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# FROM GENETIC HYPOGONADISM TO MASTECTOMY

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*Introduction*. Although it is the most common male gonadal dysgenesis, Klinefelter syndrome (KS) can often go unnoticed due to discrete clinical signs. We present a case of KS with elevated levels of gonadotropins, evaluated in multiple medical centers. *Case presentation*. A 17-year-old patient was admitted for endocrine evaluation due to minimal signs of pubertal development. Clinical examination revealed height of 187 cm, biacromial diameter of 41 cm, bitrochanteric diameter of 35 cm, crown-to-pubis length of 93 cm, pubis-to-floor length of 94 cm, absent facial and cervical hair, bilateral gynecomastia, hyperpigmented scrotum, with both testicles present in the normal position, right testicle volume of 2 ml, left testicle volume of 1 ml, corresponding to Tanner puberty stage G2P3. The hormonal profile showed elevated gonadotropins, testosterone at the lower limit of the normal range, normal estradiol and prolactin levels. Genetic testing revealed a positive Barr test, with 47, XXY karyotype. Breast ultrasound described bilateral gynecomastia with a diameter of 40 mm on the left and 45 mm on the right. Mastectomy and testosterone replacement therapy were recommended. *Conclusion.* Even though testosterone replacement therapy significantly improves the development of secondary sex characteristics, prevents gynecomastia and ensures a normal sex life, infertility is permanent.

*Keywords:* Klinefelter syndrome, gynecomastia, hypogonadism, mastectomy.

## INTRODUCTION

KS is a complex chromosomal condition affecting males, that occurs due to the presence of two or more additional X chromosomes. The incidence of KS is estimated at 1 in 650 males[1,2].

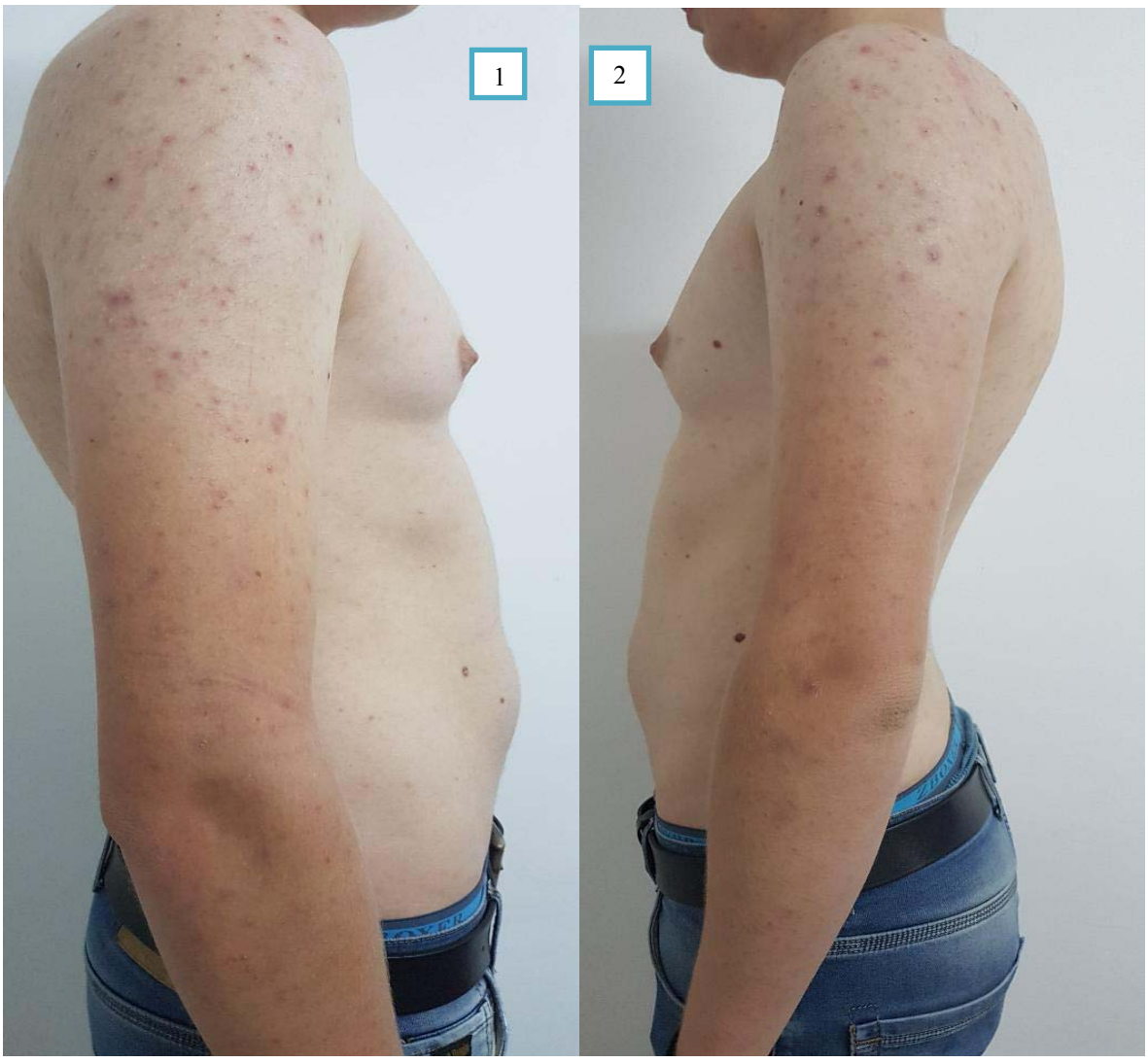
The phenotype associated with XXY karyotype has great variability, but there are some common features such as hypogonadism, gynecomastia, fertility problems, disorders of executive function, tall stature, language-based learning disabilities[3].

Most often, patients with KS have tall stature, small testes, gynecomastia in late puberty, gynoid aspect of hips, sparse body hair, signs of androgen deficiency and low serum testosterone coupled with elevated gonadotropins, and finally azoospermia or oligospermia with hyalinization and fibrosis of the seminiferous tubules[3,4,5].

## CASE PRESENTATION

A 17-year-old non-smoking patient, without significant past medical history, was admitted for endocrine evaluation due to minimal signs of pubertal development and discrete joint pain, predominantly at the level of the knees. Clinical examination revealed height of 187 cm, weight of

74 kg, BMI (body mass index) of 21.2 kg/m$^2$, normal blood pressure of 110/65 mmHg, relatively proportional body segments: biacromial diameter of 41 cm, bitrochanteric diameter of 35 cm, crown-to-pubis length of 93 cm, pubis-to-floor length of 94 cm, absent facial and cervical hair, bilateral gynecomastia, Tanner puberty stage G2P3: hyperpigmented scrotum, with both testicles present in the normal position, right testicle volume of 2 ml, left testicle volume of 1 ml (Figures 1,2). The endocrine profile revealed elevated gonadotropins: LH (Luteinizing Hormone) of 35.2 U/L (normal: 0.8-7.6 U/L), FSH (Follicle Stimulating Hormone) of 72.6 U/L (normal: 1-11.5 U/L), testosterone at the lower limit of the normal range (of 1.8 ng/mL, normal: 1.8–9 ng/mL), normal levels of estradiol and prolactin (Table 1). The patient underwent genetic testing that revealed a positive Barr test with 47, XXY karyotype. Breast ultrasound described bilateral gynecomastia with a diameter of 40 mm on the left and 45 mm on the right. Biochemical workup showed high alkaline phosphatase levels, normal liver function tests and hematological parameters (Table 1). After three months of testosterone therapy (250 mg i.v. testosterone every two weeks), normalization of serum testosterone (of 8.32 ng/ml), lower levels of FSH (of 53.3 U/L) and LH (of 17.7 U/L) were achieved, with no adverse effects on liver function and hematological parameters (Table 1). PSA (anti-prostate specific antigen) levels were also within the normal range (0.72 ng/mL, normal < 4 ng/mL). Mastectomy and continuation of testosterone therapy were recommended.




Figures 1, 2. Bilateral gynecomastia in a 17-year-old boy diagnosed with Klinefelter Syndrome.

*Table 1*

The endocrine and biochemical parameters of a young boy diagnosed with Kninefelter Syndrome: with and without specific medical treatment

| Parameter | Before therapy | 3 month after testosterone therapy | Normal limits | Units |
|---|---|---|---|---|
| Testosterone | 1.8 | 8.32 | 1.8–9 | ng/mL |
| FSH | 72.6 | 53.3 | 1–11.5 | U/L |
| LH | 35.2 | 17.7 | 0.8–7.6 | U/L |
| Estradiol | 25.1 | 31.6 | < 60 | pg/mL |
| Prolactin | 9.24 | 14.3 | 1.8–17 | ng/mL |
| AST | 13.9 | 19 | < 50 | U/L |
| ALT | 19.4 | 23 | < 50 | U/L |
| Alkaline phosphatase | 137 | | 30–120 | U/L |
| Hemoglobin | 13.9 | 15.5 | 13–17 | g/dL |
| Hematocrit | 43.6 | 46.3 | 40–54 | % |
| PSA | 0.68 | 0.72 | < 4 | ng/mL |

## DISCUSSIONS

Current guidelines recommend prescribing testosterone therapy in the majority of KS cases[6].

Despite the lack of studies regarding the effect of testosterone treatment in KS patients, there is a unanimous consent that treatment should be started around puberty for most patients and that the testosterone level should reach values that are placed in the upper side of the normal range[7]. In our patient's case treatment was initiated somewhat later, at the age of 17, due to late referral.

Based on some observational studies, testosterone treatment in patients with KS comes with positive effects such as improved libido, decreased fatigue, improved endurance and strength and also an overall improved mood with less irritability and better sleep[8,9]. After three months of treatment, the patient reported improvement in well-being, increased self-confidence, discrete appearance of facial hair and acne.

Nevertheless, testosterone therapy is not indicated in patients with breast or prostate cancer and symptomatic heart failure[6,10].

Being born with the 47 XXY karyotype has many implications in all aspects of life, such as learning disabilities, poor social integration, infertility and even increased morbidity and reduced lifespan. Although not rare, it is a condition severly underdiagnosed[11,13–16].

Generally delayed puberty in both females and males need to be diferentiated from central hypogonadism related to genetic defects, pituitary tumors including prolactin producting neoplasia[17,18,19]. In males any of these conditions may associate gynecomastia and prolonged lack of testosterone, even treateble, my not reverse the breast chnages and thus surgery is needed[17,18,19].

At present, the patient has completed high school and has an acceptable social integration, although the problem of infertility is not yet fully accepted.

## CONCLUSION

Although testosterone treatment significantly improves the development of secondary sex characteristics, prevents gynecomastia and ensures a normal sex life, infertility is permanent.
Klinefelter syndrome patients have both significant physical symptoms of hypogonadism and neurocognitive, psychosocial and behavioural problems that should be managed as a whole.

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## REFERENCES

1. Bojesen A, Juul S, Gravholt CH. Prenatal and postnatal prevalence of Klinefelter syndrome: a national registry study, J Clin Endocrinol Metab **2003**; 88:622–626.
2. Abramsky L, Chapple J. 47,XXY and 47, XYY: estimated rates of and indication for postnatal diagnosis with implications for prenatal counseling, Prenat Diagn **1997**;17:363–368.
3. Groth KA, Skakkebæk A, Høst C, Gravholt CH, Bojesen A. Klinefelter syndrome – a clinical update, J Clin Endocrinol Metab **2013**;98:20–30.
4. Morris JK, Alberman E, Scott C, Jacobs P. Is the prevalence of Klinefelter syndrome increasing?, Eur J Hum Genet **2008**;16: 163-170.
5. Lanfranco F, Kamischke A, Zitzmann M, Nieschlag E. Klinefelter's syndrome, Lancet **2004**; 364(9430):273–283.
6. Tuttelmann F, Gromoll J. Novel genetic aspects of Klinefelter's syndrome, Mol Hum Reprod **2010**;16: 386-395.

7. Bhasin S, Cunningham GR, Hayes Fj, *et al.* Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline, J Clin Endocrinol Metab **2010**; 95: 2536-2559.
8. Host C, Skakkebaek A, Groth KA, Bojesen A, The role of hypogonadism in Klinefelter syndrome, Asian J Androl **2014**;16: 185-191.
9. Miner M, Canty DJ, Shabsigh R. Testosterone replacement therapy in hypogonadal men: assessing benefits, risks, and best practices, Postgrad Med **2008**; 120(4):114.
10. Carsote M. Capatina C, Valea A, Dumitrascu A. Vanishining testes syndrome-related osteoporosis and high cardio-metabolic risk in an adult male with long term untreated hypergonadotropic hypogonadism. Arch Endocrinol Metab **2016** Feb;60(1):79-84.
11. Darby E, Anawalt BD. Male hypogonadism: an update on diagnosis and treatment, Treat Endocrinol **2005**;4(5):293-309.
12. Viuff MH, Stochholm K, Uldbjerg N, Nielsen BB. Danish Fetal Medicine Study Group, Gravholt CH, Only a minority of sex chromosome abnormalities are detected by a national prenatal screening program for Down syndrome, Hum Reprod **2015**;30: 2419-2426.
13. Bonomi M, Rochira V, Pasquali D, Balercia G, Jannini EA, Ferlin A. Klinefelter syndrome (KS): genetics, clinical phenotype and hypogonadism, J Endocrinol Invest **2016**; 40(2): 123–134.
14. Chang S, Skakkebæk A, Gravholt CH. Klinefelter Syndrome and medical treatment: hypogonadism and beyond, Hormones (Athens) **2015**;14(4): 531-48.
15. Nieschlag E, Werler S, Wistuba J, Zitzmann M. New approaches to the Klinefelter syndrome, Ann Endocrinol (Paris) **2014**;75(2):88-97.
16. Okolie K, Perampalam S, Barker A, Nolan CJ. A case of Klinefelter syndrome with hypersexual desire, Endocrinol Diabetes Metab Case Rep 2017; **2017**: 17-0082.
17. Gheorghisan-Galateanu AA, Carsote M, Valea A. Incidentaloma: from general practice to specific endocrine frame. J Pak Med Assoc. **2017** Jun; 67(6):917-922 [17-16].
18. Carsote M, Chirita C, Dumitrascu A, Hortopan D, Fica S, Poiana C. Pituitary incidentalomas--how often is too often? J Med Life. **2009** Jan-Mar;2(1):92-7.
19. Poiana C, Chirita C, Carsote M, Hortopan D, Goldstein A. Galactocele and prolactinoma--a pathogenic association? Maturitas. **2009** Jan 20;62(1):98-102. doi: 10.1016/j.maturitas.**2008**.10.015.