

# Chronic Cold Agglutinin Disease: A Case Report with Review of Literature

R. KALYANI, M J THEJ, AK THOMAS, A RAVEESHA

## ABSTRACT

Chronic cold agglutinin disease (CAD) is a sub-group of autoimmune haemolytic anaemia (AIHA). Cold reactive immunoglobulins (cold agglutinins) which are directed against erythrocyte surface antigens ('I' antigen) are essential for the pathogenesis of CAD. Classically, the patients with CAD present with chronic anaemia and acrocyanosis. Several factors like the antibody titre and the temperature range determine the ability of cold agglu-

tinins to induce haemolysis. The specific problems that occur in the laboratory due to pathologic cold agglutinins need to be kept in mind for the accurate diagnosis and treatment of the patient. Novel immuno-suppressive therapies are being tried, both to reduce cold agglutinin production as well as to cure CAD. Here, we are reporting a case with repeated episodes of haemolysis due to cold agglutinins in a middle aged man.

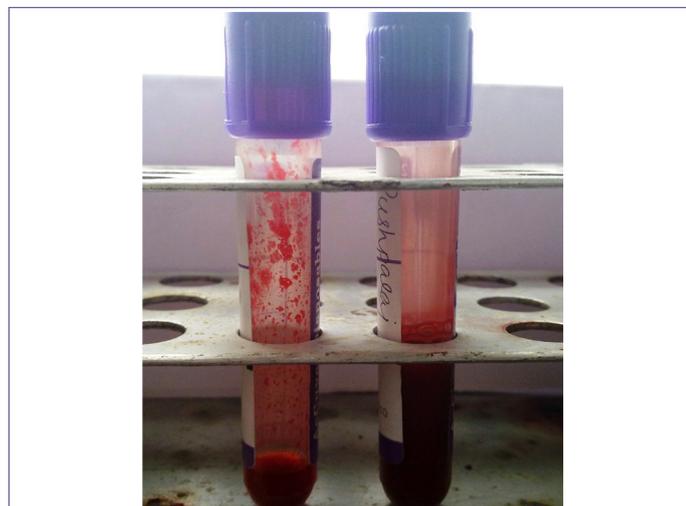
**Key Words:** : Auto-immune haemolytic anaemia, cold agglutinin disease

## INTRODUCTION

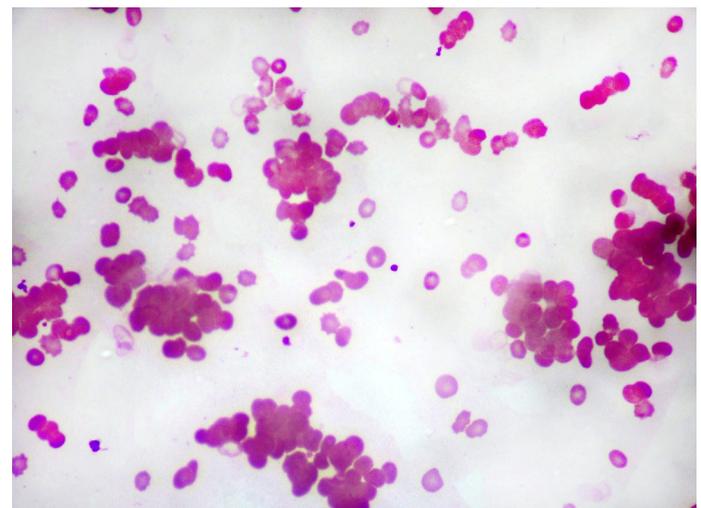
Auto-immune haemolytic anaemia (AIHA) is a complex and incompletely understood process which is characterized by an immune reaction against red blood cell (RBC) self antigens [1]. AIHA is classified into the warm and cold reactive antibody types. Aetiologically it is classified as primary (idiopathic) and secondary (co-existing with other diseases or is drug induced) [2]. The entities which are included in the cold antibody group are chronic cold agglutinin disease (CAD), acute cold antibody mediated AIHA complicating mycoplasma pneumoniae or viral infections and paroxysmal cold haemoglobinuria [3].

## CASE REPORT

A 45 year male presented with severe anaemia, acrocyanosis on exposure to cold, splenomegaly and mild hepatomegaly. The automated haematology analyzer showed erratic mean corpuscular



**[Table/Fig-1]:** Photograph shows anti-coagulated blood sample of patient with spontaneous agglutination along the wall of the test tube on left side compared with that of normal sample on right side.



**[Table/Fig-2]:** Microphotograph of peripheral blood smear showing spontaneous agglutination of RBCs. (Leishman stain X1000)

volume (MCV: 114fl), mean corpuscular haemoglobin concentration (MCHC: 69.7) and red cell distribution width (RDW: 18.1) values along with a very low RBC count (0.81 million/cu mm). This problem was encountered while his blood group was being determined. The patient was B positive but he was reported as AB positive due to the spontaneous agglutination on the slide. The spontaneous agglutination of RBCs was also appreciated along the sides of the test tube which contained the patient's blood sample [Table/Fig-1]. The peripheral blood smear showed RBC agglutination [Table/Fig-2]. The patient also had leucopaenia and thrombocytopenia. The Coomb's test was positive. The patient also gave a history of similar episodes which occurred during the winter months and febrile illnesses over the past four years for which he underwent many hospital admissions. His bone marrow examination did not reveal any abnormality. His protein electrophoresis was normal and his liver enzymes were mildly elevated. The patient tested negative for

hepatitis, malaria, Dengue and Brucella infections. His cold agglutinin titre was 1:1024 at 25°C. The patient did not give his consent for a splenic biopsy and hence the further assessment of splenomegaly could not be done. He had elevated lactate dehydrogenase levels (1500U/L). A diagnosis of primary CAD was made. The patient refused further intervention or workup, got discharged against medical advice and was lost to follow-up.

## DISCUSSION

The incidence of AIHA is estimated to be approximately 1:100,000 in adults [4]. Among these, warm-reactive antibodies are responsible for 87% of the cases and cold reactive antibodies are responsible for 13% of the cases [4]. In contrast, the south Indian data shows that cold AIHA is rare and that it contributes to only 1% of the total cases of AIHA [5].

Cold agglutinins (CAs) were first described by Landsteiner in 1903 [6]. The association of cold haemagglutination with haemolysis was described in 1937 by Rosenthal and Corten [3]. In the 1950s, Schubothe coined the term CAD. Primary or idiopathic CAD is typically an affliction of older adults with a peak incidence at around 70 years of age and both sexes are affected, with a slight female predominance [2].

Cold agglutinins (CAs) may be found in the sera of healthy subjects as well as in patients with cold AIHA. Benign cold agglutinins occur in titres which are less than 1:64 at 4°C and they have no activity at temperatures which are higher than that, while pathologic cold agglutinins typically have titres well over 1:1000 and they may react at 28 to 31°C or even up to 37°C. The term "cold" is primarily derived from the immune biology of CAD and not from its clinical features, as has been frequently misunderstood [3].

In the CAD patients, nearly all the cold agglutinins are of the IgM type and most of them are directed against the 'I' antigen on the RBC membranes [2]. The cooling of blood during its passage through the acral parts of the body allows the CAs to bind to the erythrocytes, precipitate the agglutination and activate the complement via the classical pathway. On the subsequent warming of blood upto 37°C in the central parts of the body, the CAs detach from the cell surface, allowing the agglutinated erythrocytes to separate, while the C3b remains bound [3]. These C3b-coated erythrocytes are sequestered and destroyed by the C3-receptor bearing reticuloendothelial cells, mainly in the liver [2]. In contrast, in warm AIHA, the sequestration mainly occurs in the spleen [3]. Despite the presence of the complement on the red cell surface, intravascular lysis is rare, distinguishing the cold agglutinin disease from paroxysmal cold haemoglobinuria, in which intravascular haemolysis occurs [7]. The thermal amplitude, which is defined as the highest temperature at which the antibody binds to the antigen, appears to be more important than the titre with respect to the pathogenicity of CAD [3]. When the thermal amplitude is higher, the agglutination starts occurring at room temperature.

Mild, chronic haemolytic anaemia exacerbates in the winter, which is a general rule for CAD [2]. Acrocyanosis occurs due to the agglutination of cells in the cooler vessels of the hands and feet. The first suspicion of CAD comes from the haematology laboratory's failed attempts to obtain a meaningful RBC count and indices [2]. The RBC counts are decreased and MCV is falsely elevated, producing an unbelievably high MCHC [2]. This problem can be avoided by prewarming the samples to 37°C before feeding them into the

analyzer [8]. Bilirubin is mildly elevated and it is rarely more than 3 mg/dl [2]. The direct antiglobulin test is positive with polyspecific and anti complement anti-sera [1].

Patients with high titres or wide thermal amplitude antibodies can pose extremely difficult serological problems for the blood bank laboratories, which happened in the present case. Often, incompatible units are released due to the residual agglutination from the cold auto-antibody [2]. These problems can be overcome by washing the patients' cells with warm saline in the direct grouping and by using normal AB positive serum on the control slide [8].

The paradox in CAD is the exacerbations that occur during febrile illnesses, which were seen in our patient. The most plausible explanation for these observations is that a majority of the CAD patients have low levels of C3 and C4 during their steady states, due to continuous complement consumption. During acute phase reactions, the C3 and C4 levels increase due to their enhanced production, resulting in the exacerbation of haemolysis [3]. A minority of the CAD patients have mild splenomegaly and hepatomegaly. In few cases, a palpable spleen suggests a lymphoma or infectious mononucleosis [2]. However, splenectomy is not helpful in this situation as the site of sequestration is the liver. The patients present with leucopaenia and thrombocytopaenia, which can be explained by the presence of the 'I' antigen on these cells [2].

Lymphoma induced diseases like Waldenstrom's Macroglobulinaemia and B-cell neoplasms may produce monoclonal anti-RBC antibodies with cold reactivity. Viral infection induced infections like Mycoplasma pneumonia and infectious mononucleosis can lead to production of polyclonal IgM cold reacting antibodies, which can also lead to RBC clumping and destruction. The other differential diagnoses which can be considered are paroxysmal nocturnal haemoglobinuria and cryoglobulinaemia [2,3].

The treatment modality which can be used to suppress the production of these antibodies is immunosuppressive therapy with cyclophosphamide or chlorambucil. Rituximab, a monoclonal CD 20 antibody, and Fludarabine, a purine analogue, have proven to be of therapeutic use. Plasmapheresis can be used as a temporary measure for the removal of the antibodies. Blood transfusions can be useful to tide over acute illnesses. Since the major haemolysis occurs in the liver, splenectomy is of minimal use [3].

In the present case, a 45-year male presented with acrocyanosis of the hands and feet, that used to get exacerbated in the winter, with hepatomegaly and splenomegaly. The haemogram showed erratic values of the RBC count and the blood indices. The peripheral blood smear showed the spontaneous agglutination of RBCs, leucopaenia and thrombocytopaenia. This problem was encountered while the patient's blood group was being determined, due to the spontaneous agglutination on the slide. His CA titer was 1:1024 at 25°C. This was one of the rare cases seen in our settings.

## CONCLUSION

CAD is not an indolent disease in terms of the major clinical symptoms and the quality of life [3]. The plethora of problems that occur during the laboratory testing of CAD should be known to the pathologist to make an early and accurate diagnosis. The recent treatment modalities which use rituximab and fludarabine have shown good results, thus emphasizing the need for an early diagnosis of CAD.

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