Cold Haemagglutinin Disease in Systemic Lupus Erythematosus

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A 34-year-old lady presenting with features of cold agglutinin disease during the course of systemic lupus erythematosus is described. Cold antibody titer was very high (1 in 4096) with specificity for 'I' antigen. Even though she had poor prognostic factors like high titer of cold antibodies with low thermal amplitude, she responded well to prednisolone.

Key Words: Cold haemagglutinin disease, systemic lupus erythematosus

Autoimmune hemolytic anaemias are characterized by the presence of antibodies recognizing antigens on the individual’s own erythrocytes resulting in immune-mediated hemolysis. Hemolytic anaemia is most often due to autoimmune hemolysis. Hemolytic anaemia is found to occur in 10% of cases of systemic lupus erythematosus (SLE) and rarely it may be the presenting manifestation of the disease. It is usually of the warm antibody type. Occurrence of cold haemagglutinin disease (CHAD) is very rare. We report a case of SLE presenting with cold haemagglutinin disease.

CASE REPORT

A 34-year-old female presented with history of progressive pallor, irregular fever of one month and polyarthritus of 2 years duration. There was no history of swellings in the neck, Raynaud’s phenomena, sore throat, skin rash, acrocyanosis or livedo reticularis. On physical examination, she was afebrile, pulse rate was 70/min and BP was 130/80 mmHg. She had pallor, alopecia, mild icterus and oral ulcers. Spleen was palpable 3 cms below the costal margin. Ocular fundi and other systems were within normal limits.

The blood Hgb was 6 gm%, WBC count 14×10^9/l with a differential count of polymorphs 74, lymphocytes 22 and eosinophils 4. ESR was 136 mm/1st hr, platelets 88×10^9/1 and reticulocyte count 10%. Urine analysis was normal except for the increased urobilinogen.

Serum bilirubin was 2.7 mg% with direct bilirubin 0.7 mg%. Peripheral smear showed anisocytosis, pochromasia and features of autoagglutination (Fig. 1). Pure saline preparation showed autoagglutination which disappeared on incubation at 37°C. Blood grouping at room temperature showed autoagglutination. On repeating the test at 37°C agglutination disappeared. The direct Coombs’ test was positive with polyspecific antisera. Cold agglutinin titer was 1 in 4,096 at 4°C with specificity for 'I' antigen. Lupus erythematosus (LE) cell test and anti-double stranded DNA antibody test were positive. Paul

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Bunell test and Donath Landsteiner antibody test were negative. VDRL, prothrombin time (PT) and activated partial thromboplastin time (APTT) were normal. From the clinical and laboratory findings a diagnosis of SLE with CHAD was made. The patient was started on prednisolsone 60 mg/day and was gradually tapered over the next 3 months. She responded very well and is remaining in remission during the last 12 months of follow up. She is now maintained on prednisolone 10 mg on alternate days.

**DISCUSSION**

Autoimmune hemolytic anaemias are classified into warm and cold antibody type depending upon the thermal properties of the red cell antibody (Foerster, 1993). Cold autoimmune haemolytic anaemias are of two types—cold haemagglutinin disease (CHAD) and paroxysmal nocturnal haemoglobinuria. CHAD may be idiopathic or secondary. Common causes of secondary CHAD are lymphoma, leukemia and infections with mycoplasma pneumonia, Epstein-Barr virus and cytomegalovirus.

Hemolytic anemia is found to occur in about 10% of cases of SLE. Of the different hemolytic anaemias, warm antibody type of autoimmune hemolytic anaemia is the most common in SLE. CHAD is rare, although described in SLE. A study by Crisp and Pruzanski (1982) on the prevalence of cold agglutinin in collagen vascular diseases, could not detect any cases of CHAD in SLE. There is a paradox that cold lymphocytotoxins, i.e. antibodies cytotoxic to human lymphocytes are commonly found in 30–90% of patients with SLE (Thomas, 1973; Winfield et al. 1975; Pruzanski and Shumak, 1977). These antibodies do not agglutinate RBC to produce hemolysis and are thus distinct from cold agglutinins (Thomas, 1973; Pruzanski and Shumak, 1977).

Cold agglutinins are of two types - they are assigned ‘I’ specificity when they react more strongly with adult red cells than with cord blood cells and ‘i’ specificity when the reverse is true (Foerster, 1993). The agglutinins that react equally with cord and adult red cells are known as ‘Pr’ (Protease sensitive). The amount of lysis induced by cold agglutinins is related most directly to the ability of a given antibody to initiate complement activation and this is dependent on the thermal amplitude of the antibody. The site of hemolysis is mainly intravascular. The antibody is usually IgM which induces sensitization of red cells by attachment of C3b. C3b sensitized erythrocytes attach to phagocytic cells and undergo hemolysis. C3b inactivator cleaves one C3b molecule to C3c and C3d fragments. The survival of C3d coated cells is normal, because the presence
of C3d appears to interfere with the fixation of fresh C3 molecules, thereby protecting the cells from further damage by complement mediated mechanisms (Foerster, 1993). Thus, the anemia of CHAD is usually mild.

Treatment of secondary CHAD is mainly treatment of the underlying disorder as in our patient, where successful treatment of SLE has controlled CHAD. Warmth and bed rest may suffice for moderate exacerbations. Blood transfusions are found to exacerbate the hemolytic process due to the suplementation of fresh complements. The use of washed red cells through a 'inline' blood warmer has been recommended. Cross matching must be done at 37°C. Splenectomy is usually not effective as the site of clearance of antibody coated red cells in the liver (Atkinson et al. 1973; Foerster, 1993).

The most rational therapy for CHAD centers on the suppression of antibody production by using cyclophosphamide, chlorambucil or steroids. Plasmapheresis at temperatures above the thermal amplitude of the patients antibody may benefit acutely ill patients, because the IgM antibodies are predominantly intravascular. Intravenous immunoglobulin though useful in warm AIHA is not effective in CHAD (Besa, 1988; Jefferies, 1994). The favorable factors for responsiveness to steroids in CHAD are low antibody titer, high thermal amplitude and mixed (IgG-IgM) antibodies (Jeffries, 1994). Our patient had continued complete remission of CHAD, though she had a high titer of cold antibodies. This is not usual and is probably because her primary disease, SLE was well controlled with corticosteroids. This case reminds the physician to investigate further when problems arise during grouping and cross matching of blood and also to look for rarer complications of SLE.

REFERENCES


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