

# A CASE REPORT OF PRIMARY COLD AGGLUTININ DISEASE

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## INTRODUCTION

Autoimmune hemolytic anemias (AIHAs) are divided into Warm Antibody type (IgG mediated), Cold Antibody Type, Paroxysmal Cold Hemoglobinuria (Donath Landsteiner antibody)<sup>1</sup>. Out of which Cold AIHA or Cold Agglutinin Disease (CAD) is rare, accounting for 15% of AIHA cases<sup>2</sup>. CAD has chronic & indolent course. It is mediated by Monoclonal IgM antibody. In the body core, circulating IgM remains unbound from the RBC surface. Optimal temperature needed for binding is 0<sup>o</sup> to 4<sup>o</sup>C. However, as blood shifts toward the peripheral circulation and exposed to less than 4<sup>o</sup> temperature, IgM transiently binds the RBC membrane. Once bound, the IgM molecule activates the complement cascade, binding C3b to the cell surface. As C3b-coated cells return toward the body core, IgM dissociates. C3b-coated cells subsequently lose surface membrane by receptor-specific macrophages present predominantly in the liver (but also to a lesser degree in the spleen), resulting in extravascular hemolysis and perhaps some degree of intravascular hemolysis. The severity of hemolysis depends on the thermal amplitude, rather than the serum concentration of IgM<sup>3-4-5</sup>.

## Rouleaux vs Agglutination



**Rouleaux:** Cells are arranged 'like stacks of coins'



**Agglutination:** Cells are randomly clumped together

## Causes<sup>8</sup>:

1. Primary or Idiopathic CAD.
2. Monoclonal secondary CAD : Waldenstrom Macroglobulinemia, CLL.
3. Polyclonal secondary CAD : Mycoplasma pneumoniae infection, Infectious Mononucleosis, HIV, HCV, Syphilis, Malaria<sup>6,7</sup>.
4. Drug induced : Lenalidomide.

Patient can present with Acrocyanosis (painful and purple fingers/toes), Chronic fatigue, Hemoglobinuria, Lymphadenopathy, Fever, Respiratory symptoms, Livedo reticularis.

Work up for CAD is done with Complete Blood Count (CBC), urine analysis, Serum LDH, S. Bilirubin, Direct Coomb's Test with polyvalent and monovalent sera, Chest X ray/CT scan and infectious disease testing to rule out secondary causes and Bone Marrow aspiration and biopsy to rule out malignancy.

## CASE REPORT

- A 17 year old Hindu female patient admitted with chief complaint of generalised weakness and low grade fever since 3 days. Patient also complaint of easy fatigability, giddiness since 10 days with abdominal pain and dark colored urine. Patient had similar complaint in December 2021 with history of 6 packed cell volume transfusions, but no

documents were available. Patient did not had cough, history of weight loss, vomiting, diarrhoea or any significant drug history. No past history of any other disease. No significant family history.

- ON EXAMINATION: patient was conscious and oriented to time place and person. Patient was febrile 101 f. Pulse was 102/min, BP 102/64 mmhg and Saturation was 98% on room air. Pallor was present with mild icterus. There was no cyanosis, clubbing, pedal edema. Neck rigidity was not present. Cervical and inguinal lymph nodes were not palpable. Patient's Respiratory system and Central nervous examination was normal. On per abdomen examination there was splenomegaly. On cardiovascular system examination mild systolic murmur was heard at mitral region.
- On INVESTIGATION: CBC revealed 2.6 hemoglobin, RBC count 0.62 mill/cumm, 9300/cu mm, platelet 294000/cu mm.
- On peripheral smear RBC's agglutination was seen with anisocytosis, few microcytic RBCs and polychromatic cells.
- Patient's MCV was 138.70, MCH was 42.10, MCHC was 30.40.
- On investigating further patient's Retic count was 25% and RPI (reticulocyte production index) 2.5 with Serum Iron 83.8, Serum LDH 788.5, Total bilirubin was 3.11 and direct 0.41, indirect bilirubin 2.70, Serum TSH was 6.782 with free T3- 2.39 and free T4 0.79.
- Patient's direct coomb test was positive on polyvalent antihuman immunoglobulin. On testing with monovalent antihuman globulin it was positive for Anti C3 and negative for Anti IgG.
- Patient's Complement C3 level was 0.637.
- Patient's G6PD was normal, stool occult blood test was positive and urine routine micro shows 2-3 pus cells.
- Patient's Malarial Antigen test, Dengue NS1 antigen, IgG and IgM, HIV, HCV, VDRL were negative.
- Usg abdomen showed splenomegaly.
- Chest x ray was normal
- There was evidence of hemolysis high reticulocyte count, High LDH, High indirect bilirubin, high RPI.
- Positive direct antiglobulin for Anti C3 only with peripheral smear showing RBC agglutinin and history of similar episode in winter season (on exposure to cold)

With negative ANA profile to rule out SLE and RA confirmed the diagnosis of Primary Cold Agglutinin Disease.

Patient was initially given Methylprednisolone pulse therapy for 3 days and repeat CBC was performed which showed Hemoglobin 2.6 gm/dl. Then after consulting with hematologist. Patient was given Injection Rituximab 500 mg for 3 days then once a week for 2 weeks.

After Rituximab therapy patient's Hemoglobin improved to 8.7 gm/dl. Patient advised for Rituximab monotherapy once a week for total 4 weeks.

## DISCUSSION:

Cold agglutinin Disease is rare and most common presentation is anemia of undetermined origin. Cold Agglutinin Disease is diagnosed on basis of Hemolysis, Positive Direct Coomb's Test with monovalent Anti C3, Positive cold agglutinin titers<sup>1</sup>. It can be secondary due to many infectious causes so it should be ruled out. Treatment of Cold Agglutinin Disease consistence of avoidance of cold with adequate clothing, avoid icy drinks, cold shower. In hospitalised patient Application of body warming blankets, pre warming of IV fluids and blood products. Mainstay of treatment is Rituximab, which is considered in severe anemia and if patient is symptomatic. Other drugs that can be used are Bendamustine, Fludarabine, Ibrutinib and Bortezomib. These drugs are used with Rituximab as a second line therapy if patient is not responding with Rituximab monotherapy.<sup>8</sup> Steroids is not much useful in Cold Agglutinin Disease. So it is important to differentiate it from Warm AIHA.

## CONCLUSION:

Patient's with AIHA and Anemia of undetermined origin Cold Agglutinin Disease should be considered in differential diagnosis and work up should be done as treatment of Cold Agglutinin disease differs from Warm AIHA.

## REFERENCE:

1. Berentsen S. How I manage cold agglutinin disease., *Br J Haematol*, 2011, vol. 153 3(pg. 309-317)
2. Lechner K, Jäger U. How I treat autoimmune hemolytic anemias in adults., *Blood*, 2010, vol. 116 11(pg. 1831-1838)
3. Jaffe CJ, Atkinson JP, Frank MM. The role of complement in the clearance of cold agglutinin-sensitized erythrocytes in man., *J Clin Invest*, 1976, vol. 58 4(pg. 942-949)
4. Zilow G, Kirschfink M, Roelcke D. Red cell destruction in cold agglutinin disease., *Infusionsther Transfusionsmed*, 1994, vol. 21 6(pg. 410-415)
5. Kirschfink M, Knoblauch K, Roelcke D. Activation of complement by cold agglutinins., *Infusionsther Transfusionsmed*, 1994, vol. 21 6(pg. 405-409)
6. Khan FY, A yassin M. Mycoplasma pneumoniae associated with severe autoimmune hemolytic anemia: case report and literature review., *Braz J Infect Dis*, 2009, vol. 13 1(pg. 77-79)
7. Karunarathne S, Weerasinghe S, Govindapala D, Fernando H, Jayaratne B. Cold autoimmune haemolytic anaemia secondary to Epstein Barr virus infection presenting with peripheral gangrene; case report., *Thromb J*, 2012, vol. 10 1pg. 4
8. 21<sup>st</sup> Edition, Harrison's Principles of Internal Medicine.