Case Report

B Cell Loss Leading to Remission in Severe Systemic Lupus Erythematosus

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ABSTRACT. Systemic lupus erythematosus (SLE) pathogenesis is mediated in part by autoantibodies. We describe a patient with central nervous system lupus who developed a loss of B cells with associated hypogammaglobulinemia and sinopulmonary infections requiring intravenous immunoglobulin. The SLE went into complete remission. Of 18 reported patients with SLE developing persistent hypogammaglobulinemia, only 5 patients including ours had a nearly complete loss of circulating B cells. Of those whose SLE and B cell status was reported, 5/5 with B cell loss and 1/10 without B cell loss experienced a durable response of SLE ($p = 0.002$). These cases illustrate that B cell ablative therapies may have efficacy for SLE. (J Rheumatol 2003;30:412–4)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS
HYPOGAMMAGLOBULINEMIA
B CELL ABLATION
COMMON VARIABLE IMMUNODEFICIENCY
INTRAVENOUS IMMUNOGLOBULIN

Autoantibodies clearly play an important role in the pathogenesis of systemic lupus erythematosus (SLE). Recently, anti-CD20 antibodies used to selectively deplete mature B cells have been effective at treating autoantibody mediated diseases, including autoimmune or idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, and myasthenia gravis. These results suggest that B cell ablative therapies may also be effective for SLE[1].

We describe the clinical course of an individual with SLE who developed a loss of circulating B cells and a long-lasting, complete remission of SLE (no disease activity by examination and laboratory evaluation, including autoantibodies). Our review of the literature revealed reports of 4 other individuals with SLE who had a durable response (no disease activity requiring treatment) in SLE associated with B cell loss, and a fifth report of an individual who had a decrease in B cells, but the SLE activity after B cell loss was not reported[2-6]. We also discuss the implications of our findings for the use of B cell ablative therapy to treat refractory SLE.

CASE REPORT

A 27-year-old female physician diagnosed with SLE in March 1996 had a syndrome of fever, fatigue, malar rash, arthritis, proteinuria (773 mg/24 h), serositis, hypocomplementemia, and positive antinuclear (1:1280), anti-dsDNA, anti-Smith, and anti-RNP antibodies. She was treated with glucocorticoids until May 1997, when she developed neuropsychiatric lupus with a generalized tonic-clonic seizure and a brain magnetic resonance imaging finding of lesions in the left frontal and right posterior parietal lobes. Infectious and hypercoagulation investigations including lupus anticoagulant and anticardiolipin antibodies were negative. She was treated with steroids, phenytoin, gabapentin, and intravenous (IV) cyclophosphamide 880 mg. After hospital discharge, she received monthly IV cyclophosphamide for 6 months, and a single dose of 1125 mg IV at 9 months. At this time, she found she was pregnant, and cyclophosphamide therapy was discontinued. The pregnancy was remarkable for a herpes zoster infection a few weeks before the delivery of a healthy infant in October 1998.

After pregnancy and cessation of cyclophosphamide, she had no exacerbations of SLE, but developed bilateral conjunctivitis, bilateral otitis media, and pneumonia requiring hospitalization in September 1999. She developed neutropenia and lymphopenia with an absolute neutrophil count of 40 (normal 1700–7000) and an absolute lymphocyte count of 900 (normal 1000–4800). In November 1999, she was found to have hypogammaglobulinemia (IgG undetectable at < 33 mg/dl, IgA undetectable at < 7 mg/ml, and IgM decreased at 9 mg/dl (normal 43–238 mg/dl). Flow cytometric analysis showed normal neutrophil counts, but < 1% B cells, and a reversed CD4/CD8 ratio. With severe sinopulmonary infections and hypogammaglobulinemia, replacement IVIG therapy (400 mg/kg every 28 days) was initiated and all immunosuppressives discontinued in December 1999. All autoantibodies became negative. She has remained B lymphopenic and has had no serious infections or evidence of SLE for over 2 years.

DISCUSSION

SLE is routinely associated with hypergammaglobulinemia, autoantibody formation, and inflammation. In rare instances, individuals with SLE have developed hypogammaglobulinemia requiring passive immunotherapy with IVIG[2-14]. In those 17 individuals whose SLE status has been reported (Table 1), 7 experienced a durable response of SLE; 3, including our patient, had a remission.

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Table 1. Clinical characteristics of individuals with SLE who developed hypogammaglobulinemia..

Patient	SLE Onset and Characteristics	Treatment	Hypogammaglobulinemia Onset, Characteristics, Ig Levels (mg/dl)	Circulating B Cells	Other Immunologic Abnormal	Persistent SLE
1, this report	Female age 27, ANA (1:1280), anti-DNA, anti-Smith, anti-RNP antibodies	Glucocorticoids, CYC, phenytoin, gabapentin	30 yrs, no detectable autoantibodies IgG < 33, IgM 9, IgA < 7	Decreased, < 1%	Reversed CD4/CD8 ratio	No
2[2]	Male age 15 ANA (1:80)	Glucocorticoids, phenytoin, phenobarbital	18 yrs, ANA+, anti-DNA+, complement normal, IgG 6, IgM undetectable, IgA undetectable	Decreased, 1–2%	Impaired DTH, T cell anergy to tetanus toxoid	No
3[3]	Female age 11 ANA+, +LE prep, anti-DNA +, anti-RNP +	Prednisone, carbamazepine	17 yrs, IgG211, IgM 0, IgA 0	Decreased undetectable	Decreased proliferation to pokeweed mitogen	No
4[4]	Female age 36, ANA+, false + RPR, Positive LE prep	Prednisone, azathioprine	46 yrs, ANA+ IgG < 200, IgM 0, IgA 0	Decreased, 1.6%	Increased T suppressor cells, decreased CD4/CD8 ratio	No
5[5]	Female age 28, ANA 1:640, anti-DNA +	Prednisone, CYC	30 yrs, ANA neg, IgG 340, IgM 704	Varying levels, < 1–5%	Elevated IgM	No
6[6]	Female age 41, +LE prep	Prednisone, azathioprine, carbamazepine	ANA neg, anti-DNA neg, IgG 0, IgM 113 IgA 0	Decreased, 2.8%		Not known
7[7]	Female age 11, Anti-DNA +	Prednisone, azathioprine	15 yrs, IgG 387, IgM normal, IgA normal	Normal, 5%	Increased suppressor T cells	Yes
8[7]	Female age 49, ?	Prednisone	61 yrs, IgG 496, IgM decreased, IgA normal	Mild decrease, 3%		Yes
9[7]	Female age 15, Anti-DNA +	Prednisone, CYC	20 yrs, IgG 132, IgM normal, IgA normal	Normal levels,10%	Decreased T cells	Yes
10[7]	Female age 51, Anti-DNA +	Prednisone, CYC	58 yrs, IgG 524, IgM normal, IgA normal	Mild decrease, 3%	Inverted CD4/CD8 ratio	Yes
11[7]	Female age 28, Anti-DNA +	Prednisone	29 yrs, IgG 280, IgM normal, IgA normal	Normal levels, 8%	Inverted CD4/CD8 ratio	Yes
12[8]	Female age 16, ANA+ Anti-DNA+	Prednisone chlorambucil	26 yrs, ANA+ IgG 300, IgM 944, IgA < 3	Not stated	Elevated IgM, decreased CD4/CD8 ratio	No
13[8]	Female age 32, ANA+ Anti-DNA+	Prednisone azathioprine	39 yrs, ANA neg,IgG 600, IgM 20, IgA 0	Not stated	Decreased CD4/CD8 ratio	Yes
14[9]	Female age 42, ANA+ C3 70, C4 5	Prednisone, azathioprine, phenytoin	42 yrs, ANA+ IgG 150, IgM 37, IgA 20	Normal levels, 10%	B cells did not express CD19	Yes
15[10]	Female age 37, C2 deficiency ANA – Anti–DNA	Glucocorticoids, phenytoin, carbamazepine	39 yrs, IgG, IgM, IgA initially decreased, but IgG and IgM returned to normal levels after 2 yrs	Normal levels, 5%	Opsonization defect to *H. influenza*	Yes
16[11]	Female age 10, LE prep+ Anti-DNA+ C3 41	Prednisone, CYC	16 yrs, Anti-DNA+ IgG 200, IgM 50, IgA normal	Normal levels, 10%	Decreased T cell number, EBV induced suppression reduced	Yes
17[12]	Male age 34, ANA+ (1:1024) Anti-DNA+ CH50 < 12	Prednisone, phenytoin, azathioprine	41 yrs, ANA+ (1:16), anti-DNA neg IgG 127, IgM 61, IgA 10	"Normal levels"	Decreased proliferation to *S. aureus,* decreased T cell number	No
18[13]	Female 21, ANA+ Anti-DNA +	Prednisone, chloroquine	33 yrs, IgG < 2g/l	Normal levels, 20%	Increased T suppressor cells	Yes

CYC: cyclophosphamide, RPR: rapid plasma reagin, DTH: delayed-type hypersensitivity, EBV: Epstein–Barr virus, LE prep: lupus erythematosus cell preparation.

We investigated the clinical features associated with durable responses of SLE. Preceding herpes zoster infection, as in our patient, has been described as a potential association[5], but insufficient information is available to determine if this association is valid. Decreased CD4:CD8 ratios[2-4,7-9,13] and decreased T cell numbers[7,11,12] were also observed, but none of these consistently conferred protection from SLE ($p > 0.05$, Fisher's exact test). However, a loss of B cells (undetectable or < 2% of the lymphocyte population at any point in the clinical course) correlated highly with protection from SLE ($p = 0.002$): 5/5 individuals with B cell loss and 1/10 without documented B cell loss experienced a durable

response of SLE. Indeed, 3/5 individuals with B cell loss and 0/10 without documented B cell loss experienced a remission of SLE ($p = 0.02$). IVIG has been thought to be an immunomodulatory agent with possible efficacy in SLE[15]. It is possible that IVIG therapy could be contributing to protection from SLE, but since 9 of 10 evaluable individuals without B cell loss did not experience a durable response, it is unlikely that IVIG therapy compared to B cell loss leads to remission of SLE.

The mechanisms by which B cell loss and hypogammaglobulinemia occur in SLE are not known. Some have suggested that patients with SLE may develop B cell-specific autoantibodies, early senescence of hyperactive B cells[6], or a B cell maturation defect[3]. The immunosuppressive medications, particularly cyclophosphamide and phenytoin, have also been proposed as a potential mechanism of hypogammaglobulinemia[2,4,5,10-12,14]. The diversity of cases described, medications to which the patients were exposed, and immunologic aberrations noted illustrate that the mechanism is likely multifactorial. Although the mechanism remains inconclusive, SLE responsiveness correlates significantly with a decrease in the number of circulating B cells to negligible (< 2%) or undetectable levels. Thus, it is plausible that B cell ablative immunotherapy may be a therapeutic alternative in patients with SLE.

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