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CASE REPORT

Marked alteration of glycemic profile surrounding lanreotide administration in acromegaly: A case report

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ABSTRACT

Whether somatostatin analogs for acromegaly improve or worsen a patient's glycemic profile is controversial. A risk of hypoglycemia should be presumed, especially when patients receive insulin therapy, as the package inserts caution. However, a detailed clinical course of such a case has never been reported in research articles. An 80-year-old Japanese female diabetes patient treated with insulin therapy was diagnosed with acromegaly, and the somatostatin analog, lanreotide, was given. On day 4 of lanreotide treatment, repeated hypoglycemia as a result of exogenous insulin arose and the patient required inpatient care. After lanreotide treatment, the total daily insulin dose could be reduced, but her fasting C-peptide level decreased from 1.6 to 0.4 ng/mL, implying improved insulin resistance and impaired endogenous insulin secretion. In the present case, marked alteration surrounding lanreotide administration was observed; careful co-administration with insulin therapy is required, as the package insert cautions.

INTRODUCTION

Acromegaly is an endocrine disorder characterized by overgrowth with subsequent metabolic complications in response to a chronic excess of growth hormone (GH) and insulin-like growth factor-1 (IGF-1)[1]. Impaired glucose metabolism is a frequent complication.

Lanreotide, a somatostatin analog (SSA), is frequently used for acromegaly. However, whether SSAs improve or worsen glycemic profiles is controversial[2–4]. Furthermore, although the package insert clearly cautions the risk of hypoglycemia, especially in patients receiving insulin therapy, a detailed clinical course of such a case has never been reported in research articles[5].

Herein, we report an acromegaly patient whose glycemic profile was markedly altered after lanreotide administration.

CASE REPORT

An 80-year-old Japanese woman with diabetes mellitus presented at the Nihon University Itabashi Hospital, Tokyo, Japan. Diabetes was diagnosed at 50 years-of-age, which was finally treated with multiple daily insulin injections (MDII) from 72 years-of-age onwards. Glycated hemoglobin was 7.1%, maintained with 56 units of a total insulin daily dose: 20 units of insulin degludec at bedtime, and 10–14 units of insulin aspart before meals. She did not take any medicine, including oral hypoglycemic agent, other than insulin.

The patient's body mass index was 22.2 kg/m^2 (height 153 cm, weight 52 kg). Her vital signs were unremarkable. Acromegalic facies and enlarged extremities were observed. Cushingoid signs were not evident. Hormones under the above MDII were measured (Table 1). GH and IGF-1 were pathologically high. Adrenocorticotropic hormone and cortisol were not consistently high, and midnight serum cortisol was atypical for Cushing's disease (Table 2). Magnetic resonance imaging showed a tumor on the pituitary, and the patient was diagnosed with acromegaly. Pituitary hormones, other than GH, were unremarkable in pituitary function tests. Acute octreotide suppression test was positive.

An intramuscular injection of 90 mg lanreotide was given, and blood glucose declined (Figure 1). The patient continued MDII as aforementioned, and was admitted because of repeated hypoglycemia on the fourth day. Insulin injections were temporarily suspended, and dextrose was intravenously infused to prevent a hypoglycemic attack. Levels of immunoreactive insulin (0.2 μU/mL; measured using Roche's Cobas 8,000 modular analyzer, which does not detect exogenous insulin analogs),

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Table 1 | Hormones regulating glucose surrounding lanreotide administration

	Before	After	
Glucose	7.9	8.2	(4.0–6.0 mmol/L)
GH	8.72	3.26	(<5.0 ng/mL)
IGF-1	403	128	(49–158 ng/mL)
Serum C-peptide	1.6	0.4	(1.5–3.5 ng/mL)
Urine C-peptide	Not measured	17.5	(41–145 μg/day)
Glucagon	Not measured	134	(40–180 pg/mL)
ACTH	83.3	54.7	(9–52 pg/mL)
Cortisol	17.1	17.3	(3.8–18.4 μg/dL)
TSH	0.18	0.12	(0.4–4 μIU/mL)
Free T3	3.20	2.80	(2.2–4.5 pg/dL)
Free T4	1.84	1.62	(0.8–1.9 ng/dL)

Hormones were examined after overnight fasting, and before and after lanreotide administration. Diabetes was treated with multiple daily insulin injections using 52 units of total insulin daily dose (before) and vildagliptin 100 mg/day (after), respectively. ACTH, adrenocorticotropic hormone; GH, growth hormone; IGF-1, insulin-like growth factor-1; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone.

serum C-peptide (0.1 ng/mL) and plasma glucose (1.4 mmol/L) implied exogenous insulin-induced hypoglycemia. With this hypoglycemic event as a trigger, the patient hoped to avoid use of antidiabetic medicine with hypoglycemic risk, including insulin. To maintain glucose without hypoglycemia, vildagliptin (100 mg/day) and metformin (500 mg/day) were given instead of insulin. However, a response to an oral hypoglycemic agent was not achieved. Then, 4 units of insulin aspart before each meal was restarted, and the patient's preprandial blood glucose (an average of glucose levels before each meal) was maintained.

With vildagliptin (100 mg/day), hormones were measured on the seventh day, but the results of serum and urine C-peptide were obtained on the 11th day (Table 1). GH and IGF-1 were naturally lower; meanwhile, serum and urine C-peptide showed low values.

DISCUSSION

Acromegaly is an endocrine disease characterized by inappropriate systemic overgrowth[1]. Impaired glucose metabolism is a frequent complication, with half of patients showing glycemic intolerance[2,4,6]. SSA is frequently used, but whether SSA improves or worsens glycemic profiles is controversial. Indeed, lanreotide multifariously modified glucose in 30–40% of patients[2,3]. Its risk of causing hypoglycemia, especially in patients receiving insulin therapy, is clinically well-recognized. However, a detailed clinical course of such a case has never been reported in research articles[5].

The 44-unit reduction in total insulin daily dose implied a marked alteration of this patient's diabetes. As insulin secretion was impaired after administration, this improvement was attributed to increasing insulin sensitivity. GH influences glucose metabolism through two contradictory pathways; while IGF-1 mediated by GH plays a similar role to insulin, GH interferes with insulin receptor substrate 2, phosphatidylinositol 3-kinase and Akt activation, resulting in insulin resistance, a dominant factor for glucose intolerance in acromegaly[1,7]. Similar to somatostatin inhibiting hormone release through binding somatostatin receptor (SSTR) 1–5, lanreotide binds SSTR2 strongly and SSTR5 weakly, to inhibit hormone release, including GH, thus modifying glucose[1,8]. Disease controllability and a lower body mass index are predictors for glycemic improvement in lanreotide therapy for acromegaly[3,4]. The early normalization of IGF-1 and non-obesity in the present case did not conflict with an improvement. Furthermore, the patient's race was also possibly implicated in the her response to treatment: East Asians have high insulin sensitivity, suggesting improved insulin resistance can be more easily attained[9].

Table 2 | Repeated measurement of adrenocorticotropic hormone and cortisol level

	ACTH (9–52 pg/mL)	Cortisol (3.8–18.4 μg/dL)
Morning	37.0	14.2
	83.3	17.1
	18.8	6.6
	29.6	13.7
Midnight	12.0	4.8

Adrenocorticotropic hormone (ACTH) and cortisol were measured at four different early morning fasting times and midnight before lanreotide administration.

The impaired insulin secretion after lanreotide administration was also of interest. Low levels of serum and urine C-peptide imply lanreotide altered the patient's diabetes to an insulin-dependent state. Serum glucagon remained unaltered; however, it was presumed that lanreotide severely impaired β-cell function through SSTR5. While it is well recognized that pasireotide binds with high affinity to SSTR5 and causes hyperglycemia, lanreotide also has certain affinities to SSTR5[10,11]. From another angle, the decreased C-peptide level to that before lanreotide treatment probably meant decreased insulin resistance. Ohkura reported that '20 / (fasting C-peptide × fasting plasma glucose)' correlates well with insulin resistance estimated by a glucose infusion rate evaluated by euglycemic clamp[12]. Although insulin therapy makes a fair judgment difficult, the regression equation in that article estimated the glucose infusion rate of the present case at 5.64 mg/kg/min (before) and 18.38 mg/kg/min (after).

The present case included several limitations. First, with regard to an oral glucose tolerance test, the standard diagnostic method for acromegaly, tests on insulin resistance and glucose stimulated insulin secretion were not carried out, because severe hyperglycemia was predicted based on the high-dose insulin requirement of the patient's MDII regimen. Second, the transient withdrawal of insulin injections and environmental factors, such as physical activity and diet, that become altered on admission, might have affected the clinical course. Therefore, the reduction observed in the total insulin daily dose might not simply reflect the influence of lanreotide.

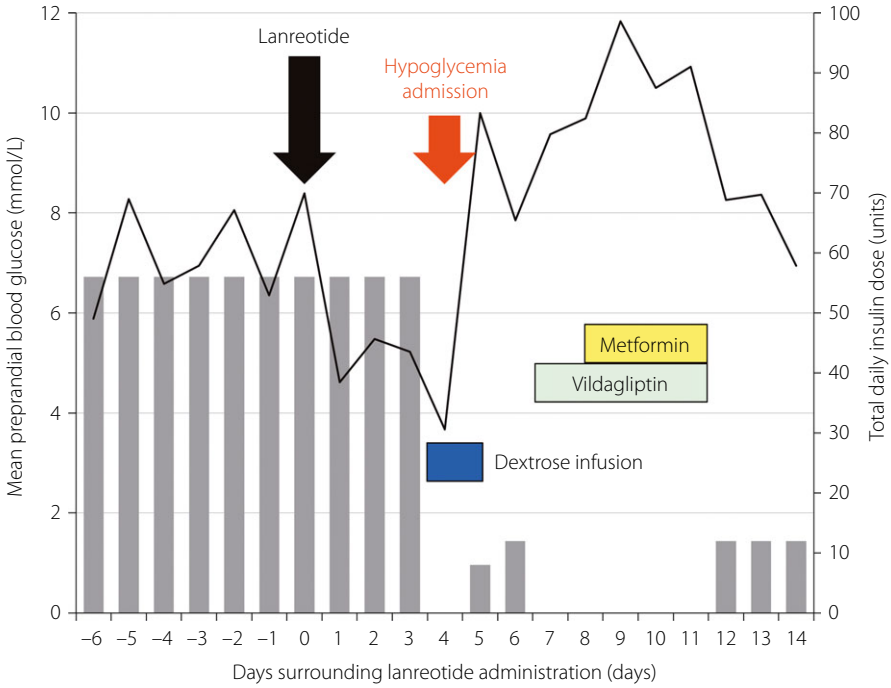

Figure 1 | Clinical course surrounding lanreotide administration. The black line indicates mean preprandial glucose (an average of blood glucose levels before each meal), and the vertical gray bar indicates the total daily insulin dose, respectively. Dosages of vildagliptin and metformin were 100 and 500 mg/day, respectively.

Importantly, SSAs should be administered with inpatient medical care to ensure appropriate treatment for any altered glycemic profile, if they are administered to diabetes patients receiving high-dose insulin therapy.

DISCLOSURE

The authors declare no conflict of interest.

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