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NOTE

Multiple Endocrine Disorders and Rathke's Cleft Cyst with Klinefelter's Syndrome: A Case Report

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Abstract. A 46-year-old Japanese male was admitted for the evaluation of severe hypertension. He was obese and had a eunuchoidal body habitus. Chromosomal analysis revealed a 46, XY/47, XXY karyotype. Serum LH, FSH and testosterone levels were low, indicating hypogonadotropic hypogonadism. Endocrinological dynamic tests disclosed presence of hypothalamic panhypopituitarism, partial diabetes insipidus, type 2 diabetes mellitus and low renin essential hypertension. Brain computed tomography and magnetic resonance imaging revealed intra- and extrasellar masses. Histological examination of the tissue obtained at transsphenoidal surgery showed a Rathke's cleft cyst (RCC). To the best of our knowledge, this is the first case report of mosaic Klinefelter's syndrome accompanied by symptomatic RCC, type 2 diabetes mellitus and low renin essential hypertension.

Key words: Rathke's cleft cyst, Klinefelter's syndrome, Partial diabetes insipidus, Type 2 diabetes mellitus, Low renin essential hypertension

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KLINEFELTER'S syndrome (KS) is a well-recognized form of male hypogonadism and feminization related to aberration of sex chromosomes, which is characterized by small, firm testes, azoospermia, gynecomastia and elevated levels of plasma gonadotropins [1]. Chromosomal analysis of patients with KS commonly reveals a 47, XXY karyotype, although mosaicism occurs in about 20% [2]. In addition to the manifestation of gonadal insufficiency, dysfunction of the hypothalamus, pituitary, thyroid and endocrine pancreas has been found in this syndrome [3–5].

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On the other hand, Rathke's cleft cysts (RCCs) are usually asymptomatic. They are observed in 12–33% of normal pituitary glands in routine autopsies [6–9]. Symptomatic RCCs, however, are very uncommon [10, 11]. Goldzieher [12] presented first autopsy findings in a patient who had clinical symptoms arising from the cystic enlargement. Until 1977 only 35 cases had been reported [10], but by 1992 the number of histologically confirmed RCCs had more than doubled (87 cases) [13]. This recent increase in the incidence of diagnosed RCCs is attributed to the prevalence of magnetic resonance imaging (MRI) [14].

In the present report, we describe an uncommon case of mosaic KS associated with RCC, which presumably caused a variety of endocrinological abnormalities.

Case Report

A 46-year-old Japanese male was referred to our hospital for the evaluation of severe hypertension (218/126 mmHg) in July 1996. He was married yet infertile and his general appearance seemed eunuchoidal. Therefore, a question of Klinefelter's syndrome was raised and chromosomal analysis in peripheral venous blood specimen was performed. The result showed that his karyotype was 46, XY/47, XXY, which confirmed Klinefelter's syndrome with mosaic form of karyotype. The patient was readmitted on December 1996 for further study.

On admission, the patient, 173 cm in height weighing 81.5 kg, had a eunuchoidal habitus (total arm span 175 cm, with an upper half to lower half ratio of 0.9). His blood pressure was 200/120 mmHg and pulse rate 67/min. There was no gynecomastia, and the olfactory sense was normal, but his visual acuity was diminished with vision on the right 20/40 and on the left 20/40. Pubic hair showed a female type distribution. Testes were 1.5 × 1 × 1 cm in size and phallus 3 cm in length. Laboratory examinations including biomedical variables showed within normal limits. Urinalysis was also normal with specific gravity of 1.017. However, fasting plasma glucose and serum triglycerides elevated to 127 mg/dl and 378 mg/dl, respectively. Serum glycosylated hemoglobin A_1c (HbA_1c) was high (7.6%; normal range, 4.3–5.8%).

Endocrinological examination revealed low levels of testosterone (<5.0 ng/dl), estradiol (<10 ng/ml), LH (<0.5 mIU/ml) and FSH (0.9 mIU/ml) in serum, indicating hypogonadotropic hypogonadism. The other basal hormone levels are shown in Table 1.

Table 2 summarizes the major results of endocrinological dynamic tests. Poor responses were observed of serum LH, FSH, TSH, PRL and GH as

Table 1. Basal hormone values of the patient

Pituitary
GH = 0.14 ng/ml (<0.42), ACTH = 44 pg/ml (9–52), TSH = 1.8 μg/ml (0.24–3.70), PRL = 120 ng/ml (15–97), ADH = 0.9 pg/ml (0.3–3.5)
Thyroid
free triiodothyronine = 2.1 pg/ml (2.4–4.3), free thyroxine = 0.8 ng/dl (0.9–1.8)
Adrenal
cortisol (09:00) = 1.6 μg/dl (4.0–18.3), adrenaline = 16 pg/ml (<100), noradrenaline = 50 pg/ml (100–450), DHEAS <20 ng/ml (400–3,500), urinary 17-hydroxycorticosteroid = 2.5–3.7 mg/day (3.4–12.0), urinary 17-ketosteroid = 2.6–3.9 mg/day (4.6–18.0), urinary cortisol 15 μg/day (30–100), urinary adrenaline = 6.4–9.7 μg/day (3.0–15.0), urinary noradrenaline = 42.1–104.3 μg/day (26.0–121.0)

Figures in parentheses indicate ranges of normal values in our laboratory.
DHEAS = dehydroxy epiandrosterone sulfate.

Table 2. Responses to several stimuli of the pituitary, adrenal and pancreatic endocrine secretion

TRH test

Time (min)	0	30	60	90	120
TSH (μU/ml)	1.2	9.6	9.8	9.2	7.6
PRL (ng/ml)	15	26	23	20	20

CRH test

Time (min)	0	15	30	60	90	120
ACTH (pg/ml)	36	310	180	150	130	70
Cortisol (μg/dl)	2.8	6.0	8.2	11.4	13.2	11.5

GRH test

Time (min)	0	30	60	90	120
GH (ng/ml)	0.15	3.69	4.13	2.75	0.86

LH-RH test

Time (min)	0	30	60	90	120
LH (mIU/ml)	<0.5	<0.5	0.6	0.6	0.5
FSH (mIU/ml)	0.9	1.2	1.7	1.7	1.8
LH (mIU/ml)*	<0.5	11	10	9.9	7.7
FSH (mIU/ml)*	3.1	6.2	5.9	8.2	7.8

*Values after 8 days of LH-RH priming (400 μg/day)

Insulin tolerance test

Time (min)	0	30	60	90	120
GH (ng/dl)	0.09	0.12	0.10	0.08	0.08
ACTH (pg/ml)	15	14	17	18	13
Cortisol (μg/dl)	2.5	2.2	2.6	2.8	3.0
Glucose (mg/dl)	101	40	53	89	108

75 g oral glucose tolerance test

Time (min)	0	30	60	90	120
Glucose (mg/dl)	127	185	259	272	226
IRI (μU/ml)	5.1	16.1	30.0	36.2	22.0

well to their appropriate stimuli. ACTH responded exaggeratedly to CRH with a delayed response of plasma cortisol. Urinary excretion of cortisol was low (15 μg/day; normal range, 30–100 μg/day) and increased markedly to 2250 μg/day after a bolus intramuscular injection of synthetic $ACTH_{1-24}$ (1 mg /day for 3 days). An hCG loading test (5000 U/day for 3 days, intramuscular injection) resulted in no response of serum testosterone. After 8 days of LH-RH priming (400 μg/day), both FSH and LH increased only slightly.

Insulin-induced hypoglycemia (regular insulin 0.1 U/kg, intravenous injection) failed to increase serum cortisol, GH or ACTH levels. A 75 g oral glucose tolerance test revealed a diabetic pattern.

Serological studies including autoantibodies against thyroid, pituitary, and adrenal were all negative. Anti-glutamic acid decarboxylase antibodies and islet cell antibody were also negative.

A water-deprivation test was performed while the patient was receiving hydrocortisone (40 mg/day) and levothyroxine sodium (50 μg/day). Baseline plasma osmolality was 285 $mOsm/kgH_2O$, while the urine osmolality was 398 $mOsm/kgH_2O$. Seventeen hours after water deprivation, the urine output was 800 ml and 3% loss of body weight occurred at that time. Although the plasma osmolality increased to 297, the simultaneous urine osmolality increased to only 467 $mOsm/kgH_2O$. One hour after subcutaneous injection of 5 units of vasopressin, the urine osmolality increased to 611 $mOsm/kgH_2O$ yet plasma osmolality remained unaltered. These results are consistent with the diagnosis of centrally mediated partial diabetes insipidus.

Both urinary and plasma catecholamines were within the normal limits. Baseline PRA was extremely low (<0.1 ng/ml/h; normal range, 0.3–2.9 ng/ml/h) and plasma aldosterone concentration (PAC) was 6.1 ng/dl (normal range, 3.0–15.9 ng/dl). Both PRA and PAC were unchanged after intravenous injection of furosemide (1 mg/kg) and upright posture for 2 h. These results together with plasma cortisol value indicated etiologically that hypertension of this patient was primary, i.e. low-renin type of essential hypertension.

Although skull radiography was normal, computed tomography of the brain revealed a cystic mass in the intra- and suprasellar regions. On MRI this lesion showed a marked "hyperintensity" in the brain on T_1 weighted images (Fig. 1a), and focal "hypointense" component was seen in the posterio-inferior part of the region on T_2 weighted images (Fig. 1b). Ring enhancement was not shown after gadolinium-diethylenetriamine penta-acetic acid (Gd-DTPA) administration. The pituitary gland was examined by contrast enhancement and was better visualized with Gd-DPTA (Fig. 1c). Neuroophthalmological examination with Humphrey instruments showed a bitemporal hemianopsia, consistent with optic chiasm compression.

Transsphenoidal surgery was carried out on February 1997. The cyst contained yellowish fluid. A solid, cholesterin-like material was found in the posterio-inferior part of the cyst, corresponding to the above mentioned "hypointense" component. Histological examination confirmed RCC consisting of a single layer of cuboidal epithelium (Fig. 2).

The postoperative course was uneventful. His vision improved rapidly and he was discharged with vision on the right 20/30 and on the left 20/30, in addition to the visual fields. However, hypopituitarism persisted. The appropriate hormone replacement (levothyroxine sodium 50 μg/day and hydrocortisone 15 mg/day) induced biochemical normalization and clinical improvement. This patient was subsequently

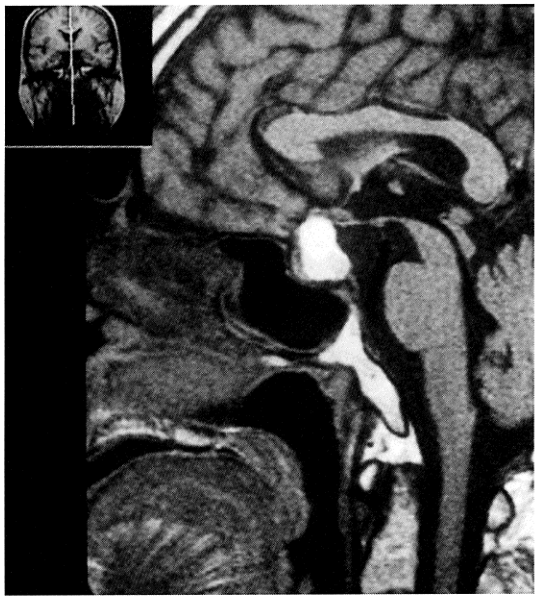

Fig. 1a. Sagittal T_1-weighted MR images showing a high intense intra- and suprasellar mass and a focal isointense component in the posterio-inferior part of the lesion.

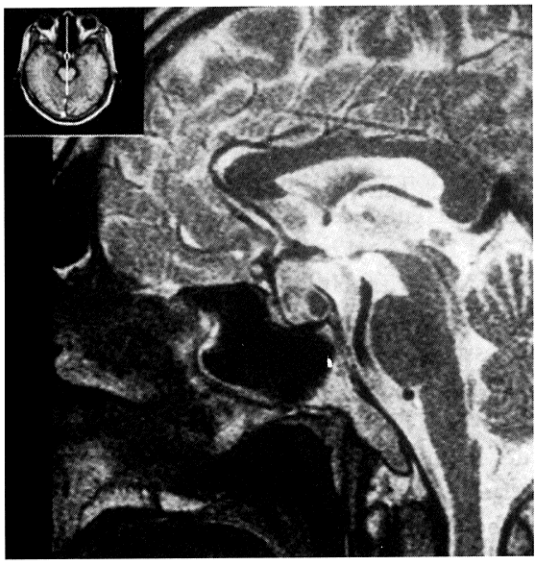

Fig. 1b. Sagittal T_2-weighted MR images showing an isointense intra- and suprasellar mass and a focal low intense component in the posterio-inferior part of the lesion.

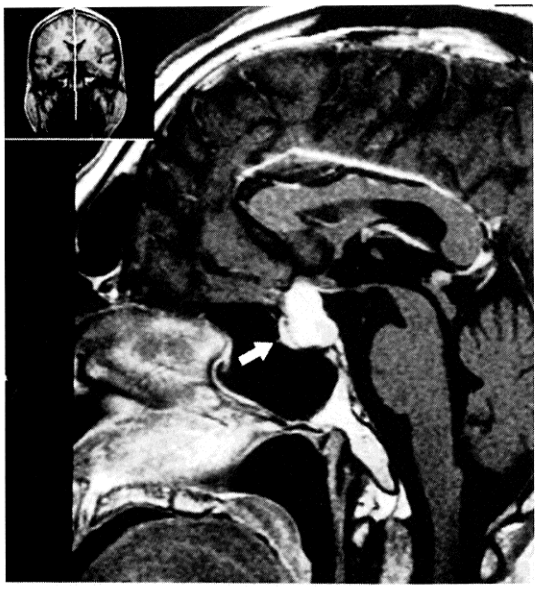

Fig. 1c. Sagittal T_1-weighted MR images after Gd-DTPA administration showing enhancement of the partially compressed pituitary gland (arrow) but not the lesion.

treated as an out-patient. For about 5 years, diabetes mellitus has been controlled well by diet alone as judged by HbA_1c (5.8–6.2%). In addition, antihypertensive drugs, a calcium entry blocker nifedipine (40 mg/day) and an angiotensin-converting enzyme inhibitor, temocapril hydrochloride (1 mg/day), resulted in a marked improvement of hypertension; blood pressure ranged from 122/70 to 134/84 mmHg on the regimen.

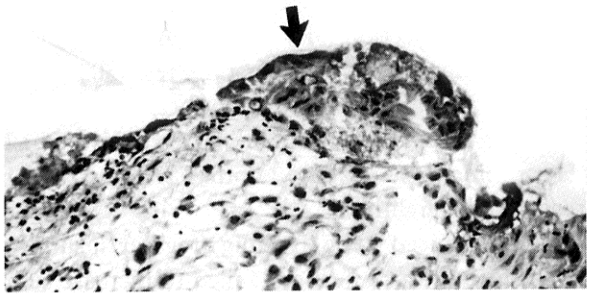

Fig. 2. Light photograph showing the cyst wall lined by a single layer of cuboidal epithelium (arrow). (Hematoxylin and eosin stain, × 400)

Discussion

The patient clearly demonstrated the features which have been diagnosed as non-reported RCC accompanied with panhypopituitarism, partial diabetes insipidus, type 2 diabetes mellitus, low renin essential hypertension and mosaicism KS. While these abnormalities have been previously described singly in individual patients, coexistence of such the multiple disorders occurring in the same patient has never been reported.

On the other hand, patients with KS are well recognized to have several accompanying endocrine and /or metabolic disorders involving the pituitary and thyroid [3–5]. As to metabolic disorders, type 2 (non-insulin dependent) diabetes mellitus is the most common complication in KS [15], as observed in our patient.

Our patient showed a 46, XY/47, XXY mosaicism. The incidence of mosaicism is reported approximately 10% of the patients with KS, estimated by the chromosomal karyotype of peripheral blood leukocytes. The physical manifestation of the mosaic form is usually less severe than that with the non-

mosaic form (i.e., 47, XXY karyotyope) and the testes of KS with mosaic form have been found to be almost normal in size [16] as observed in our patient. The endocrine abnormalities are also less severe, and either gynecomastia or azoospermia is less common. Some patients with the mosaic form may even be fertile [17]. In some cases, KS may not be suspected because of the minor degree of the associated abnormalities.

Our patient showed a large RCC. In this context, the pituitary fossa has been reported to be abnormally large in KS patients [18]. The etiology and exact relationship between the large RCC and enlarged fossa remains obscure. Chronic hypersecretion of gonadotropin due to primary hypogonadism could partly explain the hypertrophic alternation of the tissue.

The number of cases of KS associated with hypopituitarism seems to be greater than would be expected from a chance association of the two entities. Investigators [19–27] have suggested that the failure of hypothalamic or pituitary function might be related to a congenital defect in the central nervous system. The clinical relevance to endocrine dysfunction of the complex sex chromosomal mosaicism found in our patient is uncertain. Of the 9 cases associated with hypothyroidism quoted above [19–27] where karyotype analysis was carried out, 4 were mosaics (XY/XXY for 3 and XXY/X/XY for one).

Observations on randomly examined pituitary glands at autopsy have shown the incidence of small (less than 7 mm in diameter) RCCs to be between 13% and 33%. These are unsymptomtic [10]. RCCs are rarely symptomatic even when they are greater than 1 cm in diameter [10]. In some cases they are responsible for hypopituitarism, visual defects and headache [10, 11, 13, 28, 29] when a pituitary mass has reached an extrasellar level.

Hyperprolactinemia [30] and diabetes insipidus [31] have been described in patients with lesions involving the stalk. Preoperative hormonal studies reported in the previous review show that 46.4% of the cases have a variety of hormonal abnormalites to a lesser or greater extent [9, 13, 32]. These include hyperprolactinemia (the most common finding), gonadotropin deficiency, panhypopituitarism, hypothyroidism, and hypocorticoidism.

Our patient was somewhat unique in that he presented symptoms of endocrine dysfunction and exhibited multiple pituitary abnormalities including secondary adrenal insufficiency, hypogonadotropic hypogonadism, hyperprolactinemia, and partial diabetes insipidus. In addition, low peripheral thyroid hormones in conjunction with a delayed peak of TSH after administration of TRH suggested mild secondary hypothyroidism. Although the exact cause of the abnormalities remains to be determined, hypothalamic dysfunction is most likely responsible. This idea is supported by the following findings: 1) primary hypothalamic location of cyst, 2) presence of partial diabetes insipidus, 3) hyperprolactinemia presumably due to diminished delivery of prolactin-inhibitory factor(s) from the hypothalamus, 4) delayed peak response of TSH after administration of TRH, 5) markedly enhanced responses of plasma ACTH to CRH and ITT in association with low levels of plasma cortisol, and 6) deteriorated response of gonadotropin to LH-RH after LH-RH priming. Considering the typical elevation of serum LH and FSH levels in KS, the decreased basal serum gonadotropin level in our patient was indicative of the presence of severe hyposecretion.

RCC arises from the remnants of Rathke's pouch, and is formed by a single layer of ciliate cuboidal or columnar epithelium, often with interspersed mucin secreting goblet cells [33, 34]. When symptomatic, it is usually successfully operated by simple drainage and partial excision of the wall [13, 29]. Inflammation [35] and mechanical compression [13] of the pituitary gland may play an important role in causing pituitary dysfunction in patients with RCC. In our case, visual disturbances recovered relatively soon, but panhypopituitarism did not recover even after surgery, implying that pituitary dysfunction is irreversible if the pituitary is severely injured.

Finally, we emphasize that men presenting with hypogonadism accompanying KS should be investigated in sufficient detail to exclude the possibility of associated hypopituitarism due to space occupying lesions.

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