Rare Case of Monozygotic Twins Diagnosed With Klinefelter Syndrome During Evaluation for Infertility

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Although neither Klinefelter syndrome nor monozygotic twins are particularly rare (1/667 male births and 3-4/1000 live births, respectively), the occurrence of both in the same pregnancy (ie, identical twins with Klinefelter syndrome) is exceedingly rare and has only been reported three times previously in the literature. This report describes the fourth ever reported case of monozygotic twins with Klinefelter syndrome (who presented to our male fertility clinic with failure to conceive) and sheds interesting light on the reproductive concordance observed with this rare clinical entity. To our knowledge, this is the first reported case of monozygotic twins with Klinefelter syndrome that describes the infertility workup and outcomes of microsurgical testicular sperm extraction.

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KEY WORDS

Klinefelter syndrome • Microsurgical testicular sperm extraction • Azoospermia • Sertoli only syndrome • Germ cell aplasia

Klinefelter syndrome, the most common sex chromosome disorder in men, is the clinical result of an additional X chromosome in human males. This syndrome, which affects an estimated 1 in 667 live male births, most commonly manifests as 47,XXY, but may also take the form of 46,XY/47,XXY (Klinefelter mosaicism), 48,XXXY, or 49,XXXXY.[1] Typical clinical manifestations of the syndrome include primary infertility, atrophic testes, hypergonadotropic hypogonadism, gynecomastia, eunuchoidism, and decreased facial and body hair.[1] This condition often goes undiagnosed in prepubertal boys, and even in adult men, despite the physical hallmarks of the syndrome; many cases

come to light only during the evaluation of primary male factor infertility. The andrologist, therefore, plays a central role in the diagnosis, work-up, and management of men with Klinefelter syndrome.

With an incidence approximately twice that of Klinefelter (3-4 per 1000 live births worldwide),[2] monozygotic (identical) twinning occurs when one fertilized egg splits and divides into two embryos. Monozygotic twins have been observed with various karyotypic abnormalities, including trisomy 21,[3] trisomy 18,[4] and trisomy 13.[5] However, the presentation of monozygotic twins with Klinefelter syndrome (a fertilized egg with a 47, XXY karyotype splitting to produce identical embryos with Klinefelter syndrome) is exceedingly rare. In this report, we discuss one case of identical twin brothers diagnosed with Klinefelter syndrome at our fertility clinic (Glickman Urological & Kidney Institute, Cleveland, OH) as part of a work-up for inability to conceive.

Case Report

A 29-year-old man was referred to our male fertility clinic in July 2011 secondary to failure to conceive. Two prior semen analyses performed at an outside hospital had demonstrated azoospermia. Results of the patient's review of systems were negative for a prior history of mumps orchitis, trauma, cryptorchidism, urinary tract infections, prostatitis, epididymitis, or sexually transmitted infections. He denied any past surgical history, past medical history, and family history of first-degree relatives with infertility, and was not currently taking any prescribed medications or supplements. The patient was a married electrician without known occupational exposures, a social smoker, and occasional beer drinker, and denied any history of illicit drug or testosterone use. His review of systems was otherwise unremarkable. On physical examination, he was noted to have a well masculinized body habitus without gynecomastia; however, examination of his genitals revealed bilateral nontender 4-mL testes with a palpable and nontender epididymis and vas deferens on each side. The patient was referred for scrotal ultrasound, karyotype, Y chromosome microdeletion, and hormone profile testing, which confirmed a diagnosis of azoospermia secondary to nonmosaic Klinefelter syndrome (47,XXY) with elevated gonadotropins and sustained testosterone production (follicle-stimulating hormone [FSH] 34.2 mU/mL, luteinizing hormone [LH] 14.2 mU/mL, total testosterone 396 ng/dL). Y chromosome microdeletion test results were negative for any deletion of the azoospermia factor (AZF) a, b, or c regions, and scrotal ultrasound confirmed bilateral atrophic testes (right testis, 3.5 × 1.6 × 1.8 cm; left testis, 3.6 × 1.3 × 1.6 cm) without focal masses or calcifications and with normal arterial and venous flow on Doppler imaging.

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Results of a three-generation pedigree performed by a geneticist were negative for known genetic disease, birth defects, malformation syndromes, chromosomal disorders, metabolic disorders, developmental delay, mental retardation, infertility, recurrent pregnancy loss, stillbirth, unexplained infant death, or consanguinity in the patient's first-degree relatives. However, the patient described having an identical twin brother with unproven paternity, thus raising the possibility of a second case of undiagnosed Klinefelter syndrome in the family.

As the patient and his wife were eager to conceive, a decision was made to proceed with microsurgical testicular sperm extraction (micro-TESE). Unfortunately, at the time of surgery, biopsied testis tissue demonstrated tubular atrophy with markedly sclerotic seminiferous tubules and scattered small clusters of Leydig cells; no sperm was identified.

The patient's family history was significant for an identical twin brother (unconfirmed monozygoticity) with unproven fertility. In light of his sibling's recent karyotype and failed micro-TESE, the patient's brother also presented to our fertility clinic for an evaluation. Like his brother, this man was also 29 years old and on questioning admitted that he, too, had been unsuccessfully trying to conceive for the past year with his wife. Review of systems and past medical and social histories were entirely unremarkable. On physical examination, this individual was identical in appearance to his twin brother and similarly well masculinized. He was also found to have nontender, bilaterally atrophic testes (each measuring 4 mL in size). Semen analysis demonstrated normal volume azoospermia with rare sperm heads, and genetic testing confirmed the patient had nonmosaic Klinefelter syndrome (47,XXY) without any Y chromosome microdeletions. Endocrine evaluation similarly demonstrated elevated gonadotropins and sustained testosterone production (FSH 34.9 mU/mL, LH 12.3 mU/mL, total testosterone 369 ng/dL).

Despite his brother's failed micro-TESE, this man and his wife expressed a desire to proceed with sperm retrieval as well. Unfortunately, his testes were similarly fibrotic and rubbery in consistency, with only diminutive seminiferous tubules identified under the operating microscope. No sperm or sperm parts were identified despite extensive microsurgical sampling, and formal histologic analysis confirmed the presence of testicular parenchyma with sclerotic seminiferous tubes, aggregates of hyperplastic Leydig cells, and no evidence of spermatogenesis bilaterally.

Discussion

We conducted a systematic literature search using PubMed and MEDLINE to identify any previously reported cases of monozygotic twins with Klinefelter syndrome undergoing an infertility evaluation. Although monozygotic twinning has been observed with various karyotypic abnormalities, including trisomy 21, 18, and 13,[3-5] monozygotic twinning with sex chromosomes appears to be far less prevalent. An extensive review of the literature yielded only three other reported cases of identical twins with 47,XXY Klinefelter syndrome, one in which concordant chordee was present,[6] and two in which the twins were discordant for systemic lupus erythematosus.[7,8] With the exception of these three cases, no additional reports were available in the literature.

Klinefelter syndrome is the most common sex chromosome abnormality (occurring in 1 of every 500-700 human males) and the most common etiology of primary hypogonadism in men.[9] Although the degree of androgen deficiency and eunuchoidism varies from patient to patient, the syndrome is almost uniformly characterized by the finding of extremely small testes with at least some degree of androgen deficiency and elevated gonadotropin levels after the onset of puberty.[9]

The principal karyotype abnormality in Klinefelter syndrome is the presence of one or more extra X chromosomes resulting from either maternal or paternal nondisjunction, primarily during meiosis I. Nondisjunction most commonly results in the karyotype 47,XXY (90% of men); however, mosaic Klinefelter syndrome (47,XXY/46,XY) occurs when postfertilization mitotic nondisjunction occurs. In these cases, some cells/tissues carry the normal 46,XY karyotype, whereas others contain a supernumerary X chromosome.[9]

Although a handful of case reports have described monozygotic twins with Klinefelter syndrome, as previously mentioned, none report on the fertility outcomes of identical twin men with this condition. Therefore, our case is unique in that it not only describes the occurrence of this rare entity and its clinical presentation, but provides deeper insight into the surgical findings and outcomes of monozygotic twins carrying this diagnosis.

Although a handful of case reports have described monozygotic twins with Klinefelter syndrome, as previously mentioned, none report on the fertility outcomes of identical twin men with this condition.

MAIN POINTS

- Klinefelter syndrome is the most common sex chromosome disorder in men and is the clinical result of an additional X chromosome in human males; it affects an estimated 1 in 667 live male births.
- Typical clinical manifestations of the syndrome include primary infertility, atrophic testes, hypergonadotropic hypogonadism, gynecomastia, eunuchoidism, and decreased facial and body hair; many cases only come to light during the evaluation of primary male factor infertility.
- Although the degree of androgen deficiency and eunuchoidism varies from patient to patient, the syndrome is almost uniformly characterized by the finding of extremely small testes with at least some degree of androgen deficiency and elevated gonadotropin levels after the onset of puberty.
- The principal karyotype abnormality in Klinefelter syndrome is the presence of one or more extra X chromosomes resulting from either maternal or paternal nondisjunction. The presentation of monozygotic twins with Klinefelter syndrome (a fertilized egg with a 47,XXY karyotype splitting to produce identical embryos with Klinefelter syndrome) is exceedingly rare.

Conclusions

The present case represents the fourth case ever reported of monozygotic twins with Klinefelter syndrome. Our case is particularly unique because both men elected to undergo micro-TESE. Although micro-TESE has been associated with a 68% rate of successful sperm retrieval in men with this karyotypic abnormality,[9] neither of our attempts was successful. Whether this would hold true for another sibling pair with Klinefelter syndrome remains unknown, as this clinical entity is almost unheard of. Nonetheless, our findings are noteworthy in that they demonstrate that men with Klinefelter syndrome are not only identical in their physical appearance, but appear to also exhibit similar endocrine profiles and phenotypic concordance with respect to their testicular histology. ■

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