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Spontaneous remission of common variable immunodeficiency of 20 years duration

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The manifestations of CVI are mainly pyogenic paranasal sinusitis and pneumonia, characteristic of Ab deficiency. Circulating B-lymphocytes are present, and T-lymphocyte abnormalities occur in about 50% of patients.^{1,2}

Few patients have benefitted from treatment with cimetidine.^{3,4} Spontaneous reversal of CVI has been reported in two HIV-infected patients.⁵ Short-lived immunoglobulin and Ab production occurred in two patients with CVI.⁶ We describe a patient with CVI

Abbreviations used

CVI: Common variable immunodeficiency
Ab: Antibody
HIV: Human immunodeficiency virus

for 20 years, who has maintained a low-normal IgG for 2 years, and has the ability to produce specific Ab.

CASE REPORT

A 25-year-old white woman was found to have hypo- γ -globulinemia in 1969 after recurrent upper respiratory tract infections and two hospitalizations for bronchopneumonia. She denied previous recurrent infections.

Results of a physical examination at that time were unrevealing except for obesity (height, 64 inches; weight, 195 pounds). Results of a complete blood count and chemistry were normal. Hypo- γ -globulinemia was present (Table I),

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TABLE I. Total immunoglobulins

Date	Method	IgG (mg%)	IgA (mg%)	IgM (mg%)	IgE (IU)
1969	RID	<269	0	0	ND
1980	RID	169	<10	12	ND
7/23/87	Neph	209	<1.4	60	ND
4/25/88	Neph	396	<8	64	ND
3/20/89*	Neph	919	<8	55	0†
2/28/90‡	Neph	731	1.4	57	ND
4/19/91‡	Neph	632	<7	151	ND

RID, Radial immunodiffusion; ND, not done; Neph, nephelometry.

*Receiving 20 ml of γ -globulin, intramuscularly, at biweekly intervals.

†Performed by PRIST.

‡ γ -Globulin was stopped in April 1989.

whereas the serum albumin concentration was 3.6 g/dl. A delayed-type hypersensitivity skin test to histoplasmin was positive at 48 hours. She was administered 20 ml of γ -globulin, intramuscularly, and antibiotics but continued to suffer from recurrent respiratory infections. Evaluation in 1980 revealed a serum IgG ranging from 87 to 169 mg/dl (Table I), and she started receiving erythromycin, 1 g/day for 10 days of each month. Biweekly intramuscular injections of 20 ml of γ -globulin were started, but she received them irregularly, since several IgG levels between 1982 to 1985 were unchanged. Because of occasional wheezing and intolerance for dust, fumes, and strong odors, she was treated with inhaled corticosteroids and bronchodilators. However, results of pulmonary function tests from 1969 to 1989 were normal.

She was referred to the Allergy-Immunology Clinic of the University of Missouri-Columbia in May 1988 for consideration of intravenous γ -globulin. Results of physical examination were unremarkable, except for obesity (weight, 200 pounds). Serum albumin concentration was 4 g/dl. Results of sinus series were normal, and a chest roentgenogram revealed a stable small calcification. Five inhalations of 0.25 mg of methacholine caused a 30% decline in FEV₁. Serum IgG was 396 mg/dl (Table I). Biweekly intramuscular injections of 20 ml of γ -globulin were continued. In March 1989, serum IgG became normal, and replacement therapy was stopped. She responded normally to several immunizations. She felt reasonably well, although she complained of having recurrent "infections" without any fever and produced intermittently purulent sputum. In October 1989, rales were heard at the left lung base and persisted for 3 months. Result of a chest roentgenogram was normal, and a sputum culture revealed normal flora. In January 1990, she developed a bilateral maxillary sinusitis with complete clearing of the sinus roentgenogram after antibiotic therapy. No other infections occurred as of April 1991.

For the last 2 years, the patient has been receiving intermittent cimetidine for heartburn at a dose of 300 mg every other day.

Immunologic evaluation

Serum protein electrophoresis (twice), C3, C4, and total hemolytic complement determinations were normal.

Immunoglobulins (Table I). Hypo- γ -globulinemia had been present from 1969 to 1988. IgG and IgM normalized, whereas IgA was low and IgE was undetectable.

Specific Ab responses. Normal responses were obtained to the following vaccines: (1) influenza A and B, titers increased from <1:2 to 1:8 measured by hemagglutination. (2) IgG response to booster injections of tetanus and diphtheria toxoids; titers rose from 1:1 to 1:10 for diphtheria and 1:24 for tetanus-measured by ELISA. Tetanus IgM titers were normal before immunization and have not changed. (3) Four serotypes of pneumococci were tested after pneumococcal vaccine (Pnu-Immune; Lederle Laboratories, Pearl River, N.Y.). Titers increased from 1:5 to 1:17, 1:22, 1:56, and 1:68 measured by ELISA. (4) *Haemophilus influenzae* type b (ProhiBit; Connaught Laboratories, Inc., Swiftwater, Pa.); two doses were required to increase IgG level from 0.2 to 2.7 ng/ml (measured by ELISA). Abs to HIV and p24 Ag were undetectable. Isohemagglutinins were undetectable (blood group, A and Rh+).

Cellular immunity (1990). Delayed-type hypersensitivity skin tests to mumps Ag and *Candida* were positive.

Immunophenotypic analysis of peripheral blood by flow cytometry revealed normal numbers of leukocytes (2112/mm³); T-lymphocytes and subsets, expressed as absolute numbers per cubic millimeter: CD2, 1863; CD4, 725; CD8, 745; DR⁺ T-lymphocytes, 62; natural killer cells (CD57, 642; CD16, 269); B-lymphocytes (CD20), 83; surface IgG-positive cells, 331; IgA-positive cells, 14; and IgM-positive cells, 311. Lymphocyte transformation in response to phytohemagglutinin was borderline low, compared to the response of three simultaneous control subjects, and normal to concanavalin A and pokeweed mitogen.

DISCUSSION

This patient is unique in that serum IgG and IgM became normal 20 years after diagnosis of CVI. Ab responses were normal when the patient was evaluated in 1989. No such studies have been performed previously, probably because of persistent hypo- γ -globulinemia and recurring infections. No other studies of long-term spontaneous remissions of CVI have been

reported in the literature. In one HIV-infected patient, IgG rose to subnormal levels, whereas HIV Ab titer was high; in the second HIV-infected patient, IgG increased to 1.95 gm/dl, IgA and IgM normalized, and specific Abs to several viruses developed.⁵ Two other patients with CVI had a transient rise in immunoglobulin concentrations, and one patient produced antitetanus Abs for several months after immunoglobulins had returned to baseline.⁶ Our patient had no risk factors to HIV infection, no Abs to the virus, nor antigenemia. She was studied at a time when her ability to produce specific Abs to several Ags was demonstrated and has maintained a low-normal IgG and normal IgM for 2 years.

Cimetidine has been tried in several patients with CVI^{3,4} and has been demonstrated to inhibit the activity of suppressor lymphocytes in vitro.^{3,4} In vivo, cimetidine led to a clinical improvement with³ or without⁴ a concomitant rise in serum IgG in very few patients. In both studies, 1200 mg/day of cimetidine was required for clinical improvement.^{3,4} Even with this dose, only one of six patients had a significant increase in serum IgG. Six hundred milligrams of cimetidine was ineffective, with clinical worsening in the previously responding patient and had no effect on suppressor lymphocytes.³

Our patient had been receiving 300 mg of cimetidine every other day for about 1 year when she was

initially observed. This dose is considerably smaller than the dose that resulted in a significant response in the above studies. Hence, it is unlikely that cimetidine caused the current patient's improvement.

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