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【 CASE REPORT 】

Type 1 Diabetes Mellitus and Klinefelter Syndrome

Teruaki Sakurai[1], Katsumi Iizuka[1,2], Takehiro Kato[1] and Jun Takeda[1]

Abstract:
A 60-year-old male patient with type 1 diabetes mellitus (T1DM) was admitted for glycemic control. The patient exhibited abdominal adiposity, osteoporosis, and high insulin requirement (>100 U), and we suspected hypogonadism. A physical examination revealed small testes and thin pubic hair, laboratory examination found high luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels and low testosterone levels, and a chromosome analysis (47, XXY) indicated hypogonadism due to Klinefelter syndrome (KS). KS is associated with autoimmune diseases and patients positive for diabetes related auto-antibodies. In male patients with T1DM and abdominal adiposity, the concurrence of KS should be taken into consideration.

Key words: Klinefelter syndrome (KS), type 1 diabetes mellitus (T1DM), osteoporosis, abdominal adiposity

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Introduction

Klinefelter syndrome (KS) is the most common chromosomal aneuploidy affecting males (1:650 newborn males) and is defined by the 47, XXY karyotype (1). This syndrome is characterized by hypogonadism, gynecomastia and azoospermia (1). Patients with KS may show abdominal obesity and the prevalence of metabolic syndrome (MS) in KS patients is up to 44% (1, 2), which leads to an increased incidence of type 2 diabetes mellitus (T2DM) (1, 2). The concurrence of KS and autoimmune diseases such as type 1 diabetes mellitus (T1DM) is known (3). However, cases of KS and T1DM are rarely reported because the concurrence of KS with T1DM is often overlooked (4). We report a case of KS in a patient previously diagnosed with T1DM.

Case Report

A 60-year-old man with a history of T1DM was admitted to our hospital for the purpose of glycemic control. His body weight was 48 kg at 20 years of age and increased to 88 kg at 32 years of age. At 39 years of age, he experienced polydipsia, polyuria and body weight loss (10 kg/year). He was diagnosed with type 1 diabetes mellitus and intensive insulin therapy was initiated. His glycemic levels were as high as 8%, and he had a very high insulin (>100 U) requirement. He had been married for 30 years, but had no children. A physical examination revealed that his height was 170 cm, his body weight was 63.2 kg, and his body mass index was 21.8 kg/m^2. His body pressure (BP) was 145/59 mmHg [on telmisartan (20 mg)]. His waist circumference was 88 cm and his abdomen was distended. The patient had micro testes and thin pubic hair, but his penis was within the normal size range and gynecomastia was not observed. Other systemic examinations revealed no changes. A laboratory examination revealed that his circulating luteinizing hormone (LH) [19.71 (0.79-5.72 mIU/mL)] and follicle stimulating hormone (FSH) [27.5 (2.00-8.30 mIU/mL)] levels were elevated and that his total testosterone level [0.74 (2.71-7.61 ng/mL)] was reduced (Table). The intramuscular administration of a total of 15,000 U of human chorionic gonadotropin over 3 days produced no increase in circulating testosterone levels (Table), suggesting primary hypogonadism (5). Abdominal CT showed bilateral testicular atrophy, a renal stone, and subcutaneous abdominal adiposity (Fig. 1A-C). A chromosome analysis indicated the 47, XXY chromosome karyotype and he was diagnosed with KS (Fig. 2). KS is known to be associated with osteoporosis (1). The examination of his bone mineral density [T score -3.3, 62% of young adult mean (YAM)] revealed osteoporosis and risedronate was administered monthly (75 mg/month).

[1]Department of Diabetes and Endocrinology, Graduate School of Medicine, Gifu University, Japan and [2]Gifu University Hospital Center for Nutritional Support and Infection Control, Japan
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Correspondence to Dr. Katsumi Iizuka, kiizuka@gifu-u.ac.jp

Table. Labolatory Findings at Diagnosis.

Urinalysis		Metabolism	
Protein	-	A1c	9.8 (4.9-6.2) %
Glucose	4+	Glucose	247 mg/dL
Hb	-	C-peptide	<0.01 (0.61-2.09) ng/mL
Ketone body	2+	Urinary C-peptide	undetectable
Blood			
WCC	6.1 (3.3-8.6) $\times 10^3/\mu L$	Anti-GAD Ab	19.8 U/mL
RBC	3.97 (4.35-5.55) $\times 10^6/\mu L$	Anti-IA-2 Ab	<0.4 (<0.4) U/mL
Hb	13.5 (13.7-16.8) g/dL	Anti-Insulin Ab	16.8 (<0.4) U/mL
Ht	40 (40.7-50.1) %		
MCV	100.8 (83.6-98.2) fL	LDLc	88 (65-140) mg/dL
MCHC	33.8 (31.7-35.3) %	TG	86 (40-150) mg/dL
Plt	32.4 (15.8-34.8) $\times 10^4/\mu L$	HDLc	96 (40-90) mg/dL
Biochemistry		Hormones	
TP	7.2 (6.6-8.1) g/dL	GH	0.98 ng/mL
Alb	4.5 (4.1-5.1) g/dL	IGF-1	80 ng/mL
AST	23 (13-30) U/L	PRL	8.63 (3.58-12.78) ng/mL
ALT	20 (10-42) U/L	ACTH	66.0 (7.2-63.3) pg/mL
ALP	376 (106-322) IU/L	Cortisol	16.9 (6.24-18.0) μg/dL
γGTP	98 (13-64) U/L	DHEA-S	128 (38-313) μg/dL
LDH	171 (124-222) U/L	11-OH Corticosteroid	22.9 (7.0-23.0) μg/dL
CK	129 (59-248) U/L	TSH	0.82 (0.35-4.94) μIU/mL
Cre	0.45 (0.65-1.07) mg/dL	FT4	1.48 (0.70-14.8) ng/dL
BUN	15.1 (8.0-20.0) mg/dL	FT3	3.09 (1.71-3.71) pg/mL
UA	2.8 (3.7-7.0) mg/dL	LH	19.30 (0.79-5.72) mIU/mL
Na	138 (138-145) mEq/L	FSH	27.41 (2.00-8.30) mIU/mL
K	5.0 (3.6-4.8) mEq/L	Testosterone	0.45 (2.07-7.61) ng/mL
Cl	105 (101-108) mEq/L	Human Chorionic Gonadotropin loading Test (15,000 Units/3 days)	
Ca	10.1 (8.8-10.1) mg/dL	LH (pre/day4)	19.71/21.46 mIU/mL
Pi	3.6 (2.7-4.6) mg/dL	FSH (pre/day4)	27.5/34.39 mIU/mL
		Testosterone (pre/day4)	0.74/0.96 ng/mL

As typical with T1DM, the patient was positive for anti-glutamic acid decarboxylase(GAD) (19.8 U/mL) and anti-insulin [16.8 U/mL (<0.4)] antibodies and negative for anti-IA-2 antibodies (<0.4 U/mL) (Table). His plasma and urinary C-peptide levels were undetectable. He displayed simple diabetic retinopathy and normoalbuminuria (urinary albumin: 27 mg/day). His thyroid function was within the normal range (Table). The patient's adrenal function was also normal [ACTH 66.0 (7.2-63.3) pg/mL and his cortisol level was 16.9 (6.24-18.0) μg/dL]. After titration of the insulin dosage, the patient's fasting plasma glucose level was approximately 120 mg/dL with 40 U insulin. Dyslipidemia was controlled (LDLc 88 mg/dL) by pitavastatin (Table).

Discussion

In this case report, we predicted hypogonadism in the KS patient based on his abdominal adiposity and the requirement of >100 U insulin. Low serum testosterone levels are a predictor of increased visceral fat in Japanese-American men (6). Moreover, KS patients exhibit the phenotypes of insulin resistance and hyperinsulinemia (7). Epidemiological studies have demonstrated a 5-fold higher prevalence of MS among KS males in comparison to age-matched controls (1). Abdominal adiposity in KS causes insulin resistance and hyperinsulinemia, resulting in the increased incidence of T2DM and cardiovascular diseases (1). Among 895 Japanese KS patients, 61 were diagnosed with diabetes mellitus and at least 20 were treated with insulin (8). In the current case, the patient displayed abdominal adiposity and insulin resistance, and was insulin deficient due to T1DM. Thus, the abnormal fat distribution and the requirement of a high insulin titer may provide diagnostic indicators of the coexistence of hypogonadism.

The association between KS and autoimmune syndrome has been previously reported. A retrospective study demonstrated that KS was associated with a significantly increased risk of Addison's disease (RR 11.7), T1DM (RR 6.1), Sjögren's syndrome (RR 19.3) and systemic lupus erythematosus (RR 18.1) in comparison to controls (3). Interestingly, the majority of the above conditions are more frequently observed in females. Moreover, some groups have shown that testosterone replacement for hypogonadism is associated with reduced levels of inflammatory markers C-reactive protein (CRP), interleukin-1β (IL-1β) and tumor necrosis factor-α (TNFα) (9). This suggested that hypogonadism due

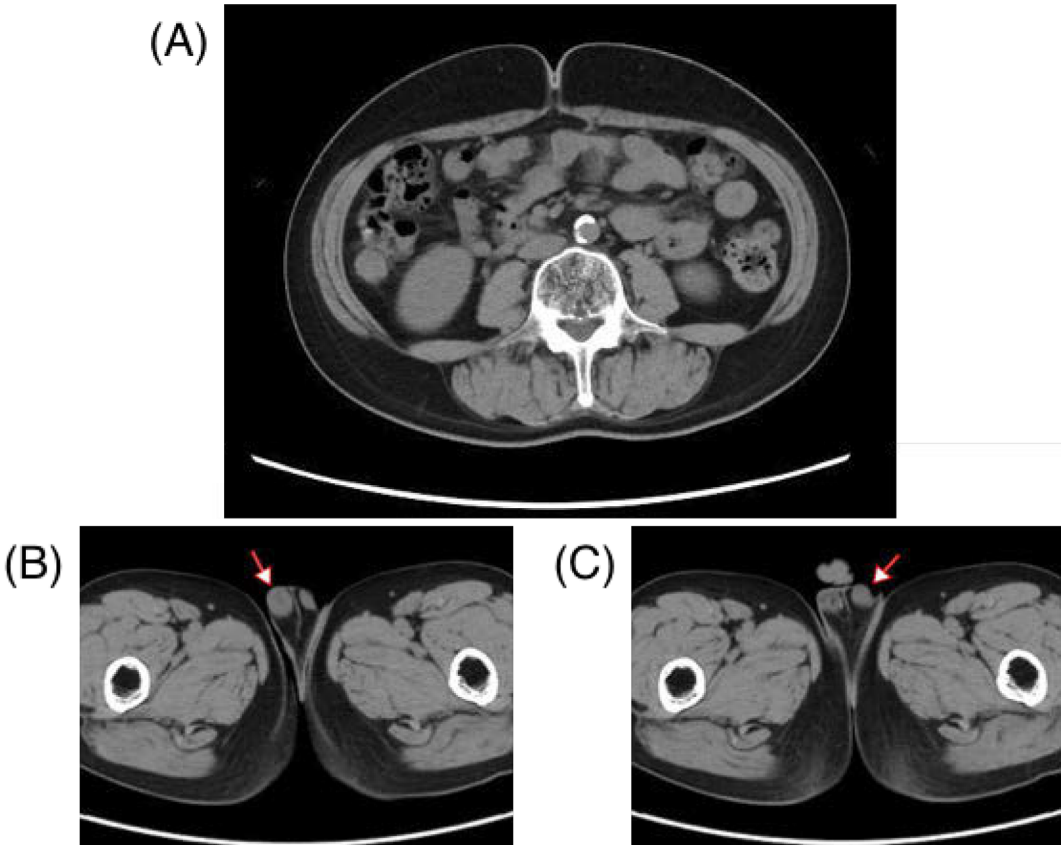

Figure 1. **An X-ray CT image at the position of the omphalic part (A), the right testis (B), and the left testis (C).**

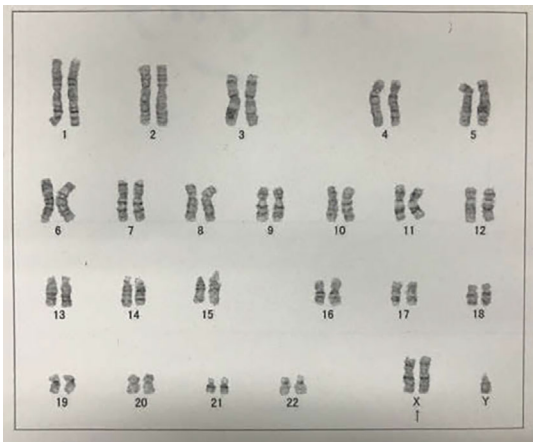

Figure 2. **Chromosome analysis of the present patient. A chromosome analysis indicated the 47, XXY chromosome karyotype. Based on this finding, he was diagnosed with KS.**

to KS might cause autoimmune syndrome; however, the precise mechanism remains unclear.

Some studies have reported that the positive detection of diabetes-related autoantibodies is much higher in KS patients than in healthy males (8.2% vs. 0.01%, respectively; p=0.016) (10). In a Danish study, out of 832 patients with KS, 15 had T1DM (11). In contrast, among 260 patients diagnosed with T1DM, five patients (1.9%) had KS, which was higher than the incidence in the normal population (12). There is no established causal link between KS and T1DM. However, considering the possibility that insulin resistance may promote beta cell destruction, the clinical examination of KS patients should include testing for the presence of diabetes-related antibodies, and further follow-up may be needed for autoantibody-positive KS patients.

The coexistence of insulin deficiency and insulin resistance in this KS patient made it difficult to obtain glycemic control. Some groups reported that testosterone replacement therapy (TRT) was beneficial for treating insulin resistance and dyslipidemia in T2DM (13). Thus, TRT may reduce the level of administered insulin. However, in patients with KS, TRT was not as effective-with regard to improving body proportions and bone mineral density-in 46, XY hypogonadal males (14). In addition, TRT may increase the risk of prostate cancer (15). Thus, we did not administer TRT to this patient. One study reported that pioglitazone was effective in a patient with KS and T2DM (8). In addition, thiazolidines may reduce the insulin requirement in T1DM (16). In the current KS patient, such treatments may be beneficial for at least reducing the insulin requirement.

In this report, the bone mineral density of the KS patient was much lower than that of normal healthy subjects (1). A recent study found that the proportion of KS patients with osteopenia and/or osteoporosis was 42.5% (1, 17). Another study reported that the oral administration of alendronate (10 mg) significantly increased spine, hip, and total body

bone mineral density, and reduced the incidence of vertebral fractures in men with osteoporosis, 36% of whom were hypogonadal (18). It was also reported that KS patients were particularly prone to 25OH-vitamin D fluctuation, and that they presented with insufficient levels more frequently than controls. Although we did not measure 25 OH-vitamin D because of health insurance limitations, vitamin D supplementation may be beneficial (19).

In conclusion, we reported a case of combined T1DM and KS. In male patients displaying abdominal adiposity and an excessive insulin requirement with type 1 diabetes mellitus, it is possible that conditions associated with hypogonadism, such as KS, may be overlooked. However, KS is not a rare disease and approximately 70% of men with KS may remain undiagnosed. There is no universal guideline regarding the follow-up of KS patients; however, we will continue to counsel this patient with respect to the increased incidence of malignancies, such as breast and hematological cancers (20, 21), bone fracture, and cardiovascular diseases (22), and continue to control his glycemic level.

The authors state that they have no Conflict of Interest (COI).

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