CASE REPORT

Diabetic ketoacidosis in a patient with acromegaly and central diabetes insipidus treated with octreotide long-acting release

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Abstract A 43-year-old man was diagnosed with acromegaly due to pituitary GH-secreting macroadenoma, and underwent craniotomy surgery. After surgery, he was given octreotide long-acting release (LAR) to treat the residual tumor. Eighteen months later, he presented polydipsia and polyuria due to diabetic ketoacidosis (DKA) and central diabetes insipidus (CDI). His casual plasma glucose level was 570 mg/dL, his HbA1c was 14.9%, and his urine was strongly positive for ketone bodies. We discuss a causal relationship among DKA, CDI, and treatment with LAR in this case with residual GH-secreting tumor from the perspective of insulin secretion and resistance.

Keywords Diabetic ketoacidosis · Acromegaly · Central diabetes insipidus · Octreotide LAR

Introduction

Patients with acromegaly often develop glucose intolerance due to an excess of growth hormone (GH) secreted from the tumor [1]. About 19–56% of patients with acromegaly have been reported to have diabetes mellitus (DM) [1]. GH also increases fat metabolism and thus the production of ketone bodies [2].

Octreotide long-acting release (LAR) has been widely used to treat endocrine tumors and pituitary tumors, including those associated with acromegaly [3]. Somatostatin receptors (SSTRs) are known receptors for

octreotide. They belong to a family of G-protein coupled receptors with an extracellular domain, a seven-transmembrane domain, and an intracellular domain. Five different SSTRs have been identified, and octreotide LAR predominantly binds to SSTR2 and SSTR5 [3]. Since SSTR2 and SSTR5 are expressed in 96 and 86%, respectively, of GH-producing pituitary adenomas, octreotide LAR has been used for the treatment of acromegaly [3]. Octreotide LAR alters glucose tolerance because either hyperglycemia or hypoglycemia may occur depending on the individual's medical status [4–8]. Central diabetes insipidus (CDI) sometimes develops after pituitary surgery, causing polydipsia and polyuria. The clinical symptoms of CDI, such as polydipsia and polyuria, are similar to those of hyperglycemia, thus DM is difficult to diagnose in patients with CDI. In this report, we discuss a case of diabetic ketoacidosis (DKA) and CDI during the course of acromegaly treated with octreotide LAR.

Case

A 43-year-old man presented with bitemporal hemianopsia, and a pituitary tumor (52 × 30 mm) had been observed in MRI 18 months before. His serum level of GH was elevated to 6.2 ng/mL, and his IGF-1 level was increased to 800.1 ng/mL (±2SD: 92–255) (Fig. 1, period A; Fig. 2; Table 1, period A). The levels of other anterior pituitary hormones, except for central hypogonadism, were normal. His serum osmolality was 289 mOsm/L, his urinary osmolality was 748 mOsm/L, and his plasma level of arginine vasopressin (AVP) was 0.4 pg/mL, suggesting normal posterior pituitary function. He was diagnosed as having a GH-secreting pituitary tumor and underwent craniotomy. Because the tumor was too large,

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Fig. 1 Clinical course after the diagnosis of acromegaly is shown. After craniotomy, L-T4, hydrocortisone, a nasal drip of 1-desamino-8-arginine vasopressin (*¹DDAVP), and octreotide acetate long-acting release (*²LAR) were commenced. After the onset of diabetic

ketoacidosis, subcutaneous insulin infusion was commenced. The periods are represented as follows: A before craniotomy; B immediately after craniotomy; C at current admission; D 5 months after the cessation of LAR; and E 5 months after resumption of LAR

approximately 25% of it was not removed. His preoperative level of fasting plasma glucose (FPG) was 104 mg/dL and his HbA1c was 6.2%. Insulin secretion measured as fasting immunoreactive insulin (IRI) was preserved before surgery (Table 1). In a 75-g oral glucose tolerance test, he was classified as having impaired glucose tolerance (IGT), with a plasma glucose level of 187 mg/dL at 120 min after loading. The insulinogenic index was 0.61 (normal: >0.4), HOMA-R was 2.23 (normal: <1.6), and QUICKI was 0.124 (normal: 0.348–0.430). Both the increased HOMA-R and the decreased QUICKI suggested insulin resistance. The normal insulinogenic index and the fasting insulin level of 8.7 µU/mL suggested that insulin secretion was preserved (Table 1, period A). The basal level of GH decreased from 3.5 to 1.5 ng/mL 12 h after subcutaneous infusion of octreotide (100 µg). After craniotomy, the diagnosis of CDI was made based on elevated serum osmolality (320 mOsm/L), decreased urine osmolality (88 mOsm/L), and polydipsia and polyuria

(>5000 mL/day). Those abnormalities normalized rapidly after the administration of a nasal drip of 1-desamino-8-arginine vasopressin (DDAVP) (Fig. 1, period B). Endocrinological examination immediately after craniotomy showed panhypopituitarism due to the surgery (Table 1, period B). The panhypopituitarism was treated with L-T4 at 50 µg/day, oral hydrocortisone (15 mg in the morning and 5 mg in the evening), and a nasal drip of DDAVP (5 µg in the morning, and 7.5 µg in the evening). Octreotide LAR 20 mg/month treatment was commenced for the residual GH-secreting pituitary tumor (Fig. 1, period B). After treatment with octreotide LAR, serum GH decreased to less than 1 ng/mL. HbA1c levels measured 5 months after surgery were 6.2%, similar to those pre-surgery. His body weight increased over time.

Eighteen months after surgery, the patient consumed a large amount of soft drink on a daily basis for a couple of weeks. He presented polydipsia and polyuria, and visited our hospital. He did not have family history of diabetes and

Fig. 2a–h MRI, GH, and IGF-1 levels during the course. *Arrows* indicate the pituitary tumor. **a, b, c, and d** are coronal MRI images, whereas **e, f, g, and h** are sagittal MRI. All images, data, and periods correspond to the clinical course shown in Fig. 1. **a** and **e** are MRI images taken before surgery. The pituitary tumor (52 × 30 mm) extended to the cerebral ventricles. **b** and **f** MRI images taken on

admission showed an approximately 75% reduction in the tumor after surgery. **c** and **g** MRI images taken 5 months after the cessation of octreotide LAR indicated an enlarged tumor. **d** and **h** Eight months after the resumption of octreotide LAR, shrinking of the tumor was observed. The levels of serum IGF-1 appeared to be proportional to the tumor size

his history was unremarkable. His casual plasma glucose (PG) was 570 mg/dL, his HbA1c was 14.9%, and the level of ketone bodies in his urine was 3+, so he was admitted (Fig. 1, period C). The patient had lost 5 kg within the previous 2 months. At admission, he was alert, his blood pressure was 98/69 mmHg, his heart rate was 65 beats/min, and his body temperature was 37.6 °C. His body height was 177 cm, his body weight was 84 kg, and his BMI was 26 kg/m². No anemia or jaundice was seen in the conjunctiva. His heart and breath sounds were normal. No abnormal abdominal findings or edema were seen. Bilateral achilles tendon reflexes were normal. Vibration time was 12 s for both the right and left. Acromegalic facial features were seen (distension of the arcus superciliaris, thickness of the lips and nose, mandibular protrusion, and megaloglossia). The amount of underarm hair and pubic hair was reduced. No headaches, excessive sweating, dysesthesia, or joint pain were seen. In laboratory tests at admission, the complete blood count was normal, but mildly increased BUN and uric acid suggested dehydration (Table 2, period C). Serum sodium level was increased to 156 mEq/L, and serum osmolality was increased to 358 mOsm/L. Urine osmolality was also elevated to 624 mOsm/L. Endocrinological examination (Table 1, period C) indicated a decreased serum fasting CPR level: 0.5 ng/mL. Anti-GAD

antibody was negative. Serum level of IGF-1 was within the normal range (235 ng/mL), but serum GH was slightly increased to 2.8 ng/mL. Despite receiving L-T4 at 50 µg/day, the levels of TSH, FT3, and FT4 were decreased due to central hypothyroidism. Serum cortisol (F) level was increased to 32.7 µg/dL 3 h after taking oral hydrocortisone. TRAb, TPOAb, and TgAb were all negative. The plasma level of BNP was normal at 4.2 pg/mL. In urinary analysis, he showed increased specific gravity (SG) and was positive for ketone bodies (Table 2). Acidemia and metabolic acidosis were present at arterial blood gas examination. Electrocardiogram showed a normal sinus rhythm (71 beats/min). Chest X-rays revealed no cardiomegaly. No abnormal shadow was seen in the lungs and mediastinal lesion. Echocardiography revealed that wall movement was normal and the ejection fraction was 64.5%. In abdominal CT with contrast enhancement, no abnormal findings were detected except for fatty liver. Regarding diabetic complications, no retinopathy, nephropathy, or neuropathy were seen. The residual pituitary tumor was approximately 25% compared with that of before surgery, and was almost the same size as that immediately after surgery (Fig. 2b, f).

He was diagnosed with DKA, and continuous insulin infusion was started. After normalizing PG and the serum

Table 1 Endocrinological examinations during the course

Period	A	B	C	D	E	Units
IRI	8.7	N/A	N/A	N/A	N/A	μU/mL (2.7–10.4)
CPR	N/A	N/A	<u>0.5</u>	1.5	<u>0.8</u>	ng/mL (1.5–3.0)
GH	<u>6.2</u>	<u>2.9</u>	<u>2.8</u>	0.6	0.3	ng/mL
IGF-1	<u>800.1</u>	<u>452</u>	235	<u>321</u>	154	ng/mL (±2SD: 92–255)
PRL	16.3	21	19.2	18.8	N/A	ng/mL
LH	<u>0.6</u>	<u><0.2</u>	<u><0.2</u>	<u><0.2</u>	<u><0.2</u>	mIU/mL
FSH	<u>1.8</u>	<u><0.1</u>	<u><0.1</u>	<u><0.1</u>	<u><0.1</u>	mIU/mL
T	<u>55.9</u>	<u>4.9</u>	<u><4.3</u>	<u><4.3</u>	<u><4.3</u>	ng/dL (225–1039)
TSH	0.57	<u>0.03</u>	<u>0.034</u>	<u>0.18</u>	0.042	μIU/mL (0.35–4.94)
FT3	3.13	1.76	<u>1.19</u>	1.74	N/A	pg/mL (1.71–3.71)
FT4	0.97	0.92	<u>0.62</u>	0.7	0.71	ng/dL (0.70–1.48)
ACTH	29.8	13.6	<u>2.1</u>	<u>1.3</u>	<u>2</u>	pg/mL (7.2–63.3)
F	7.8	<u>2.6</u>	<u>32.7</u>	11.6	17.2	μg/dL (4.0–19.3)

The periods are represented as follows: A, before craniotomy; B, immediately after craniotomy; C, at current admission; D, 5 months after the cessation of octreotide LAR; and E, 8 months after resumption of octreotide LAR

Underlining indicates an abnormal value

IRI immunoreactive insulin, *CPR* C-peptide immunoreactivity, *PRL* prolactin, *T* testosterone, *N/A* not applicable, *TSH* thyrotropin, *FT3* free triiodothyronine, *FT4* free thyroxine, *ACTH* adrenocorticotrophic hormone, *F* serum cortisol

sodium level, self-administration of insulin (two injections of premixed short- and intermediate-acting insulins) was started. In addition to hyperglycemia, deterioration of CDI was initially suspected, so sufficient extracellular fluid infusion and an appropriate amount of DDAVP were supplemented. As mentioned above, the fasting level of CPR had deteriorated at admission, but incremental serum CPR gradually improved at discharge, four weeks after discontinuation of octreotide LAR (at admission: basal PG, 135 mg/dL and basal CPR, 0.4 ng/mL; after glucagon stimulation test: PG, 154 mg/dL and CPR, 2.2 ng/mL; accordingly, incremental CPR was 1.8). Octreotide LAR was then discontinued temporarily until stable glycemic control was achieved. However, since the pituitary tumor grew and the IGF-1 level increased to 321 ng/mL after 5 months, octreotide LAR was recommenced (Fig. 1,

period D; Fig. 2c, g; Table 1, period D). Fasting CPR recovered to 1.3 ng/mL and other endocrinological findings remained unchanged. Eight months after the resumption of octreotide LAR, the levels of GH and IGF-1 decreased and the tumor shrank in size (Fig. 1, period E; Fig. 2d, h; Table 1, period E). Fasting CPR worsened to 0.8 ng/mL while other endocrinological findings remained unchanged. After discharge, the level of HbA1c was well controlled at around 7% (Fig. 1).

Discussion

Novel observations for the current case compared with other cases of soft-drink-induced ketosis in type 2 diabetes are as follows (shown in Fig. 3). (1) Increased insulin resistance caused by GH, (2) increased insulin resistance due to obesity, and (3) decreased insulin and incretin secretion induced by LAR contributed to hyperglycemia. In contrast, decreases in GH and glucagon secretion and improved insulin resistance caused by LAR seemed to prevent hyperglycemia. (4) Finally, soft-drink-induced ketosis triggered critical hyperglycemia.

As shown in Fig. 1, body weight increased over time, suggesting insulin resistance, based on HOMA-R. Insulin secretion, measured as fasting immunoreactive insulin (IRI), was preserved before surgery but deteriorated (fasting CPR: 0.5 ng/mL) after the use of octreotide LAR (Table 1). Temporary insulin secretion evaluated as fasting CPR improved after the cessation of octreotide LAR (period D),

Fig. 3 Possible causal relationship

Table 2 Laboratory data on admission

WBC	7170	/ μ L
Hb	12.9	g/dL
Plt	13.1	$\times 10^4/\mu$ L
TP	7	g/dL
Alb	4.4	g/dL
T-Bil	0.9	mg/dL
AST	16	IU/L
ALT	14	IU/L
BUN	<u>20</u>	mg/dL
Cr	0.85	mg/dL
UA	<u>13.4</u>	mg/dL
Na	<u>156</u>	mEq/L
K	4	mEq/L
Cl	<u>115</u>	mEq/L
TG	<u>954</u>	mg/dL
LDL-c	103	mg/dL
HDL-c	31	mg/dL
S-osm	<u>358</u>	mOsm/L
CRP	<u>0.77</u>	mg/dL (<0.30)
FPG	<u>570</u>	mg/dL
HbA1c	<u>14.9</u>	%
BNP	4.2	pg/mL (<18.4)
Urinalyses		
U-osm	624	mOsm/L
SG	<u>1.032</u>	
Protein	<u>+</u>	
Glucose	<u>4+</u>	
Ketone	<u>3+</u>	
U-Alb	4.2	mg/day
Arterial blood examination in room air		
pH	7.338	
pCO ₂	30.8	mmHg
pO ₂	78.2	mmHg
SaO ₂	95.6	%
BE	-8.6	mmol/L
HCO ₃ ⁻	17.8	mmol/L

Underlining denotes an abnormal value

S-osm serum osmolality, U-osm urine osmolality

while the secretion worsened again after resuming octreotide LAR (period E). However, as described above, complicated mechanisms were involved in both insulin resistance and insulin secretion in the current case (Fig. 3).

In our patient, a significant volume of the pituitary tumor was not removed, even after surgery. Thus, a considerable amount of residual GH-secreting tumor appeared to contribute to the development of DKA due to the glycemic toxicity and fat toxicity of GH [2]. Furthermore, dietary and exercise therapy were insufficient to prevent the development of DM.

Octreotide LAR is reported to inhibit the secretion of insulin and incretin; 3.9% of patients treated with octreotide LAR developed DM while 8.3% of patients had hyperglycemia after octreotide LAR treatment [4]. The glucose intolerance seen in the present case may relate to this effect of octreotide LAR. In contrast, octreotide LAR inhibits the production of GH and glucagon [5], and octreotide LAR can improve insulin resistance [6]. Valea et al. reported that cases with IGT or DM after 12 months of octreotide LAR therapy exhibited better glucose metabolism due to improved insulin resistance, similar to those without DM [7]. The authors concluded that octreotide LAR therapy induced an improvement in glycemic control in patients with active acromegaly with and without DM, consistent with decreased levels of GH and IGF-1. They also suggested that the partially increased glucose level was due to inadequate suppression of GH and IGF-1.

Baldelli et al. reported the effects of long-acting somatostatin analogs (14 patients received lanreotide, while 10 patients received octreotide) on glucose metabolism in 24 consecutive acromegalic patients [8]. The authors measured plasma glucose and insulin levels during OGTT before and after the administration of the somatostatin analog, and demonstrated that insulin resistance was clearly improved whereas insulin secretion deteriorated after therapy. Higher glucose levels after somatostatin analog therapy were observed in the normal glucose tolerance group, while there was no notable change in glucose levels after treatment in IGT/DM patients. However, predicting the onset of DM in acromegalic patients during somatostatin analog therapy remained difficult because of the diversity of insulin resistance/secretion in individuals. Kahara et al. reported that a patient with octreotide LAR did not show an improvement in insulin sensitivity (QUICKI: 0.33 before treatment, 0.35 during octreotide LAR treatment) but did exhibit a reduction in insulin secretion (insulinogenic index: 0.28 before treatment, 0.08 during octreotide LAR treatment) [9]. The current patient exhibited IGT before octreotide LAR treatment and had a lower QUICKI than the patient in the study of Kahara et al., suggesting insulin resistance. In contrast, the insulinogenic index of our patient was higher than in the patient in the previous study. Insulin secretion was impaired after octreotide LAR therapy in the current case, and the excess soft drink intake may have triggered the development of DKA. Incremental CPR was improved at discharge, suggesting that insulin secretion recovered after the cessation of octreotide LAR.

Intriguingly, the patient in the study by Sato et al. [6] recovered both insulin sensitivity and early insulin secretion after surgical removal of the tumor, suggesting that both GH and octreotide LAR may play essential roles in the attenuation of glucose control.

Since the effect of octreotide LAR on glucose metabolism varies among individuals [8], it is important to closely monitor blood glucose levels during octreotide LAR therapy. Shin et al. reported a case with type 2 DM and idiopathic CDI, and also mentioned difficulty with diagnosing DM and CDI [10]. The concurrence of DM with CDI after pituitary surgery in the present case may be related to the deterioration of polydipsia and polyuria (Fig. 3).

The frequency of hyperglycemia was reported to be higher when pasireotide (a more effective agent than octreotide) was used compared to when octreotide was used (28.7 vs 8.3%, respectively), as was the frequency of DM (19.1 vs 3.9%, respectively) [4, 11]. In subjects administered with pasireotide, DPP-4 inhibitors and GLP-1 analogs were reported to be effective for lowering blood glucose [12]. In the current case, those anti-diabetic agents may be considered the first-line therapy for DM with octreotide LAR. Octreotide LAR was reported to have an inhibitory effect on GH and IGF-1 production, in addition to suppressing tumor growth [13], as seen in the current case. Somatostatin receptor ligands are recommended as the first-line medical therapy for acromegaly. Pegvisomant or dopamine agonist may be used as an adjuvant therapy in cases with uncontrolled acromegaly (such as GH > 1 ng/mL, elevated IGF-1 levels, presence of clinical activity suggesting acromegaly) and DM [14]. Although the patient was treated for CDI, urinary osmolality at admission was high. The reasons were hyperglycemia-induced elevated urinary osmolality and dysregulation of the thirst center, which caused dehydration (Fig. 3).

In conclusion, we encountered a patient who developed DKA and CDI during the course of acromegaly treated with octreotide LAR. As octreotide LAR is a widely used agent in the treatment of endocrine tumors, including pituitary tumors, physicians should check for the onset of DM during octreotide LAR therapy in the presence of CDI.

Compliance with ethical standards

Disclosure statement There is nothing to disclose.

Human rights statement and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or a substitute for it was obtained from all patients before they were included in the report.

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