

Successful treatment of type B insulin resistance with mixed connective tissue disease by pulse glucocorticoids and cyclophosphamide

Hongbo Yang¹, Jiuliang Zhao², Yuepeng Li¹, Fang Lv¹, Songyun Zhang³, Yuxiu Li^{1*}

Departments of ¹Endocrinology, ²Rheumatology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, and ³Department of Endocrinology, The Second Affiliated Hospital of Hebei Medical College, Shijiazhuang, China

Keywords

Mixed connective tissue disease, Treatment, Type B insulin resistance

*Correspondence

Yuxiu Li
 Tel.: +86-10-6915-5073
 Fax: +86-10-6915-5073
 E-mail address: liyuxiu@medmail.com.cn

J Diabetes Investig 2017; 8: 626–628

doi: 10.1111/jdi.12619

ABSTRACT

Type B insulin resistance syndrome is a very rare condition caused by autoantibodies against the insulin receptor. We report the successful treatment of a patient with refractory type B insulin resistance with pulse glucocorticoids and cyclophosphamide. The medical record of a patient with type B insulin resistance was reviewed. A 36-year-old Chinese woman presented with menopause, weight loss and refractory hyperglycemia for 3 months, which could not be controlled by up to 972 of insulin units per day. Mixed connective tissue disease was diagnosed with high titers of antinuclear antibody, ribonucleoprotein antibody and interstitial lung disease. Type B insulin resistance was diagnosed with positive immunoprecipitation assay of anti-insulin-receptor antibodies in serum. We started one cycle of pulse methylprednisolone (1,000 mg/day for 3 days) then tapered to prednisone 1 mg/kg/day, and cyclophosphamide 0.4 g/week was added on. Three weeks after pulse glucocorticoid therapy, fasting glucose returned to 4.4 mmol/L. Fasting insulin decreased from 647.27 to 12.95 uIU/mL 6 weeks later. The patient had gained 15 kg during 20 months of uneventful following up, and glycosylated hemoglobin decreased from 10.1 to 5.1%. In this patient with type B insulin resistance, a combination of pulse glucocorticoids and cyclophosphamide was successful in inducing a complete remission. Close cooperation between endocrinologists and rheumatologists will ensure an individualized regimen for this rare condition.

INTRODUCTION

Type B insulin resistance syndrome is an extremely rare condition, as a consequence of circulating polyclonal autoantibodies directed against the insulin receptor¹. Patients usually present with refractory hyperglycemia, weight loss, hyperandrogenism, widespread acanthosis nigricans and manifestations of underlying autoimmune disorders including systemic lupus or scleroderma². Though the diagnosis of type B insulin resistance is not difficult, medical treatment of refractory hyperglycemia is always challenging. There is no standardized protocol for the treatment of type B insulin resistance so far. Here, we evaluate the clinical lessons in a Chinese patient with type B insulin resistance induced by mixed connective tissue disease.

CASE REPORT

A 36-year-old Chinese woman presented with menopause, polydipsia, polyuria and weight loss of 8 kg in December 2014.

She also complained of Raynaud's phenomenon. Laboratory investigation in the local hospital found that glycosylated hemoglobin (HbA1c) was 10.1%, and random blood glucose was 18.7 mmol/L. The fasting glucose levels fluctuated from 12.1 to 18.1 mmol/L, despite 972 units of continuous intravenous insulin per day combined with metformin, pioglitazone, acarbose and glimepiride tablets.

On admission to Peking Union Medical College Hospital (Beijing, China) in March 2015, her body mass index was 18.7 kg/m². There was mild acanthosis nigricans on the neck, axilla and abdomen. There was mild tenderness in the metacarpophalangeal joints and proximal interphalangeal joints. She had no family history of diabetes. Laboratory test results are shown in Table 1. As she had overt hyperglycemia for a long period of time and the risk of ketotic acidosis was not high, the 75-g oral glucose tolerance test was used to evaluate islet β-cell function. The baseline insulin was 647.27 uIU/mL and peak value insulin was 992.33 uIU/mL (Table 2). An immunoprecipitation assay was clearly positive for anti-insulin-receptor

Received 27 September 2016; revised 8 December 2016; accepted 6 January 2017

Table 1 | Laboratory findings from 8 weeks before combination therapy of pulse glucocorticoids with cyclophosphamide to 52 weeks later

	-8 weeks	-1 weeks	0 weeks	2 weeks	3 weeks	4 weeks	6 weeks	12 weeks	26 weeks	32 weeks	52 weeks
FBG (mmol/L)	13	14.9	16.2	15.1	8.6	4.4	3.8	4.0	4.4	4.3	5.33
2hPBG (mmol/L)	22	19.2	25.5	25.5	16.6	14.5	6.0	5.8	6.2	6.0	5.6
Urine ketone (mmol/L)		3.9	≥7.8	NEG	NEG	NEG	NEG	NEG	NEG	NEG	NEG
HbA1c, % (4.5–6.3)	10.1	9.1							5.2	5.1	5.1
Fasting INS, uIU/mL (5.2–17.2)	>300		647.27	392.97		43.43	12.95		7.88	11.80	9.50
C-peptide, ng/mL (0.8–4.2)			6.6							1.55	2.09
INS infusion (unit/day)	972	480	0	0	0	0	0	0	0	0	0
Oral antidiabetic agents	4	3	1	1	2	0	0	0	0	0	0
Testosterone (ng/mL)		0.92		0.29		0.0			<0.1	<0.1	
ANA		+S1:1280								+S 1:1280	
Ro52		++++165								+++150	
RNP		++++138								+++106	
SSA		++++72								+++72	
C3, g/L (0.73–1.46)			0.517	0.428		0.941			0.866	0.910	
C4, g/L (0.1–0.4)			0.088	0.088		0.117			0.096	0.101	
ESR (mm/h)			23			26				8	
PA, mg/L (200–400)			70	119		274			254	231	
Wt (kg)	57	48			45.7				65		72

2hPBG, 2-h plasma blood glucose; ANA, antinuclear antibody; ESR, erythrocyte sedimentation rate; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; INS, insulin; NEG, negative; PA, prealbumin; RNP, antiribonucleoprotein antibody; SSA, anti-SSA antibody; Wt, weight.

Table 2 | Serum levels of blood glucose, insulin, C-peptide and pre-insulin in 75 g oral glucose tolerance test before and after pulse glucocorticoids and cyclophosphamide therapy

	0 h		0.5 h		1 h		2 h		3 h	
	0 weeks	26 weeks	0 weeks	26 weeks	0 weeks	26 weeks	0 weeks	26 weeks	0 weeks	26 weeks
Glucose (mmol/L)	13.5	4.2	18.8	5.7	21.7	5.9	25.6	5.2	24.6	4.8
Insulin (mmol/L)	647.27	7.88	832.29	112.43	992.33	153.20	887.03	61.28	572.03	37.62
C-peptide (ng/mL)	6.6	1.05	8.49	6.92	9.63	9.75	9.58	6.56	5.5	5.43

antibodies, confirming the diagnosis of type B insulin resistance. Extensive examinations including computed tomography of the lungs and abdomen, bone scintigraphy, and biological investigation failed to show any neoplastic disorders. Mild interstitial lung disease was diagnosed by high-resolution computed tomography and pulmonary function test results. High titers of antinuclear antibody (1:1,280), anti-Ro52 antibody (++++), antiribonucleoprotein antibody (++++), and anti-SSA antibody (++++), were shown. Mixed connective tissue disease was diagnosed according to the Sharp diagnosis criteria³.

We stopped intensive insulin therapy, as she had been treated with insulin infusion in the local hospital for two more months with no improvement of hyperglycemia, and persistent hyperinsulinemia was shown in her serum. Blood glucose levels did not

increase further after discontinuation of insulin infusion. After one cycle of pulse methylprednisolone (1,000 mg/day for 3 days), glucocorticoid therapy was tapered to prednisone 1 mg/kg/day, and cyclophosphamide 0.4 g per week was added on. Two weeks after pulse glucocorticoids therapy, fasting insulin began to decrease and urine ketone bodies turned to negative. Testosterone also returned to the normal range. Four weeks later, fasting glucose decreased to the normal range, with neither insulin infusion nor oral antidiabetic drugs, and her fasting insulin levels further decreased to 43.43 uIU/mL. The patient's postprandial glucose level returned to the normal range 6 weeks later. She had normal periods 2 months later. The patient has been followed up for 18 months until now. She has gained 15 kg and her HbA1c decreased from 10.1 to 5.1%.

DISCUSSION

In most reported cases of type B insulin resistance, hyperglycemia is poorly responsive to exogenous insulin therapy. In a previous report, up to 18,000 units of insulin per day did not make a difference to blood glucose control⁴. Insulin sensitizers are usually prescribed, but the efficacy has not been studied. In the present patient, we believe that intensive insulin therapy was not helpful, as there was persistent hyperinsulinemia in the circulation. In fact, the blood glucose level did not increase further after insulin was stopped before pulse glucocorticoids therapy. We were also concerned about the potential risk of unpredictable hypoglycemia with intensive insulin therapy, as titers of anti-insulin receptor autoantibodies will decrease during immune suppression treatment. At high titers the antibody acts as an antagonist at the receptor, whereas at low titers it acts as a stimulatory agonist, resulting in differing degrees of both hyperglycemia and/or hypoglycemia^{5,6}.

Treatment for the underlying autoimmune condition is critical for both primary disease and refractory hyperglycemia. The most commonly used therapeutic intervention for underlying disease includes steroids, cyclophosphamide, plasmapheresis and intravenous immunoglobulin⁷. In 2010, a group at the National Institutes of Health (USA) published the largest case series in which a new treatment protocol with rituximab was tested in their patient population⁸, and it was reported to be effective in one case from Europe⁹. In Asia, there was one case reported from Japan in which rituximab was not efficient for disease control¹⁰. As there is no clinical experience of rituximab in type B insulin resistance in the Chinese population so far, and the patient had interstitial lung disease, which is usually steroid resistant, combination therapy of pulse glucocorticoids and cyclophosphamide was used after careful evaluation by our rheumatologist.

Two weeks after pulse glucocorticoids, the patient's fasting insulin decreased from 647.27 to 392.97 uIU/mL, followed by normalization of fasting blood glucose levels. Thus, we suppose that a decrease of fasting insulin levels is an early sign of remission. The present patient has been followed up for 20 months, uneventfully. Glucocorticoids had been tapered off, and she is still taking tacrolimus 1 mg daily now for mixed connective tissue disease. Thus, initiation of intervention for underlying disease should be as early as possible for correction of metabolic disturbance.

In summary, in the present patient with type B insulin resistance, a combination of pulse glucocorticoids and cyclophosphamide was successful in inducing a complete remission. Close cooperation between endocrinologists and rheumatologists will ensure an individualized regimen for this rare condition.

ACKNOWLEDGMENT

We thank Dr Robert K Semple from Wellcome Trust-MRC Institute of Metabolic Science (Cambridge, UK) for helping to detect the anti-insulin receptor antibody.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Kahn CR, Flier JS, Bar RS, *et al.* The syndromes of insulin resistance and acanthosis nigricans. Insulin-receptor disorders in man. *N Engl J Med* 1976; 294: 739.
2. Huang Q, Yan Y, Zhao H, *et al.* A systemic lupus erythematosus patient presenting as type B insulin resistance complicated with cryoglobulinemia. *Lupus* 2016; 26: 95–97.
3. Sharp GC, Irvin WS, Tan EM, *et al.* Mixed connective tissue disease—an apparently distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antigen (ENA). *Am J Med* 1972; 52: 148–159.
4. Yang GQ, Li YJ, Dou JT, *et al.* Type B insulin resistance syndrome with Scleroderma successfully treated with multiple immune suppressants after eradication of *Helicobacter pylori* infection: a case report. *BMC Endocrine Disorders* 2016; 16: 20.
5. Mantzoros CS, Flier JS. Insulin resistance: the clinical spectrum. *Adv Endocrinol Metab* 1995; 6: 193–232.
6. Buhaescu I, Rhee S, York MR, *et al.* A woman with severe lupus nephritis and difficult to control diabetes mellitus. *Arthritis Care Res* 2011; 63: 623–629.
7. Zhang S, Wang G, Wang J. Type B insulin resistance syndrome induced by systemic lupus erythematosus and successfully treated with intravenous immunoglobulin: case report and systematic review. *Clin Rheumatol* 2013; 32: 181–188.
8. Malek R, Chong AY, Lupsa BC, *et al.* Treatment of type B insulin resistance: a novel approach to reduce insulin receptor autoantibodies. *J Clin Endocrinol Metab* 2010; 95: 3641–3647.
9. Manikas ED, Isaac I, Semple RK, *et al.* Successful treatment of type B insulin resistance with rituximab. *J Clin Endocrinol Metab* 2015; 100: 1719–1722.
10. Takei M, Ishii H, Kawai Y, *et al.* Efficacy of oral glucocorticoid and cyclosporine in a case of rituximab-refractory type B insulin resistance syndrome. *J Diabetes Investig* 2015; 6: 734–738.