INTERNAL MEDICINE

□ CASE REPORT □

Acromegaly Accompanied by Turner Syndrome with 47,XXX/45,X/46,XX Mosaicism

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Abstract

A 33-year-old woman was hospitalized for examination of edematous laryngopharynx. She was acromegalic. A pituitary adenoma with elevated serum levels of growth hormone (GH) and insulin-like growth factor-I (IGF-I) was detected, indicating acromegaly caused by GH-secreting pituitary adenoma. Multiple pigmented nevi were also noted without overt short stature and cubitus valgus. Chromosome analysis revealed that she had contracted Turner syndrome with 47,XXX/45,X/46,XX mosaicism. Transsphenoidal resection of the tumor decreased serum GH and IGF-I levels, but the edema was not improved. Both premature ovarian failure and hypertension appeared after surgery. This case may indicate the important relationships between GH/IGF-I and Turner syndrome.

Key words: acromegaly, Turner syndrome, mosaicism, 47,XXX

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Introduction

Turner syndrome is a disorder in women with absence of a normal second sex chromosome. The typical clinical features are short stature, gonadal dysgenesis and some anatomical anomaly. This syndrome involves mental retardation, natural abortion, autoimmune disease, impaired hearing, and multiple pigmented nevi. Endocrinologically, hypogonadism, autoimmune thyroid diseases, and diabetes mellitus are often manifested. Major karyotype is monosomy X (45,X), and 5 to 10% have a duplication of the long arm of one X (46,X,i (Xq)). Most of the rest have mosaicism for 45,X, and 3 to 4% are mosaic for a triple X (47,XXX) (1-5).

Acromegaly is a rare disease caused by excess of GH secretion, resulting from a pituitary tumor in more than 99% of all cases. Oversecretion of GH develops not only overgrowth of soft tissue and bone but also hormonal and metabolic changes (6). Pituitary tumor is a very rare complication in Turner syndrome. We herein report a novel case of acromegaly in an early adult woman with Turner syndrome.

Case Report

A 33-year-old woman with a 6-year-old son was presented for dysphagia caused by edema of the soft palate and epiglottis. Her menarche was at the age of 12 and irregularity of menstrual cycles appeared at the age of 30. She was 151 cm in height and 50.2 kg in weight. Blood pressure was 103/63 mmHg. Her nose, hands and feet were enlarged. Pigmented nevi were systemically scattered, but any other external anomaly was not noted. Diffuse goiter was also observed. According to Tanner's classification, breast development and pubic hair growth were grade III and grade IV, respectively.

In the laboratory data, hemoglobin level was decreased in relation to iron deficiency (Table 1). Acromegaly was strongly suggested because levels of serum GH and IGF-I were markedly elevated with a slight increase in serum prolactin (PRL) (Table 2). This diagnosis was also supported by the following results of provocation tests; no suppression of GH secretion in OGTT; paradoxical response of GH secretion after stimulation with protirelin; and sufficiently de-

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Table 1. Laboratory Data on Admission

CBC			Alb	4.0	md/dL
WBC	4730	/μL	BUN	7.0	mg/dL
RBC	4.68	$\times 10^6$/μL	Cre	0.36	mg/dL
Hb	8.8	g/dL	Na	136	mEq/L
Ht	30.7	%	K	3.6	mEq/L
MCV	65.6	fL	Cl	104	mEq/L
MCH	18.8	pg	Ca	8.6	mg/dL
MCHC	28.7	%	iP	3.8	mg/dL
PLT	26.0	$\times 10^4$/μL	T-Chol	202	mg/dL
Urine			TG	89	mg/dL
glucose	(−)		HDL-C	47	mg/dL
protein	(−)		Fe	24	μg/dL
occult blood	(−)		TIBC	543	μg/dL
Blood Chemistry			Ferritin	1	μg/dL
ALT	9	U/L	Glucose	79	mg/dL
AST	10	U/L	Hb_{A1c}	4.7	%
LDH	114	U/L	1,25-$(OH)_2$D	60.9	pg/mL
ALP	256	U/L	***Urinary Chemistry***		
γ-GTP	13	U/L	Ca	110	mg/day
TP	7.4	mg/dL	iP	450	mg/day

Table 2. Endocrinological Data before or 2 Weeks after Surgery

	Before surgery	After surgery	Normal range	
GH	11.5	0.4	< 5.0	ng/mL
IGF-I	867	385	121 - 436 (adult female)	ng/mL
IGF-BP3	4.96	–	2.29 – 4.17 (17 - 34 years old)	μg/mL
T3	131	110	84 - 180	ng/dL
T4	7.1	7.6	5.1 - 12.8	μg/dL
TBG	19.5	17.4	10.4 - 26.1	μg/mL
TSH	1.59	1.91	0.20 - 4.00	μIU/mL
TPOAb	3.0	–	< 10	IU/mL
TgAb	3.4	–	< 10	IU/mL
TRAb	5.1	–	< +15	%
PTH-high sensitive	470	660	160 - 520	pg/mL
LH	0.7	6.9	0.9 - 15.5 (follicular phase)	mIU/mL
FSH	1.8	24.2	3.1 - 23.9 (follicular phase)	mIU/mL
Estradiol (E2)	38	< 10	10 - 78 (early follicular phase)	pg/mL
Progesterone	3.2	0.4	< 1.7 (follicular phase)	ng/mL
PRL	38.3	28.8	1.4 - 14.6	ng/mL
Cortisol (early morning)	11.3	13.5	5 - 15	μg/dL
ACTH (early morning)	32.8	35.7	9 - 60	pg/mL

Table 3. Results of Provocation Tests before or 2 Weeks after Surgery

75gOGTT

Before surgery

minute	0	30	60	90	120
GH (ng/mL)	7.6	4.8	7.0	8.0	7.8
Glucose (mg/dL)	90	122	139	118	115
IRI (μIU/mL)	6.0	38.2	37.6	30.9	46.7

After surgery

minute	0	30	60	90	120
GH (ng/mL)	0.5	0.2	0.1	0.2	0.4
Glucose (mg/dL)	76	111	98	79	75
IRI (μIU/mL)	1.8	26.2	26.0	17.1	9.7

Protirelin 0.5mg iv

Before surgery

minute	0	15	30	60	120
GH (ng/mL)	9.2	198	112	36.2	8.1
TSH (μIU/mL)	2.17	17.90	18.10	13.80	7.25
PRL (ng/mL)	25.5	73.6	65.2	50	34.3

After surgery

minute	0	15	30	60	120
GH (ng/mL)	1.1	0.8	0.5	0.5	1.3
TSH (μIU/mL)	2.36	12.65	12.93	9.24	5.02
PRL (ng/mL)	29.1	61.7	55.5	41.4	29.6

Gonadorelin acetate 0.1mg iv

Before surgery

minute	0	15	30	60	120
GH (ng/mL)	3.2	6.7	6.7	6.4	7.9
LH (mIU/mL)	6.3	6.1	8.9	9.0	7.5
FSH (mIU/mL)	16.2	18.2	20.4	22.5	24.2

After surgery

minute	0	15	30	60	120
GH (ng/mL)	0.9	0.4	0.4	1.7	1.9
LH (mIU/mL)	17.1	32.5	43.4	43.6	33.6
FSH (mIU/mL)	36.0	42.7	49.2	51.4	53.0

Bromocriptine 2.5mg po

hour	0	1	2	4	6	12
GH (ng/mL)	5.5	3.8	1.2	0.9	1.8	8.7
PRL (ng/mL)	36.6	29.3	21.7	16.2	11.2	6.0

creased serum GH levels after oral administration of bromocriptine (Table 3). Magnetic resonance imaging (MRI) of the pituitary detected a mass of around 1 cm in diameter, indicating GH-secreting pituitary adenoma (Fig. 1).

Thyroid function was normal, and both anti-thyroid peroxidase and anti-thyroglobulin antibodies were negative. Ultrasonography showed diffuse swollen thyroid with multiple cystic lesions, indicating adenomatous goitor. Basal levels of 17β-estradiol (E2) were not markedly reduced (Table 2), but gonadotropin secretion was insufficient in provocation test with gonadorelin acetate (Table 3). Osteoporosis was not noted because bone mineral density was normal in lumbar spine, hip portion of femoral bones, and forearm bones, respectively. Abnormal bleedings were not found in esophagus, stomach, duodenum, colon, or reproductive organs in endoscopical or gynecological examination.

G-band chromosomal analysis on peripheral blood lymphocytes (PBLs) showed 47,XXX[44] 46,XX[4]/ 45,X[2]. Subsequently, fluorescence *in situ* hybridization (FISH) analysis using an α satellite specific probe to X chromosome was performed on 500 cells from PBLs and buccal smear. The major cell line in PBLs was 47,XXX (71.8%), and that in buccal smear was 45,X (47.4%). Around half of cells had 45,X in buccal smear, but not in PBLs (Table 4). These findings were not contradicted with the diagnosis of Turner syndrome. We could not detect any cardiovascular diseases, renal disorders, ophthalmic disorders, bone abnormalities, or mental disorders.

Transsphenoidal removal of the pituitary tumor was performed successfully. The soft tumor was 12 mm in size with durable capsule. Histological examination revealed that eosinophilic granules were found in proliferated tumor cells with relatively pale cytosol. GH-positive cells were diffuse spread, and 20 to 30% of cells were PRL-positive in immunostaining analysis. Two weeks after surgery, circulating levels of GH and IGF-I were decreased (Table 2). GH secre-

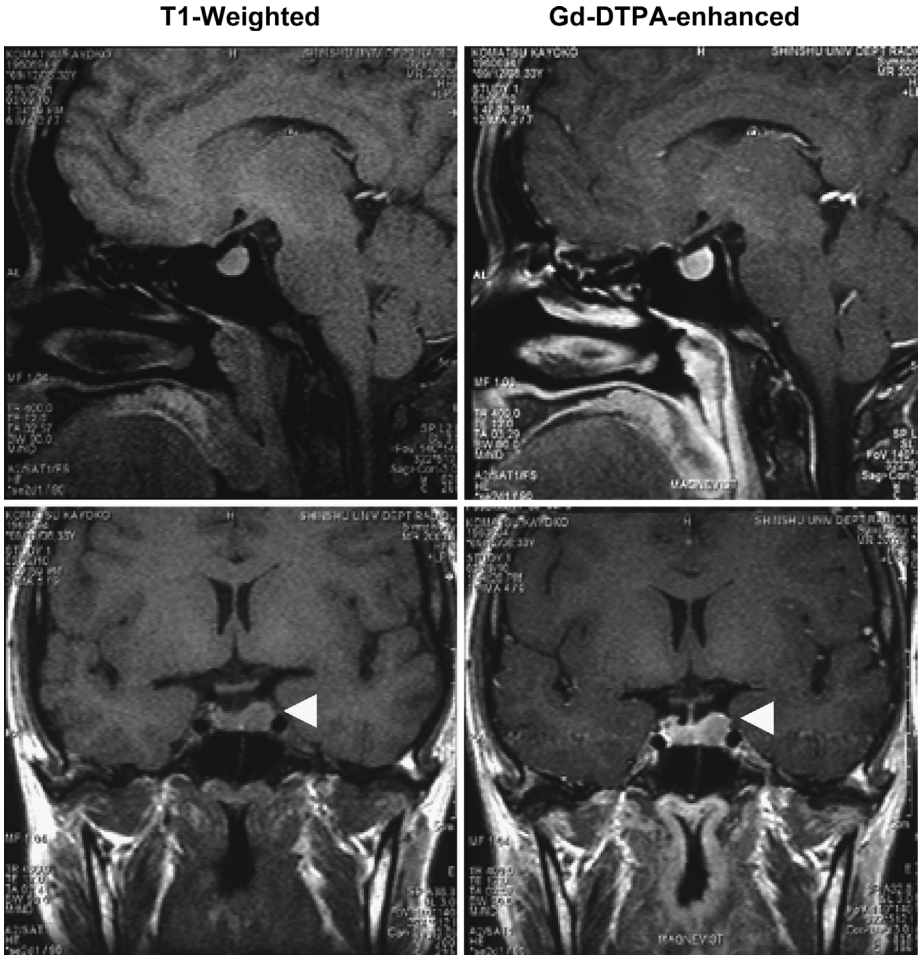

Figure 1. **Pituitary MRI. Pituitary tumor is noted (arrowheads).**

Table 4. **FISH Analysis**

Number of X chromosome	X	XX	XXX	XXXX
Peripheral blood lymphocytes (%)				
Patient	25.6	2.6	71.8	0
Normal female subject*	1.4	97.6	0.8	0.2
Buccal smear (%)				
Patient	47.4	10.6	42.0	0
Normal female subject*	1.4	98.4	0.2	0

* A specimen was derived from a woman with normal karyotype.

tion was sufficiently suppressed in OGTT, and paradoxical response of GH secretion was not seen in the protirelin stimulation test (Table 3). Serum high sensitive PTH levels were slightly elevated (Table 2). Basal levels of gonadotropin were increased after surgery, whereas serum E2 concentrations were low (Table 2). Gonadotropin secretion after provocation with gonadorelin acetate was slightly recovered, but not normalized (Table 3). About one year after surgery she was affected with hypertension, which was not related to drug, chronic kidney disease, renovascular disease, primary aldosteronism, Cushing syndrome, pheochromocytoma, thyroid dysfunction, hypercalcemia, or coarctation of the aorta. She also developed premature ovarian failure. Edematous laryngopharynx hardly improved although the recurrence of the tumor was not observed.

Discussion

Clinical characteristics in our case are shown in Table 5.

The karyotype determined by X chromosome is linked to the difference in clinical features. Congenital malformations are found more frequently among women with the 45,X karyotype, whereas endocrine disease, acquired heart disease, hypertension, and arteriosclerosis are more frequent in women with other karyotype of Turner syndrome (5). Non-mosaic triple X is generally associated with increased stat-

Table 5. Clinical Features of Turner Syndrome with Acromegaly

	The present case	Bolanowski et al.[22]
Age of diagnosis		
Acromegaly	33	33
Turner syndrome	33	6
Karyotype	47,XXX/45,X/46,XX	45,X/46,X,i(X) (q10)
Final height (cm)	151	140
Ovarian failure	+	+
History of pregnancy	+	−
Anormaly		
Heart	−	+[1]
Kidney	−	+[2]
Others	multiple pigmented nevi	shortened neck
Skeletal change	−	+[3]
Edema of pharynx/larynx	+	−
Hypertension	+	−
Iron deficiency anemia	+	−
Osteopenia/Osteoporosis	−	+
Secondary hyperparathyroidism	+	−
Impaired glucose tolerance	−	−
Autoimmune disease	−	Hashimoto thyroiditis
Impaired hearing	−	+
Mental disorder	−	−
GH replacement	−	−

[1] mixed aortic valve defect, prolapse of the anterior mitral capsid valve

[2] duplication of left renal system

[3] Most changes are caused by acromegaly.

Table 6. Pituitary Tumors in Turner Syndrome

Types of tumor	Karyotype	Reference
microprolactinoma	45,X/46,XX	[16]
macroadenoma	45,X	[17]
microadenoma	not described	[18]
macroadenoma	45,X	[19]
prolactinoma	45,X/46,XX	[20]
ACTH-producing microadenoma	not described	[21]
GH-producing macroadenoma	45,X/46,X,i(X) (q10)	[22]

ure, normal fertility, decreased intellectual ability, and increase in psychiatric problem. Conversely, this phenotype is not observed in the case combined with a monosomy X cell line (7). In a previous review, women with the mosaic karyotype of Turner syndrome containing triple X develop short stature, anomaly, and mental retardation with almost the same frequency as women in the 45,X karyotype, and are predisposed to premature ovarian failure after having natural menarche and/or the secondary sex characteristics (8). The SHOX gene, which is located in the pseudoautosomal region 1 on the distal end of the X and Y chromosome and encodes a homeodomain transcription factor in developing skeletal tissues, may be partly affected on the final height. Haploinsufficiency of SHOX leads to short stature, while overdosage may be implicated in a tall stature (9). Therefore the severity of short stature is correlated with the distribution of cell lines in 47,XXX/45,X/46,XX (10). Although the analysis of SHOX gene was not done, clinical features in our patient seem to satisfy the features mentioned above regarding abnormal menarche, pregnancy, premature ovarian failure, and borderline short stature.

In patients with Turner syndrome hypoplastic lymphatics generate lymphedema, which is worse during infancy and slowly resolves as they grow older. Multiple pigmented nevi are caused by some aging-related factors and skin dysfunction associated with lymphedema peculiar to Turner syndrome (11). Rarely, lymphedema may persistent or recur in late childhood or later in adult life (12). In patients with ac-

romegaly, edema and hypertrophy are often presented in the mucosa of laryngopharyngeal cartilages (13). Although serum levels of GH and IGF-I were decreased after surgery, laryngopharyngeal edema was not improved in the present case. This fact may indicate that the edema is caused mainly by lymphedema in Turner syndrome.

In the present patient an increase in serum high sensitive PTH levels was apparent after surgery, even though renal function did not worsen. Reduced levels of serum calcium and increased plasma PTH concentrations are generally observed in patients with Turner syndrome. Circulating levels of 1,25-dehydroxy-vitamin D (1,25-$(OH)_2$D) and 25-hydroxyl-vitamin D (25-OHD) are normal or lower than in normal age-matched female control, indicating normal conversion of 25-OHD to 1,25-$(OH)_2$D, but either diminished intake of 25-OHD or reduced uptake of the compound (3). These facts suggest that the verification of calcium intake and/or absorption is needed in our case.

Iron deficiency anemia was found in our patient. Exclusion of bleeding from the small intestine may be required because anemia in Turner syndrome is caused mainly by intermittent gastrointestinal bleeding from intestinal telangiectasia (1). It is also necessary to consider iron malabsorption (14), a part of which may be caused by celiac disease (15).

Major causes of secondary hypertension were excluded in our case. Up to 50% of adult patients with Turner syndrome have clinical hypertension with an abnormal diurnal blood pressure profile and in some patients treatment with female hormone replacement can induce a significant reduction in diastolic blood pressure (3, 5). We are confirming whether hypogonadism is a cause of hypertension by replacement of estrogen and progestin.

Development of various pituitary tumors in Turner syndrome has been reported, as shown in Table 6 (16-22). There was one report on acromegaly caused by GH-secreting adenoma in a patient with Turner syndrome (22). Most clinical features seem to be strongly related to the karyotype, but the relationship between karyotypes and tumorigenesis is not clarified (Tables 5, 6). GH/IGF-I insensitivity may be a clue to the association between GH-secreting pituitary tumor and Turner syndrome. Girls with Turner syndrome needed larger doses of GH for several years than GH deficient patients and others to reach predicted height (3). This fact indicates that there exists a certain extent of GH/IGF-I insensitivity (3, 23). GH insensitivity resulting from IGF-I insensitivity in Turner syndrome is supposedly due to defects in SHOX gene (24). The estimation on the spontaneous and stimulated GH secretion in Turner syndrome is equivocal because it is affected by secretion of estrogen. Decreased circulating levels of estrogen does not preserve GH secretion (25). However, our patient seems to have secreted estrogen sufficiently because she had her periods before the tumor developed. Therefore GH secretion may have been promoted probably because of increased GHRH secretion if she was in a state of GH/IGF-I insensitivity (26, 27). A previous study showed that excessive GH secretion resulted in upregulated somatotrope proliferation and neoplastic transformation in animal models and human (28). In addition to some genetic events in neoplastic transformation, increased GHRH secretion has a possible role for somatotrope tumorigenesis. A case report of acromegaly in a patient with anorexia nervosa, which causes functional GH insensitivity, is meaningful and helpful to consider somatotrope tumorigenesis in GH insensitivity syndrome (29). We believe that the present case is highly suggestive to elucidate the mechanism of GH/IGF-I action in Turner syndrome. Accumulating similar cases is needed to clarify the important relationships between GH/IGF-I and Turner syndrome.

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