



A Case Report: Non-Obstructive Azoospermia and Normal Phenotype in a Thirty-Eight Year Old Male with a Rare Klinefelter's Syndrome Genotype

Mia Letterie¹, Janet L Kennedy^{2*} and R Dale McClure²

¹Whitman College, USA

²Department of Reproductive Medicine, Seattle Reproductive Medicine, USA

Abstract

Background: Klinefelter's syndrome (KS) is the most common genetic cause of infertility in males. KS is characterized by non-obstructive azoospermia (NOA) most often accompanied by physical signs including small testes, tall stature, and gynecomastia. The most common karyotype is 47, XXY. We describe a patient with a rare supernumerary isochromosome of X and relatively normal phenotype. We provide evidence regarding the approach to treatment of infertility in these patients.

Case Summary: We describe an infertile male who presented only with non-obstructive azoospermia and small testes with no other phenotypic manifestations of Klinefelter's Syndrome. His karyotype, 47, X,i(Xq),Y, includes a rare isochromosome of X. Given the absence of physical evidence of hypogonadism, the patient and his wife held some hope that sperm would be found on testicular biopsy. No sperm were identifiable after bilateral microsurgical testicular sperm extraction (mTESE). Alternative treatment options were suggested and the couple eventually conceived via insemination with donor sperm.

Conclusion: Given the rarity of this presentation, this information may provide direction in future treatment by confirming that surgical sperm retrieval remains futile even in KS patients with a supernumerary isochromosome X despite a relatively normal phenotype. Treating directly with therapeutic donor insemination has a far higher pregnancy rate and avoids an unnecessary and expensive treatment attempt.

Keywords: Klinefelter's syndrome; Non-obstructive azoospermia; Isochromosome; Microsurgical testicular sperm extraction

Abbreviations

KS: Klinefelter's Syndrome; NOA: Non-Obstructive Azospermia; TESE: Testicular/Epididymal Sperm Extraction; mTESE: Microsurgical Testicular Sperm Extraction

Introduction

Klinefelter's syndrome is the most common form of male hypogonadism and the most common genetic cause of infertility in males (4% of newborn males) [1]. KS is characterized by non-obstructive azoospermia (NOA) most often accompanied by a variety of clinical signs. The three most common physical attributes that suggest the diagnosis include: small testes, tall stature and gynecomastia [2]. The most common karyotype is 47, XXY accounting for 80% to 90% of patients with KS [3]. Rare variants of this karyotype have been described with varying clinical features. We describe an infertile male who presented only with NOA and small testes with no other phenotypic manifestations of Klinefelter's Syndrome. His karyotype, 47 X, i(Xq), Y, includes a rare isochromosome of X. Given the absence of physical evidence of hypogonadism, the patient and his wife held some hope that sperm would be found on testicular biopsy. No sperm were identifiable after bilateral microsurgical testicular sperm extraction (TESE). Alternative treatment options were suggested and the couple eventually conceived via insemination with donor sperm.

Case Presentation

The 38 year old patient presented for evaluation of azoospermia after a semen analysis was performed as part of an infertility evaluation. He and his 29 year old spouse had been attempting

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*Correspondence:

Janet L Kennedy, Department of Reproductive Medicine, Seattle Reproductive Medicine, 1505 Westlake Ave, Suite 400, Seattle, WA 98109, USA,
E-mail: janet.kennedy@integrated.com

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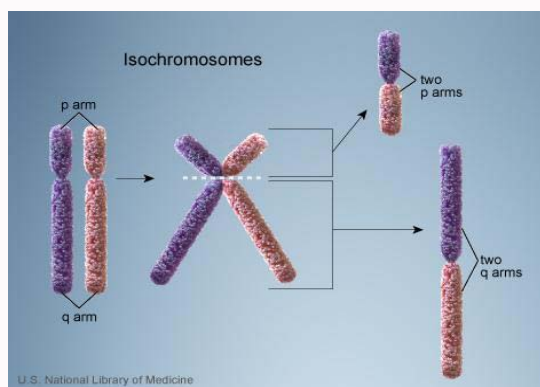


Figure 1: Formation of an isochromosome.

During either meiosis or mitosis, there is a transverse separation of chromatids just above or below the centromere rather than the usual longitudinal separation. The isochromosome consisting of the two short arms (p) is usually lost. The remaining isochromosome consists of two long (q) arms that are mirror images of each other.

pregnancy for approximately 36 months. Additional inquiry after discovery of this finding revealed a history of delayed (age 16) but otherwise normal puberty and a clinical exam that demonstrated bilateral small testicular volume. No further diagnosis was given and the subject was referred to our clinic.

On physical examination by one of the authors, the patient was 71 inches tall, a normal stature for his family, had no signs of gynecomastia and exhibited normal virilization. There was no deficit in cognition. Ultrasound examination with testicular measurements indicated dimensions of 2.0 cm × 2.0 cm on the left and 2.0 cm × 1.0 cm on the right. No hyperechoic foci were noted by ultrasound [4]. Laboratory evaluation indicated a normal total testosterone level (415 ng %), elevated serum FSH (36.8 mIU/mL) and LH (25.3 mIU/mL) concentrations, and a normal TSH (1.3 mIU/ml) level. His karyotype was found to be 47, X,i(Xq),Y (Figure 1).

The couple initially refused treatment with donor sperm and elected to proceed with testicular sperm aspiration. A bilateral scrotal exploration and attempted microsurgical sperm retrieval was performed by one of the authors. On the left side, dissection was carried down to the testis itself. The tunica vaginalis was opened and the testis was bivalved horizontally. Microscopic examination of ten biopsies revealed no sperm present. On the right side a similar procedure was performed. Again, more than 10 biopsies were taken and no sperm were identified.

After the testicular exploration failed to identify sperm, the couple decided to proceed with donor sperm insemination, achieved a pregnancy and term delivery.

Discussion

KS is characterized by heterogeneity in its clinical and genetic presentation [2,3]. Various phenotypic expressions have been described. The most common presenting phenotype is hypogonadism, gynecomastia, azoospermia or oligospermia, and increased levels of gonadotropins. The most common genotype is 47, XXY [2]. Genotypic variants of Klinefelter Syndrome are rare and usually consist of a multiplicity of normal X chromosomes in each cell, eg 48, XXXY or 49, XXXXY [5]. The occurrence of a supernumerary isochromosome of X is extremely rare. Only a few cases have been

reported describing microsurgical testicular exploration and biopsy results in this rare genotype [6,7]. In addition, this patient's normal phenotypic profile including normal virilization, normal serum testosterone concentrations and normal height is unusual. This subject's laboratory testing indicating elevated FSH and LH suggest a lower likelihood of sperm retrieval by TESE which proved to be the case here. Karyotypes, however, are not always predictive of the likelihood of sperm retrieval in NOA. The sperm retrieval rate for patients with 46, XY karyotype, KS, and other chromosomal anomalies were 27.1%, 22.5%, and 15.4% respectively [6]. However, among the samples collected from the 13 patients with NOA due to chromosomal anomalies other than 47,XXY, only those from the two patients with the normal variant 46, XY,inv(9)(p12;q13) contained spermatozoa [6].

Conclusion

This case report adds to our current knowledge on the possibility of sperm retrieval by mTESE for NOA due to a supernumerary X isochromosome [8]. This case suggests that despite a normal phenotype and rare genotype, attempts at testicular sperm retrieval may be futile and reproductive planning may best be achieved using alternate approaches.

Authors' Contributions

Mia Letterie wrote the article. Janet L Kennedy, M.D. contributed suggestions for revision, the figure, and confirmed the references. R Dale McClure performed the microsurgical testicular sperm aspiration.

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