

A case of Graves' disease associated with Klinefelter's syndrome**Hong LI^{1*}, Yi-li LUO¹, Sharvan RAMPERSAD¹, Peng Yang¹, Chun-yan Li¹, Xiao-li Zhang¹, Chun-jun Sheng¹, Le Bu¹, Fei Yu², Shen Qu¹**¹Department of Endocrinology, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai 200072, China²Department of Nuclear Medicine, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai 200072, China***Corresponding author**

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Abstract: This is the first time a case of Graves' disease associated with Klinefelter's syndrome is being reported in a Chinese patient. We report the case of a 41-year male patient who was diagnosed as Graves' disease with Klinefelter's syndrome. The patient, a known 10-year history of hyperthyroidism, presented with an increase in the severity of his symptoms, which were hyperhidrosis, palpitations, and heat intolerance, together with the appearance of fine finger tremors, with some feminizing features such as feminine voice, absent laryngeal prominence and beard, smaller than normal testes. Chromosomal study (47, XXY) confirmed the diagnosis of Klinefelter's syndrome.**Keywords:** Graves' – Klinefelter's syndrome – hyperthyroidism.

INTRODUCTION

Graves' disease is one of the most common thyroid diseases in human, and it represents 50 to 80% of all thyrotoxicosis cases. It is an autoimmune disorder resulting in an overproduction of thyroid hormones, frequently associated with goiter. Klinefelter's syndrome (KS), also known as Congenital Testicular Dysgenesis Syndrome, with the chromosomal study (47XXY), is one of the commonest types of congenital chromosomal disorder in males. It has an incidence of 1.72 per 1000 male births [1], causing hypogonadism and infertility. This genetic disorder is characterized by having at least an excess X chromosome to the normal male chromosomes (XY), such as 47XXY, 48XXXY or 49XXXXXY. The excess X chromosome causes a blunting in the expression of the male characteristics, thus giving rise to the feminine features. It is often associated with congenital malformation or some organ dysfunction. The possibility that a patient suffers from both Graves' disease and KS is extremely rare, only a few cases have been reported till date. Here, we are reporting the case of a 41-year-old male patient diagnosed as Graves' disease associated with Klinefelter's syndrome, and it is the first report of a Chinese patient having these two conditions.

CASE REPORT

We are reporting the case of a 41-year-old male patient, a known case of hyperthyroidism on methimazole, who attended our hospital with the complaints of hyperhidrosis, palpitation, heat

intolerance and fine hand tremors for the past 6 months. However, his symptoms have been more serious since 1 month after he had a common flu. The patient has been off any medicines for the past 6 months, which correlates with the appearance of his symptoms. The patient had similar symptoms, except for the fine hand tremors, 10 years before and he was then diagnosed as hyperthyroidism. He was given methimazole. Unfortunately, the patient was not regular with his treatment. His past medical history reveals he had a 14 year old history of bronchial asthma. In addition, he was found genitalia agenesis after adolescence and never did medical inspection. His intelligence was normal. His family history was not relevant; no consanguinity, no thyroid disorder, no KS was noted. From his social history, it was noted that he was unmarried and childless. On admission, his blood pressure was 150/95 mmHg, his pulse rate was 130 beats per minute, his respiratory rate was 22 times per minute, his temperature was 36°C. His B.M.I. was calculated as 15.37 kg/m² from a height of 190cm and a weight of 55.5 kg. The patient was conscious and alert. He had moist skin. The patient was found to be having a feminine voice with no beard or laryngeal prominence. No exophthalmos was noted. His neck examination revealed a Grade 3 thyroid enlargement without any tenderness or bruit. He had sparse axillary hair and had a feminine pubic hair distribution. Pulmonary, cardiac and abdominal examinations were normal. The length of his penis was 4cm, the volume of his testes were 3-4mL (GAI[2] et al reported that penis length was

6.27±0.83cm in the fertile group and testicular volume was 17.54±3.41mL), and with his feminine pubic hair distribution, his genitals were graded as Tanner G2[3] according to the Tanner Staging.

Laboratory findings at the time of admission: biochemical analysis of serum showed that liver function and kidney function were within normal range. Free fatty acid was 0.90mmol/L (NR: 0.1-0.6mmol/L) while other blood lipid levels were within normal range. Random blood glucose level was 12.5mmol/l (NR:<11.1mmol/L). Thyroid hormones were elevated with TT3 being 6.35nmol/L (NR:1.2-3.4nmol/L), TT4 being 311.9nmol/L (NR: 54-174nmol/L), FT3 being 20.9pmol/L (NR:3.5-6.5pmol/L), FT4 being 51.89pmol/L (NR: 10.2-31pmol/L), TRAb >40IU/L(NR:0-1.75IU/L), TPOAb>340IU/L (NR :< 40IU/L) and reverse triiodothyronine (r-T3) being 2.42 ng/ml (NR: 0.16-0.95 ng/ml) and a suppressed TSH level of 0.006mU/L (NR:0.35-5.5mU/L). Serum testosterone level was decreased (1.0 nmol/L; NR:9.9-27 nmol/L) while the serum estradiol (76.6 pmol/L; NR:28-156pmol/L) and progesterone (0.84nmol/L; 0.7-4.3pmol/L) levels were within the normal range. FSH and LH levels were both elevated to 25.08 IU/L (NR: 1.5-12.4IU/L) and 19.45IU/L (NR: 1.7-8.6IU/L) respectively.

Radioactive iodine (¹³¹I) uptake in the thyroid gland was 53.3% after 2 hours, and was 64.1% after 24 hours. Thyroid ultrasound showed diffuse enlargement in both lobes. According to the formula for estimating thyroid individual lobe volume[4], the volume of the left lobe was 31.02ml, and the right lobe 35.51ml. Testes ultrasound showed right testis 28×13×18mm and left testis 26×14×17mm. Chromosomal study showed the presence of 47 XXY (as showed in fig.1).

Treatment:

As per the results obtained, the patient was diagnosed with Graves' disease in thyrotoxicosis, associated with KS. As patient was in a thyrotoxic state, he needed rapid relief. However, his drug compliance was poor. Hence radioactive iodine was deemed as the treatment of choice. He was given a dose of 11mCi of ¹³¹I. For KS, he was given Andriol testocaps, 40mg bid. He was given a review after 1 month and after 3 months. When he attended hospital after 3 months, his serum thyroid hormones levels were still above normal. He was then given methimazole 10 mg bid, and was again reviewed in 1 month. His serum thyroid hormones levels were now almost near normal values.

DISCUSSION

Klinefelter first reported KS and named it in 1942[5]. Many patients suffering from KS remains undiagnosed or not promptly diagnosed [6, 7]. Males

suffering from KS has one or more excess X chromosome, which inhibits the maturation of convoluted seminiferous tubules of testis resulting in its degeneration. The more X chromosomes present, the more serious are the symptoms [8].

Most patients suffering from KS have small hard testes [9], delicate skin, decrease muscle tonicity, mammary gland development, short penis, unobvious laryngeal prominence, no or little beard and axillary hair, or female pubic hair distribution [10]. Furthermore, KS is often combined with other diseases[11-21], such as mental retardation, congenital malformations and teratoma. KS has no definite cure, and medication can be given only to alleviate the symptoms. Androgen is suggested to be given as soon as possible[22, 23], to inhibit FSH in serum without effect on the reproductive ability [24]. Meanwhile, freezing sperm or sperm cell samples provides the possibility of these patients to have their own offsprings later in life[25].

In our patient, he was above average height, with absence of secondary sexual characteristics. His serum testosterone level was markedly decreased while his FSH level was increased, with the result of his chromosomal study confirming the diagnosis of KS. Then he was prescribed Andriol testocaps 40mg bid. The resulted increase in serum testosterone cause a regression in the feminizing features, while causing the appearance of some masculinizing features, such as appearance of beard, axillary hair, and to some extent an increase in libido.

Hyperthyroidism, if not properly controlled will eventually lead to thyrotoxicosis. This is a life threatening condition and adequate treatment should be promptly started.

In our patient, he had a 10 year history of hyperthyroid, and he was prescribed methimazole. Because of his poor compliance, radioactive iodine (¹³¹I) was chosen as the best option. Even after 3 months, his serum thyroid hormones level was still elevated, there has only been a mild decrease. Hence, he was prescribed methimazole 10mg bid and was reviewed in 1 month. It is then that his thyroid function has returned to an almost normal value.

Till date, only a few cases of thyroid diseases associated with KS have been reported. The first one was a case of KS associated with micro follicular adenoma of the thyroid in 1954. The manifestation of hyperthyroidism with KS is an even rarer occurrence. In PubMed, there are 4 cases of hyperthyroidism associated with Klinefelter's syndrome reported in English. One reported case was of a Caucasian boy of

15 years of age, diagnosed as Klinefelter's syndrome in 1965. His height was 193 cm and weight was 54.9 kg. He had no other obvious symptoms of hyperthyroidism except chest distress [26]. The second one was reported in 1990 about a 41 year old Japanese male [27] while the third one was reported in 2001 about a 35 year old Korean male [28]. These three patients were all 47 XXY. The last case was an extra gonadal germ cell tumor associated with Klinefelter's syndrome and hyperthyroidism [29]. There has been no similar case reported in Chinese.

The mechanism of hyperthyroidism associated with Klinefelter's syndrome is not clear. According to the reported cases, the clinical manifestations of hyperthyroidism associated with KS vary from mild chest distress to typical hyper metabolic symptoms. Thyroid disease associated with KS often showed an euthyroid state, a low iodine uptake and a poor TSH response [26]. The patient in this case had obvious thyrotoxicosis, such as goiter, high iodine uptake rate and elevated TRAb titer, supporting the diagnosis of Graves' disease [30]. Davis believed that the number of extra X chromosomes is related to thyroid dysfunction [31]. Engel pointed that the deletion of the short arm of X chromosomes causes autoimmune thyroid diseases [32]. Like KS, Turner syndrome is frequently associated with thyroid dysfunction [33, 34]. The abnormality of X chromosomes seems to contribute to the development of thyroid disease. However, Plunkett thought that thyroid dysfunction was not influenced by the extra X chromosomes [35]. Up to now, the mechanism has not been discovered.

Following treatment with ^{131}I , it is expected that the thyroid function reaches a near normal value, or is mildly above or below normal, or a marked decrease compared to initially. Given the dose of ^{131}I used was high, it was expected that the thyroid function will decrease considerably. However, only a slight change was noted. Can the presence of KS associated with Graves' disease be the cause why the patient was refractory to the treatment of ^{131}I ? To be able to reach a conclusion, more similar cases have to be analyzed.

CONCLUSION

To conclude, for the time being, there is no updated research or discovery being done about the KS. Graves' disease associated with KS is even rarer, and not many cases have been reported. To better understand this association, more data needs to be collected and analyzed.

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