuria. Blood cultures returned negative for growth and urine culture was contaminated. COVID-19 PCR testing was positive. Chest x-ray (CXR) showed reticular mesh-like opacifications with questionable left middle lobe opacification, although grossly unchanged from a prior study two months ago. The EKG showed left anterior fascicular block, but in normal sinus rhythm. Given that the patient was hypoxemic on room air and required 4-6 L NC, she was started on a 10-day course of dexamethasone 6 mg and 5-day course of remdesivir. Community acquired pneumonia treatment was held since the left middle lobe consolidation on CXR appeared chronic. Repeat labs a few hours after admission revealed a hemoglobin of 6.3, requiring one unit of packed red blood cells. Fecal occult blood test was negative. Of note, the patient has a long-standing history of anemia and recommended outpatient bone marrow biopsy by a hematologist, for which the patient refused. She also denied any recent melena or hematochezia.

On the second day of admission, the hematology/oncology team was consulted in the context of hemolytic anemia suggestive by elevated bilirubin, LDH, and reticulocyte count with low haptoglobin and slight schistocytes on peripheral smear. Direct antiglobulin test was positive for anticomplement (C3) and negative for anti-immunoglobulin G and cryoglobulins. Epstein-Barr virus panel showed past infection and hepatitis screen was negative. Per the hematologist, this finding was likely related to infectious/inflammatory source (positive COVID-19 PCR and elevated ferritin, procalcitonin, and CRP). Moreover, total bilirubin and LDH appeared to be decreasing suggesting mild disease. As a result, the decision was made to withhold plasmapheresis and/or rituximab for hemolytic anemia treatment. The primary team was instructed to maintain a higher transfusion goal of Hgb > 8 and cold avoidance (e.g. intravenous solutions and blood products should be warmed prior to infusion, use of blankets and heat packs, no ice chips).

The patient's hospital course was complicated by worsening hypoxemic failure that required ICU transfer for mechanical ventilation. Moreover, she developed hemodynamically unstable atrial fibrillation with rapid ventricular response, which required two cardioversion attempts (both unsuccessful) and initiation of amiodarone and metoprolol tartrate. Given the higher hemoglobin threshold, the patient was transfused five additional units of packed RBCs. The total bilirubin decreased from 4.6 to 2.2 mg/dL with near normalization in haptoglobin levels. Unfortunately, the palliative care team was consulted given poor overall prognosis and the decision was ultimately made for terminal weaning off the ventilator. The patient passed from cardiopulmonary failure.

Table 1. Laboratory data

Variable	Reference Range	On ED presentation
Sodium (mEq/L)	135-145	138
Potassium (mEq/L)	3.5-5.3	3.7
Chloride (mEq/L)	96-108	98
Carbon dioxide (mEq/L)	22-31	27
Anion Gap	5-17	13
Creatinine (mg/dL)	0.50-1.3	1.24
Glucose (mg/dL)	70-99	144
Calcium (mg/dL)	8.4-10.5	9.1
Magnesium (mg/dL)	1.6-2.6	1.9
Aspartate Aminotransferase (U/L)	10-40	25
Alanine Aminotransferase (U/L)	10-45	9
Total Bilirubin (mg/dL)	0.2-1.2	4.6
Direct bilirubin (mg/dL)	0.0-0.2	1.0
Indirect bilirubin (mg/dL)	0.2-1.0	3.4
WBC Count (K/µL)	3.80-10.50	10.38
Hemoglobin (g/dL)	13.0-17.0	7.5
Hematocrit (%)	34.5-45.0	22.7
Reticulocyte (%)	0.5-2.5	3.46
Platelet Count (K/µL)	150-400	308
D-Dimer (ng/mL)	<230	198
C-Reactive Protein (mg/dL)	0.00-0.40	17.62
Ferritin (ng/mL)	30-400	1673
Procalcitonin (ng/mL)	0.02-0.10	0.38
Lactate Dehydrogenase (U/L)	50-242	461
Haptoglobin (mg/dL)	34-200	< 10
Lactate, blood (mmol/L)	0.5-2.0	1.3
Serum Pro-Brain Natriuretic Peptide (pg/mL)	0-300	2955

3. Discussion

This case serves to contribute to current medical understanding of AIHA as a complication of COVID-19. AIHA is characterized by the presence of autoantibodies that bind to a patient's red blood cells (RBCs) and cause hemolysis. The estimated incidence is 1-3 per 100,000 persons per year and the estimated prevalence is 17 per 100,000 persons [8]. When the rate of destruction far exceeds that of replacement, AIHA may present with symptomatic anemia, symptoms of jaundice, and signs of heart failure. RBC destruction may occur intravascularly via complement-mediated hemolysis or extravascularly in the spleen and/or liver via antibody and complement phagocytic activity [9]. AIHA is classified based on the thermal reactivity of autoantibodies, hence the nomenclature "warm" and "cold" agglutinins. Warm AIHA is generally caused by IgG antibodies that bind to RBCs at 37°C, with 40% of those cases being idiopathic. It is associated with infectious diseases such as HIV and medications such as antibiotics, antipyretics, and anti-cancer drugs. Moreover, warm AIHA can be seen in lymphoproliferative diseases including leukemia, non-

Hodgkin lymphoma, and myelomas. In contrast, cold AIHA is characterized by hemolysis due to cold sensitive antibodies (usually IgM) with optimal activity between 0 and 4 °C but also react at temperatures greater than 30°C. Cold agglutinins lead to RBC destruction by binding to their membrane and activating complement. They are associated with infections that include mycoplasma pneumoniae, hepatitis C virus, Epstein-Barr virus, and cytomegalovirus, and also B-cell lymphoproliferative disorders [8]. Of note, Raynaud's phenomenon can be seen in CAD [10].

After confirming hemolysis via laboratory tests (CBC, peripheral smear, bilirubin, lactate dehydrogenase, haptoglobin), the diagnosis of immune-mediated hemolysis then made via antiglobulin testing (DAT/Coombs test) by looking for anti-immunoglobulin G (IgG) and anti-C3d. Management of cold agglutinin disease (CAD) involves avoiding cold exposure, treating symptomatic anemia with blood transfusions, and rituximab [10]. More than 70% of patients require therapy, but those with mild disease may not. Additionally, underlying conditions contributing to secondary CAD should be treated according to recommended treatment guidelines for the condition. For warm AIHA management, treatment is dependent on hemodynamic stability and transfusion goals. After stabilizing the patient, it is imperative perform thorough medication reconciliation and discontinue any drug-induced warm AIHA. The patient should also be screened for VTE. Most experts then initiate glucocorticoids plus rituximab, especially in symptomatic patients. Once the hemoglobin has stabilized and hemolytic markers are improving (typically over two to three weeks), a steroid taper can be initiated [10].

Researchers postulate that molecular mimicry is a potential cause for AIHA in the COVID-19 subset due to shared epitopes (750-SNLLLQYGSFCTQL-763) between Ankyrin 1 (ANK-1) and viral spike protein. ANK-1 is an erythrocyte membrane protein that is involved with red cell differentiation and function, thereby providing the primary connection between the plasma membrane and the membrane skeleton. Notably, ANK-1 defect is seen in hereditary spherocytosis, which is a common cause of hemolytic anemia [4].

As determined by our patient's laboratory results (anemia, low haptoglobin, high LDH, positive anticomplement) this patient likely had cold agglutinin disease. An argument against this complication was her baseline hemoglobin of 8.1 prior to hospitalization. Her peripheral smears did reveal abnormal red cell morphology, smudge cells, and giant platelets, all of which may point towards undiagnosed hematological malignancy. Per outpatient records dated from last year, however, serum bilirubin and LDH levels were within normal limits, thereby favoring new onset cold AIHA. Given that the patient had clinical improvement (reduced LDH and bilirubin levels) after the first packed RBC transfusion, the hematology team did not recommend rituximab treatment. In retrospect, the patient may have benefitted from rituximab since she required repeated blood transfusions and clinically deteriorated. Volume supplementation should be judiciously used in COVID cases since patients can quickly develop flash pulmonary edema and exacerbate ventilation to perfusion mismatch.

4. Conclusion

Aside from respiratory failure, COVID-19 is known for thromboembolic and inflammatory complications that further burdens care in the inpatient and outpatient setting. Patients with severe COVID-19 present with elevated inflammatory markers – D-dimer, ferritin, CRP, cytokines – that are associated with poor prognosis. AIHA is a rare disorder that can result from this infection, but remains poorly characterized. Studies have shown AIHA can develop from a myriad of conditions such as drugs, cancers, and certain infectious diseases. Case reports, such as this, call for thorough investigations and increased awareness to improve clinical outcomes in patients with COVID-19 infection.

References

[1] John Hopkins Coronavirus Resource Center. (n.d.). Global Cases. Johns Hopkins University & Medicine. Retrieved January 13, 2021, from https://coronavirus.jhu.edu/map.html.

[2] Jacobs J, Eichbaum Q. COVID-19 associated with severe autoimmune hemolytic anemia. *Transfusion*. 2020; 1-6.

[3] Lazarian G, Quinquenel A, Bellal M, et al. Autoimmune haemolytic anaemia associated with COVID-19 infection. *Br J Haematol*. 2020; 190(1):29-31.

[4] Hindilerden F, Yonal-Hindilerden I, Akar E, Yesilbag Z, Kart-Yasar K. Severe Autoimmune Hemolytic Anemia in COVID-19 İnfection, Safely Treated with Steroids. *Mediterr J Hematol Infect Dis*. 2020; 12(1): e2020053.

[5] Bass, G. F., Tuscano, E. T., & Tuscano, J. M. (2014). Diagnosis and classification of autoimmune hemolytic anemia. *Autoimmunity Reviews*. 2013; *13*(4-5): 560-564.

[6] Campos-Cabrera G, Mendez-Garcia E, Mora-Torres M, et al. Autoimmune Hemolytic Anemia As Initial Presentation of COVID-19 Infection. Blood. 2020; 136(1): 8.

[7] Maslov DV, Simenson V, Jain S, Badari A. COVID-19 and Cold Agglutinin Hemolytic Anemia. *TH Open*. 2020; 4(3): e175-e177.

[8] Patil NR, Herc ES, Girgis M. Cold agglutinin disease and autoimmune hemolytic anemia with pulmonary embolism as a presentation of COVID-19 infection. *Hematol Oncol Stem Cell Ther*. 2020; S1658-3876(20)30116-3.

[9] Engelfriet CP, Borne AE, Beckers D, Van Loghem JJ. Autoimmune haemolytic anaemia: serological and immunochemical characteristics of the autoantibodies; mechanisms of cell destruction. *Ser Haematol*. 1974; 7(3): 328-347.

[10] Hill QA, Stamps R, Massey E, et al. The diagnosis and management of primary autoimmune haemolytic anaemia. *Br J Haematol*. 2017; 176(3): 395-411.