# A Case of Fatal Cold Agglutinin Disease with Malaria

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ABSTRACT

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The authors report a case of a 55 yr old male who presented with fever, yellowish discoloration of the eyes and altered mental status to the Emergency Department. On examination, pallor, icterus and Splenomegaly were present. Hemoglobin (Hb) was 9.5 gm. % and peripheral smear revealed ring forms of Plasmodium vivax. Serum LDH and Serum bilirubin (Indirect and Direct) were high. This patient's blood group couldn't be found out correctly as there was spontaneous agglutination in all the test and control cells. Indirect Antiglobulin Test (IAT), antibody screening and antibody identification showed pan agglutination. Direct Antiglobulin Test was also positive. The specific but rare problems that can occur due to these pathologic cold agglutinins are to be kept in mind for the accurate diagnosis and early management of these patients.

**Keywords:** Cold agglutinin disease, Malaria

*See End Note for complete author details

Auto Immune Hemolytic Anemia is classified into warm antibody and cold antibody types.[1] Cold agglutinins were first described by Landsteiner in 1903. The association of cold agglutination with hemolytic anaemias was described by Rosenthal and Corten in 1937.

Cold antibody hemolytic anemia can be of two types

1) Cold Agglutinin Diseases (CAD)

2) Paroxysmal Cold Hemoglobinuria (PCH).

A 55 yr old male presented to the Emergency Department with fever, chills, rigor and yellowish discoloration of eyes and urine. He had a history of travel to Chennai. He was a known case of Diabetes Mellitus on irregular treatment. He was also a chronic alcoholic & smoker. On examination the patient was disoriented and drowsy. He had pallor, icterus and hepatosplenomegaly.

## INVESTIGATIONS

A complete blood count **(Table 1)** and other investigations were done **(Table 2).**

Malaria rapid card test showed plasmodium vivax positivity which was later confirmed by peripheral smear examination also. Peripheral smear also showed auto agglutination **(Figure 1).**

As the patient's condition demanded red cell transfusion, the sample for grouping, typing and cross matching was brought to the Transfusion Medicine Department.

**Table 1. Complete Blood Count**

| | | | |
|---|---|---|---|
| HB | 9.5 gm/dl | MCH | 49.7 pg |
| HCT | 19.4 % | MCHC | 49 g/dl |
| TC | 12,900 x $10^3$ /ul | RBC | 1.91x$10^6$ /ul |
| DC | 73/18/9 % | ESR | 106 mm 1st hr |
| RDW | 14 % | PLC | 2.99 x$10^3$ /ul |
| MCV | 101.5 fl | MPV | 9.9 fl |

**Table 2. Blood Investigations**

| | |
|---|---|
| RBS | 362 mg/dl |
| HbA1C | 9.1 % |
| TOTAL BILIRUBIN | 8.6 mg/dl |
| DIRECT BILIRUBIN | 4.08 mg/dl |
| PROTEIN | 7.9 g/dl |
| ALBUMIN | 3.7g/dl |
| GLOBULIN | 4.2g/dl |
| SGOT | 47 IU/L |
| SGPT | 54IU/L |
| ALP | 142 IU/L |
| A/G RATIO | 0.9 |
| CREATININE | 1.1 mg/dl |
| UREA | 41 mg/dl |
| AMMONIA | 21 umol/l |
| SODIUM | 129 mEq/l |
| POTASSIUM | 4.2 mEq/l |
| CHLORIDE | 92 mEq/l |
| MP CARD | Positive ( Pl. Vivax) |

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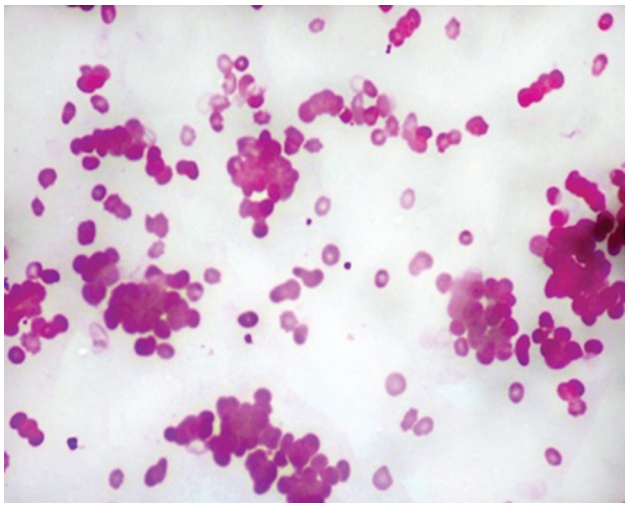

Figure 1. **Peripheral Smear Showing Auto Agglutination**

Patient's blood group could not be confirmed as pan agglutination was found in both forward and reverse grouping. The auto control also showed agglutination.

### Immunohematology workup

Blood grouping of the patient sample was done **(Table 3)** which showed pan agglutination. Direct and Indirect Coumb's Test was also done **(Table 4)** which showed a positive reaction along with a positive auto control.

A. Blood grouping

B. COOMBS Testing

**Table 3. Blood grouping**

| Anti A | Anti B | Anti D | A cells | B cells | O cells | Auto control |
|---|---|---|---|---|---|---|
| ++ | ++ | ++++ | ++ | ++ | ++ | ++ |

**Table 4. Coumb's Test and Auto control**

| | |
|---|---|
| DAT | Positive |
| IAT ( ID DIACELL I-II-III ) | Positive |
| AUTOCONTROL | Positive |

**Table 5. Radiological Investigation**

| |
|---|
| USB ABSOMEN |
| Hepatomegaly (17.5 cm) with hypo-echoic coarse parenchyma<br>& minimal Splenomegaly (13.7 cm)<br>No ascites /gall bladder wall edema |
| CT HEAD |
| No Abnormality detected |
| Echo Cardiogram |
| Normal LV systolic function<br>No RWMA<br>Type 1 LV diastolic dysfunction<br>Mild TR<br>Mild PAH |

A complete workup nor a full diagnosis could be made and unfortunately the patient succumbed to death in the mean time.

## DIAGNOSIS

Alcoholic Liver Disease, Type 2 Diabetes Mellittus,

Malaria- Plasmodium Vivax, Cold Agglutinin Disease

## DISCUSSION

CAD can be either primary or secondary. There are different causes of secondary CAD which is shown below.

### Some causes of Secondary CAD

1. Mycoplasma Pneumonia
2. Staphylococcemia
3. Influenza
4. Trypanosomiasis
5. Hemolytic Anemia
6. Malaria
7. CMV Infection
8. Congenital Syphilis

The cold agglutinin/antibody is found to have anti-I or anti-i specificity, which is present in all adult RBCs. These autoantibodies are present to a lesser or greater degree in the serum of normal, healthy individuals. However, these auto agglutinins are not considered significant in normal, healthy individuals, as most of these cold autoantibodies are present in low concentration in the serum

These agglutinins do not react at body temperature and are reactive optimally at lower temperatures, and are often too weak to be detected in serologic procedures. It is only significant in patients with the cold agglutinin disease.

### Pathogenesis of cold agglutinins in CAD

When a person with this disease is exposed to the cold, the cold autoantibody is activated, which causes agglutination of RBCs and fixes complement as the RBCs flow through the capillaries of the skin. This results in auto agglutination and signs of acrocynosis (bluish tinge in extremities). Complement fixation may result in intravascular hemolysis. Patients usually display weakness, pallor, and weight loss, which are characteristic of chronic anemia

Physical findings such as hepatosplenomegaly are frequent owing to the mechanism of hemolysis. Other clinical features of cold hemagglutination diseases include jaundice and Reynaud's phenomenon

(symptoms of cold intolerance, such as pain and a bluish tinge in the fingertips and toes, owing to vasospasm

In this case of secondary CAD, the cause was malaria. Shoron Georgy et al have mentioned that Hyperactive Malarial Splenomegaly (HMS) is an immunopathologic complication of recurrent malaria infection. Patients with HMS develop Splenomegaly acquired clinical immunity to malaria, high serum concentration of anti-plasmodium antibodies and high titre of IgM, with a complement fixing IgM, that acts as cold agglutinin

### Laboratory Findings

Often the first indication of the presence of cold agglutinins is the failure to obtain a meaningful RBC count and indices. The hemoglobin and hematocrit results do not match. The RBC count will be decreased due to doublet erythrocytes being counted as a single cell, thus resulting in a falsely high MCV. Hematocrit will also be lowered. The MCHC and MCH values will be increased due to decreased hematocrit and RBC count. Other causes of invalid red cell indices have to be ruled out. Other laboratory findings include reticulocytosis, positive DAT, auto agglutination and/or rouleaux on peripheral blood smear, polychromasia, and mild to moderate anisocytosis and poikilocytosis. Agglutinates can also be visible in the specimen tube and can be pronounced as to give the appearance of a large clot **(Figure 2).**

Spherocytes may be present in the peripheral blood smear. The leukocyte and platelet counts are usually normal. Bilirubin is mildly elevated and rarely more than 3 mg/dL. The LDH levels may be increased, reflecting RBC destruction; and complement and haptoglobin can be low or absent.

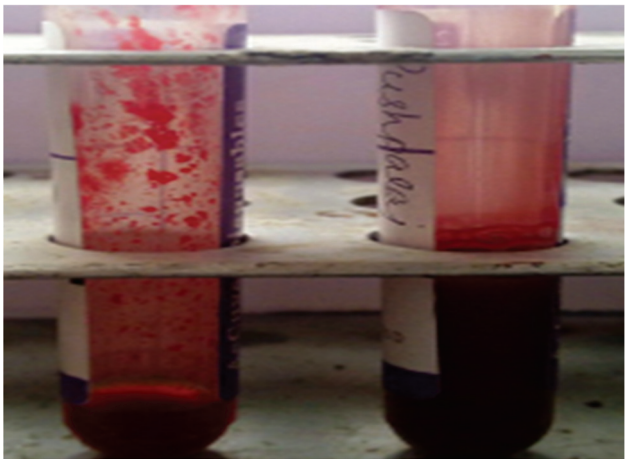

Figure 2. **Tube showing Macroscopic agglutinates**

## DEALING WITH COLD AGGLUTININS

### Laboratory Perspective

The specimen can be collected in a prewarmed tube

1. The specimen can be placed in a 37°C incubator for at least 5 minutes and then tested right away or in severe cases, the blood needs to be maintained at 37°C
2. until it can be tested by using a portable water-bath or by using a heel-warmer.
3. If possible, the phlebotomist should draw the patient near the instrument so that the specimen can be run immediately.
4. For patients with really strong cold agglutinins, the reagents on the instruments may be warmed if the instrument allows it

## CLINICAL PERSPECTIVE

The most common and easiest treatment for cold agglutinin disease is to avoid the cold, keep warm, or move to a warmer climate. In more severe cases, plasma exchange may be performed. Other methods include prescribing corticosteroids for patients whose RBCs have been highly sensitized with C3. Alkylating drug chlorambucil has some favorable results as well. If blood transfusion is required, blood should be transfused warm.

## CONCLUSION

Although cases of mild cold agglutinins are routinely met in the laboratory, strong cold agglutinins are not. Knowledge of this phenomenon can help prevent too much time being wasted on solving the problem. Preventing exposure to cold can also be done in dealing with such cases.

## END NOTE

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**Conflict of Interest:** None declared

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