

Severe Insulin-resistant Diabetes due to Insulin Antibodies Associated with Eosinophilia

Makiyo Takaya¹, Mototsugu Nagao¹, Shuji Takemitsu¹, Yasushi Nakajima¹,
Hitoshi Sugihara¹, Yasuko Uchigata² and Shinichi Oikawa¹

Abstract

A 66-year-old man with type 2 diabetes on hemodialysis treatment was admitted due to poor glycemic control. His serum insulin level and the ¹²⁵I-insulin binding rate were extremely high with an increased eosinophil count, although he did not have an allergic reaction to insulin or an elevation of specific IgE for human insulin. A Scatchard analysis revealed that the patient's insulin antibodies had a low affinity constant and a high binding capacity. Prednisolone administration decreased the eosinophil count and ¹²⁵I-insulin binding rate; accordingly, the glycemic control improved. Corticosteroid therapy may be a potent therapeutic strategy for insulin antibody-induced severe insulin resistance with eosinophilia.

Key words: insulin antibodies, eosinophilia, corticosteroids

(Intern Med 54: 2367-2371, 2015)

(DOI: 10.2169/internalmedicine.54.4022)

Introduction

Insulin antibodies in insulin treated patients generally do not affect glycemic control (1). However, there have been several reports of severe insulin resistance mediated by insulin antibodies (2-4). We recently treated a patient with severe insulin resistance due to a marked elevation of insulin antibodies during insulin therapy. A Scatchard analysis showed that the characteristics of the insulin antibodies were similar to those of insulin autoimmune syndrome (IAS). The patient also had a persistently elevated eosinophil count.

Case Report

A 66-year-old man with type 2 diabetes was admitted to our hospital in October 2009 due to poor glycemic control despite treatment with multiple daily injections of insulin analogs. He was first diagnosed with diabetes in 1997 and had been treated with oral hypoglycemic agents. In July 2008, insulin therapy was initiated with regular human insulin and neutral protamine Hagedorn (NPH) insulin. Hypereosinophilia (2,968/ μ L) was initially noted in January

2009 just before the insulin medication was replaced by insulin aspart to improve the blood glucose control. The fasting serum C-peptide level was 1.98 ng/mL and the urine C-peptide level was 17 μ g/day in January 2009. After starting insulin aspart, the eosinophil counts and the blood glucose level gradually increased. The patient had also received hemodialysis for chronic renal failure caused by diabetes since March 2009.

At the time of admission in October 2009, the patient had been treated with voglibose (0.9 mg/day) and four daily insulin injections: three of insulin aspart (48 U/day) and one of insulin detemir (20 U/day). He had no previous history of treatment with α -lipoic acid or any other drugs containing a sulfhydryl group. His height was 157.0 cm and body weight was 49.8 kg (body mass index: 20.2 kg/m²). A physical examination revealed slight anemia in the palpebral conjunctiva and pitting pedal edema. Lymphadenopathy and hepatosplenomegaly were not present. Additionally, there was no indication of a flare reaction or subcutaneous induration at the insulin injection sites. The laboratory data showed a white blood count (WBC) of 12,300/ μ L with 62% eosinophils (7,626/ μ L), hemoglobin of 12.0 g/dL, platelet count of 152,000/ μ L, and glycated hemoglobin (HbA1c, NGSP) of

¹Department of Endocrinology, Diabetes and Metabolism, Graduate School of Medicine, Nippon Medical School, Japan and ²Diabetes Center, Tokyo Women's Medical University School of Medicine, Japan

Received for publication September 1, 2014; Accepted for publication January 25, 2015

Correspondence to Dr. Mototsugu Nagao, s8067@nms.ac.jp

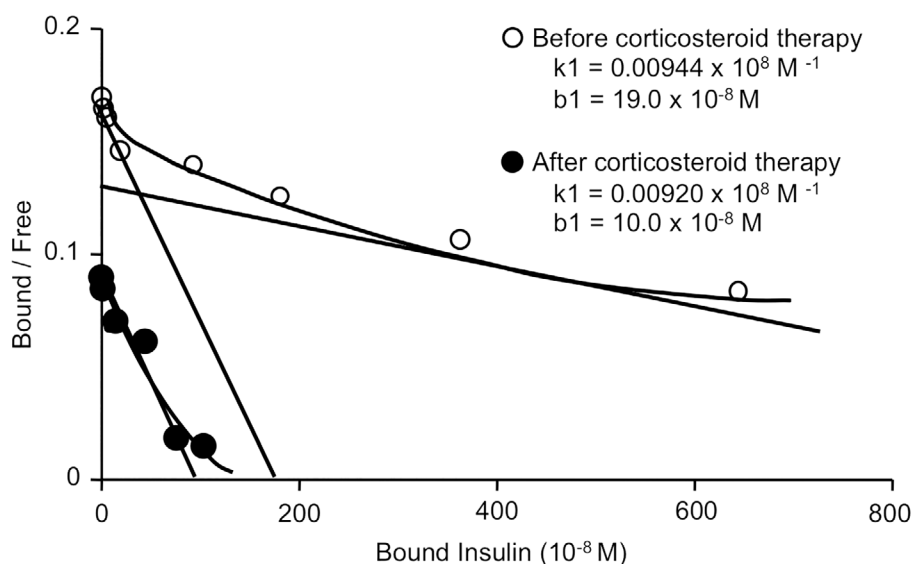


Figure 1. A Scatchard analysis of insulin antibodies before and after corticosteroid therapy. k_1 (I/U insulin), affinity constant of high-affinity binding sites; b_1 (U insulin/I), binding capacity of high-affinity binding sites.

11.9%. The tests for anti-glutamic acid decarboxylase (GAD) antibody, anti-insulinoma associated protein 2 (IA-2) antibody, and anti-islet cell cytoplasmic antibody (ICA) were all negative. The results of the liver function tests and the levels of growth hormone, insulin-like growth factor-1 (IGF-1), adrenocorticotrophic hormone (ACTH), and cortisol were within the normal ranges. Thyroid stimulating hormone (TSH) was slightly increased with normal ranges of thyroid hormones. The serum total immunoreactive insulin (IRI) concentration was 3,251.6 μ U/mL, fasting serum C-peptide was 5.24 ng/mL, and the ^{125} I-insulin binding rate was 83.5%. A Scatchard analysis showed that the patient's insulin antibody had a low affinity constant and a high binding capacity in the high-affinity binding sites (Fig. 1). Neither insulin receptor antibody nor specific immunoglobulin E (IgE) for human insulin was detected in his serum; however, soluble interleukin-2 receptor (sIL-2) and interferon γ (IFN- γ) were elevated (1,944 U/mL and 748.1 pg/mL, respectively). HLA typing of the class II haplotypes were DRB1*04:05-DQB1*04:01 and DRB1*09:01-DQB1*03:03. Echocardiography showed a preserved cardiac function with a 78.0% ejection fraction.

After the insulin analogs (aspart and detemir) were changed to human insulin (regular and NPH) or other analogs (insulin lispro, glulisine or glargine), the eosinophil counts gradually decreased (Fig. 2). However, refractory hyperglycemia persisted with an elevated ^{125} I-insulin binding rate (Fig. 2) despite the high-dose human regular insulin administration (>150 U/day) and the high IRI titer (2,830.2 μ U/mL) (Fig. 2). A reduction in dosage of insulin resulted in an increase in the blood glucose level (Fig. 2). Accordingly, we decided to initiate corticosteroid therapy for insulin antibody-mediated insulin resistance. After the oral administration of prednisolone (60 mg/day), the eosinophil

count rapidly decreased. Subsequently, the blood glucose levels gradually decreased accompanied by the reduction of the ^{125} I-insulin binding rate (Fig. 2, 3), sIL-2 (1,314 U/mL), and IFN- γ (253.6 pg/mL). Meanwhile, the insulin antibody characteristics (affinity constant and binding capacity) were not affected by the corticosteroid therapy (Fig. 1).

The patient was discharged in January 2010 with good glycemic control (Fig. 3) on 25 mg/day of prednisolone and four daily insulin injections: three of insulin glulisine (28 U/day) and one of insulin glargine (12 U/day). After discharge, we tapered the prednisolone dose to 10 mg/day and the ^{125} I-insulin binding rate has remained at <4% with stable glycemic control.

Discussion

Eosinophilia is generally accompanied by allergic diseases and adverse drug reactions (5). Hemodialysis treatment has also been reported to cause eosinophilia through allergic reactions to dialysis equipment and anticoagulants (6, 7). In the present case, the eosinophil count had increased with the use of human insulin before initiating hemodialysis treatment, suggesting that exogenous human insulin initially induced eosinophilia. Subsequently, eosinophilia and the insulin resistance became remarkable after hemodialysis treatment with the use of insulin aspart. Thus, insulin aspart, hemodialysis treatment, or both possibly exacerbated eosinophilia and accelerated the insulin antibody production. To the best of our knowledge, only one case of insulin antibody-induced insulin-resistant diabetes with concomitant hypereosinophilic syndrome (HES) has been reported to date (4). HES is characterized by persistent eosinophilia and/or end-organ damage without secondary causes of eosinophilia. In the previous case, eosinophilia and hepa-

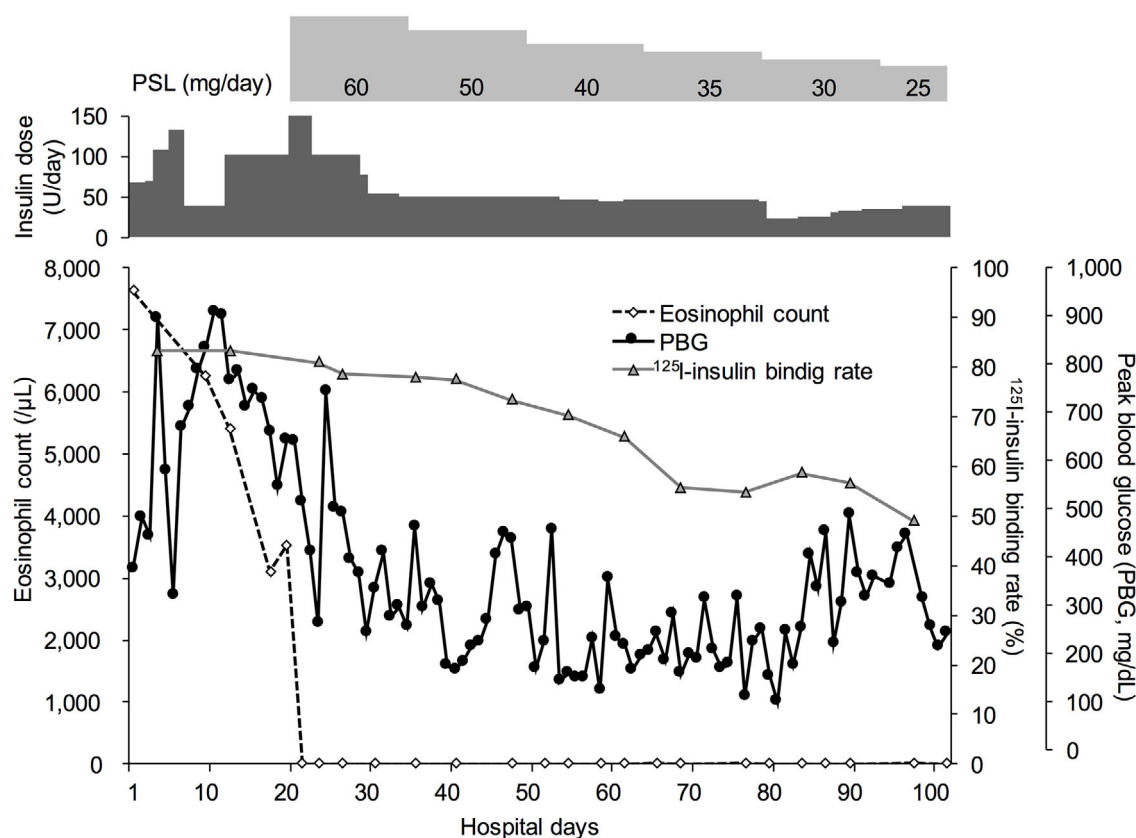


Figure 2. Changes in the daily peak blood glucose (PBG) concentration, eosinophil count, and ^{125}I -insulin binding rate during the clinical course. The doses of prednisolone (PSL) and external insulin are shown at the top.

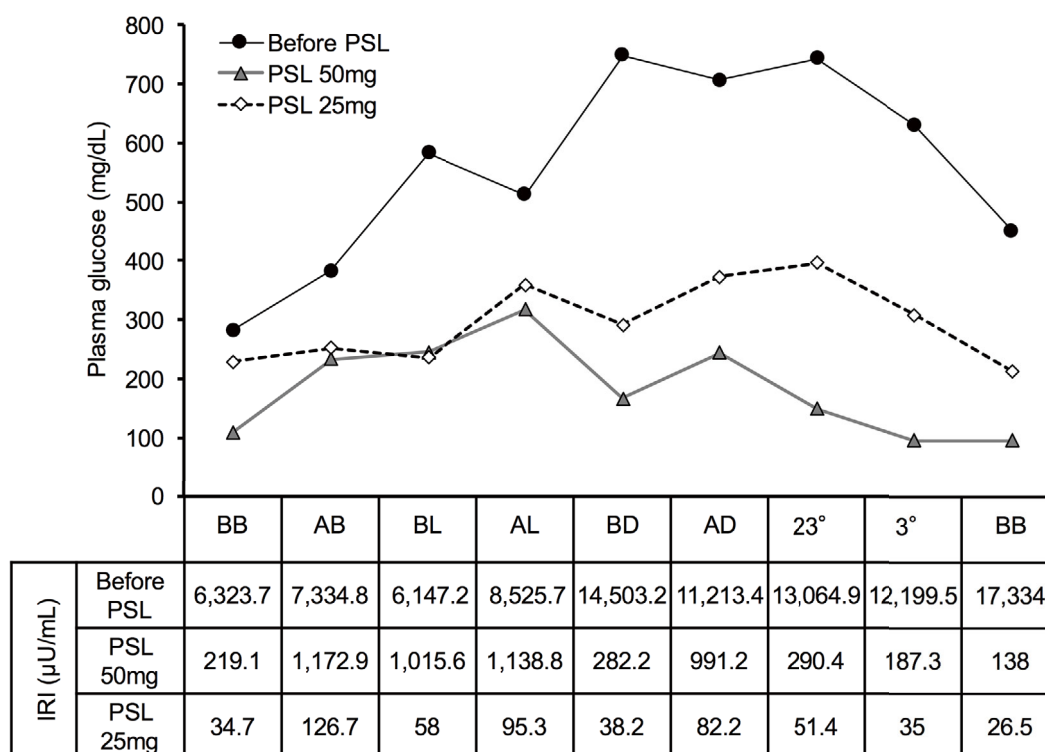


Figure 3. Representative daily profiles of the plasma glucose and serum insulin levels before (before PSL) or during corticosteroid therapy (on PSL 25 mg or PSL 50 mg). BB: before breakfast, AB: after breakfast, BL: before lunch, AL: after lunch, BD: before dinner, AD: after dinner, 23°: 23:00, 3°: 3:00, PSL: prednisolone, IRI: serum total insulin

tosplenomegaly had already been noted before initiating insulin therapy and insulin antibody-induced insulin resistance emerged with multiple organ damage by eosinophilic infiltration after insulin therapy. In contrast, in the present case, exogenous insulin was strongly suspected as the cause of eosinophilia, and no signs of organ dysfunction by eosinophilic infiltration were observed even at the peak of the eosinophil count (at the time of admission), indicating that the present case has a different etiology of eosinophilia from the previously reported case.

The cessation of insulin was reported to be a useful therapeutic option for patients with unstable glycemic control due to insulin antibodies (2). In the present case, the fasting serum C-peptide level was 1.97 ng/mL despite a decreased urine C-peptide level (17 µg/day) before starting insulin analog treatments and hemodialysis. The discrepancy between the serum and urine C-peptide levels may be the result of renal failure (8). In addition, probably due to interference by insulin antibodies (9, 10), the serum C-peptide concentration in the immunoassay had further increased (5.24 ng/mL) at the time of admission. It was therefore difficult to evaluate the endogenous insulin secretion capacity accurately during the admission period; accordingly, we decided to continue insulin therapy. Even after the change of insulin preparations, a high ¹²⁵I-insulin binding rate and severe insulin resistance persisted, and the reduction in the dosage of insulin resulted in an increased blood glucose level. Hence, an additional treatment to suppress the insulin antibody production was necessary to achieve acceptable glycemic control.

For the additional treatment, we selected corticosteroid therapy because it is the mainstay treatment for eosinophilia (5, 11). A few previous reports have suggested that corticosteroid therapy has favorable effects on the insulin antibody-induced insulin resistance (4, 12). As expected, both eosinophilia and insulin resistance were ameliorated after the treatment with prednisolone. Corticosteroid therapy was previously reported to modify the characteristics of insulin antibodies, especially in the binding capacity (12). In contrast, the characteristics of insulin antibodies were not strongly affected by prednisolone in the present case; the binding capacity remained high ($b_1=10.0 \times 10^{-8}$ M) even after the treatment. We therefore assumed that the reduction in the insulin antibody concentration, reflected by the decrease in the ¹²⁵I-insulin binding rate, chiefly contributed to the improvement of glycemic control after the prednisolone treatment.

Insulin allergy with marked eosinophilia has been reported to accompany the elevation of specific IgE for human insulin (13). However, in the present case, we could not detect total IgE elevation or specific IgE for human insulin. In this respect, the previous case of insulin antibody-induced insulin resistance associated with HES was similar to the present case (4). The interaction between eosinophilia and insulin antibody-induced severe insulin resistance still remains unclear. Activated T-lymphocytes may play a critical role in eosinophilia (14). In the present case, persistent T-

lymphocyte activation may have induced the insulin antibody production since the ¹²⁵I-insulin binding rate was reduced with the decrease in activated T cell markers sIL-2R and IFN-γ after corticosteroid therapy. In addition, the patient had HLA-DR4, which is relevant for a strong immune response to insulin (15). These factors may trigger an immunological disorder of producing insulin antibodies and concomitant eosinophilia.

In summary, we herein reported a case of insulin antibody-induced severe insulin-resistant diabetes associated with eosinophilia. Corticosteroid therapy ameliorated both the insulin resistance and eosinophilia. Further accumulation of such cases is warranted not only to elucidate the interaction between eosinophilia and insulin antibody production, but also to establish the efficacy and safety of corticosteroid therapy for insulin antibody-induced insulin resistance.

The authors state that they have no Conflict of Interest (COI).

References

1. Van Haeften TW. Clinical significance of insulin antibodies in insulin-treated diabetic patients. *Diabetes Care* **12**: 641-648, 1989.
2. Hara K, Tobe K, Uchigata Y, et al. Antibody-mediated insulin resistance treated by cessation of insulin administration. *Intern Med* **39**: 143-145, 2000.
3. Greenfield JR, Tuthill A, Soos MA, et al. Severe insulin resistance due to anti-insulin antibodies: response to plasma exchange and immunosuppressive therapy. *Diabet Med* **26**: 79-82, 2009.
4. Uriuhara A, Morita S, Kuroda S, et al. Severe insulin-resistant diabetes mellitus associated with hypereosinophilic syndrome. *Intern Med* **33**: 632-636, 1994.
5. Roufosse F, Weller PF. Practical approach to the patient with hypereosinophilia. *J Allergy Clin Immunol* **126**: 39-44, 2010.
6. Nakanishi K, Kaneko T, Yano F, et al. Marked eosinophilia induced by nafamostat mesilate, an anticoagulant in a hemodialysis patient. *Nephron* **62**: 97-99, 1992.
7. Diskin CJ, Strokes TJ, Dansby LM, Radcliff L, Carter TB. The prevalence and meaning of eosinophilia in renal disease on a nephrology consultation service. *Nephron Dial Transplant* **26**: 2549-2558, 2011.
8. Akalın N, Köroğlu M, Harmankaya Ö, Akay H, Kumbasar B. Comparison of insulin resistance in the various stages of chronic kidney disease and inflammation. *Ren Fail* **37**: 237-240, 2015.
9. Arzamendi AE, Rajamani U, Jialal I. Pseudoinsulinoma in a white man with autoimmune hypoglycemia due to anti-insulin antibodies: value of the free C-Peptide assay. *Am J Clin Pathol* **142**: 689-693, 2014.
10. Basu A, Service FJ, Yu L, Hesser D, Ferries LM, Eisenbarth G. Insulin autoimmunity and hypoglycemia in seven white patients. *Endocr Pract* **11**: 97-103, 2005.
11. Ogbogu PU, Bochner BS, Butterfield JH, et al. Hypereosinophilic syndrome: a multicenter, retrospective analysis of clinical characteristics and response to therapy. *J Allergy Clin Immunol* **124**: 1319-1325, 2009.
12. Honda M, Kawashima Y, Kawamura H, et al. Acute liver dysfunction complicated with uncontrollable glycemia due to insulin antibody: successful treatment with glucocorticoid and lispro insulin. *Intern Med* **45**: 1225-1229, 2006.
13. Nagai Y, Mori T, Abe T, Nomura G. Immediate-Type allergy against human insulin associated with marked eosinophilia in type 2 diabetic patient. *Endocr J* **48**: 311-316, 2001.

- 14.** Prin L, Plumas J, Gruart V, et al. Elevated serum level of soluble interleukin-2 receptor: a marker of disease activity in the hypereosinophilic syndrome. *Blood* **78**: 2626-2632, 2001.
- 15.** Kahn CR, Rosenthal AS. Immunologic reaction to insulin: insulin allergy, insulin resistance and the autoimmune insulin syndrome. *Diabetes Care* **2**: 283, 1979.

© 2015 The Japanese Society of Internal Medicine
<http://www.naika.or.jp/imonline/index.html>