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IDIOPATHIC COLD ANTIBODY AUTOIMMUNE HEMOLYTIC ANEMIA – A CASE REPORT. WHERE WAS THE INFECTION LURKING?

Medicine

Dr Sangita D Kamath*

MBBS, M.D (General Medicine), Consultant, Department of Internal Medicine, Tata Main Hospital, Tata Steel, Jamshedpur *Corresponding Author

ABSTRACT

Autoimmune hemolytic anemia (AIHA) is characterized by shortened red blood cell survival and positive direct Coombs' test. The responsible autoantibodies may be either warm reactive or cold reactive and are directed against the RBC antigens. The rate of hemolysis and the severity of the anemia may vary from mild to severe and life-threatening. Cold antibody mediated AIHA or cold agglutinin disease (CAD) is characterized by the presence of autoantibodies which exhibit affinity for RBCs optimally at temperatures below body temperature. In adults, most of the cold-reactive antibodies are agglutinins of IgM isotype. When AIHA occurs as a manifestation or complication of another disease, it is termed as secondary AIHA. In the absence of any disease, it is termed primary or idiopathic. Primary CAD is generally a disease of elderly, while in young adults and children, it is usually secondary to infections due to mycoplasma, chicken pox, or Ebstein Barr virus. We report a case of a young girl who developed cold agglutinin induced AIHA in absence of any obvious cause and showed good response to steroid.

KEYWORDS

autoimmunity, hemolysis, infections, auto agglutination, corticosteroids

INTRODUCTION

Cold agglutinin disease (CAD), or cold antibody autoimmune hemolytic anemia (AIHA), is characterized by anemia, positive direct Coombs test, and high titers of cold agglutinin [1]. It may manifest as a primary disease, or secondary to B-cell malignant lymphoma, autoimmune disorder, immunological disorders or infections [2]. Primary CAD is most often seen in elderly patients (median age at onset is 67 years). Here, we report a rare case of primary CAD in a young patient with good response to steroid therapy.

CASE REPORT

An eighteen years old girl, student by occupation, was admitted to Tata Main Hospital (TMH) with history of intermittent fever and a feeling of extreme weakness for 15 days prior to hospitalization. Fever was associated with chills and rigors and would subside with anti-pyretics. She was treated outside for malarial fever with oral chloroquine for 3 days. There was no history of cough, skin eruptions, vomiting, loose stools, burning micturition, joint pains or passing of brown colored urine. Two days before admission, she became very irritable, restless, could not recognize her relatives and was admitted in critical care unit (CCU). She did not consume alcohol and tobacco in any form. She was unmarried and did not have past history of any significant medical ailment.

On admission, she was lean, incoherent, had severe pallor and mild icterus. She did not have lymphadenopathy, pedal edema, cyanosis, bleeding into the skin or oral cavity. She was afebrile, with pulse rate of 126/minute, blood pressure 90/60 mm Hg, and respiratory rate of 24/minute. Examination of cardiovascular system revealed normal first and second heart sounds, grade 3 ejection systolic murmur (ESM) along the left sternal border. Examination of respiratory system was normal. Mild splenomegaly of 3cm below the left costal margin was noted per abdomen. Examination of central nervous system revealed irritable, restless patient. There was no focal neurological deficit. Neck was soft. Fundus examination showed pallor of the disc and Roth's hemorrhages.

Her hemoglobin, on admission was 2.5gm/dl, total WBC count 7,600/cu mm with 76% neutrophils, 16% lymphocytes, 2% monocytes, and 6% eosinophils, MCV 129.6 fl, RDW (CV) 17.9%, platelet count 128,000/cu mm and reticulocyte count 5.8%. Peripheral blood smear showed red cell hypochromia, anisocytosis, macrocytes, nucleated RBCs and agglutination of RBCs **(figure 1)** with separation of RBCs on warming the slide.

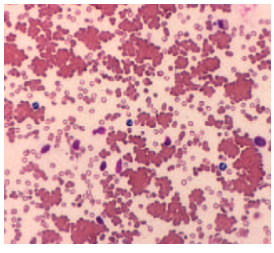

Figure1: Agglutination of RBCs in the peripheral smear

Her liver function tests revealed total bilirubin 3.11 mg/dl, direct fraction 1.55 mg/dl, indirect fraction 1.56 mg/dl, alanine transaminase (ALT) 1569.2U/L, aspartate transaminase (AST) 2007.6U/L, alkaline phosphatase (ALP) 61.6U/L, gamma glutamyl transferase (GGT) 64.8U/L, total serum proteins 7.1g/dl, serum albumin 3.53 g/dl and globulin 3.57 g/dl. Coagulation profile showed prothrombin time (PT) 19 sec, control 11sec, PT (INR) 0.99, PTTK (test) 23.2, control 26.7, serum fibrinogen 345 mg/dl and normal fibrin degradation products (FDP). Renal function tests showed blood urea 42.2 mg/dl and serum creatinine 0.72 mg/dl. Her CRP was 0.6 mg/dl, ESR (Westergren) was 56 mm1st hour. Serum iron was 65.8mcg/dl, while serum ferritin was 367.8 ng/ml. Serum lactate dehydrogenase (LDH) was elevated at 2,906U/L. Polyspecific direct anti-globulin test (DAT) was strongly positive. Further, also monospecific Coomb's test with complement C3d specificity was strongly positive. Cold agglutinin titer was not done as this facility is not available in our lab. A diagnosis of autoimmune hemolytic anemia (AIHA) due to cold autoantibodies was made in view of auto agglutination of red blood cells at room temperature and a strongly positive DAT with complement 3d specificity and evidence of hemolysis.

Further investigations were done to look for the infectious etiology. Her paracheck was negative, peripheral smear did not show malarial parasite, blood culture for aerobic organisms did not reveal growth of any organisms, Ebstein Barr virus (EBV) DNA was not detected by PCR, serology for mycoplasma was negative. Serology for Hepatitis A, E, C, viruses, HIV 1 and ll were non-reactive. HBV surface antigen was negative. Screening for tuberculosis in the form of Mantoux test, chest radiograph and sputum for acid fast bacilli was negative. Echocardiography and urine analysis were normal.

Serum protein electrophoresis did not show monoclonal antibodies. Her antinuclear antibody, rheumatoid factor and anti CCP antibody were negative. She was treated with intravenous methylprednisolone 1 g for 3 days followed by oral prednisolone 1mg/kg body weight (total of 60 mg/day) in divided doses, antibiotic (cefepime), and oxygen. She was also transfused four units group specific least incompatible four packed red cells transfusions as she had features of cerebral hypoxia due to severe anemia. Her hemoglogin remained above 10gm/dl over the next 15 days and she was discharged with advice to continue oral prednisolone 40 mg/day and avoid exposure to cold. Four weeks after discharge, she was seen in the out-patient department in stable condition with hemoglobin of 10.5g/dl. Her steroid was tapered to 30 mg/day and she was asked to follow-up after 4 weeks. A final diagnosis of idiopathic AIHA of cold antibody type with acute hemolytic crisis was made.

DISCUSSION

AIHA is a type of acquired hemolytic anemia, characterized by the presence of auto antibodies directed against the antigens on red blood cell surface, usually demonstrated by a positive direct anti globulin (Coomb's) test and shortened red blood cell (RBC) survival due to

hemolysis [1]. AIHA is classified by the temperature at which autoantibodies bind optimally to RBCs (thermal threshold) into warm antibody AIHA, cold antibody AIHA and mixed type. Cold-antibody AIHA is characterized by the presence of cold auto antibodies and constitutes about 15% cases of AIHA cases [2].

Cold auto antibodies (agglutinins) were first described by Landsteiner in1903. Their action against red blood cells resulting in hemolytic anemia was described some years later by Clough and Iwai. In 1953, Schubothe coined the term Cold Agglutinin Disease (CAD) [2,3,4]. Its incidence rate is estimated at 1 per million people per year [4,5]. It is more common in women than men [1,2].

In adults, the auto-antibody involved is usually IgM isotype, less frequently IgA or IgG, which is able to agglutinate RBCs at temperatures lower than the body temperature (maximally between 0 and 5°C), subsequently activate the complement system by the classical pathway, resulting in membrane attack complex (MAC) which causes lysis of RBCs [2,3,4]. Complement activation generally occurs between 20 and 25°C, but can also occur at normal body temperature [3]. The monoclonal IgM autoantibodies are directed against the I/i carbohydrate antigens on the RBC surface [2,4]. IgM is a 1-million-Da molecule that can simultaneously bind to many RBCs, overcoming the natural repulsive forces between them, thus allowing spontaneous agglutination of RBCs.

The cause of cold antibody type AIHA could be primary (idiopathic) or secondary to infections like mycoplasma, Epstein Barr virus [5,6] varicella [7], clonal B cell proliferation like CLL [8], lymphoproliferative disorders like Waldenstom's macroglobinemia, non-Hodgkin's lymphoma (B-cell) [9], and autoimmune disorders [4]. In a study by Swiecicki et al involving 89 patients of CAD, underlying hematologic diseases were identified in 69 patients (76%); of these, MGUS was most common (47%) [2]. Auto-IgM antibodies are monoclonal in 90% of cases of primary CAD and B-cell neoplasm, but polyclonal in post-infectious cases [2,4].

Idiopathic (primary) chronic cold agglutinin disease has its peak incidence after age 50 years [1,2] while secondary cold agglutinin disease due to infections is seen in adolescents or young adults. It is a self-limited process, lasting 1 to 3 weeks [11]. In our patient, despite an extensive search for cause of an infectious etiology, we could not find one.

The clinical features are like those of other hemolytic anemias. The severity of symptoms depends upon the rate of hemolysis. Patients have symptoms and signs of chronic anemia like pallor, jaundice, fatigue, breathlessness, palpitation or may develop acute hemolytic crisis with increasing jaundice, pallor, tachycardia, angina (in elderly) and heart failure [1,10]. Exacerbations of hemolysis are triggered by febrile illness, trauma, or surgery. Cold exposure may lead to agglutination of RBCs in the cutaneous microvasculature resulting in acrocyanosis, involving the fingers, toes, nose, and ears. After warming up, acrocyanosis disappears quickly. Livedo reticularis may be occasionally seen. Skin ulceration and necrosis are uncommon. Splenomegaly, may be observed in idiopathic cold agglutinin disease. Though Berentsen et al [6] reported cold-induced symptoms in more than 90% of patients, our patient did not report cold induced symptoms prior to this admission.

Lab diagnosis of AIHA is based on evidence of hemolytic anemia consisting of anemia, unconjugated hyperbilirubinemia, reticulocytosis, decreased haptoglobin level, increased lactate dehydrogenase (LDH) and a positive DAT [1,2,3]. Peripheral smear may show polychromasia which represents reticulocytosis, reflecting an increased production and release of reticulocytes from the marrow. In more severe cases, microspherocytes, RBC fragments and nucleated RBCs may be seen. Presence of RBC autoagglutination in the peripheral smear at temperatures <37°C is suggestive of cold-type AIHA [9]. Mild leukocytosis with neutrophilia may be present .

Once AIHA has been identified, differentiation between warm and cold antibodies can be done by monospecific DAT [10]. In cold agglutinin disease (CAD), the reaction is positive with anti C3d anti serum but negative with anti IgG. Some cases of drug-induced immune hemolytic anemia also exhibit a positive DAT only with an anti-complement reagent. A history of recent drug ingestion and absence of a significant cold agglutinin titer help to differentiate drug-induced immune hemolytic anemia from cold agglutinin disease. Our patient did not have any significant history of drug ingestion. Other acquired causes of hemolytic anemia are characterized by negative DAT test.

Corticosteroid therapy is less effective in CAD when compared to that in warm AIHA [10]. However, our patient responded well to steroids. Transfusions are of transient benefit but may be required initially because of severity of anemia. Transfusion of red cells can be complicated because of cross matching problems and rapid in vivo destruction of transfused cells due to the presence of auto antibodies. Our blood bank also encountered problems during blood grouping due to clumping of red cells. Cross matching was also difficult and 'least incompatible' A+ve red cells were transfused. We transfused four PRBCs under the cover of steroids and there were no post transfusion hemolytic episodes.

In refractory cases, immunosuppressive agents with anti-CD20 antibody like Rituximab may be tried. Splenectomy is not helpful in cold AIHA as liver is the main site of extra vascular hemolysis [3]. All these patients should strictly avoid cold, as it the most effective measure to prevent hemolysis. Appropriate warm clothing should be used. Idiopathic CAD typically has a chronic benign course, but some patients may later develop B-cell neoplasms and hence, must be regularly followed up. Death may result from infection, severe anemia or from an underlying lymphoma. Review of previous published literature revealed, secondary cold-induced AIHA due to infection, autoimmune disorders and B cell lymphoma. Also there are case reports of primary cold AIHA with megaloblastic anaemia in elderly patients. However, there are no reports of primary cold AIHA in young. The idea of reporting this case is to make the clinician aware of this rare cause of hemolytic anaemia.

CONCLUSION:

Presence of anemia with evidence of hemolysis and a positive DAT (direct antiglobulin test) test should make one suspect AIHA. The nature of the autoantibody should then be determined to further sub-classify the type of AIHA. Though literature suggests, cold AIHA in young is most often secondary to infections, while in elderly is secondary to lymphomas or autoimmune disorder, in our case, despite extensive evaluation, no infective etiology or any other cause was found. To the best of our knowledge, this is, perhaps, the first case report of idiopathic CA-AIHA in a young patient, hitherto unreported in literature.

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