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Treatment of Systemic Lupus Erythematosus–Associated Type B Insulin Resistance Syndrome With Cyclophosphamide and Mycophenolate Mofetil

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Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by loss of immunologic self-tolerance and the subsequent development of autoantibodies. These antibodies are thought to be important in relation to the clinical manifestations of the disease. One example is the development of multiple cytopenias secondary to cytolytic or cytotoxic antibodies directed toward red blood cells, platelets, and white blood cells. Other antibodies may mediate abnormal cellular mechanisms such as those seen with neuropsychiatric manifestations of SLE. We report the occurrence of autoantibodies directed toward insulin receptors and the subsequent development of type B insulin resistance syndrome in a woman with SLE. This syndrome was treated successfully with cyclophosphamide and mycophenolate mofetil.

The insulin resistance syndrome is a clinical state in which there is a subnormal cellular and metabolic response to insulin, characterized by elevated circulating insulin levels (1). Most insulin resistance is cellular or tissue based; common examples are obesity or type 2 diabetes mellitus. In these conditions, resistance results from abnormalities in insulin receptor action or signaling (1,2). The type A insulin resistance syndrome presents clinically as ovarian dysfunction and severe insulin resistance accompanied by hyperglycemia. This syndrome is caused by genetic defects in the insulin signaling system (2–5).

Serum-based insulin resistance is relatively unusual. Historically, the majority of such patients developed resistance due to insulin antibodies directed against exogenously administered insulin, especially that from bovine and porcine sources. After the introduction of human insulin produced with recombinant DNA technology, this form of resistance has declined dramatically (6–11). It also occurs in conditions associated with elevated circulating levels of autoantibodies, such as autoimmune disorders and certain medications (12–17).

Insulin receptor autoantibody formation is especially rare. The type B insulin resistance syndrome is an autoimmune phenomenon caused by polyclonal immunoglobulin G antibodies with antagonist activity directed against the insulin receptor (1,2,4). This competition results in hypersecretion of insulin to compensate, usually at insufficient levels to maintain normoglycemia (1,2,18–20). Occasionally, the receptor autoantibodies can have an insulin-like effect, which can cause hypoglycemia (21–24). The syndrome has been described in patients with systemic lupus erythematosus (SLE) and Sjögren's syndrome as well as less clearly defined autoimmune disorders (12,21,25–27). Acanthosis nigricans (a marker of insulin resistance), amenorrhea in women, and hyperandrogenism are usually present (4,12,28–30).

CASE REPORT

The patient, a 27-year-old African American woman, was in good health until October 1999, when she was in the fourth month of her second pregnancy. The pregnancy became complicated by toxemia, pericarditis, and pericardial and pleural effusions. She was treated with aspirin, and the fetus was delivered prematurely by cesarean section at 32 weeks. In April 2000, the patient developed arthritis in both hands. SLE was diagnosed based on antinuclear antibody (ANA) positivity (titer $>1:640$) with an elevated double-stranded DNA (dsDNA) antibody level (126 IU/ml) and Sm antibody positivity. In January 2001, at a routine followup visit,

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the patient reported lower extremity edema and numbness as well as weight loss. She was found to have elevated plasma glucose levels. Euglycemic therapy was initiated, but there was minimal response to multiple oral medications given at high doses, including insulin secretagogues, metformin, and a thiazolidinedione. Insulin therapy was added, but despite doses of U500 insulin of up to 1,200 units/day, she remained hyperglycemic. The patient's medical history was unremarkable except for the SLE. Her family history was notable for hypertension and breast cancer, but no autoimmune disease or diabetes.

Because of difficulty with glycemia control, the patient was referred to the University of California, San Francisco Medical Center Diabetes Clinic. Medications she was taking at the time of referral included glyburide 20 mg/day, metformin 2,000 mg/day, rosiglitazone 8 mg/day, hydroxychloroquine 400 mg/day, and prednisone 12 mg/day. On physical examination, the patient was noted to be 5 feet 8 inches tall, weighing 58 kg, with a blood pressure of 136/78 and a heart rate 105 beats per minute. There was evidence of thrush in the oropharynx. Diffuse anterior and posterior cervical lymphadenopathy was noted. There were areas of hyperpigmentation on the back of the neck, consistent with acanthosis nigricans. Trace edema was found in the extremities. Joint examination results were notable for mild synovitis of the metacarpophalangeal and proximal interphalangeal joints bilaterally. Abnormal laboratory findings included ANA titer >1:640, erythrocyte sedimentation rate (ESR) 50 mm/hour, dsDNA antibody 126 IU/ml, C3 60 mg/dl, C4 <10 mg/dl, Sm antibody positivity, RNP antibody positivity, SSA antibody positivity, SSB antibody positivity, creatinine 0.9 mg/dl, hemoglobin A_{Ic} 15.3%, C-peptide 6.4 ng/ml, thyrotropin 1.36 mIU/liter,

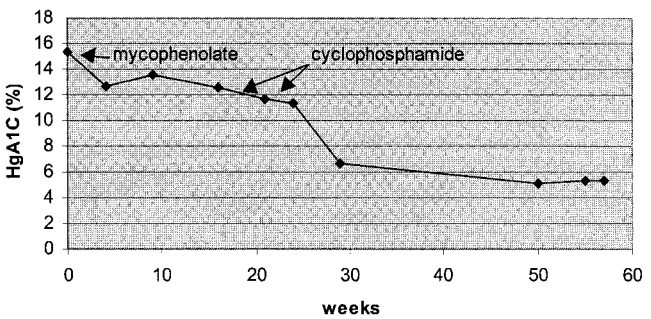

Figure 1. Change in hemoglobin A_{Ic} (HgA1C) levels with mycophenolate and cyclophosphamide (CYC) therapy. Mycophenolate was given starting at week 0 and stopped during the time of CYC therapy. (CYC at 750 mg was given in 2 infusions, 1 month apart.)

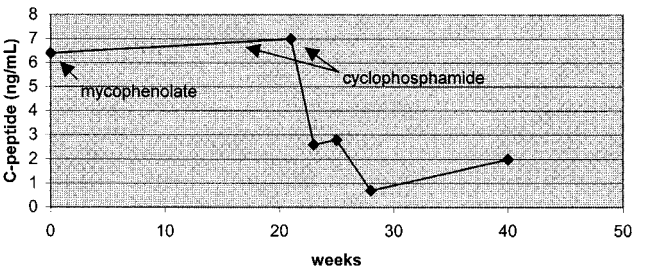

Figure 2. Change in C-peptide levels with mycophenolate and cyclophosphamide (CYC) therapy. Mycophenolate was given starting at week 0 and stopped during the time of CYC therapy. (CYC at 750 mg was given in 2 infusions, 1 month apart.)

white blood cell count 3.2×10^9/liter with lymphopenia, hematocrit 33%, platelet count 209×10^9/liter, total cholesterol 216 mg/dl, low-density lipoprotein cholesterol 123 mg/dl, high-density lipoprotein cholesterol 85 mg/dl, insulin antibodies (porcine, bovine, human) negative.

The extreme difficulty in controlling the patient's blood sugar levels despite treatment with large doses of insulin prompted consideration of the possibility that she had an insulin resistance syndrome. Elevated C-peptide and serum insulin levels and presence of anti–insulin receptor antibodies at a high titer (1:100) (tested in the laboratory of Dr. Ronald Kahn, Harvard School of Medicine, Boston, MA) confirmed the presence of type B insulin resistance syndrome associated with SLE.

The patient was referred to the University of California, San Francisco Lupus Clinic for aggressive treatment of the SLE, in the hope that this would lead to ablation of the cellular clones responsible for formation of the insulin receptor autoantibodies. Mycophenolate mofetil treatment was initiated in May 2001. Prednisone dosage during this period ranged between 8 and 15 mg/day. Despite a gradual increase of the dosage of mycophenolate mofetil to 2.5 gm/day, the patient's lupus symptoms did not abate and the hyperglycemia continued to be unmanageable with oral euglycemics and insulin. In September 2001, mycophenolate mofetil was discontinued and therapy with cyclophosphamide (CYC) was initiated. Two treatments with 750 mg CYC were given, 1 month apart. With this therapy, the patient's synovitis, arthritis, and pleuritis improved and the plasma glucose levels began to fall. She experienced moderately severe reactive hypoglycemia, with plasma glucose values between 27 and 60 mg/dl. In all instances, hypoglycemia occurred within hours after she had eaten high carbohydrate–containing foods.

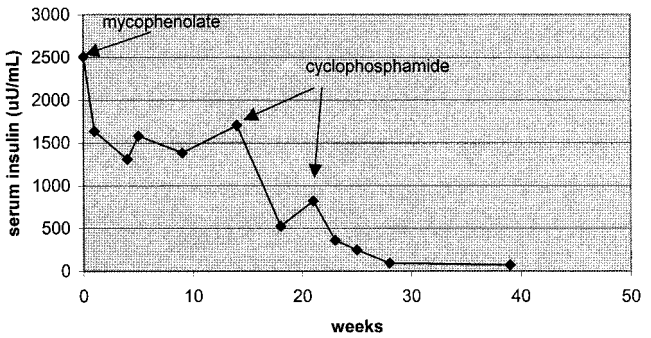

Figure 3. Change in serum insulin levels with mycophenolate and cyclophosphamide (CYC) therapy. Mycophenolate was given starting at week 0 and stopped during the time of CYC therapy. (CYC at 750 mg was given in 2 infusions, 1 month apart.)

Because of concern that she could be developing antibodies with agonist activity, the patient was briefly hospitalized for observation and consideration of plasmapheresis. In the hospital, she was able to maintain fasting glycemic control, but would exhibit early postprandial hyperglycemia, followed by late postprandial hypoglycemia. This phenomenon was reduced when she ate meals with a more limited amount of complex carbohydrates. Her insulin, hemoglobin A_{Ic}, and C-peptide levels subsequently improved and returned to baseline values (Figures 1–3). Mycophenolate was restarted as maintenance therapy. The insulin receptor autoantibody titers began to decline within 10 weeks after initiation of CYC therapy. By January 2002, no insulin receptor antibody could be detected, although other serologic findings remained abnormal (ESR 38 mm/hour, dsDNA antibody 191 IU/ml, C3 85 mg/dl, C4 13 mg/dl). At present, the patient's SLE is under good control, with minimal synovitis and arthritis and occasional pleuritic chest pain. Fasting blood glucose and hemoglobin A_{Ic} levels are normal. She still has occasional postprandial glucose elevation, and although her insulin levels are higher than normal, they are continuing to decrease toward the normal range.

DISCUSSION

We have described a novel approach to the treatment of the type B insulin resistance syndrome associated with SLE. Specifically, we advocate using pulse CYC, guided by plasma glucose and insulin levels, to accelerate the immunosuppressive response, with subsequent oral mycophenolate for maintenance suppression. Kawanishi et al described a 45-year-old woman with Sjögren's syndrome–associated type B insulin resistance syndrome that was successfully treated with prednisone and CYC. With immunosuppressive therapy for 8 months, the insulin resistance resolved and the patient became normoglycemic. However, with temporary termination of CYC treatment, glucose intolerance recurred (31). Bloise and colleagues reported the case of a 23-year-old woman with type B insulin resistance syndrome associated with scleroderma. With immunosuppressive therapy consisting of prednisone and CYC, the insulin resistance remitted and the patient became hypoglycemic (26). Eriksson et al described a 41-year-old woman with type B insulin resistance associated with SLE. The patient was initially treated with plasmapheresis and CYC. Cyclosporin A and azathioprine were used as maintenance therapy. There was a rapid improvement in insulin resistance, with response to therapy sustained at followup of >4 years (32).

The patient described herein, a 27-year-old woman, was diagnosed with type B insulin resistance syndrome associated with SLE. Despite SLE therapy with prednisone and hydroxychloroquine supplemented by aggressive treatment with oral euglycemic agents and insulin, glycemic control was inadequate. We initially attempted therapy with substantial doses of mycophenolate mofetil (up to 2.5 gm/day) with limited success: it took 10 weeks of therapy to effect a drop in the antibody titer, and there was no discernible change in the patient's glycemic control. Potent immunosuppression was achieved with CYC at a dose of 750 mg given on 2 occasions 1 month apart. As evidenced by the development of frank hypoglycemia and declining C-peptide, serum insulin, and hemoglobin A_{Ic} levels, the CYC rapidly ameliorated the insulin resistance. Anti–insulin receptor antibodies could not be detected following CYC therapy. Mycophenolate was resumed as maintenance therapy, and no recurrence of significant insulin resistance was observed during 10 months of followup.

It is possible that the disappearance of the receptor autoantibody could be part of a spontaneous remission. Even if this were the case, we believe the remission was accelerated by the CYC because of the dramatic decrease in the patient's plasma glucose level within 1–3 weeks after the first CYC treatment and definitive resolution of hyperglycemia following the second dose. We thus recommend that the possibility of insulin resistance be considered in any at-risk patients, such as those with autoimmune disorders, who exhibit excessive insulin requirements. Assuming poor compliance with insulin therapy, improper injection technique, and inadequate insulin potency have been ruled out, such patients should be evaluated for the presence of circulating

insulin autoantibodies. In individuals with marked resistance and the absence of insulin antibodies, the possible presence of insulin receptor autoantibodies should be explored. In such patients, elimination of receptor autoantibodies with aggressive immunosuppression may be a successful therapeutic strategy. We suggest a regimen of pulse CYC and maintenance mycophenolate mofetil with close monitoring of serum insulin, hemoglobin A_{Ic}, and anti–insulin receptor autoantibody levels when treating patients with severe SLE-associated type B insulin resistance syndrome.

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