Acute systemic lupus erythematosus in IgA deficiency

Mechlorethamine hydrochloride therapy

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Treatment of systemic lupus erythematosus (SLE) that has failed to respond to steroids poses a difficult problem. Various regimens involving the long-term use of cytotoxic drugs such as cyclophosphamide,[1] azathioprine,[2] or chlorambucil[3] have been proposed; such drugs are considered warranted in cases where renal involvement is severe. Occasionally, however, a patient with only mild renal involvement may have an acute attack of SLE that does not respond to moderate doses of steroid. In this situation, a short course of a fast-acting cytotoxic drug followed by more conventional therapy may be useful.

This paper reports on the effectiveness of intravenous nitrogen mustard therapy in subduing an acute attack of SLE which had been unsuccessfully treated with steroid. It also exemplifies the common occurrence of SLE in patients with IgA deficiency[4] and the modifications of the usual pathogenic mechanisms this may imply.

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Materials and methods

Fluorescent antinuclear antibody tests and lupus erythematosus cell preparations were performed by the method described by Garewal and Deodhar.[5] Anti-DNA was determined by passive hemagglutination with a modification of the method of Bankhurst, using high polymerized DNA* which was heat denatured before coupling with sheep erythrocytes in the presence of chromic chloride. C3 (B1C/B1A) levels were determined by radial immunodiffusion with the use of commercially available materials.† Hemolytic complement titers were measured by the method of Kabat and Mayer.[6]

Serum content of components of the alternate pathway to C3 activation (properdin system) was assayed as follows: 0.1 mg of zymosan, 0.1 ml of patient's serum, and 10^6 neutrophils (obtained by sedimentation of 2 volumes of normal whole heparinized blood with 1 volume of 6% dextran in saline solution at room temperature for 1 hour) were incubated at 37C for 50 minutes in medium 199. The percentage of cells containing zymosan particles was then determined immediately by microscopic examination with a Nikon microscope with phase optics at 1000× under oil.

Anti-DNA in individual immunoglobulin classes was assayed by a newly developed radioimmunoassay technique, a detailed description of which is in preparation. Dilutions of serum were each exposed to 3 aliquots of 10^8 sheep erythrocytes coated with the same DNA preparation used in the passive hemagglutination assay. After extensive washing, ^{125}I labelled specific anti-IgM, anti-IgG, and anti-IgA were added to individual aliquots of cells with their bound antibody. After washing, the cells were lysed with water and the amount of radioactivity was determined in a Picker gamma counter. All samples were absorbed with sheep erythrocytes before assay, and parallel determinations of antibody against sheep erythrocytes were done using uncoated cells. Results were expressed in antibody units equal to the percent of added counts fixed by 0.1 ml of serum corrected for dilution.

* *Nutritional Biochemical Company.*

† *Hyland Laboratories.*

Case report

This 15-year-old boy was in apparent good health until January 1973 when painful swelling developed in the right ankle, left knee, and small joints of both hands. His physician diagnosed the condition as juvenile rheumatoid arthritis and instituted salicylate therapy. However, symptoms persisted until prednisone, 10 mg/day, was substituted. He did well until April 12, 1973, when after a period of sun exposure while vacationing in Florida, he had a temperature of 104F, and an erythematous rash developed on the exposed parts of his body. Results of studies performed at that time revealed leukopenia (2,600 cells/cu mm), elevated sedimentation rate, and postive LE cell preparation. The diagnosis was SLE. He was treated with prednisone, 40 mg/day, and had good initial response, although symptoms soon recurred despite continued treatment.

He was first examined at the Cleveland Clinic on April 24, 1973, and was hospitalized with a temperature of 101F, blotchy violaceous rash over the knees and shoulders, and arthralgia, but no objective arthritis. His physical examination showed no other abnormalities.

Laboratory studies at that time disclosed the following values: hemoglobin, 11.7 g/100 ml; hematocrit, 34.5%; white

cell count, 10,900/cu mm, with 74% segmented neutrophils, 2% nonsegmented neutrophils, 13% lymphocytes, and 12% monocytes; platelets appeared normal; sedimentation rate, 1.6 mm/min (Rourke/Ernstene); plasma fibrinogen, 441 mg/100 ml; serum glycoproteins, 184 mg/100 ml (normal = 110 to 145 mg/100 ml); fluorescent antinuclear antibody, positive at a serum dilution greater than 1:160 with a homogeneous pattern; LE cell preparation, 4+; VDRL test, negative; blood urea nitrogen (BUN), 18 mg/100 ml; and serum creatinine, 0.8 mg/100 ml. Immunoglobulin levels were as follows: IgG, 1,725 mg/100 ml (normal = 1,380 ± 255); IgM, 180 mg/100 ml (normal = 145 ± 105); IgA, undetectable (normal = 156 ± 92). Urine examinations included an Addis count which revealed 2.5×10^6 red blood cells, 2.5×10^6 white blood cells, and 2.8×10^4 casts in a 12-hr specimen, and a 24-hr protein excretion of 1.58 g. The creatinine clearance was 67.3 mm/min. Results of anti-DNA and complement studies are given in the next section.

Percutaneous renal biopsy was performed and the specimen had focal membranoproliferative glomerulonephritis; immunofluorescent studies showed diffuse granular deposition of IgM, IgG, and C3, but not IgA in the glomeruli (*Fig. 1*).

Treatment was begun with mechlorethamine administered intravenously, 1 mg the first day, then in 2-mg increments daily to a total dosage of 13 mg; each dose was accompanied by 10 units of ACTH. Prednisone, 40 mg/day, was continued. The patient became afebrile on the 4th day of treatment and the rash cleared gradually over the 7-day period. Urinary sediment improved significantly. A 12-hr specimen on May 1, 1973, contained no red blood cells, 6.0×10^5 white blood cells, and 6.6×10^3 casts.

He was discharged from the hospital on May 5, 1973, on a regimen of prednisone, 35 mg/day, and hydroxychloroquine phosphate, 200 mg/day. During the next month, the dosage of prednisone was gradually reduced to 7.5 mg/day without recurrence of symptoms. He remained asymptomatic during the subsequent 27 months.

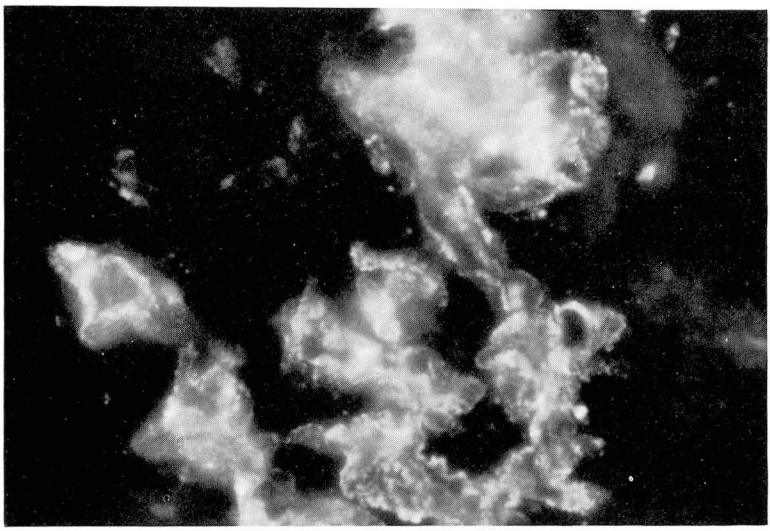

Fig. 1. Immunofluorescent study of the renal biopsy specimen showing granular deposition of IgG in the glomerulus. A similar pattern was seen for IgM and for C3, but no IgA could be found in the glomeruli.

Results

Paralleling the clinical response to treatment characterized by regression of fever, arthralgia, rash, proteinuria, and abnormal urinary sediment, there was a striking decrease in the anti-DNA titer (*Fig. 2*). This was accompanied by a rise in total hemolytic complement (*Fig. 3*). B1C/B1A (C3) levels remained in the low normal range throughout the treatment. Properdin function, as assayed by support of zymosan phagocytosis, was also normal throughout the same period.

A more detailed view of anti-DNA levels was obtained using a radioimmunoassay technique to measure anti-DNA in the individual IgM, IgG, and IgA classes. These results are shown in *Figure 4*. Consistent with the IgA deficiency, little or no anti-DNA could be found in the IgA class. Activity was found in both IgM and IgG classes; IgM anti-DNA diminished with a half-time of 2.25 days, and IgG anti-DNA with a half-time of about 4 days. During this period there was no significant change in total immunoglobulin levels.

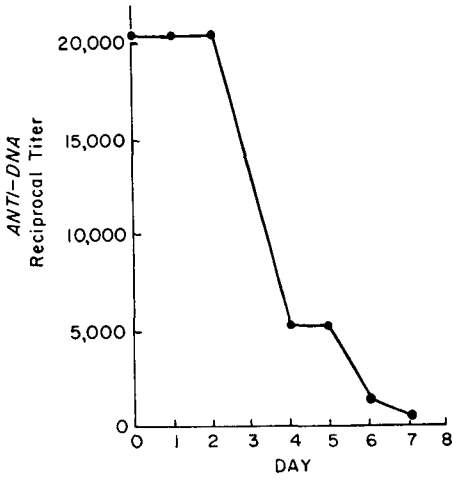

Fig. 2. Decrease in anti-DNA as determined by passive hemagglutination during mechlorethamine treatment period.

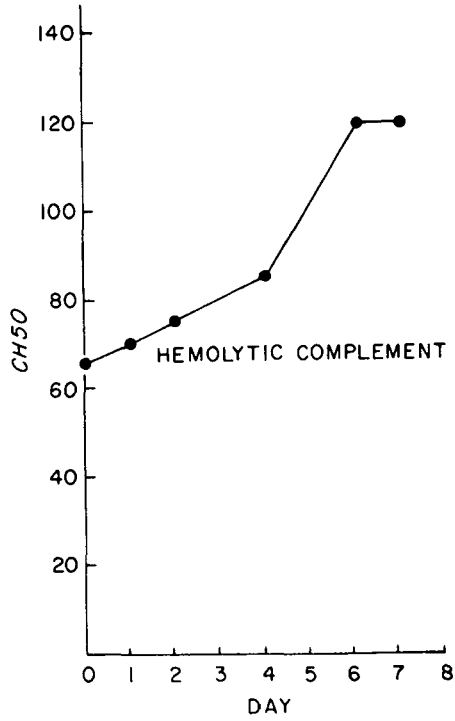

Fig. 3. Rise in total hemolytic complement titer during the treatment period.

After mechlorethamine treatment was completed, despite decreasing the dose of prednisone to 7.5 mg/day, anti-DNA titer remained within the normal range for at least 27 months and is still normal.

Discussion

The use of cytotoxic drugs for the treatment of severe inflammatory disorders, such as SLE,[1] rheumatoid arthritis,[7] polymyositis,[8] necrotizing vasculitis,[9] and Wegener's granulomatosis[10] has recently attracted widespread interest. Although such application has been prevalent in some centers for more than 20 years,[7] acceptance has

been slow because of concern about hazardous side effects and because of difficulties in establishing drug efficacy in diseases with spontaneously fluctuating and unpredictable courses. Prolonged administration of immunosuppressive doses of these agents has been emphasized, and toxicity has been a frequent problem.[1] A different approach is the use of a short course of a rapidly acting cytotoxic drug such as mechlorethamine to suppress active disease. This suppression can then often be maintained by more conventional therapy alone, despite failure of an initial trial of such therapy.*

This paper describes such a case. Mechlorethamine hydrochloride given intravenously induced rapid resolution of clinical and laboratory parameters which had failed to respond to moderate-dose corticosteroid therapy for 1 month. Remission was subsequently maintained with low-dose corticosteroid and antimalarial drug treatment.

Of additional interest is the finding that this patient had no detectable IgA, a fact which probably modified the pathogenesis of his disease and which may have had a bearing on its etiology.

The association of SLE and defective immunity, especially deficient T-cell function, and its possible etiologic importance have recently attracted considerable attention. Hahn et al[11] and Horwitz[12] reported decreased reactivity of skin tests for delayed hypersensitivity, confirming the results of Bitter et al[13] and Abe and Homma.[14] In addition, the incidence of SLE in patients with IgA deficiency is higher than the incidence in the general

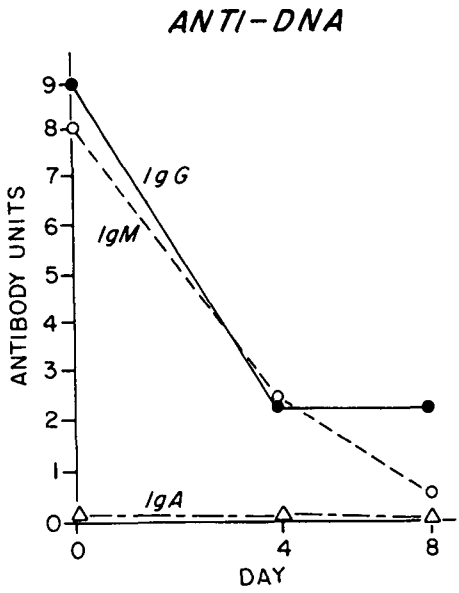

Fig. 4. Decrease in serum anti-DNA in immunoglobulin classes IgM and IgG during the treatment period; little or no IgA anti-DNA was present.

population.[4] It has been shown in several animal systems that the integrity of the thymus gland is especially important in IgA antibody production in response to "thymic dependent" antigens[15] and in the maintenance of serum IgA levels.[16] The reason for this relationship is not clear, but it has been suggested that T-cell helper function is more important in IgA antibody production than in IgM or IgG antibody production.[15] Thus, the absence of IgA may indicate a subtle T-cell defect in this patient.

The pathogenesis of SLE renal disease is thought to involve the deposition in the glomerulus of immune complexes containing DNA and anti-DNA.[17] Activation of complement via both classical and alternate pathways then leads to local inflammation and tissue destruction.[18] Classical pathway activation normally requires antibody

* *Scherbel AL: Unpublished data.*

of IgG or IgM class,[19] and alternate pathway activation may be brought about by IgA antibody.[20] Thus, in this patient, one major, postulated pathway of complement activation is absent. Although IgM, IgG, and C3 could be seen in the glomeruli by immunofluorescence, no IgA could be demonstrated. Lack of consumption of the components of the alternate pathway is suggested by normal ability of this serum to support zymosan phagocytosis by neutrophils. In contrast, consumption of components of the classical pathway is indicated by initially low total hemolytic complement titers, which generally reflect C2 levels in the absence of a primary complementopathy. Perhaps the relatively good response to treatment was in part due to the less overpowering nature of the "autoimmune" onslaught in this immunodeficiency state.

The apparent paradox of using medication capable of suppressing immunity to treat a disease in which immunodeficiency may play an etiologic role is not completely resolved. Whether the proposed defect in T-cell regulatory function allows B-cell hyperactivity,[21] or whether some less direct effect of T-cell deficiency such as viral infection[22] hyperstimulates humoral activity, it seems clear that at least some of the manifestations of SLE are caused by the production of autoantibodies, including anti-DNA.[17] To the extent that "immunosuppression" interferes with this, it should be beneficial.

The most desirable form of immunosuppression in a disease mediated by autoantibody, in this case presumably anti-DNA, would be the specific elimination of that autoantibody without affecting the patient's ability to make other more normal immune responses. This state would resemble specific immunologic tolerance. In mice, tolerance to sheep erythrocytes can be produced by giving cyclophosphamide with sheep erythrocytes.[23] The drug apparently attacks those clones of rapidly proliferating immunocytes which are specifically responding to antigen. Other clones of relatively quiescent lymphocytes, not activated by that antigen, are not affected by the drug. The data here are consistent with such an effect. Although total immunoglobulin levels were virtually unchanged during the period of administration of mechlorethamine hydrochloride, IgM anti-DNA levels decreased with a half-time of 2 days, and IgG anti-DNA decreased with a half-time of about 4 days, indicating a marked decrease in specific antibody synthesis. Wochner[24] reported average values for overall IgM and IgG (not anti-DNA) survival half-time in 16 patients with lupus erythematosus to be 8.53 ± 2.81 and 14.7 ± 3.3 days, respectively. The lower half-time values for specific antibody reported here probably reflect accelerated clearance due to continued complex formation with DNA. This state of decreased anti-DNA synthesis was maintained for at least 27 months, allowing reduction of steroid therapy and requiring no further cytotoxic intervention during that time.

The unknown, and as yet uninvestigated, danger of such treatment is that the possible underlying T-cell deficiency could be aggravated to the ultimate detriment of the patient. Nonetheless, in view of the known

immediate danger posed by the presence of such antibodies and the immune complexes they form, the judicious use of cytotoxic drugs seems indicated, especially in short, intermittent courses.

Summary

Clinical and some immunologic abnormalities in a 15-year-old IgA-deficient boy with acute systemic lupus erythematosus were ameliorated after a short course of mechlorethamine hydrochloride, a nitrogen mustard. Anti-DNA levels fell and hemolytic complement titers rose to normal during the 1-week treatment period. He was subsequently maintained on antimalarial and low-dose corticosteroid therapy without relapse for at least 27 months. The use of mechlorethamine hydrochloride to induce specific immunologic tolerance to DNA is discussed.

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