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Male infertility and Klinefelter Syndrome: case report of azoospermia associated with trisomy X

Infertilidade masculina e síndrome de Klinefelter: relato de caso de azoospermia associada à trissomia do cromossomo X

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Abstract

Klinefelter syndrome is determined by a male karyotype with an extra X chromosome. This syndrome leads to the degeneration of testicular tissue, characterized by fibrosis and hyalinization of the seminiferous tubules, as well as hyperplasia of Sertoli and Leydig cells, which regulate spermatogenesis and testosterone production, respectively. In adulthood, testosterone deficiency occurs due to an increase in luteinizing and follicle-stimulating hormones, testicular atrophy, and infertility due to azoospermia. The study aims to report the case of a 32-year-old man undergoing infertility investigation with azoospermia. During a genetic study using karyotype analysis, the patient presented 47, XXY, inv per 9[20] and was diagnosed with Klinefelter syndrome. Therefore, a spermogram and a genetic study must be performed to investigate azoospermia. Furthermore, this syndrome needs to be more frequently diagnosed, as timely and appropriate treatment and follow-up may reduce the physical complications, as well as individual and social outcomes related to this syndrome.

Keywords: Klinefelter syndrome; Azoospermia; Infertility

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Resumo

A síndrome de Klinefelter é determinada por um cariótipo masculino com um cromossomo “X” extra. Nesta, há degeneração do tecido testicular, com fibrose e hialinização dos túbulos seminíferos e hiperplasia das células de Sertoli de Leydig, as quais controlam a espermatogênese e a produção de testosterona, respectivamente. Na fase adulta ocorre deficiência de testosterona pelo aumento dos hormônios luteinizantes e folículo-estimulante, atrofia testicular e infertilidade pela azoospermia. O objetivo do estudo é relatar o caso de um homem de 32 anos, em investigação de infertilidade com azoospermia que realizou um estudo genético com análise do cariótipo cujo resultado foi 47, XXY, inv per 9[20], diagnosticando-o com Síndrome de Klinefelter. Portanto, é de suma importância a realização do espermograma e estudo genético para investigação de azoospermia. Além disso, salienta-se a importância do reconhecimento clínico mais frequente desta síndrome, visto que o tratamento e o acompanhamento em tempo hábil e adequado podem limitar as complicações físicas e os desfechos individuais e sociais dessa síndrome.

Palavras-chave: Síndrome de Klinefelter; Azoospermia; Infertilidade

INTRODUCTION

Klinefelter syndrome (KS) is characterized by a male karyotype with at least one extra X chromosome, most commonly 47, XXY, with an incidence of 1 in 500 to 1000 live births[1]. KS is underdiagnosed due to its varied phenotypes. The diagnostic hypothesis is established during the clinical profile investigation, which impacts the quality of life of patients[2].

KS may lead to psychiatric disorders and somatic alterations, especially cardiovascular, neurological, endocrine, metabolic, and respiratory disorders[1]. Patients may also present testosterone deficiency due to primary testicular failure (i.e, gonads responsible for producing testosterone), decreasing testicular volume, azoospermia, and gynecomastia[3]. The association of these alterations contributes to the infertility of these individuals, impacting their quality-of-life[3]. Moreover, KS may be a differential diagnosis in this situation, requiring further investigation.

This study aimed to report the case of a man diagnosed with KS during the investigation of azoospermia and infertility, underscoring the relevance of associating these findings for etiological elucidation.

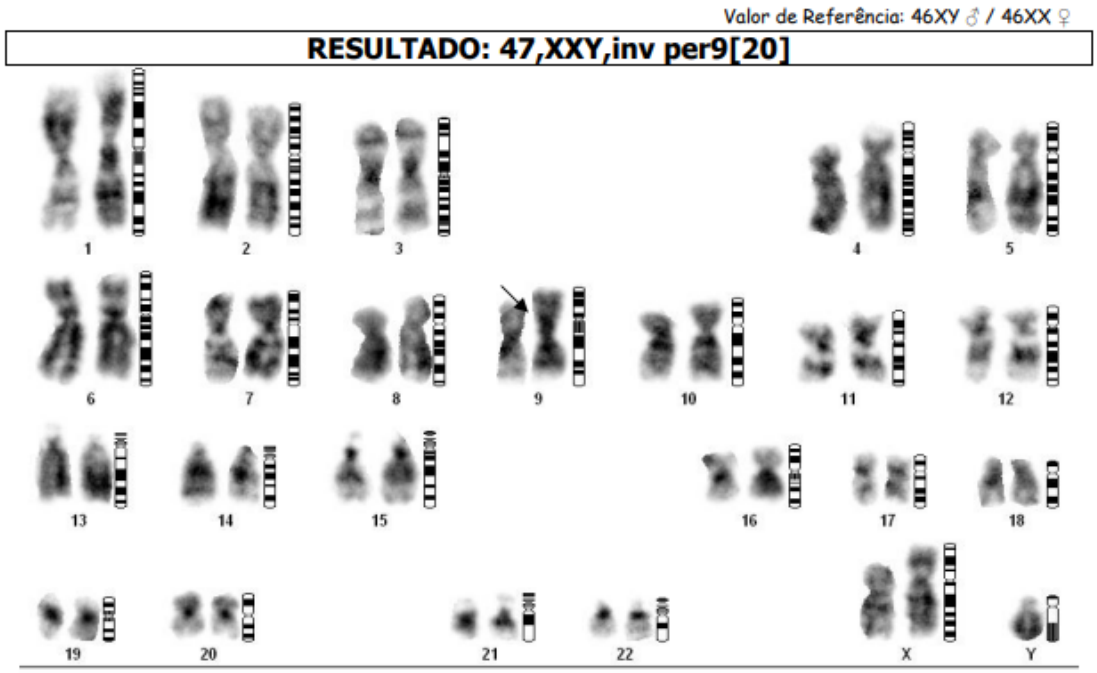
CASE REPORT

A 32-year-old male patient with level I obesity (BMI 30.12 kg/m^2) and dyslipidemia underwent a sperm analysis and was diagnosed with azoospermia at the age of 28, during an investigation of infertility after ruling out causes in the partner.

A genetic investigation for the Y chromosome detected no microdeletions, and karyotype

analysis revealed 47, XXY, with pericentric inversion of chromosome 9 (Figure 1), establishing the diagnosis of KS.

Figure 1. Result of the karyotype analysis of the patient.

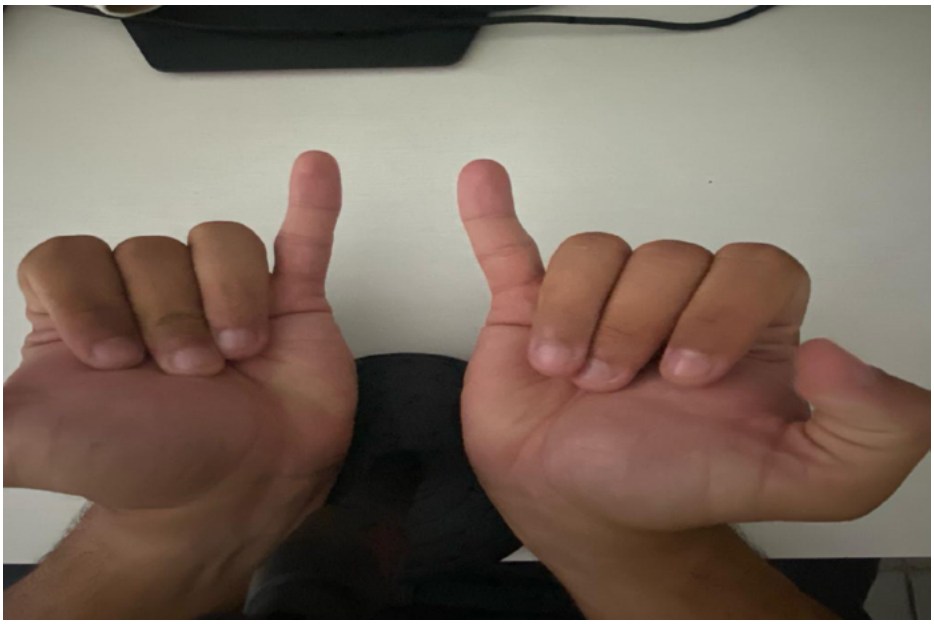


Source: test result provided by the patient. Per inv 9 = pericentric inversion of chromosome 9.

The patient presented a delayed puberty beginning at 18 years old, little facial hair and beard formation, frontal alopecia, and testicular atrophy. The patient also presented clinodactyly (Figure 2), pectus excavatum, bone elongation predominantly in the upper limbs, ligamentous laxity, a history of mandibular fracture, and limited muscle hypertrophy during physical activity. Furthermore, a diagnosis of attention deficit hyperactivity disorder was established after the KS diagnosis.

To increase serum testosterone levels, the patient began treatment with anastrozole 1 mg, followed by 2 mg for 9 months. After the dosage change, the patient developed depression, edema in the lower limbs, and worsening of ligament laxity. In this context, treatment was changed to topical testosterone for 4 to 5 months; however, androgen absorption was inadequate.

Figure 2. Bilateral clinodactyly in the fifth fingers.



Source: image provided by the patient.

During follow-up with a urologist and andrologist, aiming at the possibility of fertility, weekly doses of injectable testosterone were initiated every 12 to 16 weeks. However, the time between doses was reduced to 8 weeks until a serum testosterone level of 600 ng/dL was achieved, due to ulcerated lesions on the glans penis.

After medical advice, the couple discontinued reproductive attempts due to the risk-benefit and the potential consequences for testicular architecture and azoospermia after androgenic therapy. The couple was advised on the possibility of adoption or artificial insemination.

DISCUSSION

Described in 1942 by Harry F. Klinefelter, the KS affects about 3% of male patients with infertility and 10% to 12% in those with azoospermia (i.e., total absence of sperm in the ejaculatory fluid)[4]. The diagnosis of KS is difficult due to its varied phenotypes; thus, one-third of patients are diagnosed only when investigating infertility, as in this case report[4].

In histopathology, degeneration of testicular tissue is common, characterized by fibrosis and hyalinization of the seminiferous tubules, as well as hyperplasia of Sertoli and Leydig cells[5,6]. These gonadal changes begin during the intrauterine period and increase during puberty[7], leading to clinical and laboratory alterations, such as testosterone deficiency, hypergonadotropic hypogonadism (due to increased luteinizing and follicle-stimulating hormones), testicular atrophy, and infertility, commonly due to azoospermia[5,7].

Some patients present hyperestrogenism due to increased luteinizing hormone levels,

which elevates aromatase enzyme expression and peripheral testosterone conversion. These alterations favor abdominal fat and gynecomastia; the latter occurs in 10% to 12% of patients with azoospermia[8], but it was not observed in this case report.

During the investigation of infertility in a couple, KS can be diagnosed using karyotype analysis, which accuracy may increase when associated with fluorescent in situ hybridization or chromosomal microarray analysis, as performed in this study[9].

Testosterone supplementation is indicated to treat the classic phenotype of KS, especially the physical symptoms, such as hypogonadism, as performed in this case report. When diagnosis is confirmed early, testosterone supplementation is recommended to prevent physical changes, reduce gynecomastia, and improve cognition and behavior[9].

Azoospermia is the most serious form of infertility in men, especially when caused by KS, affecting both men and the couple[10]. Thus, due to the impact that infertility causes in the daily lives of couples, a therapeutic option is needed to alleviate this situation or provide parenthood using alternative pathways.

Currently, the therapeutic option available for couples with a carrier of KS and azoospermia is assisted reproductive technology, especially intracytoplasmic sperm injection and microdissection testicular sperm extraction, with the success rate of the latter being related to younger ages[4]. Nonetheless, managing infertility in patients with KS is challenging due to the underdiagnosis. Since the aneuploidy is commonly confirmed at older ages, it hinders the effectiveness of procedures, such as the microdissection testicular sperm extraction[5].

Furthermore, other differential diagnoses should be considered during the investigation of patients with KS, such as acromegaly, adrenogenital and secretory gonadal tumors, fragile X syndrome, hyperprolactinemia, other causes of azoospermia and hypogonadism, and Marfan syndrome[9].

Despite the diagnostic and therapeutic advances related to KS, more in-depth and early investigations are needed, preferably during the prenatal or postnatal period, based on clinical suspicion. Early diagnosis increases treatment efficacy and promotes fertility in these patients using intracytoplasmic sperm injection and microdissection testicular sperm extraction, or even with other therapeutic options.

CONCLUSION

The early diagnosis of KS is essential due to its physical and hormonal changes. Thus, performing a sperm analysis and genetic testing to investigate azoospermia is crucial. Furthermore, healthcare professionals should recognize the most common clinical presentation of KS, as timely and appropriate treatment and follow-up may reduce the physical complications, reduce outcomes and social trauma, and enable conception for couples who desire it.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTIONS

FAP: Conceptualization, Data curation, Methodology, Project administration, Resources, Supervision, Writing - original draft, Writing – review and editing; **JECS:** Conceptualization, Data curation, Methodology, Project administration, Resources, Supervision, Writing - original draft, Writing – review and editing; **TJMBSV:** Writing - original draft, Writing – review and editing; **MBA:** Writing - original draft, Writing – review and editing; **MCC:** Writing - original draft, Writing – review and editing; **FAA:** Writing - original draft, Writing – review and editing; **GBNM:** Writing - original draft, Writing – review and editing. All authors read and approved the published version of the manuscript.

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