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Case Report
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HbE Heterozygous Patient Presenting with Cold Agglutinin Syndrome with COVID-19 Infection - Case Report

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Abstract

Introduction: COVID-19 is rapidly spreading throughout the world. Several complications have been described which has been accompanying this infection. There have been few cases reported with autoimmune active hemolysis subsequently with COVID-19, most of them corresponding to Warm autoimmune hemolytic anemia.

Case Report: MRS. XX, 45 years old woman presented with complaints of generalized weakness, yellowish discoloration of skin for the last 5 days. She was incidentally found to be positive for COVID-19 after routine testing. On investigation the LFT disclosed unconjugated hyperbilirubinemia. Direct Coombe's test was found to be positive when done after washing RBC's and incubation. The patient was found to be positive for Heterozygous HbE phenotype. The patient was managed with blood transfusion and warming up the surrounding. Patient was discharged 4 days after stabilization.

Discussion: This case gives positive result with conservative treatment with blood transfusion alone that to in presence of severe anemia for cold agglutinin disease presenting with COVID-19 in presence of HbE trait.

Conclusion: This case affirms the relation between autoimmune hemolysis and COVID-19 infection. The association between HbE heterozygous with development of transient cold agglutinin disease in COVID-19 infection is yet to be ascertained.

Keywords: Autoimmune hemolytic anemia; COVID-19; Heterozygous HbE; Cold agglutinin disease

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Introduction

COVID-19 has entered its third year since its beginning in 2019. The various strains have affected the world having different virulence and infectivity. Initially starting from the Chinese province of Hubei and is still rapidly spreading throughout the world. With time we are becoming more aware of the various complications of the disease. There have been a few case reports of Autoimmune Hemolytic Anemia (AIHA) associated with COVID-19 [1]. This will be the first report of an AIHA-cold agglutinin disease associated with this viral infection and subsequently the presence of HbE phenotype to the best of our knowledge. It is important for us to be aware of the various presentations of COVID-19 which are not typical and can cause problems for the physician initially.

Acquired hemolytic anemia can be caused by mechanical destruction of cells as seen in paraprosthetic valve regurgitation and march hemoglobinuria, infection caused by malaria (most common infectious cause of hemolytic anemia) and other bacterial and viral infections, immune hemolytic anemia's, favism, drug induced and transfusion related hemolysis [2].

Autoimmune hemolysis consists of warm autoimmune hemolytic anemia, paroxysmal cold hemoglobinuria, cold agglutinin disease and drug or toxic agent induced. Two mechanisms are defined to explain the pathophysiology of autoimmune hemolysis. The first mechanism is known as innocent bystander effect in which the antibody is directed against certain molecule (drug/toxic substance) and in subsequent action leads to destruction of RBC's. The second mechanism consists of true autoantibody against the RBC's [2].

Unlike acquired, primary cold agglutinin disease is a rare disease. Countries of northern Europe

and Atlantic have the incidence of approximately 1 to 1.8 per million and the prevalence at approximately 13 to 16 per million. Females have slightly higher prevalence than males. Median age of diagnosis is in the 60s and 70s [3].

Cold agglutinin disease is less common than warm autoimmune hemolytic anemia, approximately one-fifth to one-quarter of patients with autoimmune hemolytic anemia. The disease is also known to occur in association with lymphoid malignancies and autoimmune disorders [3].

Cold agglutinins frequently occur during the course of *M. pneumoniae* and Epstein-Barr virus infection. Case reports have described cold agglutinins with other viral infections such as rubella virus, HIV, COVID-19 infection, influenza viruses, or varicella-zoster virus [3].

All individuals who have these infections does not develop cold agglutinins and will not have clinically significant hemolysis. It usually occurs approximately two weeks after onset of the primary infection. This condition is reported to resolve spontaneously after the resolution of infection. The blood parameters return to normal limits in few weeks to months. Cold agglutinins have also been reported in individuals with autoimmune disorders, i.e., rheumatoid arthritis and Systemic Lupus Erythematosus (SLE) [3].

Case Presentation

The 45 years old lady who is resident of Meghalaya, India was referred by primary care hospital for severe anemia of unexplained origin to our hospital on January 3rd, 2022. The lady presented with complaints of generalized weakness, yellowish discoloration of skin and eyes, increased thirst and urinary frequency for the last 5 days. She did not give any history of fever, body ache, respiratory symptoms, hematuria, pain abdomen, melena or hematemesis.

She did not have any significant similar past medical history. She was not on any prescribed drugs. No significant history of anemia in the family. She takes mixed diet in adequate amount. There was no history of alcohol intake. She takes tobacco product since a long time.

The general examination revealed pallor. Lymph nodes or spleen were not appreciated during examination. Further physical examination was within normal limits.

The patient was tested positive for COVID-19 infection on routine testing before admission through CBNAAT. The patient was shifted to COVID ward for further evaluation. On further testing Hemoglobin was 3.8 g/dL, MCV was 114 fL and corrected reticulocyte count was 6.3. PBS revealed clumping of RBC's, spherocytes, polychromatophilic cells, nucleated RBC's and a few Howell Jolly bodies. LFT revealed unconjugated hyperbilirubinemia. On routine urine examination RBCs and urobilinogen and bilirubin was reported.

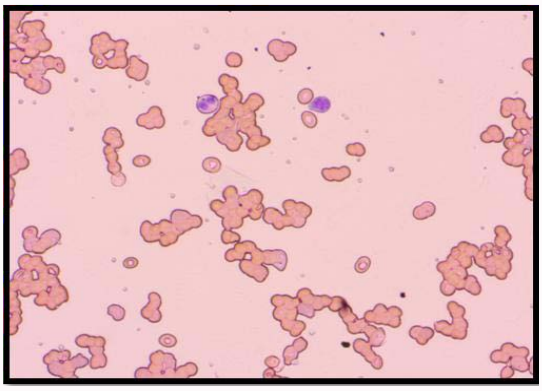

Figure 1: Peripheral blood smear stained with Leishman stain with Clumping of RBC at room temperature (40x).

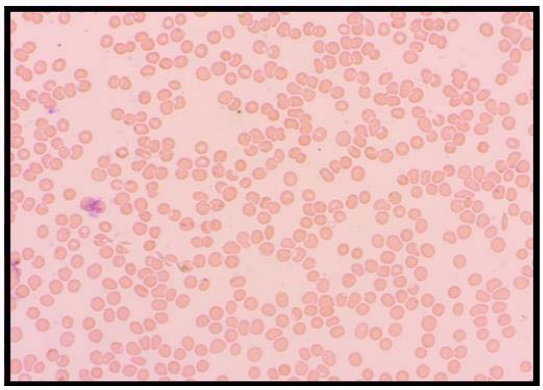

Figure 2: Peripheral blood smear stained with Leishman stain after Warming at 37ºC, No Clumping (40x).

Table 1: Liver function test findings.

Bilirubin Total	5.5	0.2-1.3 mg/dL
Bilirubin Unconjugated	4.7	0.0-1.1 mg/dL
Bilirubin Conjugated	0.8	0.0-0.3 mg/dL
SGPT	14	<35 U/L
SGOT	104	14-36 U/L
Total Protein	7.7	6.3-8.2 g/dL
Albumin	4.2	3.5-5.0 g/dL
Globulin	3.5	g/dL
A:G Ratio	1.2:1	1.5-2.0:1
Alkaline Phosphatase	67	38-126 U/L
GGT*	23	12-43 U/L

Table 2: Hemogram findings at the time of admission.

Hemoglobin	3.8	12.5-16.0 gm%
Total WBC Count	5,040	4,000-11,000/cumm
Neutrophil	61	40-80%
Lymphocyte	34	20-40%
RBC	**0.7**	4.5-6.0 million/cumm
PCV	**08**	37-47%
Reticulocyte Count	**21.5**	0.5-2.5%
Corrected Reticulocyte Count	6.3	%
MCV	**114**	78-100 fL
MCH	**48**	27-31 pg
MCHC	**48**	32-36%

The patient's blood was sent for blood grouping and matching but initially the test showed unequivocal results due to agglutination of red blood cells. After washing and incubating RBCs at 37ºC, blood grouping was performed which was reported to be A1B positive. The patient's direct coombs test came positive. Cross matching was done and compatible blood was issued and transfused to the patient.

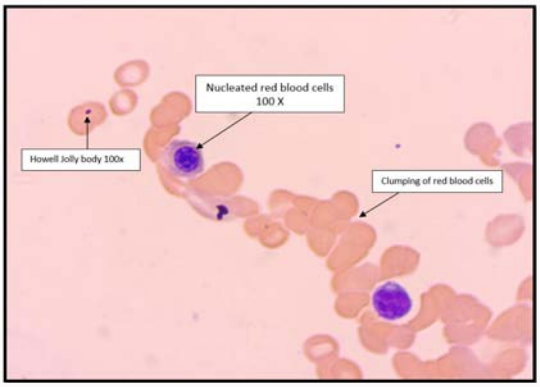

Figure 3: Peripheral blood smear stained with Leishman stain (100x).

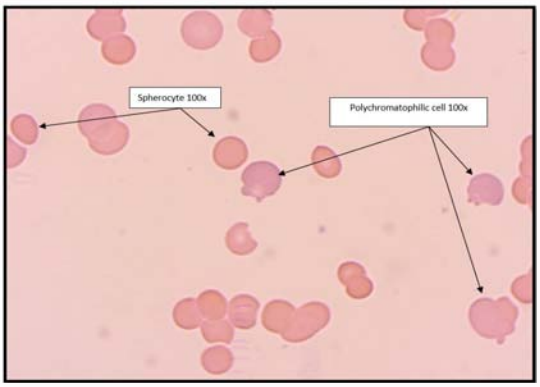

Figure 4: Peripheral blood smear stained with Leishman stain (100x).

Hemoglobin chromatography was sent to rule out hemoglobinopathy which came out positive for HbE heterozygous. ANA profile was sent to rule out association with other AI disorders which came out to be negative for common antigens. The patient was not evaluated for lymphoid malignancies as the history, examination and laboratory investigations were not demonstrating any characteristics of the disease.

Cold agglutinin disease was suspected in view of COVID-19 and algorithm followed for processing of blood in laboratory. The patient was given supportive treatment. She was kept in warm environment with the help of blankets and room heater and was advised to avoid exposure to cold. She was transfused with 3 units of whole blood. The hemoglobin levels reached 8.2 g/dL after the initial management. Oral glucocorticoids were started in view to prevent further deterioration of COVID-19 infection. The patient also received folate supplementation for her hemoglobin phenotype.

The patient was discharged with advice for home isolation in warm environment on the fourth day of admission and was asked to follow up after isolation.

Discussion

The patient was going through her first episode of autoimmune hemolysis in association with viral infection. Cold agglutinin disease is recognized as a chronic disease with predilection in old age population. It can also present as acute exacerbation on chronic condition in association with bacterial or viral infection. The antibody is predominant in the disease is IgM type and reacts poorly or not at all at 37°C, whereas it reacts strongly at lower temperatures that cause complement-mediated hemolysis by binding the I antigen on the red cell surface [3]. The average temperature in Meghalaya in December-January, 21-22 was 12.1°C; while minimum was 7.4°C and maximum being 16.9°C. The patient must have been exposed to SARS-CoV-2 virus in the preceding 2 weeks as the average incubation period of presentation is 9 days.

The pathophysiology of COVID-19 is not a fully established, cytokine storm with a hypercoagulable state, and an increased incidence of venous thromboembolism has been postulated. This hematologic dysfunction with proinflammatory infection conditions, as seen in COVID-19, leads to hemolysis [4].

Primary cold agglutinin disease and secondary cold agglutinin syndrome may be suspected in a patient with symptoms induced due to cold such as discomfort in the extremities with exposure to cold. Cold Agglutinin Disease should also be suspected in a patient with hemolysis or red blood cell agglutination in a blood collection tube which is cold when the peripheral blood smear reports the same. Presence of very high mean corpuscular volume is a spurious result caused by RBC agglutination which is seen in this case [3]. The present case demonstrated transient cold agglutinins and acute anemia in a patient diagnosed with SARS-CoV-2 Infection. This case has unconjugated hyperbilirubinemia as conjugated bilirubin was less than 15% of total bilirubin. The hemogram reported high reticulocyte count further confirming hemolysis. Cold agglutinin titer was not measured due to unavailability of the test but the symptoms of the patient, results of direct Coombe's test and peripheral blood smear, processing of the blood samples in warm temperature and subsequent supportive treatment given to the patient indicates towards the cold agglutinin phenotype.

Few case reports and case series have been published having cold agglutinin induced hemolysis in presence of COVID-19. In these cases, three fourth survived but one fourth expired due to hemolysis induced anemia and subsequent circulatory failure. According to reports those who improved were treated with Rituximab and DMARD's in addition to supportive care, while those who were managed with only blood transfusion did not survive [5]. The severity of anemia and hemolysis was not specified in few cases but this case further gives positive result with conservative treatment with blood transfusion alone that to in presence of severe anemia. Rituximab was not used for treatment as it can further impair the response of B cells against the SARS-CoV-2 infection.

Table 3: Peripheral smear finding.

RBC Series	RBC series show clumping with an anisocytosis, normocytic normochromic in nature with few macrocytes, ovalocytes, target cells, spherocytes, polychromatophilic cells and nucleated red blood cells.
WBC Series	WBC series are normal in total number and distribution.
Platelets	The platelets are adequate in number with a normal morphology.
Parasites	No parasite seen in the smear examined.
Impression:	The peripheral blood smear, showing a normocytic normochromic blood picture with macrocytes, spherocytes, increase polychromasia and a few Howell jolly bodies.

HbE variant is increasingly prevalent in South East Asia; a region endemic in malaria has been hypothesized to be providing survival advantage to the carriers of the trait with resistance to malaria, dengue virus, and very recent addition of COVID-19 infection by a study [6]. Further HbE heterozygous trait does not have any significant effect on red blood cell and its survival unless it presents in coinheritance with β thalassemia [7].

Conclusion

The case study presents the rare occurrence of cold agglutinin disease accompanying COVID-19 infection and HbE heterozygous phenotype. It also affirms that conservative treatment with blood transfusion, temperature regulation and glucocorticoids in view of COVID-19 associated inflammatory reaction can lead to positive outcome in resource limited settings.

The significance of disease in association with HbE heterozygous condition needs more reporting and further study.

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