A case of type B insulin resistance syndrome treated with low-dose glucocorticoids

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Summary

Type B insulin resistance syndrome is characterized by the presence of autoantibodies to the insulin receptor. We present a 57-year-old male admitted to a hospital due to body weight loss of 16 kg and hyperglycemia of 13.6 mmol/L. He was diagnosed with type B insulin resistance syndrome because the anti-insulin receptor antibodies were positive. We informed him that some hyperglycemic cases of this syndrome had been reported to be spontaneously remitted in 5 years, and he did not agree to be treated with high-dose glucocorticoids and/or immunosuppressive agents due to his concern for their adverse effects such as hyperglycemia and immunosuppression. He chose to be treated with insulin and voglibose, but fair glucose control could not be obtained. Six years later, he agreed to be treated with low-dose glucocorticoids practicable in outpatient settings. One milligram per day of betamethasone was tried orally and reduced gradually according to the values of glycated hemoglobin. After 30 months of glucocorticoid treatment, the anti-insulin receptor antibodies became undetectable and his fasting plasma glucose and glycated hemoglobin were normalized. This case suggests that low-dose glucocorticoids could be a choice to treat type B insulin resistance syndrome in outpatient settings.

Learning points:

- Type B insulin resistance syndrome is an acquired autoimmune disease for insulin receptors.
- This case suggested the possibility of long-lasting, low-dose glucocorticoid therapy for the syndrome as an alternative for high-dose glucocorticoids or immunosuppressive agents.
- Since the prevalence of autoimmune nephritis is high in the syndrome, a delay of immunosuppressive therapy initiation might result in an exacerbation of nephropathy.

Background

Type B insulin resistance syndrome is a rare disease that belongs to a class of autoimmune diseases against cell-surface receptors. The syndrome is caused by the production of autoantibodies against the insulin receptor. Its clinical manifestations are hyperinsulinemia, glucose intolerance, resistance to exogenous insulin, and acanthosis nigricans (1). The syndrome is usually complicated with other autoimmune diseases such as systemic lupus erythematosus (SLE), systemic sclerosis, and Sjögren's syndrome (1, 2, 3, 4). Since the aim of managing the syndrome is to reduce anti-insulin receptor antibodies, combinations of immunosuppressive agents, such as cyclophosphamide, rituximab, and pulse glucocorticoids, are recently used as the remission induction therapy in severe cases (4, 5, 6). Here we describe a rare case of type B insulin resistance syndrome improved by a low-dose glucocorticoid therapy in outpatient settings.

Case presentation

The case was a 57-year-old Japanese male. After flu-like symptoms for two weeks, he presented thirst, polyuria,

and body weight loss (16 kg) over three months. His height, body weight, and BMI were 1.67 m, 59 kg, and 21 kg/m², respectively. Acanthosis nigricans was not observed.

Investigation

Table 1 shows his laboratory findings on admission. His fasting plasma glucose was 13.6 mmol/L and glycated

Table 1 Laboratory findings on admission.

Laboratory tests (normal values)	Results
White blood cell (3.30–8.60 × 10⁹/L)	2.80 × 10⁹/L
Red blood cell (4.35–5.55 × 10¹²/L)	4.48 × 10¹²/L
Platelets (158–348 × 10⁹/L)	60 × 10⁹/L
Total protein (66–81 g/L)	85 g/L
Albumin (41–51 g/L)	40 g/L
Creatinine (57.5–94.6 μmol/L)	61.9 μmol/L
Sodium (138–145 mmol/L)	138 mmol/L
Potassium (3.6–4.8 mmol/L)	3.9 mmol/L
Total bilirubin (6.8–25.7 μmol/L)	13.7 μmol/L
Aspartate aminotransferase (0.22–0.50 μkat/L)	0.96 μkat/L
Alanine aminotransferase (0.17–0.70 μkat/L)	1.05 μkat/L
Lactate dehydrogenase (2.07–3.70 μkat/L)	2.17 μkat/L
Alkaline phosphatase (1.77–5.37 μkat/L)	6.72 μkat/L
γ-Glutamyltranspeptidase (0.22–1.07 μkat/L)	2.85 μkat/L
Cholinesterase (4.0–8.1 μkat/L)	4.05 μkat/L
HbA1c (26.8–44.3 mmol/mol)	119.7 mmol/mol
Fasting plasma glucose (3.9–6.1 mmol/L)	13.6 mmol/L
Immunoreactive insulin (12.9–5.4 pmol /L)	1189.3 pmol/L
C-peptide (0.20–0.69 nmol/L)	0.96 nmol/L
Immunoreactive insulin/C-peptide ratio	1.23
IgG (8.6–17.5 g/L)	26.1 g/L
IgA (0.9–3.9 g/L)	7.3 g/L
IgM (0.3–1.8 g/L)	0.7 g/L
Anti-insulin receptor antibodies (negative)	Positive
Insulin autoantibodies (negative)	Negative
Anti-GAD antibodies (<0.02 nmol/L)	<0.02 nmol/L
Anti-IA-2 antibodies (negative)	Negative
Anti-nuclear antibodies (1:<40)	1:320
Anti-dsDNA antibodies (negative)	Negative
Anti-SS-A/Ro antibodies (negative)	Negative
Anti-mitochondrial antibodies (negative)	Negative
Anti-smooth muscle antibodies (negative)	Negative
Anti-platelet antibodies (negative)	Negative
Anti-Scl-70 antibodies (negative)	Negative
Anti-Jo-1 antibodies (negative)	Negative
Anti-RNP antibodies (negative)	Negative
Urine glucose (negative)	(++++)
Urine protein (negative)	(+)
Urine occult blood (negative)	(++)
Urine ketone bodies (negative)	(+)
Urine C-peptide (9.7–55.7 nmol/day)	44 nmol/day

dsDNA, double stranded DNA; GAD, glutamic acid decarboxylase; Hb, hemoglobin; IA-2, insulinoma-associated protein-2; Ig, immunoglobulin; RNP, ribonucleoprotein; SS, Sjögren syndrome.

hemoglobin (HbA1c) was 119.7 mmol/mol. The urinalysis showed glycosuria, proteinuria, microscopic hematuria, and ketonuria. The quantification of urinary C-peptide showed considerable insulin secretion. The blood count showed slight neutropaenia and thrombocytopaenia. The blood chemistry showed slight hepatic dysfunction and hyperglobulinemia of immunoglobulin (Ig) G and IgA as a polyclonal gammopathy. The marked hyperinsulinemia as compared with the serum C-peptide level suggested the prolonged half-life of insulin in this case. Anti-insulin receptor antibodies were detected by a radio receptor assay using IM-9 cells (BML, INC., Tokyo, Japan) (7), and he was diagnosed with type B insulin resistance syndrome. In addition, the positive anti-nuclear antibodies, proteinuria, neutropaenia, thrombocytopaenia, and a high IgA level suggested that the case might be complicated with other autoimmune and/or kidney diseases.

Treatment

He was introduced with s.c. injections of exogenous insulin (60 U/day) and oral administration of voglibose (0.9 mg/day). His plasma glucose before and after meal ranged approximately 3.9~6.7 mmol/L and 19.4~27.8 mmol/L, respectively. We informed him that intensive combination therapies with high-dose glucocorticoids, immunosuppressive agents and/or plasmapheresis were recommended in spite of their adverse effects of hyperglycemia and immunosuppression. We also informed him that some hyperglycemic cases of this syndrome had spontaneously remitted within five years in the literature (4). Rituximab, an anti-CD20 MAB, was reported to be a new therapeutic choice for type B insulin resistance syndrome (5, 6), but it was not approved for the syndrome in Japan. He did not accept intensive combination therapies, but agreed to be treated with insulin and voglibose in outpatient settings for, at least, a few years.

Outcome and follow-up

Figure 1 shows his clinical course after the discharge. Eleven months after the discharge, his HbA1c values were markedly elevated, and exogenous insulin was increased from 60 to 75 U/day. Hypoglycemic events were observed up to once a week. When 4 years had passed since the onset of the syndrome, anti-insulin receptor antibodies were still positive and his hyperglycemia was not improved. We recommended him hospitalization to receive intensive treatments because it might be difficult
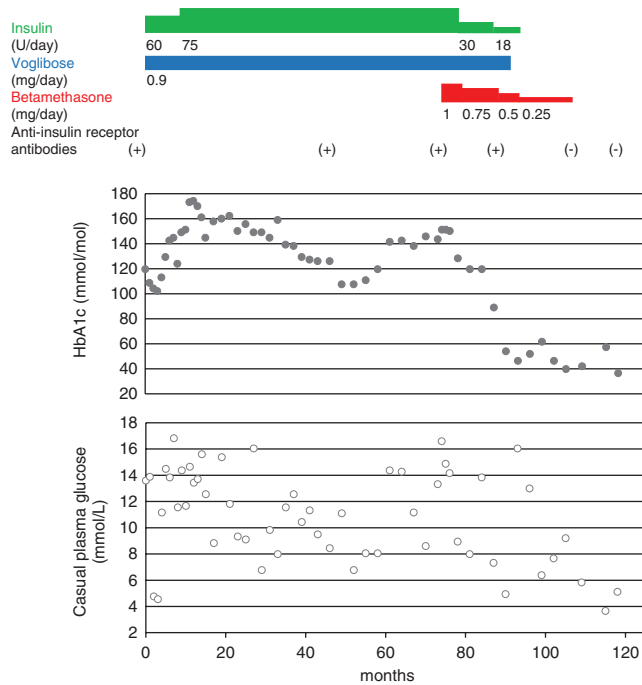
Figure 1
Clinical course of the case with type B insulin resistance syndrome after discharge. At the top part, colored boxes indicate periods of treatments with insulin (green), voglibose (blue), and betamethasone (red). Numbers indicate doses of each medicine. At the middle part, changes in anti-insulin receptor antibodies are shown. At the bottom part, changes in HbA1c values (closed circles) and casual plasma glucose levels (open circles) are shown. The time of discharge was set for 0 months.

Table 2 Laboratory findings after 30 months of the betamethasone treatment.

White blood cells	2.80×10^9/L
Red blood cells	3.76×10^{12}/L
Platelets	115×10^9/L
Total protein	72 g/L
Albumine	35 g/L
Creatinine	67.2 µmol/L
Aspartate aminotransferase	0.58 µkat/L
Alanine aminotransferase	0.40 µkat/L
Lactate dehydrogenase	3.48 µkat/L
Alkaline phosphatase	3.65 µkat/L
γ-Glutamyltranspeptidase	0.57 µkat/L
Cholinesterase	4.13 µkat/L
HbA1c	39.8 mmol/mol
Casual plasma glucose	8.9 mmol/L
Immunoreactive insulin	220.5 pmol/L
C-peptide	0.86 nmol/L
Immunoreactive insulin/C-peptide ratio	0.25
Total cholesterol (3.11~5.66 mmol/L)	3.22 mmol/L
Triglyceride (0.56~1.69 mmol/L)	0.31 mmol/L
IgG	19.6 g/L
IgA	7.1 g/L
IgM	0.3 g/L
Anti-insulin receptor antibodies	Negative
Insulin autoantibodies	Negative
Anti-GAD antibodies	<0.02 nmol/L
Urine glucose	(−)
Urine protein	(++)
Urine occult blood	(++)
Urine ketone bodies	(−)

to expect his spontaneous remission of the syndrome (4). He refused the intensive treatments worrying about the adverse effects of the therapies, but agreed to be treated with glucocorticoids within doses, which would not exacerbate the hyperglycemia. Then, we tried 1 mg/day of betamethasone. After 4 months of the therapy, a slight improvement in HbA1c values was obtained, and betamethasone doses were then gradually reduced by 0.25 mg when HbA1c was reduced more than 15 mmol/mol (Fig. 1). Dose reduction intervals were greater than 1 month. Insulin doses were gradually reduced from 75 to 30, then to 18 U/day, and finally stopped. Voglibose was also stopped due to hypoglycemic events. Fourteen months after the beginning of the glucocorticoids therapy, his HbA1c value was decreased to 88.0 mmol/mol, although anti-insulin receptor antibodies remained positive (Fig. 1). After 16 more months, anti-insulin receptor antibodies became undetectable and his postprandial plasma glucose, HbA1c, serum immunoreactive insulin (IRI), and C-peptide levels were 8.9 mmol/L, 39.8 mmol/mol, 220.5 pmol/L, and 0.86 nmol/L, respectively (Table 2). Except for slightly high IRI levels, the syndrome almost remitted, and betamethasone

was stopped. He showed proteinuria (+ ~ 2+) and microscopic hematuria (+ ~ 2+) in semi-quantitative urinalysis from the admission to the end of the glucocorticoids therapy. Although his metabolic markers were improved, the proteinuria was rapidly increased to 4+. His serum albumin levels decreased to less than 30 g/L. Because the chronic kidney disease was rapidly exacerbated, we referred him to another hospital with a department of nephrology. At the next hospital, he received a kidney biopsy. The pathology was compatible with diabetic nephropathy, and no signs of glomerulonephritis were observed (data not shown). Two years later, his HbA1c values remained less than 42.1 mmol/mol without antidiabetic medicine, and anti-insulin receptor antibodies were undetectable. However, his serum creatinine unfortunately elevated to approximately 265 µmol/L under the treatment with diuretics and an angiotensin-converting-enzyme inhibitor.

Discussion

We experienced a case of type B insulin resistance syndrome, which was characterized by anti-insulin receptor antibodies (1). The case was treated with a low-dose

glucocorticoid therapy in outpatient settings and the remission was achieved. The glucocorticoid doses, which were determined by the informed consent with the patient, was lower than those usually used for other cases of the syndrome in the literature (5, 6, 8, 9, 10). The cumulative dose of betamethasone given to the case was approximately 450 mg. As 4 mg betamethasone is equivalent to 25 mg of prednisolone (11), the cumulative dose is equivalent to 2.8 g of prednisolone, which is almost comparable to those used in usual high-dose glucocorticoid therapies for the syndrome (5, 6). Rebound worsening of blood glucose control could be avoided by the gradual dose reduction protocol similar to that for other autoimmune diseases. Steroid therapies tend to cause or worsen atherosclerosis and arteriolosclerosis due to metabolic derangements, but it usually takes metabolic derangements many years to cause vascular complications. Since it was reported that the mortality of patients with type B insulin resistance syndrome was high (4), we decided that the benefit of betamethasone therapy was greater than its risk. We selected a low dose of 1 mg as the start dose, in order to reduce the metabolic risk of hyperglycemia.

In this case, type B insulin resistance syndrome remitted, but the progression of diabetic kidney disease could not be prevented. It is recognized that damages to renal glomeruli, which covertly develops during long-lasting diabetes mellitus, results in the decline of glomerular filtration, and that it is difficult to stop the progression of diabetic kidney disease to end-stage renal disease, once the decline of glomerular filtration has begun (12). It took almost 10 years for remission of the syndrome to occur after diagnosis in our patient. Earlier introduction of glucocorticoid therapies might lead to better renal outcomes in this case.

According to the review of clinical courses of type B insulin resistant syndrome in 24 cases of the National Institute of Health, over half of the patients had proteinuria. Most cases were complicated with lupus glomerulonephritis, but no cases were pure diabetic nephropathy, although a case had a mixed picture of glomerulonephritis and diabetic nephropathy, as diagnosed by a renal biopsy (4). This case fulfilled three criteria for SLE (13, 14): renal disorder (persistent proteinuria greater than 3+), hematologic disorder (neutropaenia less than 4.00×10^9/L and thrombocytopaenia less than 100×10^9/L), and abnormal titers of anti-nuclear antibodies (Table 1). In the 24 cases of the National Institute of Health, six cases fulfilled three criteria for SLE and a case was complicated with myeloma (4). A monoclonal gammopathy was not observed in this case. Although this case was diagnosed

with diabetic nephropathy by a renal biopsy, it cannot be completely denied that this case was complicated also with some autoimmune diseases, renal complication of which was exacerbated after the cessation of the glucocorticoid therapy.

In conclusion, we experienced a rare case of type B insulin resistance syndrome that improved with low-dose glucocorticoids in outpatient settings. As the syndrome is very rare, further accumulations of therapeutic experiences are necessary for the better understanding of the syndrome.

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