INTERNAL MEDICINE

□ CASE REPORT □

Type B Insulin Resistance Complicated with Systemic Lupus Erythematosus

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Abstract

Type B insulin resistance is characterized by the appearance of autoantibodies to the insulin receptor. We present a 59-year-old Japanese man with type B insulin resistance complicated with systemic lupus erythematosus (SLE). A high titer of anti-insulin receptor autoantibodies was revealed when SLE was defined as active disease. Intravenous boluses of cyclophosphamide (IVCY) with oral prednisolone and cyclosporin A induced remission of SLE, and a subsequent disappearance of anti-insulin receptor autoantibodies, followed by a recovery of glucose intolerance. This is a rare and important case report showing a clear correlation between anti-insulin receptor autoantibodies of type B insulin resistance and SLE disease activity.

Key words: type B insulin resistance, anti-insulin receptor antibody, systemic lupus erythematosus

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Introduction

Type B insulin resistance is an uncommon autoimmune disease characterized by autoantibodies to the insulin receptor (1). These antibodies are related to clinical manifestations of the disease. The majority of patients present with marked hyperglycemia and compensated hyperinsulinemia, but some patients may present with hypoglycemia caused by an insulin-like effect of the receptor autoantibodies. Type B insulin resistance sometimes is complicated by other autoimmune diseases, and systemic lupus erythematosus (SLE) is the most common complication (2, 3). We describe herein a patient with type B insulin resistance complicated with SLE who was successfully treated with immunosuppressants.

Case Report

The patient was a 59-year-old Japanese man who had Raynaud's phenomenon in 1997 and polyarthralgia in 2005. In August 2006, he was admitted to our hospital with pulmonary hemorrhage. At that time immunologic testing showed a positive result for anti-nuclear antibodies (titer 1: 80) without definite classification of autoimmune disease. In early 2007, pancytopenia gradually progressed. In March 2007, he presented general fatigue, weight loss, and modest hyperglycemia. In April 2007, the patient was readmitted to our hospital. He had no family history of diabetes. His weight was 45 kg, height 167.8 cm, and body mass index 16 kg/m^2. Cervical and inguinal lymphadenopathy, Raynaud's phenomenon, and arthritis of bilateral wrists were presented. Biochemical and serological data are shown in Table 1. The blood count showed pancytopenia. Hemolytic anemia was diagnosed by a positive test for urine urobilinogen and direct Coombs' test, and a low level of haptoglobin. Increments of IgG, IgA, and IgM, decrements of serum complements, and positivity of a number of autoantibodies including antinuclear antibodies, anti-DNA antibodies, anti-cardiolipin antibodies, anti-SS-A antibodies, and proteinase-3 (PR3)-anti-neutrophil cytoplasmic antibody (ANCA) led to a diagnosis of SLE. Fasting glucose concentrations were low, 67 mg/dL. Anti-glutamic acid decarboxylase (GAD)

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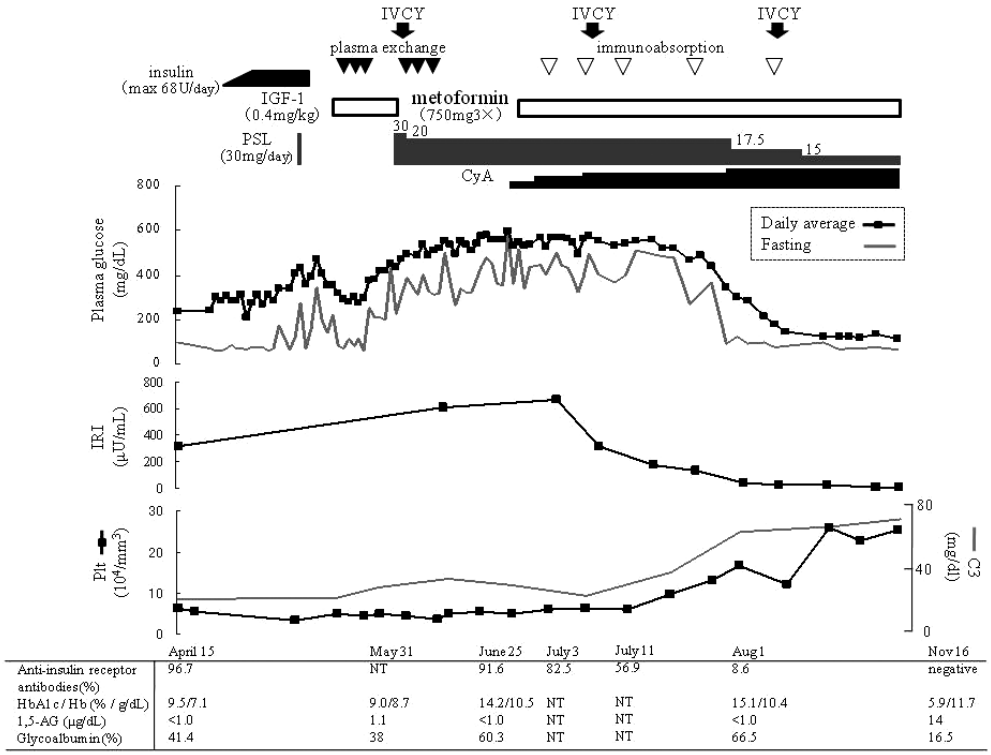
Table 1. Biochemical and Serological Evaluation

Laboratory test	Result	Laboratory test	Result
Urine glucose	Positive	Antinuclear antibodies	1:160 (homogenous pattern)
Urine protein	Positive		1:160 (cytoplasmic pattern)
Urine urobilinogen	Positive	Anti-dsDNA	6.7 U/mL
Urine C protein	637 μg/day	Anti-ssDNA	32.3 U/mL
White cell count	2,900/mm^3	Anti-Sm	4.8 U/mL
Hemoglobin	7.1 g/dL	Anti-RNP	25.3 U/mL
Platelets	29,000/mm^3	Anti-cardiolipin antibodies	43.2 U/mL
Sodium	134 mEq/L	MPO-ANCA	Negative
Potassium	3.9 mEq/L	PR3-ANCA	99 EU
Chloride	103 mEq/L	Sjögren antibodies: SSa	99.3
BUN	9.0 mg/dL	Sjögren antibodies: SSb	11.4
Creatinine	0.54 mg/dL	Rheumatoid factor	Negative
Albumin	3.0 g/dL	C reactive protein	0.91 mg/dL
Total cholesterol	110 g/dL	IgA	413 mg/dL
Triglyceride	81 g/dL	IgG	2,760 mg/dL
Glucose	67 mg/dL	IgM	274 mg/dL
IRI	316 μU/mL	C3	24.4 mg/dL
C peptide	3.08 ng/mL	C4	3.0 mg/dL
Hemoglobin A1c	9.5 %	CH50	15.6 U/mL
1,5-anhydroglucitol	<1.0 μg/mL	Direct Coombs' test	Positive
Glycoalbumin	41.4 %	Indirect Coombs' test	Negative
Haptoglobin	<3.7 mg/dL	Anti-platelet antibodies	Positive
Free thyroxine	1.11 ng/mL	Platelet surface immunoglobulin G	53.1 ng/10^7cell
TSH	1.63 μU/mL	Anti-GAD	Negative
		IAA	Negative
		Anti-insulin antibodies	7.6 %
		Insulin receptor antibodies	Positive
			(inhibition by 96.7 %)

IRI: immunoreactive insulin, TSH: thyroid stimulating hormone, Anti-dsDNA: anti-double stranded DNA antibodies, Anti-ssDNA: anti-single stranded DNA antibodies, Anti-Sm: anti-Smith antibodies, Anti-RNP: anti-ribonucleoprotein antibodies, MPO: myeloperoxidase, PR3: proteinase-3, GAD: glutamic acid decarboxylase, IAA: insulin autoantibodies

and anti-insulin antibodies were negative, but anti-insulin receptor antibodies were detected (inhibition by 96.7%). The response to a 75-g oral glucose tolerance test (75 g-OGTT) was clearly abnormal: at 0, 30, 60, 90, 120, 180 minutes, respective plasma glucose concentrations were 71, 149, 216, 280, 311, and 351 mg/dL, respective plasma insulin concentrations were 396.5, 409.2, 427.6, and 588.7 μU/mL, and respective plasma C-peptide concentrations were 4.22, 6.57, 8.90, 11.48, and 13.49 ng/mL; indicating marked hyperglycemia and hyperinsulinemia. According to the above manifestations, the patient was diagnosed with type B insulin resistance complicated with SLE. The SLE disease activity index (SLEDAI) at that time was 8, thus indicating an active disease status of SLE. Figure 1 showed the clinical course. Treatment with rapid-acting insulin was not effective. Treatment with oral prednisolone was initiated, but it was discontinued due to hyperglycemia. Subcutaneous injection of human recombinant insulin-like growth factor type 1 (hrIGF-1) at 0.4 mg/kg, instead of insulin was also not effective. He was then treated with 6 cycles of plasma exchange to remove anti-insulin receptor antibodies, but they were not effective in treating the diabetes. Intravenous boluses of monthly cyclophosphamide (IVCY; 1,000 mg per body) were given 3 times in late May 2007. Oral prednisolone (PSL) was restarted, and it was tapered by concomitant use of oral cyclosporin A (CyA, maximum 250 mg/day). Metoformin, 250 mg twice daily, was induced to attenuate insulin resistance. Immunoabsorption was initiated in late June 2007 5 times, once per week. At the end of July, pancytopenia and low levels of serum complements had improved to a SLEDAI of 0. The patient tested negative for anti-insulin receptor antibody in early August 2007. The binding inhibition of anti-insulin receptor antibodies decreased in parallel with the normalization of glycemic control, and his body



	April 15	May 31	June 25	July 3	July 11	Aug 1	Nov 16
Anti-insulin receptor antibodies(%)	96.7	NT	91.6	82.5	56.9	8.6	negative
HbA1c / Hb (% / g/dL)	9.5/7.1	9.0/8.7	14.2/10.5	NT	NT	15.1/10.4	5.9/11.7
1,5-AG (μg/dL)	<1.0	1.1	<1.0	NT	NT	<1.0	14
Glycoalbumin(%)	41.4	38	60.3	NT	NT	66.5	16.5

Figure 1. **Clinical course of the present case. Abnormal data by SLE disease activity such as thrombocytopenia and low C3 were recovered by the immunosuppressive therapy in accordance with normalization of glucose intolerance. IVCY: intravenous boluses of monthly cyclophosphamide, IGF-1: insulin-like growth factor type 1, PSL: prednisolone, CyA: cyclosporin A, IRI: immunoreactive insulin, Plt: platelets, 1,5-AG: 1,5-anhydroglucitol, NT: not tested.**

weight increased. PSL and CyA were resumed as maintenance therapy. During follow-up in the last 15 months, the patient has had no further recurrence of SLE disease activity or hyperglycemia.

Discussion

Type B insulin resistance caused by serum anti-insulin receptor antibodies was first defined by Kahn et al in 1976 (1). Type B insulin resistance has been reported to be complicated with SLE (2, 3), but the actual number of patients with this condition is extremely low. As far as we know, there have been only two case reports of type B insulin resistance complicated with SLE in Japan (4, 5), and the precise therapeutic course of disease activity of SLE, in relation to glucose metabolism, has not yet been fully reported (6-8).

In the present case, it was clear that type B insulin resistance and SLE occurred concomitantly. SLE is an autoimmune disease characterized by a loss of immunologic self-tolerance and the subsequent development of autoantibodies. We speculate, in the present case, that anti-insulin receptor antibody formation was stimulated through the active disease status of SLE. This hypothesis may be supported by the clinical course, in which immunosuppressive therapies, including IVCY, improved both SLEDAI and type B insulin resistance. In fact, anti-insulin receptor antibodies completely disappeared in this case.

In summary, we showed a case of type B insulin resistance complicated with SLE that was successfully treated by immunosuppressants. Control of the disease activity of SLE is suggested to be important in treating glucose intolerance.

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