

CASE REPORT

Long-term follow-up of insulin autoimmune syndrome in an elderly patient

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Abstract

An 84-year-old man was admitted to our hospital. His blood glucose level was 20 mg/dL. Since laboratory tests showed high titers of insulin antibodies, insulin autoimmune syndrome (IAS) was diagnosed. In order to avoid hypoglycemia, steroids can be effective in the long-term management of IAS in elderly patients.

KEYWORDS

anti-insulin antibodies, elderly, insulin autoimmune syndrome, steroid

1 | INTRODUCTION

An 84-year-old man was admitted to our hospital. His blood glucose level was 20 mg/dL. Since laboratory tests showed high titers of insulin antibodies, insulin autoimmune syndrome (IAS) was diagnosed. In order to avoid hypoglycemia, steroids can be effective in the long-term management of IAS in elderly patients.

Insulin autoimmune syndrome (IAS), also called Hirata's disease (HD), was first reported in 1970.¹ IAS is a disease characterized by hyperinsulinemic hypoglycemia, elevated insulin autoantibody titers, without prior exposure to exogenous insulin and no pathological abnormalities of the pancreatic islets. However, the pathophysiology of IAS is still poorly understood. It is likely to be associated with autoimmune diseases or plasma cell dyscrasias. It has been suggested that sulfhydryl group drugs divide the disulfide bound of insulin and enhance its immunogenic properties.² From the first IAS report up to 2007, 380 cases of IAS were identified by

Uchigata et al.³ IAS is known to be more common among the Asian population. We reported a case of IAS in an elderly patient in 2015⁴ and follow-up of the patient thereafter. Seven years after his diagnosis, his high titer of anti-insulin antibodies decreased significantly due to steroid therapy. Furthermore, some critical points for successful long-term control of blood glucose in IAS patients are discussed.

2 | CASE PRESENTATION

In December 2012, an 84-year-old man was admitted to Shin-suma General Hospital. On arrival, he was unconscious and his blood glucose level was 20 (range 70-110) mg/dL. Laboratory investigations revealed: glycated hemoglobin (HbA1c:NGSP) 6.6 (range 4.7-6.2) %, high titers of insulin antibodies ($\leq 5\%$: bound/total), and immunoreactive insulin (IRI) 7800 (range 5-15) mU/L. A 75 g oral glucose tolerance test (OGTT) showed impaired glucose tolerance

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(Table 1). The patient experienced persistent hypoglycemia (Figure 1A). Low affinity constant and a high binding capacity of autoantibodies were revealed by Scatchard analysis (Figure 2A). Moreover, his human leukocyte antigen (HLA) was DRB1*04:03, which has been reported to be associated with IAS previously. Therefore, he was diagnosed with IAS.⁴ He had hypertension, prostatic hypertrophy, and constipation. Onset of cerebral infarction occurred 2 years previously. Before admission to the hospital, clopidogrel, eicosapentaenoic acid, magnesium oxide, cilostazol, irbesartan, and sildenafil were prescribed. After admission, eicosapentaenoic acid and magnesium oxide were discontinued. The patient was maintained on frequent small meals to prevent rapid elevation of plasma glucose levels. However, a month later, the patient still experienced attacks of hypoglycemia and his insulin-binding antibody titer remained elevated. We initiated

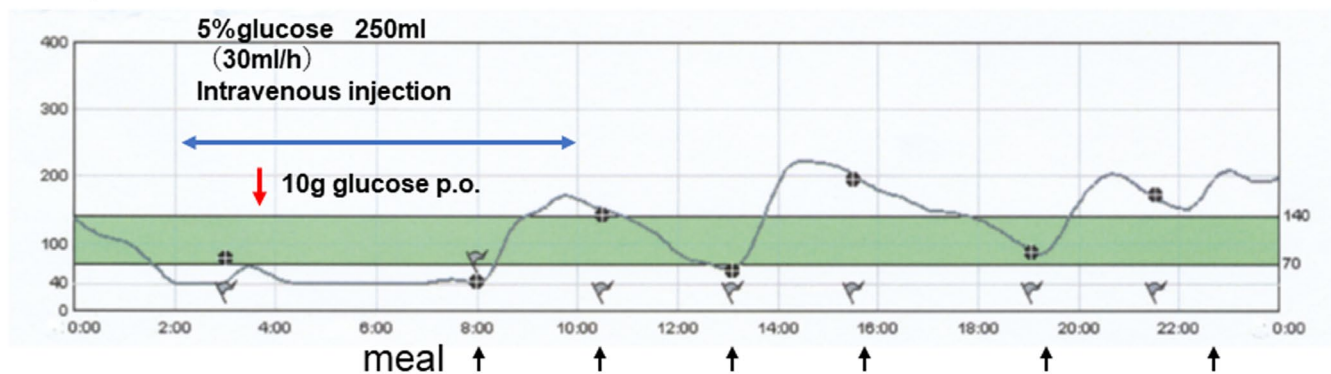
steroid therapy to suppress production of the autoimmune antibodies causing the hypoglycemia attacks. Prednisolone (PSL) was started at a dose of 30 mg/d for the first 5 days, and the dosage was tapered 5 mg/d at 5-day intervals. He did not experience any further hypoglycemic episodes (Figure 1B). The affinity constant and binding capacity of the autoantibodies also improved (Figure 2B). There were no new cerebrovascular disorders. Therefore, clopidogrel was withdrawn in February 2013. PSL was reduced to 2.5 mg/d in September 2013. The patient did not experience any steroid-related side effects such as, osteoporosis, hypertension, serious infection, or muscle weakness. His anti-insulin antibody levels decreased gradually. In January 2019, the patient's anti-insulin antibodies were significantly reduced to 18.1% (Figure 3) and his IRI was 7.0 mU/L. His fasting blood glucose was maintained between 88 and 92 mg/dL. The patient did not experience any hypoglycemic episodes. Therefore, dose reduction of PSL was commenced. Simultaneously, his adrenal function was monitored to avoid adrenal insufficiency. Basal plasma adrenocorticotropic hormone (ACTH) was 99.8 (range 7.2-63.3) pg/mL with serum cortisol of 16.2 (range 2.7-15.5) µg/dL. Rapid-ACTH stimulation test revealed that his adrenal function was normal (serum cortisol was 13.6,

TABLE 1 75 g oral glucose tolerance test (OGTT)

Time (min)	0	60	120	180
BG (mg/dL)	28	204	180	84
IRI (µIU/L)	7800	7720	8890	9570

Abbreviations: BG, Blood glucose; IRI, Immunoreactive insulin.

(A) Day 12



(B) After 9 months

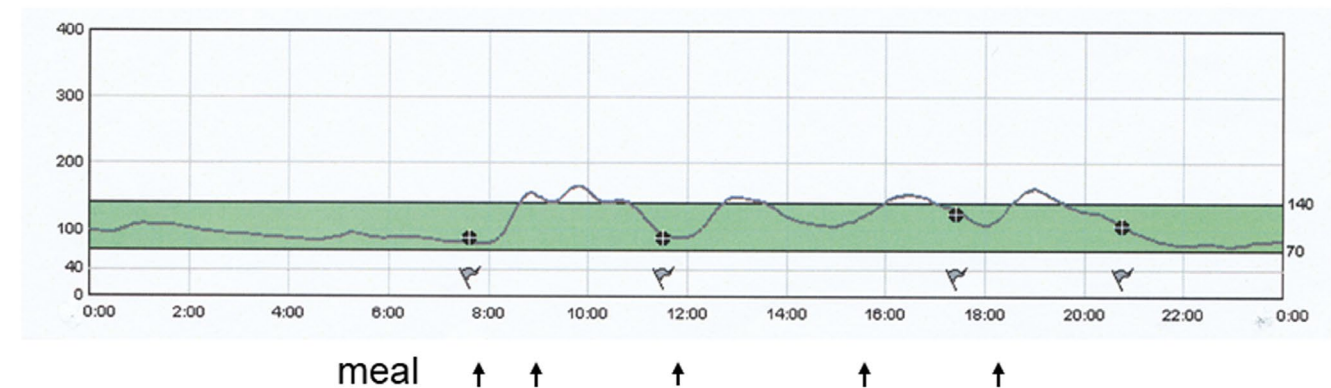


FIGURE 1 Twenty-four-hour glucose profile using a continuous glucose monitoring system. A, On admission. B, After 9-mo follow-up. Blue arrow indicates intravenous injection of 5% glucose. Red arrow indicates p.o of 10 g glucose. Black arrows indicates divided meal intake. p.o, per os

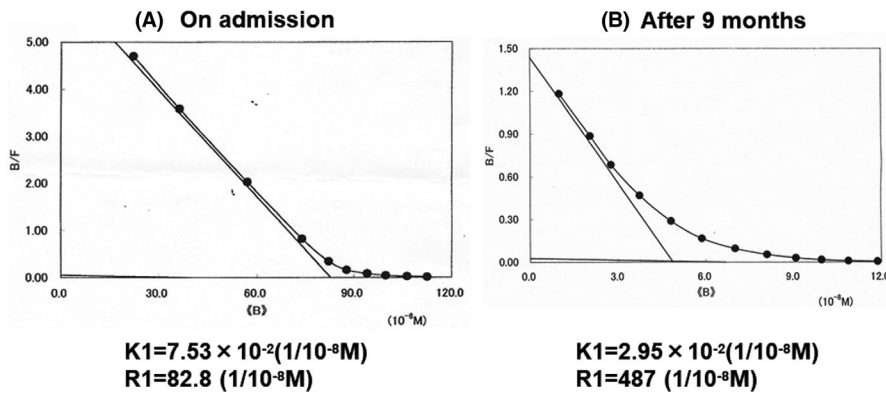


FIGURE 2 Scatchard analysis for insulin autoantibodies. A, Low affinity constant and a high binding capacity of the autoantibodies were revealed. B, An affinity constant and binding capacity of the autoantibodies were also improved

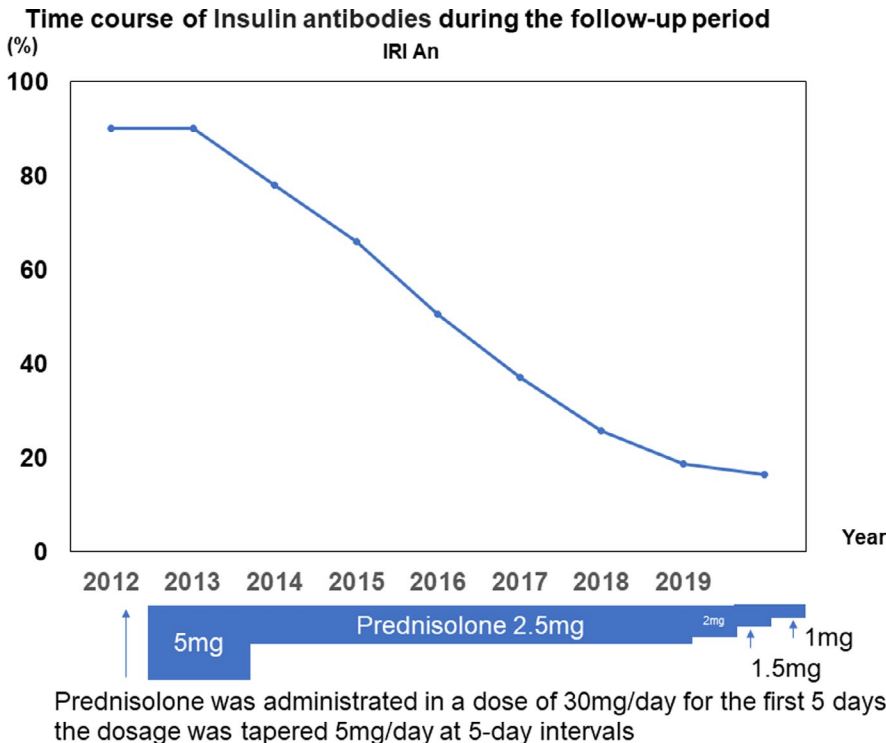


FIGURE 3 Time course of insulin antibodies (%) during the follow-up period. The relationship between suppression of anti-insulin antibodies and the dose reduction rate of prednisolone was indicated. IRI An, immunoreactive insulin antibodies (%)

15.8 and 18.6 $\mu\text{g/dL}$ at 0, 30, and 60 minutes, respectively). Finally, PSL dose was tapered to 1 mg/d in September 2019 (Figure 3).

3 | DISCUSSION

From 1994 to 2010, Kondou et al⁵ reported 120 IAS cases, 14% of which were elderly patients aged 75 years or older, and there were no cases of typical drug-related IAS. In 2017, Rajapal et al⁶ reported a case of clopidogrel-induced IAS. The chemical structure of clopidogrel does not include sulfhydryl, but its active metabolite possesses a sulfhydryl group. Management of IAS may include: discontinuation of the offending drug, a low-carbohydrate diet, or often the use of glucocorticoids. Recently, IAS was successfully managed with rituximab.⁷ Oral steroid therapy is one of the lines of treatment of IAS.⁸ It has been attempted to lower the titer of

insulin-binding antibody,^{9,10} but some cases showed a high titer of insulin-binding antibody or high immunoreactive insulin for long periods.^{8,11} Our case also had a high titer of insulin-binding antibody. Therefore, low-dose PSL therapy was continued to avoid relapse of hypoglycemia. According to Gomez et al,¹² one of the mechanisms of glucocorticoids in the management of IAS is through the elevation of blood glucose caused by insulin resistance. Other factors involved in this mechanism are unclear to our knowledge. In 1987, a Japanese case report mentioned IAS patients under chronic exogenous glucocorticoid excess. Therefore, insulin binding to monocytes increased due to increased receptor numbers. In addition, under endogenous steroid excess, increased affinity for insulin receptors leads to increasing insulin binding to monocytes.¹³ Therefore, glucocorticoid therapy could reduce the levels of insulin autoantibodies. Glucocorticoid therapy revealed a significant effect in our case. However, glucocorticoid-induced adrenal insufficiency is a serious adverse

effect of steroid therapy.¹⁴ Before reducing the dose of PSL, we evaluated adrenal function. According to Fujio et al,¹⁵ in the low-dose (5–20 mg/d PSL) group, basal ACTH and cortisol levels were also significantly decreased by glucocorticoid therapy, but the amount of change of ACTH and cortisol was unchanged for at least 4 weeks.

4 | CONCLUSION

Steroids can be effective in the long-term management of IAS in elderly patients. We emphasize that under physician control of steroids, dose monitoring of adrenal function is an important matter during management of IAS.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

HY is responsible for database search and writing of the article. KyK, KeK, GY, SM, and HT is responsible for correction of the article and supervision.

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