

## Graves' Disease Associated with Klinefelter's Syndrome

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Klinefelter's syndrome is one of the most common forms of primary hypogonadism and infertility in males. It is characterized by small and firm testes, gynecomastia, azoospermia, and an elevated gonadotropin level. The frequencies of diabetes mellitus, breast cancer, and germ cell neoplasia increases in Klinefelter's syndrome. We report upon a 35 year-old male patient with Graves' disease in association with Klinefelter's syndrome; as confirmed by chromosome analysis. The patient is being treated with antithyroid medication for Graves' disease and by testosterone replacement for Klinefelter's syndrome.

**Key Words:** Klinefelter's syndrome, Graves' disease, primary hypogonadism

### INTRODUCTION

Klinefelter's syndrome is the disease that most frequently causes primary hypogonadism in men, and was first reported in 1942 by Klinefelter, et al.<sup>1</sup> Klinefelter's syndrome, which is caused by a structural sex chromosome abnormality, shows hypogonadism, eunuchoidism, gynecomastia, and so on, and has the endocrinological characteristics of reduced testosterone and a GnRH increase. Klinefelter's syndrome carries a high risks of breast cancer, psychiatric disorder, learning disorder, and osteoporosis, and higher frequencies of systemic lupus erythematosus, rheumatoid arthritis, and Sjogren's syndrome. In addition, the

incidence of endocrinological diseases like diabetes and thyroid disease is higher than normal.<sup>2</sup>

In cases of Klinefelter's syndrome combined with thyroid disease, the thyroid function is normal for the most part. However, Klinefelter's syndrome has also been reported rarely to be associated with hyperthyroidism. Therefore, we report a case of a 35-year-old male patient diagnosed as having Klinefelter's syndrome combined with Graves' disease.

### CASE REPORT

A male patient aged 35 was admitted to our hospital due to a 6 kg weight loss over several months and palpitations. At the time of birth, his father was 34 years old and his mother 28 years old. His history showed that in childhood he suffered growth retardation and a learning disorder due to mental retardation. His secondary sexual characteristics didn't appear but no medical help was ought. There was no relevant family history. He had married 3 years previously but had no child.

On physical examination his height was 162 cm, weight 63 kg, body mass index 24 kg/m<sup>2</sup>, arm span 175 cm, length of pubis to the planta pedis was 87 cm, and length from pubis to the parietal area was 88cm. At the time of admission, his blood pressure was 120/80 mmHg, body temperature 36.4°C, respiration rate 19 times per minute, and pulse rate 102 times per minute. He looked acutely ill, and had neither anemic conjunctiva nor icteric sclera. Exopthalmos, beard, hirci, and pubes were absent. Physical examination of the neck, showed neither goiter nor bruit in the thy-

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roid gland. Gynecomastia was absent and no abnormal finding was evident by physical examination of the thorax or abdomen. Testicular volume of both testes was as low as 2 mL, and the penile length was 2 cm and had been implanted with a silicon brace (Fig. 1).

Laboratory findings on a peripheral blood smear at the time of admission were; hemoglobin 12.1 g/dL, hematocrit 36.2%, WBC count 7,560/mm<sup>3</sup>, and platelets 256,000/mm<sup>3</sup>. A biochemical analysis of serum revealed; calcium 10.0 mg/dL, phosphorus 4.8 mg/dL, glucose 102 mg/dL, BUN 10.5 mg/dL, creatinine 0.5 mg/dL, protein 6.2 g/dL, albumin 3.4 g/dL, total bilirubin 0.7 mg/dL, GOT 18 IU/L, GPT 31 IU/L, and alkaline phosphatase 178 IU/L. Serum thyroid hormone level showed that T3 was 615.3 ng/dL, FT4 > 7.8 ng/dL, TSH < 0.01 (IU/mL, TSH receptor antibody 18.2% (normal range 0-10%), antimicrobial antibody 1:6400 positive, and antithyroglobulin antibody negative. Serum testosterone was down to 1.0 ng/mL, and estradiol was 24.1 pg/mL, which is within the normal range. LH level was elevated to 15.2 mIU/mL and the FSH level to 31.9 mIU/mL.

Electrocardiography showed sinus tachycardia, and the chest X-ray was normal. A Tc 99 thyroid scan showed diffuse enlargement and increased uptake in both lobes (Fig. 2). By bone densito-

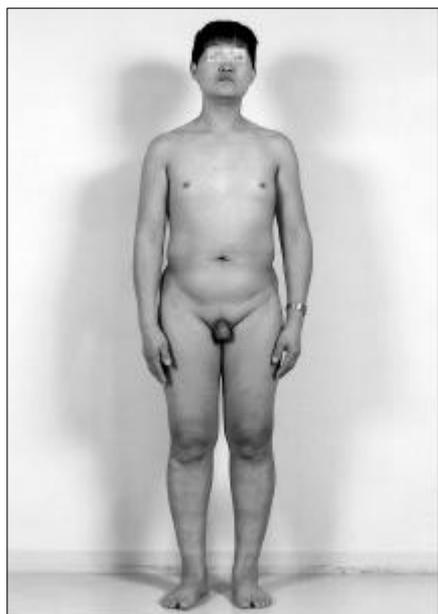


Fig. 1. Clinical photography. The small penis, diminished pubic hair and sparse body hair.

metry measured using DEXA, the T score of the lumbar spine was -3.3 and of the femur was -2.7. A chromosomal study showed 47 XXY (Fig. 3).

After being diagnosed as Klinefelter's syndrome with Graves' disease, this patient has been placed under antithyroid and osteoporosis medication, and testosterone replacement therapy for Klinefelter's syndrome. Thyroid function 1 month after therapy on an outpatient basis improved and showed T3 245.9 ng/dL, TSH 0.01  $\mu$ IU/mL, and

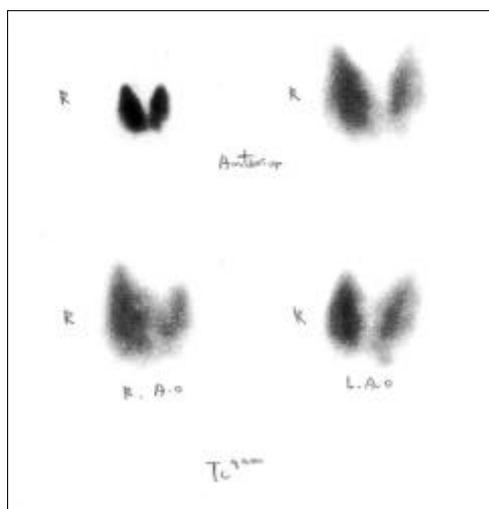


Fig. 2. Technetium 99 thyroid scan. The Tc 99 thyroid scan revealed increased mild diffuse goiter uptake.

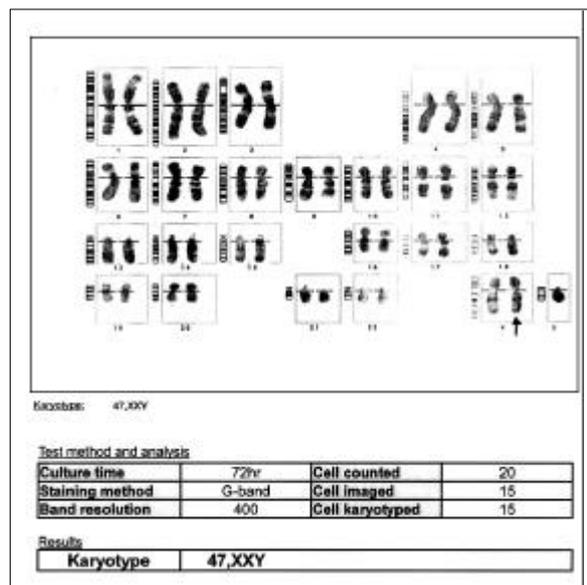


Fig. 3. Chromosomal study showing 47, XXY chromosome anomaly.

FT4 2.9 ng/dL.

## DISCUSSION

In 1942 Klinefelter first reported 9 cases of Klinefelter's syndrome, which showed gynecomastia, azoospermia, without Leydig cell defect, small sized testes, and the increased secretion of FSH in urine.<sup>1</sup> In 1959 Jacobs and Strong discovered that this syndrome has 47 chromosomes (XXY),<sup>3</sup> though 48 (XXYY), 48 (XXXY) and 49 (XXXXY) have also been reported.<sup>4-6</sup> In Korea, Song, et al. reported upon various chromosomal findings in Klinefelter's syndrome.<sup>7</sup>

Klinefelter's syndrome is the most frequent cause of male gonadal failure and is characterized by the presence of 47 chromosomes (XXY). It is known to occur in one out of 500 male births. Typical physical findings are a tall stature, eunuchoidism, gynecomastia, decreased testis size, decreased facial and pubic hair follicles, and mental retardation in 10% of cases. Laboratory findings may show decreased testosterone and increased gonadotropin.<sup>8</sup> However, our patient had a short stature and some features typical of Klinefelter's syndrome, such as eunuchoidism, and gynecomastia, were absent; however, Klinefelter characteristics like a reduced testicular size, hypergonadotropic hypogonadism, and 47, XXY by chromosomal study were evident. In addition, Klinefelter's syndrome is usually combined with other diseases. The risks of psychiatric disorder, learning disorder, osteoporosis, varicocele, and deep vein thrombosis are higher, and primary hypothyroidism,<sup>3</sup> diabetes,<sup>9,10</sup> breast cancer,<sup>11,12</sup> prostate cancer, bladder cancer, leukemia, malignant lymphoma, adrenal malignancy, thyroid cancer, lung cancer, seminoma, mediastinal germ cell tumor, and medulla oblongata germinoma have been reported with Klinefelter's syndrome.<sup>13-16</sup> Congenital heart disease is also known to be frequently associated, and Ferguson-Smith reported that congenital heart disease is 4-5 times more likely to arise in Klinefelter's syndrome than in the general population.<sup>17</sup> Rao, et al. reported Klinefelter's syndrome combined with a double outlet right ventricle, atrial and ventricular septal defect, and patent ductus arteriosus, respectively,

and Rohde, et al. reported Klinefelter's syndrome combined with atrial septal defect.<sup>18,19</sup>

Additionally, the frequencies of autoimmune diseases, such as lupus, Sjogren's syndrome, and rheumatoid arthritis are known to be increased, which are thought to be due to the sex hormone abnormality. In Klinefelter's syndrome, chronic estrogen stimulation could arise due to its metabolism,<sup>20,21</sup> and testosterone injections decrease the CD4/CD8 ratio, the level of anti-nuclear antibody, and the titer of rheumatoid factor, and clinical improvements have been reported.<sup>22,23</sup>

Burt, et al. reported in 1954 the first case of thyroid microfollicular adenoma combined with Klinefelter's syndrome, providing a connection between Klinefelter syndrome and thyroid disease.<sup>24</sup> Barr, et al. reported [<sup>131</sup>I] uptake reduction and a reduced response to TSH in 15 patients with Klinefelter syndrome and added that the majority of reports issued found that thyroid disease associated with Klinefelter's syndrome showed an euthyroid state, an iodine uptake reduction, and a reduced response to TSH.<sup>25</sup> In 1965, Green and Singer, et al. first reported upon the association between Klinefelter's syndrome and hyperthyroidism, and subsequently Klinefelter's syndrome with Graves' disease has been rarely reported.<sup>26-29</sup> Davis, et al. reported that the extra X chromosome of Klinefelter's syndrome is connected with thyroid dysfunction, and that this dysfunction deteriorates depending on the number of X chromosomes.<sup>30</sup> On the other hand, Plunkett found that number of X chromosomes is not related to thyroid function.<sup>31</sup> Many papers have suggested that Turner syndrome is associated with thyroid dysfunction, like Klinefelter's syndrome. Engel and Forbes, et al. demonstrated the deletion of the short arm of X chromosome as the cause of autoimmune thyroid disease.<sup>32</sup> The X chromosome abnormality itself seems to contribute to the development of thyroid disease, but the specifics of the mechanism are unknown.

The case described is in the course of recovery due to antithyroid medication for the Graves' disease and testosterone replacement for Klinefelter's syndrome. Testosterone replacement does not affect infertility and gynecomastia, but leads to secondary sexuality, by improving the symptoms of androgen deficiency, and increases bone

density, it also has a positive effect on mood, and activity, and improves muscle mass.<sup>2</sup>

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