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Case report

Severe autoimmune hemolytic anemia with cold agglutinin and sclerodermic features – favorable response to danazol

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Summary. A rare case of severe primary autoimmune hemolytic anemia with cold agglutinin and extensive cutaneous sclerodermic changes is reported. This association has not been previously documented in the literature. The anemia was refractory to steroids but responded to danazol treatment. Danazol may be an effective therapy in some cases of autoimmune hemolytic anemia with cold agglutinin.

Key words: Cold agglutinin disease – Scleroderma – Danazol

Introduction

Autoimmune hemolytic anemia (AIHA) with monoclonal cold agglutinins is found mostly in patients with the idiopathic form or in association with lymphoproliferative disorders [4, 9]. Rarely, monoclonal cold agglutinins are noted in association with nonhematologic malignancies [12]. We report a case of severe AIHA with cold agglutinins associated with sclerodermic features, and the favorable response of the anemia to danazol therapy.

Case report

A 45-year-old Caucasian patient was hospitalized in our Medical Center in August, 1992, because of weakness. For the past 2 years she had noticed the progressive appearance of facial skin tightening and a limitation in opening her mouth. She was otherwise healthy and was taking no medication. On admission she looked pale, and physical examination revealed a generalized cutaneous thickening, especially marked in the facial area around the mouth and on both arms. Opening of the mouth was incomplete, and conjunctival jaundice was noted. The spleen was enlarged and was palapable 8 cm below the costal margin. Laboratory findings showed: hemoglobin 8.5 g/dl, MCV 92 fl, reticulocyte count 8.9%, and normal leukocyte and platelet counts. Peripheral blood smear showed moderate poikilocytosis and anisocytosis and few normoblasts. There were no Heinz bodies. Serum bilirubin level was 3.5 mg/dl, mostly indirect; haptoglobin was 20 mg/dl (normal >80) and LDH 4170 units/l (normal up to 330). Complement levels were: C3, 3.5 mg/dl (normal 70–210), and C4, 2.6 mg/dl (normal 17–80). Direct Coombs test was negative with anti-IgG but positive in the presence of anticomplement. The presence of a monoclonal cold agglutinin of the IgM type with anti-i specificity was demonstrated in the serum. Its titer was 1:1024 using adult ii cells. Serum protein immunoelectrophoresis showed IgG 680 mg/dl (normal 800–1450), IgA 70 mg/dl (normal 180–400), and IgM 1200 mg/dl (normal 80–200). Tests for Rose-Waaler and antinuclear factor (ANF) were weakly positive. A test for G6PD B$^-$ level showed that the patient was deficient for this enzyme. A bone marrow biopsy showed severe erythroid hyperplasia, compatible with hemolysis. There was no lymphoid infiltration in the bone marrow. An abdominal CT scan showed no enlarged lymph nodes. Cervical and thoracic CT scans were normal. A biopsy of the skin showed atrophy of the epidermis with flattening of rete ridges, secondary to a considerable expansion of the dermis due to diffuse collagen infiltration.

Investigation of the gastrointestinal tract and the cardiovascular and respiratory systems showed no evidence of systemic scleroderma. Antitopoisomerase 1 antibodies were not measured. The patients was discharged in October 1992 and followed up in the Hematology Outpatient Clinics. During the following weeks, the hemoglobin level progressively decreased to 5.7 g/dl, with evidence of severe hemolysis. Oral steroid therapy (prednisone, 60 mg per day) was started. No response was noted, however, and 4 units of washed red cells were transfused during a 4-week period. There were no problems with cross-matching. No clear connection was observed between room temperature and the severity of the clinical hemolysis.

In November 1992, therapy with danazol (600 mg/day) was initiated. Within 6 weeks, the hemoglobin rose to 11.0 g/dl, the reticulocyte count dropped to 2.6%, the LDH level to 800 units/l, and the serum bilirubin to normal levels. Cold agglutinins were still found in the serum (titer 1:128). The ANF was still weakly present, while the Rose-Waaler test became negative. After 4 months of danazol therapy, the hemoglobin level was 12.5 g/dl, with no need for blood transfusions. No changes were observed in the cutaneous scleroderma.

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Discussion

Our patient had severe AIHA with cold agglutinins, presenting with sclerodermic changes. The diagnosis of AIHA with cold agglutinins was based on the occurrence of anemia with hemolysis, the presence of a monoclonal IgM cold agglutinin, and a positive direct antiglobulin test in the presence of complement. Positive tests for rheumatoid factor and antinuclear antibodies are often seen in this context [8]. Although the patient was deficient in G6PD, the appearance of a chronic severe hemolysis in a Caucasian woman without exposure to an offending agent is not typical of G6PD B$^-$-induced hemolysis. The absence of Heinz bodies further rules out this diagnosis.

The skin changes were clinically and histologically consistent with scleroderma. The Raynaud phenomenon was not present, however, and no systemic damage was demonstrated. To the best of our knowledge, the association between AIHA with cold agglutinins and scleroderma has not been reported before. Since both diseases have been reported, although rarely, in association with lymphoma [4, 10], this disease was looked for and excluded after a thorough clinical and radiological workup.

The treatment of hemolytic anemia related to primary cold agglutinin disease is often unsatisfactory. Corticosteroids are not useful in most cases, and treatment is frequently limited to blood transfusions [3]. Our patient did not respond to corticosteroid therapy and needed repeated blood transfusions. Danazol was initiated when the hemoglobin dropped to below 6 g/dl. Response to therapy was rapid: within a few weeks, the hemoglobin rose to 12 g/dl, without the need for blood transfusions. Danazol is an effective therapy for AIHA with warm antibodies [2], for autoimmune thrombocytopenia purpura, and in the prevention of hereditary angioneurotic edema attacks [1, 7]. Studies of the action of danazol in AIHA suggest that inhibition of complement activation and its binding to cell membranes is an important mechanism [2]. It is known that the amount of lysis affected by cold agglutinins is directly related to its ability to initiate complement activation [11]. It should therefore be logical to use such an "anti-complement" drug to prevent the hemolytic reaction due to complement activation by cold agglutinins. Danazol is not known as a possible therapy for AIHA with cold agglutinins [5]. Geffray and Najman [6] recently reported the favorable effect of danazol on four patients with AIHA with cold agglutinins. Response to danazol was noted within a few weeks of therapy in all four patients, who had been unresponsive to previous treatments. Maintenance danazol was given for 3–7 years with no serious side effects or complications. No relapse was observed among the four treated patients. In the light of this report and our personal experience, although limited to one patient, it seems that danazol could be an effective therapy for some patients with AIHA with cold agglutinins.

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