

A patient with type B insulin resistance syndrome, responsive to immune therapy

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SUMMARY

Background A 55-year-old woman with vitiligo, hypothyroidism, interstitial lung disease and diabetes mellitus developed severe insulin resistance during a hospital admission for respiratory failure. Before hospitalization, her HbA_{1c} level was 8.1% on ~100 U/day of insulin. Her interstitial lung disease had been treated with glucocorticoids, but after their withdrawal her insulin requirements had increased dramatically. She remained hyperglycemic (blood glucose levels 16.7–27.8 mmol/l), despite intravenous insulin at doses as high as 30,000 U/day.

Investigations The patient's serum creatinine level was 301 µmol/l and her liver function tests were normal. A mildly elevated white cell count was present. The patient was diagnosed with pneumonia due to *Pseudomonas aeruginosa*. When the patient's plasma glucose level was 22.5 mmol/l, her plasma C-peptide level was 0.9 nmol/l and her serum insulin level was 294 pmol/l. At that time the patient was on 2,600 U/day of intravenous insulin aspart. Anti-insulin and anti-islet-cell antibodies were not detected, but anti-insulin-receptor antibodies were found.

Diagnosis Type B insulin resistance syndrome.

Management The patient's insulin resistance responded to glucocorticoids and plasmapheresis. After the patient was treated with prednisone (60 mg/day), her insulin requirements decreased within 1 week to pre-admission doses. When steroids were subsequently discontinued, glycemic control deteriorated once again. Plasmapheresis was initiated, inducing a striking acute decline in insulin needs. On a maintenance dose of 10 mg prednisone/day, glucose control improved (HbA_{1c} 5.8%) with an average of 60 U of isophane insulin twice daily.

KEYWORDS anti-insulin-receptor antibodies, autoimmunity, diabetes mellitus, insulin resistance, type B insulin resistance syndrome

CME

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THE CASE

A 55-year-old African American woman with type 2 diabetes mellitus developed acute respiratory failure from aspiration pneumonia that she contracted following cataract surgery. She was intubated and transferred to the intensive care unit. The patient had been diagnosed with diabetes mellitus at 40 years of age, at which point she had begun insulin therapy. One month before cataract surgery, her HbA_{1c} level was 8.1%. She also had a history of interstitial lung disease (ILD) that required chronic oxygen therapy and treatment with glucocorticoids. The patient's other medical problems included primary hypothyroidism, vitiligo, obesity, hypertension, chronic kidney disease, gout, and arthritis. At the time of admission, her medications included isophane insulin 40 U twice daily, insulin lispro taken before meals in accordance with an adjusted scale, prednisone 5 mg twice daily, atenolol, furosemide, levothyroxine, simvastatin plus ezetimibe, metoclopramide, allopurinol, morphine sulfate, and aspirin. Previous evaluations for rheumatoid arthritis and systemic lupus erythematosus (SLE) had been negative.

On physical examination, the patient's temperature was 37.9°C. Her height was 162.5 cm and her weight was 110 kg (BMI 41.7 kg/m²). Her other vital signs were normal and she was mechanically ventilated. Crackles in the right upper lobe of the patient's lung were detected by auscultation and were found to correspond to an area of consolidation seen on her chest X-ray. The patient's cardiovascular and abdominal examinations were unremarkable. Vitiligo was present on her chest, arms, legs, and face. There was no evidence of peripheral edema, joint abnormalities, rash, or acanthosis nigricans.

In the intensive care unit, the patient was administered ceftriaxone and clindamycin to

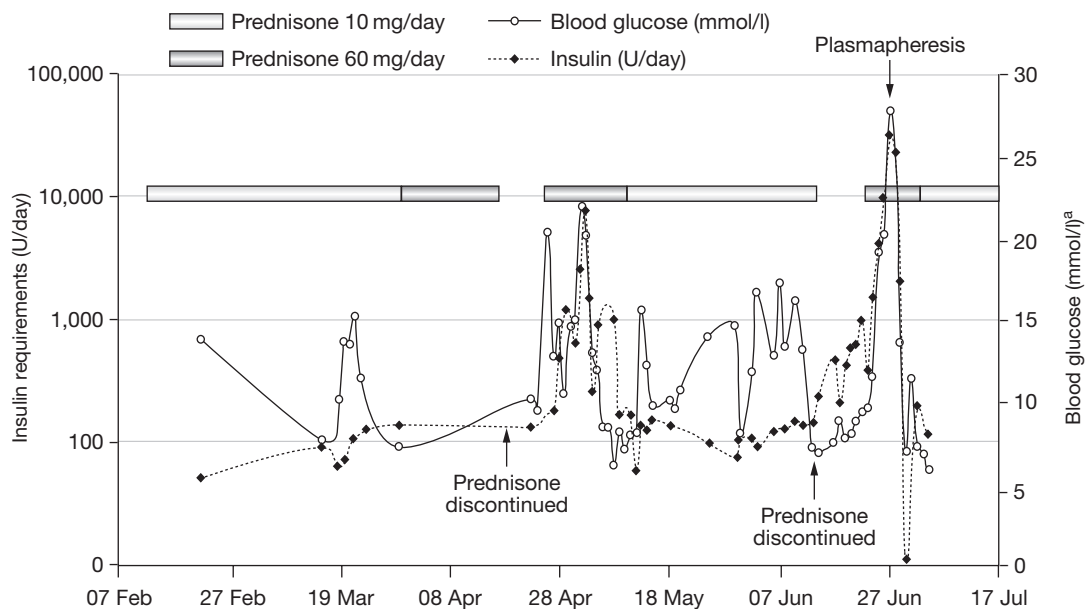


Figure 1 Changes in insulin requirements and blood glucose over time. ^aTo convert to mg/dl, multiply by 0.0555.

treat the pneumonia infection. Her outpatient medications were continued but, in lieu of subcutaneous insulin, the patient was begun on an intravenous (regular) insulin infusion to optimize blood glucose control. Continuous enteral feeding via a nasogastric tube was begun.

On admission to the intensive care unit, the patient's plasma glucose levels were in the range 6.7–13.3 mmol/l (to convert to mg/dl, multiply by 0.0555) on 50–120 U/day of intravenous insulin (Figure 1). The patient then developed acute renal failure (peak serum creatinine level 301 $\mu\text{mol/l}$ [to convert to mg/dl multiply by 0.0113]), and hemodialysis was initiated. Her enteral feeds were changed from Diabetsource[®] (Société des Produits Nestlé, Vevey, Switzerland), a high-protein formula with reduced carbohydrate content, to a high carbohydrate, low protein formula (Nepro[®]; Abbott Laboratories, Abbott Park, IL). The patient was thought to have developed drug-induced interstitial nephritis and, therefore, her prednisone dose was increased to 60 mg daily. Her creatinine levels improved, and the prednisone dose was tapered and the drug ultimately discontinued. Five days after prednisone was discontinued, the patient suffered a recurrence of fever, and a chest X-ray showed that pneumonia had recurred. A sputum culture test was positive for *Pseudomonas aeruginosa*.

Two days after the patient's fever had returned, her insulin requirements rose dramatically. The daily dose of insulin administered intravenously was increased to more than 1,000 U/h, but there was little change in her blood glucose level.

The laboratory data shown in Table 1 were collected 3 months after admission. The patient had a serum creatinine level of 301 $\mu\text{mol/l}$, but an otherwise normal serum chemistry panel, including normal liver function tests. She had a mild leukocytosis (white blood cell count $11 \times 10^9/\text{l}$) with a normal differential count. Whilst the patient was receiving intravenous insulin aspart and her plasma glucose level was 22.5 mmol/l, her plasma C-peptide level was 0.9 nmol/l (normal range 0.3–1.4 nmol/l), and her serum insulin level was mildly elevated at 294 pmol/l (the latter was measured by an assay specific for human insulin). Total and free serum insulin levels were also measured in a radioimmunoassay that detects both human and aspart insulin. As shown by this assay, the patient's total (2,580 pmol/l) and free (2,562 pmol/l) insulin levels were both elevated, which confirmed that high peripheral levels of insulin had been achieved by the administration of insulin to the patient. Anti-insulin and anti-islet-cell antibodies were not detected. The patient had a positive anti-nuclear-antibody titer (1:160 with a uniform nuclear immunofluorescence

Table 1 Results of the patient's laboratory examinations.

Parameters	Results	Normal range
Creatinine	301 $\mu\text{mol/l}$ (3.40 mg/dl)	44–106 $\mu\text{mol/l}$ (0.50–1.20 mg/dl)
White blood cell count	11×10^9 cells/l	4–10 $\times 10^9$ cells/l
Albumin	29 g/l	35–50 g/l
Alanine aminotransferase	11 U/l	(0–35 U/l)
Aspartate aminotransferase	15 U/l	(0–35 U/l)
Plasma glucose	22.5 mmol/l (405 mg/dl)	3.9–5.8 mmol/l (70–105 mg/dl)
C-peptide	0.9 nmol/l	0.3–1.4 nmol/l
Insulin measured by radioimmunoassay	2,580 pmol/l (total), 2,562 pmol/l (free)	0–102 pmol/l (for total and free)
Insulin (human)	294 pmol/l	0–102 pmol/l
Islet-cell antigen 512 antibody	<0.8 U/ml	<1 U/ml
Anti-insulin antibody	4.3 $\mu\text{U/ml}$	0–5 $\mu\text{U/ml}$
Anti-insulin-receptor antibody	Positive (titer 1:2)	Negative
IgG	9.64 g/l	8.1–17.5 g/l
Anti-nuclear antibodies	Positive (titer 1:160, with a uniform staining pattern)	Negative
Erythrocyte sedimentation rate	76 mm/h	0–20 mm/h
C3 complement factor	1.6 g/l	0.8–1.5 g/l
Anti-Smith antibody	Negative	Negative

staining pattern), but other autoimmune markers were normal (Table 1).

The patient had features commonly seen in patients with insulin resistance mediated by anti-insulin-receptor antibodies (Box 1), including female sex, African American race, and the presence of other autoimmune diseases. In addition, despite treatment for and resolution of pneumonia, the patient continued to have intractable hyperglycemia. For these reasons, the presence of anti-insulin-receptor antibodies was investigated. Anti-insulin-receptor antibodies were detected in two separate samples from the patient (Box 2). The antibodies were of low titer (1:2), but at this dilution the patient's serum inhibited binding of ^{125}I -labeled insulin by 72–88%.

On the basis of this information, glucocorticoid therapy was re-instituted at high doses (prednisone 60 mg/day). Within approximately 1 week, the patient's glucose response to insulin improved, and the insulin dose she required decreased to pre-admission baseline levels. The steroid dose was gradually tapered over the next month to a daily maintenance dose of 10 mg. Glucose control (average blood glucose level 10 mmol/l) was achieved in the patient by the

Box 1 Clinical features of type B insulin resistance syndrome.

- Hyperglycemia
- Hyperinsulinemia
- Hypoglycemia (less commonly)
- Female predominance
- Age at presentation usually 40–50 years
- African American predominance
- Other autoimmune diseases commonly present
- Acanthosis nigricans usually present

administration of 40–50 U of isophane insulin twice daily and a daily infusion of 20–40 U of regular insulin while she was receiving enteral nutrition. The patient improved clinically and was extubated, and then transferred to the general medicine ward.

Upon transfer from the intensive care unit, the patient's steroid therapy was inadvertently discontinued. She subsequently developed aspiration pneumonia for the third time. Treatment resulted in normalization of the patient's white

Box 2 Anti-insulin-receptor-antibody assays.**Binding inhibition assay**^{a,17,18}

Human lymphoblastoid cells (IM-9) are incubated with serial dilution of serum from the patient or a normal healthy control. After pre-incubation, cells are washed and resuspended in assay buffer containing ¹²⁵I-labeled insulin and incubated for 90 min at 15 °C. One set of tubes contained, in addition, 10 µg/ml unlabeled insulin. Duplicate aliquots are then centrifuged. The supernatants are aspirated and discarded, and the radioactivity in the pellet is determined in a gamma counter. Specific ¹²⁵I-labeled binding is considered to be the difference between tracer (i.e. ¹²⁵I-labeled insulin) binding in the absence or presence of 10 µg/ml of unlabeled insulin. The results are expressed as a percentage of control binding. The titer is the dilution that produces 50% of tracer binding.

Immunoprecipitation assay^{9,18}

Extract from cells expressing recombinant human insulin receptors (e.g. Cos-7 cells) is pre-incubated with patient serum overnight at 4 °C. Immunoprecipitation of the antibody-bound receptors is performed using a labeled affinity-purified F(ab')₂ fragment of a rabbit antibody that recognizes the Fc part of human IgG. After immunoprecipitation, the presence of anti-insulin-receptor antibodies can be assayed by standard immunoblot techniques.

^aThis assay (performed in the DERC Specialized Assay Core of the Joslin Diabetes Center, Boston, MA, USA) was used in the case study. There are two potential advantages to this assay: capability of measurement of the number of receptors if additional experiments are performed; and data can be compared and contrasted to historical patient cases on the basis of clinical observations because the assay was developed in the late 1970s.

blood cell count and resolution of her fever, but despite these improvements her glycemic control deteriorated once again. She remained hyperglycemic (glucose levels 16.7–27.8 mmol/l) on intravenous insulin (either regular or aspart) doses as high as 30,000 U/day. High-dose glucocorticoid therapy was re-instituted and one course of plasmapheresis was given. Within 24 h following this procedure, the patient's insulin requirements initially decreased from 2,100 U/day to 2 U/day before stabilizing at an average of 120 U/day (Figure 1).

Over the following two months, the patient's steroid dose was gradually tapered and continued at a maintenance dose (prednisone 10 mg/day). Her glucose control improved, with an HbA_{1c} level of 5.8% on treatment with isophane insulin 60 U twice daily.

DISCUSSION OF DIAGNOSIS

Deterioration of blood glucose control is common in hospitalized patients with diabetes. Such 'stress hyperglycemia', which also affects patients who are not known to have diabetes, has been attributed to counter-regulatory factors that intensify during illness and result in further insulin resistance.^{1,2} In addition, hyperglycemia can be worsened by medications, such as glucocorticoids, or by parenteral or enteral nutrition. The hyperglycemia per se might adversely affect insulin secretion through oxidative stress of β cells. Glucose control in these patients is typically manageable by intensification of their outpatient antihyperglycemic regimen. In the majority of cases, insulin resistance improves as the infection clears or the offending medications are discontinued. When escalating doses of insulin do not achieve adequate glucose control and other common causes of hyperglycemia have been addressed, rarer causes of insulin resistance should be considered.

In the case under discussion, the severity of insulin resistance seemed to increase after the infections had resolved and had no clear relationship to increasing caloric density from the change in the proprietary enteral nutritional formula. Total (2,580 pmol/l) and free (2,562 pmol/l) insulin levels (while the patient was on intravenous insulin aspart and had concurrent glucose levels of 22.5 mmol/l) were elevated when measured by radioimmunoassay, demonstrating that the patient was receiving a pharmacologically active insulin infusion.

Medications commonly used in hospitalized patients can lead to dysglycemia. β-Blockers and thiazide diuretics, for example, have been implicated in causing hyperglycemia.³ β-Blockers are postulated to cause a reduction in pancreatic β-cell insulin release.³ Thiazide diuretics are thought to induce hyperglycemia by reducing total body potassium levels, which leads to decreased insulin secretion.³ The case patient was not taking either of these classes of drugs. Some of the fluoroquinolone antibiotics have been reported to be associated with dysglycemia,^{4,5} which has been shown to be due to the actions of these agents on the K_{ATP} channels on β-cells. The case patient, however, was taking ciprofloxacin, which is a fluoroquinolone antibiotic that is not linked to hyperglycemia.⁴ Hyperglycemia also occurs in patients taking atypical antipsychotics, such as olanzapine, but this association seems to result largely from the weight gain known to

occur with these medications.⁶ The case patient was on low-dose olanzapine (2.5 mg daily), and even after discontinuation of this medication her insulin requirements rose dramatically.

Glucocorticoids are among the most common medications associated with insulin resistance and hyperglycemia. In this case patient, the anomalous increase in insulin requirements upon discontinuation of steroids, and the obvious responsiveness to higher doses of steroids and to plasmapheresis, probably reflected immunosuppressive effects on the production of anti-insulin-receptor autoantibodies. For approximately 3 years before the patient's hospital admission, maintenance doses of glucocorticoids had been used to manage her ILD. The inhibitory effect of glucocorticoids on autoantibody production might also explain the delay in the appearance of profound insulin resistance until after steroids were discontinued (which occurred during the second month of her hospital admission). Type B insulin resistance syndrome is a rare cause of insulin resistance that results from the production of autoantibodies directed against the insulin receptor. These antibodies block the binding of insulin to its receptor at the plasma membrane, which inhibits the cellular effects of insulin.⁷ Anti-insulin-receptor antibodies can also cause spontaneous hypoglycemia as a result of an insulinomimetic effect.^{8,9}

Clinical features of the syndrome include a female predominance, African American heritage, first presentation in the third to fifth decade of life, an association with other autoimmune diseases, acanthosis nigricans, and hyperinsulinemia (Box 1).^{7,8} SLE is the most common autoimmune disease associated with type B insulin resistance, occurring in approximately 50–80% of patients with the syndrome.^{8,10} Although the case patient had other autoimmune conditions, including vitiligo and a positive anti-nuclear-antibody titer, several evaluations by rheumatologists had excluded SLE.

The diagnosis of type B insulin resistance is based largely on clinical presentation and on ruling out other causes of insulin resistance. Assays for anti-insulin-receptor antibodies can confirm the diagnosis but are currently not commercially available. In another case report of type B insulin resistance, anti-insulin-receptor antibodies were not detected by the binding inhibition assay but were subsequently detected by their ability to immunoprecipitate the insulin

receptor.⁹ Anti-insulin-receptor-antibody assays have technical limitations; therefore, the absence of detection of anti-insulin-receptor antibodies with one assay does not rule out the possibility that the patient has clinically significant anti-insulin-receptor antibodies.⁹

TREATMENT AND MANAGEMENT

The initial goal when treating patients with type B insulin resistance is to manage their hyperglycemia, and this generally requires large amounts of insulin. In a review of 28 years of experience in treating patients with type B insulin resistance, the average insulin dose reported as administered was 5,100 U/day.⁸ The clinical course of patients with type B insulin resistance is variable. Many patients will have a spontaneous remission of the autoantibody syndrome but the time to remission is unpredictable. Some patients will have a biphasic course, with periods of severe insulin resistance and hyperglycemia followed by a hypoglycemic phase. A variety of immunosuppressive agents, including glucocorticoids, cyclophosphamide, azathioprine, ciclosporin, rituximab, and mycophenolate mofetil have been reported to induce remission.^{8–16} In many cases, patients have been treated with a combination of immunosuppressive therapies, making it difficult to identify which treatment was most effective. In this patient, the timely response to both glucocorticoids and plasmapheresis suggests that both approaches were effective (Figure 1).

Type B insulin resistance is a rare disease that responds in an unpredictable manner to immunosuppressive therapies; therefore, there are no treatment guidelines for the use of immunosuppressive agents for patients with the disease. Treatment strategies should, therefore, probably be individualized and made on the basis of the requirements of the medical setting. For example, steroids had been used to treat ILD in the case patient; therefore, initial management with high-dose steroids followed by maintenance with low-dose glucocorticoids was employed. Plasmapheresis was also initiated when the patient's insulin requirements rose substantially. Some of the more toxic agents were avoided because the patient had multiple underlying medical problems.

Owing to the limited availability of and technical constraints associated with anti-insulin-receptor-antibody assays, empiric use of an immunosuppressive agent might be advisable when patients who present with characteristic

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Competing interests

The authors declared no competing interests.

features of type B insulin resistance (Box 1) are unresponsive to high-dose insulin therapy after other causes of hyperglycemia have been addressed.

CONCLUSIONS

This case report demonstrates the difficulty in diagnosing an extremely rare cause of insulin resistance in a hospitalized patient whose insulin resistance was owing to multiple contributing factors. The anomalous increase in the patient's insulin requirements after discontinuation of glucocorticoids, as well as her response to re-institution of glucocorticoids and to a single dose of plasmapheresis, provided evidence for an immune-mediated mechanism for the insulin resistance. In addition, the patient's age, sex, ethnicity, and history of autoimmune disease fitted the clinical phenotype of the type B insulin resistance syndrome. Although the presence of anti-insulin-receptor antibodies was not re-evaluated after glucose homeostasis was achieved, the patient's serology data and her clinical response to immunosuppressive therapy suggested that anti-insulin-receptor antibodies were the underlying cause of the severe insulin resistance she experienced during her hospitalization.

This case of type B insulin resistance is unusual in that the endogenous insulin and C-peptide levels were not in the range that has generally been identified in individuals with this condition ($>1,200$ pmol/l and >2.0 nmol/l, respectively).^{7,8,10,12,13,15,16} The inability of the patient to generate a greater endogenous insulin response might have been due to her underlying diabetes (i.e. diminished pancreatic insulin secretory capacity). Identification of this mechanism—which would not have been detected with routine laboratory studies—nonetheless led to an effective approach to therapy. This case report underscores the importance of considering immune-mediated insulin resistance along with other, more common, contributors to decreased insulin sensitivity in hospitalized patients with marked insulin needs.

References

- Langouche L *et al.* (2007) Therapy Insight: the effect of tight glycemic control in acute illness. *Nat Clin Pract Endocrinol Metab* **3**: 270–278
- Soop M *et al.* (2007) Stress-induced insulin resistance: recent developments. *Curr Opin Clin Nutr Metab Care* **10**: 181–186
- Luna B and Feinglos M (2001) Drug-induced hyperglycemia. *JAMA* **286**: 1945–1948
- Park-Wyllie L *et al.* (2006) Outpatient gatifloxacin therapy and dysglycemia in older adults. *N Engl J Med* **354**: 1352–1361
- Yip C and Lee AJ (2006) Gatifloxacin-induced hyperglycemia: a case report and summary of the current literature. *Clin Ther* **28**: 1857–1866
- Newcomer JW (2005) Second-generation (atypical antipsychotics) and metabolic effects. A comprehensive literature review. *CNS Drugs* **19**: 1–93
- Kahn CR *et al.* (1976) The syndromes of insulin resistance and acanthosis nigricans. *N Engl J Med* **294**: 739–745
- Arioglu E *et al.* (2002) Clinical course of the syndrome of autoantibodies to the insulin receptor (Type B insulin resistance): a 28-year perspective. *Medicine* **81**: 87–100
- Taylor S *et al.* (1989) Syndromes of autoimmunity and hypoglycemia. *Endocrinol Metab Clin North Am* **18**: 123–143
- Bao S *et al.* (2007) Type B insulin resistance syndrome associated with systemic lupus erythematosus. *Endocr Pract* **13**: 51–54
- Magsino C and Spencer J (1999) Insulin receptor antibodies and insulin resistance. *South Med J* **92**: 717–719
- Eriksson J *et al.* (1998) Successful treatment with plasmapheresis, cyclophosphamide, and cyclosporin A in type B syndrome of insulin resistance. *Diabetes Care* **21**: 1217–1220
- Kawanishi Y *et al.* (1976) Successful immunosuppressive therapy in insulin resistant diabetes caused by anti-insulin receptor autoantibodies. *J Clin Endocrinol Metab* **44**: 15–20
- Coll A *et al.* (2004) Rituximab therapy for the type B syndrome of insulin resistance. *N Engl J Med* **350**: 310–311
- Gehi A *et al.* (2003) Treatment of systemic lupus erythematosus-associated type B insulin resistance syndrome with cyclophosphamide and mycophenolate mofetil. *Arthritis Rheum* **48**: 1067–1070
- Fareau GG *et al.* (2007) Regression of acanthosis nigricans correlates with disappearance of anti-insulin receptor autoantibodies and achievement of euglycemia in type B insulin resistance syndrome. *Metabolism* **56**: 670–675
- Flier JS *et al.* (1977) Autoantibodies to the Insulin Receptor. Effect on the insulin receptor interaction in IM-9 lymphocytes. *J Clin Invest* **60**: 784–794
- Flier JS *et al.* (1976) Characterization of antibodies to the insulin receptor: a cause of insulin-resistant diabetes in man. *J Clin Invest* **58**: 1442–1449