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 eueneuchoidal body habitus. Chromosomal analysis revealed a 46, XY/47, XXY karyotype. Serum LH, FSH and testosterone levels were low, indicating hypogonadotrophic 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, azospermia, 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].

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 re-admitted 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 x 1 x 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 A1c (HbA1c) 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>
<thead>
<tr>
<th>Table 1. Basal hormone values of the patient</th>
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<tr>
<td>Pituitary</td>
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<tr>
<td>GH = 0.14 ng/ml (&lt;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)</td>
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<tr>
<td>Thyroid</td>
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<td>free triiodothyronine = 2.1 pg/ml (2.4-4.3), free thyroxine = 0.8 ng/dl (0.9-1.8)</td>
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<tr>
<td>Adrenal</td>
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<td>cortisol (09:00) = 1.6 µg/dl (4.0-18.3), adrenaline = 16 pg/ml (&lt;100), noradrenaline = 50 pg/ml (100-450), DHEAS &lt;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 = 421-104.3 µg/day (26.0-121.0)</td>
</tr>
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</table>

Figures in parentheses indicate ranges of normal values in our laboratory.

DHEAS = dehydroxyepiandrosterone sulfate.
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 in-
tramuscular injection of synthetic ACTH₁–24 (1 mg
/day for 3 days). An hCG loading test (5000 U/day
for 3 days, intramuscular injection) resulted in no re-
sponse of serum testosterone. After 8 days of LH-
RH priming (400 μg/day), both FSH and LH in-
creased 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/kgH₂O, while the
urine osmolality was 398 mOsm/kgH₂O. Seventeen
hours after water deprivation, the urine output was
800 ml and 5% loss of body weight occurred at that
time. Although the plasma osmolality increased to
297, the simultaneous urine osmolality increased to
only 467 mOsm/kgH₂O. One hour after subcutane-
ous injection of 5 units of vasopressin, the urine os-
molality increased to 611 mOsm/kgH₂O yet plasma
osmolality remained unaltered. These results are
consistent with the diagnosis of centrally mediated
partial diabetes insipidus.

Both urinary and plasma catecholamines were with-
in 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 indi-
cated etiologically that hypertension of this patient
was primary, i.e. low-renin type of essential hyper-
tension.

Although skull radiography was normal, comput-
ed tomography of the brain revealed a cystic mass in
the intra- and suprasellar regions. On MRI this les-
ion showed a marked “hyperintensity” in the brain
on T₁ weighted images (Fig. 1a), and focal “hypo-
tense” component was seen in the postero-inferior
part of the region on T₂ weighted images (Fig. 1b).
Ring enhancement was not shown after gadolinium-
diethylenetriamine penta-acetic acid (Gd-DTPA)
admnistration. The pituitary gland was examined by
contrast enhancement and was better visualized with
Gd-DPTA (Fig. 1c). Neuroophthalmological examina-
tion with Humphrey instruments showed a biemporal
hemianopsia, consistent with optic chiasm
compression.

Transsphenoidal surgery was carried out on Febru-
ary 1997. The cyst contained yellowish fluid. A
solid, cholesterin-like material was found in the
postero-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 ad-
motion to the visual fields. However, hypopituitarism
persisted. The appropriate hormone replacement
(levothryoxine sodium 50 μg/day and hydrocortisone
15 mg/day) induced biochemical normalization and
clinical improvement. This patient was subsequently

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Fig. 1a. Sagittal T₁-weighted MR images showing a high in-
tense intra- and suprasellar mass and a focal iso-
tense component in the postero-inferior part of
the lesion.
treated as an out-patient. For about 5 years, diabetes mellitus has been controlled well by diet alone as judged by HbA1c (5.8–6.2%). In addition, antihypertensive drugs, a calcium entry blocker nifedi-

pine (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.

**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-

**Fig. 1b.** Sagittal T1-weighted MR images showing an iso-intense intra- and suprasellar mass and a focal low intense component in the posterior-inferior part of the lesion.

**Fig. 1c.** Sagittal T1-weighted MR images after Gd-DTPA administration showing enhancement of the partially compressed pituitary gland (arrow) but not the lesion.

**Fig. 2.** Light photograph showing the cyst wall lined by a single layer of cuboidal epithelium (arrow). (Hematoxylin and eosin stain, ×400)
mosaic form (i.e., 47, XXY karyotype) 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 fer-
tile [17]. In some cases, KS may not be suspected
because of the minor degree of the associated abnor-
malities.

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

The number of cases of KS associated with hypo-
pituitarism 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 dysfunc-
tion 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 unsymptomatic [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 extracellular 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 abnormalities to
a lesser or greater extent [9, 13, 32]. These include
hyperprolactinemia (the most common finding),
gonadotropin deficiency, panhypopituitarism, hypo-
thyroidism, and hypocorticoidism.

Our patient was somewhat unique in that he pre-
vented symptoms of endocrine dysfunction and ex-
hibited multiple pituitary abnormalities including
secondary adrenal insufficiency, hypogonadotropic
hypogonadism, hyperprolactinemia, and partial dia-
abetes 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) de-
layed peak response of TSH after administration of
TRH, 5) markedly enhanced responses of plasma
ACTH to CRH and ITT in association with low lev-
els 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 gonado-
tropin 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 ciliated 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]. Inflam-
mation [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 ir-
reversible if the pituitary is severely injured.

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

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References


