Partial In vivo Response to Corticosteroid Treatment in Common Variable Immune Deficiency

Summary: The case of a 13-year-old girl with CVI is presented who required steroid treatment for myositis. After three weeks of treatment, the serum IgM level increased about ten-fold. Specific antibodies to vaccination antigens, which despite adequate vaccination were absent prior to any kind of treatment, could be synthesized following steroid treatment. The effects observed were only transient. Steroid influences on immunoregulatory T cells may have contributed to the improvement of humoral immunity in this patient.

Introduction

The inability of patients with humoral immune deficiency syndromes to produce specific antibodies in response to foreign antigens may be due to the lack of B lymphocytes, as in X-linked agammaglobulinemia (1). However, many patients with common variable immune deficiency (CVI) do have normal values of peripheral B cells. Dysfunction of these B cells is not necessarily the consequence of an intrinsic B cell defect but may be caused by lacking helper T cell function or excessive suppressor T cell function. In the latter group of patients, antibody production can be induced in vitro following the elimination of suppressor cells. The clinical significance of these in vitro findings has not yet been fully elucidated. Glucocorticosteroids have been shown to be able to increase immunoglobulin production in vitro (2, 3). In vivo, however, administration of large doses of these drugs results in a reduction of immunoglobulin levels and levels of specific antibodies (4, 5).

In this communication we would like to present data indicating that antibody production may not always be suppressed by steroids but can be induced under certain conditions in patients with CVI due to a regulatory T cell defect.

Case Report

Family history and pregnancy were unremarkable. Until the age of nine years, the girl had been suffering from recurrent sinusitis, recurrent conjunctivitis, bronchitis and one episode of iridocyclitis. She suffered from chronic granuloma anulare on the back of both feet. The course of varicella and mumps was uncomplicated. At the age of nine years she was admitted to a regional hospital for further evaluation. At that time she had received a total of six vaccinations against diphtheria/tetanus, four against pertussis, one BCG, one against smallpox, one against measles and four oral vaccinations against poliomyelitis. All vaccinations were well tolerated.

During her first period of admission to the regional hospital, she was found to have hepatosplenomegaly and chronic hepatitis. Levels of immunoglobulins IgG and IgM were markedly reduced but no replacement therapy was initiated. By the end of 1979 she was referred to our hospital for further immunological evaluation and therapy.

On clinical examination the predominant finding was a markedly enlarged spleen (9 cm) and a slightly enlarged liver (1 cm). Granuloma anulare was present on the back of both feet. Otherwise she appeared healthy.

Laboratory tests: The ESR was normal and CBC normal except for slight leukopenia (3500/mm³) with a normal differential count. SGOT 26 U/l, SGPT 41 U/l (slightly elevated); other routine tests were normal.

Immunological findings: IgG present in traces (normal: 690-1840 mg/dl), IgA 190 mg/dl (80-452 mg/dl), IgM 28 mg/dl (51-200 mg/dl). Blood group was AB, so isohemagglutinins could not be expected. No specific antibodies could be found to vaccination antigens and children’s diseases diagnosed in the past. Surface immunoglobulin-positive B cells were 15%, E-rosette-forming T cells 48%. Lymphocyte stimulation with mitogens PHA, Con A, PWM and allogeneic cells (MLC) was normal. Skin tests for delayed type hypersensitivity, phagocytic functions and hemolytic complement were within the normal range.

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Replacement therapy was initiated using a β-propiolactone-treated gammaglobulin preparation (Intraglobin F, Biotest, Frankfurt, FRG) at a dose of 200 mg/kg bw intravenously every three weeks. Infusions were well tolerated and IgG levels between 100-800 mg/dl could be maintained. Despite this therapy she had two documented episodes of bronchitis, two of sinusitis maxillaris, one of lymphadenitis colli, zoster and two minor purulent skin infections on her upper lip and one finger during the following three years. Liver enzymes remained slightly elevated. CBC revealed a tendency to develop mild leukopenia, thrombocytopenia and reticulocytosis without further signs of hemolysis. In January 1982, six days after the last gammaglobulin infusion, she became febrile and complained of proximal muscle weakness and pain. She was unable to walk. At that time the liver was 3 cm, the spleen 14 cm below the costal margin. Neurological findings suggested myositis, although CK was normal. Myositis was confirmed by electromyography and muscle biopsy. Minor calcifications could be noticed on X-rays of her pelvis around her left hip joint. Virus cultures of muscle tissue were negative, as were cultures of saliva and stool (further details in the Results section). Prior to steroid treatment she was markedly leukopenic (WBC 700/mm^3), anemic (Hb 8.7 g/dl) and thrombocytopenic (platelets 48,000/mm^3) with increased reticulocyte count (92%). The direct Coomb’s test was negative. These data and the results of the muscle biopsy suggested some kind of “autoimmune” complication. As the predominant immunoglobulin present in immune deposits of the muscle biopsy specimen was IgG (the only immunoglobulin not produced by the patient), replacement therapy was discontinued because it was possible that IgG derived from the preparation had mediated muscle inflammation. Thus, the in vivo response of a CVI patient to steroid treatment could be studied without gammaglobulin infusions influencing Ig levels. Myositis treatment using 0.5 mg/kg bw methylprednisolone was successful, as judged by muscle strength and EMG. CBC returned to normal. Further results are mentioned in the Results section. Fifteen months after the first episode of myositis, she had a recurrence associated with aplastic anemia and staphylococcal septicemia. Complete remission could be achieved by treatment with oxacillin, methylprednisolone and oxymetholone. However, at this time no antibody production could be induced. As this second crisis had occurred without replacement therapy, it was proven that it was not responsible for the myositis. Therefore we started the girl on gammaglobulin again. At present she is doing well.

Materials and Methods

Immunoglobulins were measured by single radial immunodiffusion according to Mancini et al. (6) using commercially available immunodiffusion plates (Behring, Marburg, FRG). Tetanus-specific and diphtheria-specific antibodies were determined by indirect hemagglutination methods (7, 8). The differentiation between specific IgM and IgG antibodies was carried out by column chromatography separation of serum proteins using a polyacrylamide agarose gel (Ultrogel AcA 34, LKB, Bromma, Sweden). Serum samples were additionally examined by hemagglutination prior to and following the destruction of IgM with mercaptoethanol or dithiothreitol. Lymphocyte surface markers for B cells, T cells and lymphocyte subpopulation were analyzed by established techniques (9). Lymphocyte transformation tests using antigens, mitogens and allogeneic cells have been described in detail elsewhere (10, 11). The results are expressed as cpm increment values by subtracting the spontaneous thymidine incorporation from the respective stimulated values.

For the immunohistological examination a specimen of freshly obtained muscle tissue was incorporated into a drip of Tissue-Tek II (Miles Lab., Naperville, Ill., U.S.A.) and immediately frozen in liquid nitrogen. Further treatment of the tissue sample has been described by Seelig (12).

Results

Microscopic examination of the muscle biopsy revealed a pathological pattern with lymphocyte infiltration, muscle

![Figure 1: Development of immunoglobulin levels and WBC counts in a 13-year-old girl with CVI and myositis following treatment with methylprednisolone at a dose of 0.5 mg/kg bw orally. Replacement therapy with intravenous gammaglobulin had been discontinued two weeks earlier. The shaded areas indicate the respective normal values.](image-url)