Austin Journal of Invitro Fertilization

Open Access

Austin Publishing Group

Case Report

47, Xyykaryotype Associated with Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Mutation in an Infertile Man Presenting with Obstructive Azoospermia: Spermal Retrieval and *In Vitro* Fertilization Feasibility with Preimplantation Genetic Diagnosis

Lopes LS[1,2], Pane CEV[1,2] and Ghirelli-Filho M[1,2]*

[1]IdeiaFértil Institute, ABC Medical School, Brazil

[2]Department of Urology, ABC Medical School, Brazil

***Corresponding author:** Ghirelli-Filho M, Ideia Fértil Institute, ABC Medical School, Av. Príncipe de Gales, 840 – Santo André, SP, Brazil

Received: October 05, 2014; **Accepted:** March 15, 2015; **Published:** March 17, 2015

Abstract

A 41-year-old man presented with a 5-year history of primary infertility. The patient denied any hypogonadism symptoms. There was no family history of infertility. His 34-year-old wife presented with no infertility factor. Physical examination demonstrated Body Mass Index (BMI) of 24, normal phallus and bilateral descended testes measuring approximately 21cc. No evidence of clinical varicocele. Vas deferens were non palpable. Three semen analysis with hipospermia and Azoospermia were obtained. Total serum testosterone was 910 ng/dL (normal range 220-1000 mg/dl), Follicle Stimulating Hormone (FSH) 6,15mU/mL (normal 1-10 mU/mL), prolactin was 9,1 ng/mL (normal 2-18 ng/mL). Genetic evaluation presented 47,XYY[95]/46,XY[5] karyotype and Phe508del CFTR heterozygous mutation and normal Y-linked microdeletion assay. The partner´s karyotype confirmed 46, XX and no CFTR mutations. Sperm retrieval was possible only through Testicular Sperm Extraction (TESE). In the first IVF cycle performed, two embryos were obtained: one with degraded DNA and other with hatching 44,X-20 after PGD. In the second and third cycles 46, XX embryos were obtained and transferred, but pregnancy wasn´t achieved.

Keywords: Chromosome aberrations; Fertilization *in vitro*; Cysticfibrosis; Male infertility

Introduction

Infertility is defined as a couple's failure to conceive after having sexual intercourse without contraception for 1–2 years and male factors because approximately half of these cases [1]. Male infertility can be attributed to several factors including medication and illegal drug side effects, exposures to toxic compounds, erectile dysfunction, endocrine disorders, varicocele, systemic diseases and anatomic malformations [1]. In addition, it has been known for several decades that cytogenetic and molecular abnormalities such as autosomal abnormalities, micro deletions of the Y-chromosome and sex chromosome aberrations affect male fertility including [1,2].

The development of ICSI in 1992 revolutionized the treatment of male infertility and was rapidly adopted in IVF clinics worldwide [2]. Given the aforementioned risk of chromosomal abnormalities, it would be wise to perform routine karyo typing prior to IVF/ICSI in infertile men with unexplained spermatogenic failure and a reduced sperm count (less than 10 million sperm per ml); and Y chromo some micro deletion analysis in men with severe oligozoospermia (less than 5 million sperm per ml) or Azoospermia [2,3].

The 47,XYY sex chromosome variation is the most common sex chromosome anomaly after Klinefelter syndrome (47,XXY),occurring in approximately 1 out of 1000 live male births [3]. Studies have increasingly reported an association between 47,XYY and fertility problems, noting an increased incidence of chromosomally abnormal spermatozoa in the semen of men with 47,XYY syndrome [3-5].

Male patients with Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene heterozygous mutation are infertile mostly due to Congenital Bilateral Absence of the Vas Deferens (CBAVD) and obstructive Azoospermia [6]. CFTR gene studies represent one of the most frequent genetic analyses routinely performed worldwide [6,7]. More than 1500 sequence variations have been reported in the CFTR gene, often with geographic or ethnic variations in frequency [7].

Recently advances in genetic evaluation, with embryo biopsy and Preimplantation Genetic Diagnose (PGD) may allow patients that carry chromosomal rearrangements to transfer only chromosomally normal embryos [2].

Methods

IVF protocols

Ovarian stimulation of multiple follicles was carried out using

Ghirelli-Filho et al. © All rights are reserved

Citation: Lopes LS, Pane CEV and Ghirelli-Filho M. 47, Xyykaryotype Associated with Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Mutation in an Infertile Man Presenting with Obstructive Azoospermia: Spermal Retrieval and *In Vitro* Fertilization Feasibility with Preimplantation Genetic Diagnosis. Austin J In Vitro Fertili. 2015;2(1): 1015.

purified or recombinant gonadotropins, and GnRH agonists or antagonists were used to suppress endogenous secretion of gonadotropins. Individual doses of each medication varied for each case, taking into account the age of the wife and clinical exams. Patients presenting at least three follicles with at least 17 mm in diameter on ultrasound after ovarian stimulation received hCG injection. The oocyte aspiration guided by Transvaginal ultrasonography was performed 36 hours after hCG injection. The gametes handling was performed according to routine protocols, following the ICSI technique for IVF using semen recovered by PESA [8].

Testicular sperm extraction (TESE)

Testicular sperm recovery for IVF was performed by testicular biopsy, with the patient under local anesthesia with lidocaine and sedation.

Genetic evaluation

Both karyotype and CFTR mutation search were made with peripheral blood. Karyotype evaluation was made with Giemsa staining (G-bandidng) [9].

Case Report

A 41-year-old man presented with a 5-year history of primary infertility. The patient denied any hypogonadism symptoms. There was no family history of infertility. His 34-year-old wife presented with no infertility factor.

Physical examination demonstrated Body Mass Index (BMI) of 24, normal phallus and bilateral descended testes measuring approximately 21cc. No evidence of clinical varicocele. Vas deferens were non palpable.

Three semen analysis with hipospermia and azoospermia were obtained. Early morning total serum testosterone was 910ng/dL (normal range 220-1000mg/dl), follicle stimulating hormone (FSH)6,15mU/mL (normal 1-10 mU/mL), prolactin was 9,1 ng/mL (normal 2-18 ng/mL).

Genetic evaluation presented 47,XYY[95]/46,XY[5] karyotype and Phe508del CFTR heterozygous mutation and normal Y-linked microdeletion assay.The partner´s karyotype confirmed 46, XX andno CFTR mutations.

Sperm retrieval was possible only through testicular sperm extraction (TESE).

In the first IVF cycle performed, two embryos were obtained: one with degraded DNA and other with hatching 44,X-20 after PGD. In the second and third cycles 46, XX embryos were obtained and transferred, but pregnancy wasn´t achieved.

Discussion

The cumulative frequency of autosomal abnormalities in infertile males is 3,5%, compared to 0,42%within the normal population.1,7% of infertile males are reported to have re arrangements of sex chromosomes, compared to 0,10% among the normal male population.[1]In cases of unexplained spermatogenic failure and a reduced sperm count (less than 10 million sperm per ml) it is recommended to perform routine karyotyping prior to IVF/ICSI; and Y chromosomal microdeletion analysis is recommended in men with severe oligozoospermia (less than 5 million sperm per ml) or Azoospermia [2,3].

The reported patient presented with a 47,XYY mosaic karyotype. Many men with 47,XYY karyotype are fertile in spite of their sex chromosome abnormalities [3]. Some researchers have suggested that the extra Y chromosome is lost before meiosis, thus conserving fertility in these patients. Studies comparing sperm aneuploidy between fertile and infertile XYY men revealed that most sperm produced by XYY men have a normal karyotype [3]. Conversely, multiple studies demonstrated that XYY men have a significant percentage of sperm mosaicism, aneuploidy, or hyperdiploidy ranging from 0, 57% to 77,8% [3,10].

Some studies indicate that 47,XYY syndrome may present with impaired spermatogenesis or with severe oligospermia [3,5,10]. Impaired spermatogenesis in this condition may be due to persistence of the extra Y chromosome during meiosis, hypogonadism or an associated condition such as varicocele [3-5,10].

Our patient presented with obstructive Azoospermia due to a CBAVD. In male infertility due to obstructive azoospermia, documented cases with CBAVD have been shown to be commonly linked to CFTR mutations [6,7]. Cystic Fibrosis (CF) is a relatively common hereditary disease caused by mutations of the CFTR gene (a cAMP-activated anion channel), with clinical manifestations of progressive lung disease, pancreatic insufficiency and infertility in both sexes [6,7]. When men are confirmed with CFTR mutations their partners must be evaluated and genetic counseling must be given [6,7].

More and more laboratories are now offering CFTR genetic testing; the number of indications for referrals has increased, in particular in the field of male infertility. The extensive heterogeneity in the distribution of CFTR gene mutations in European populations[7] makes the goal of a mutation detection rate of over 95% very hard to achieve, except with a combination of scanning methods. Efforts should be made to provide tests with reasonably high sensitivity to detect all CF-causing mutations with a frequency above 1% in the local population [7].

Aneuploidy screening of embryos was first performed using FISH analysis of cells biopsied from day-3 embryos, trophectoderm cells biopsied from blastocyst stage embryos or polar bodies biopsied from oocytes or zygotes.[2]FISH-based testing was able to analyze between 5 and 12 chromosomes in each oocyte or embryo, but was unable to provide a full evaluation of all 24 chromosomes.

Comparative Genomic Hybridization (CGH), a technique related to FISH, was first applied to day-3 embryo biopsies in 1999 [2,4]. This technique allowed the analysis of 24 chromosomes from a single cell and was a great leap forward from FISH-based testing. However, conventional CGH is time-consuming and incompatible with day-3 biopsy and fresh embryo transfer in the same cycle.

More recently, two new testing platforms have come into use, microarray CGH (array-CGH (aCGH)) and Single Nucleotide Polymorphism (SNP) microarrays. These tests platforms allow comprehensive chromosomal analysis of single cells from day-3 biopsy and yield results in 24 h [2].

These new tests allowed performing PGD preventing from lost IVF cycles using aneuploid embryos and consequent less miscarriage rates or potentially morbid and mortal diseases in offspring.

Conclusion

Infertile men should be genetically screened according to correct clinical and laboratorial evaluation. IVF could be offered when spermal retrieval is possible, and in some genetic conditions with PGD association pregnancy could be feasible.

References

1. Hofherr SE, Wiktor AE, Kipp BR, Dawson DB, Van Dyke DL. Clinical diagnostic testing for the cytogenetic and molecular causes of male infertility: the Mayo Clinic experience. J Assist Reprod Genet. 2011; 28: 1091-1098.
2. Harton GL, Tempest HG. Chromosomal disorders and male infertility. Asian J Androl. 2012; 14: 32-39.
3. Kim IW, Khadilkar AC, Ko EY, Sabanegh ES. 47,XYY Syndrome and Male Infertility. Rev Urol. 2013; 15: 188-196.
4. Lim AS, Fong Y, Yu SL. Analysis of the sex chromosome constitution of sperm in men with a 47, XYY mosaic karyotype by fluorescence in situ hybridization. Fertil Steril. 1999; 72: 121-123.
5. Abdel-Razic MM, Abdel-Hamid IA, ElSobky ES. Nonmosaic 47,XYY syndrome presenting with male infertility: case series. Andrologia. 2012; 44: 200-204.
6. Xu WM, Shi QX, Chen WY, Zhou CX, Ni Y, Rowlands DK, et al. Cystic fibrosis transmembrane conductance regulator is vital to sperm fertilizing capacity and male fertility. Proc Natl Acad Sci USA. 2007; 104: 9816-9821.
7. Dequeker E, Stuhrmann M, Michael A Morris, Teresa Casals, Carlo Castellani, Mireille Claustres, et al. Best practice guidelines for molecular genetic diagnosis of cystic fibrosis and CFTR-related disorders – updated European recommendations. European Journal of Human Genetics. 2009; 17: 51–65.
8. Gianaroli L, Plachot M, van Kooij R, Al-Hasani S, Dawson K, DeVos A, et al. ESHRE guidelines for good practice in IVF laboratories. Committee of the Special Interest Group on Embryology of the European Society of Human Reproduction and Embryology. Hum Reprod. 2000; 15: 2241-2246.
9. Shaffer LG, Tommerup N. (eds). ISCN 2005 – An International System for Human Cytogenetic Nomenclature. Basel, Karger. 2005; Chapter 2-6: 6–52.
10. Shi Q, Martin RH. Multicolor fluorescence in situ hybridization analysis of meiotic chromosome segregation in a 47,XYY male and a review of the literature. Am J Med Genet. 2000; 93: 40-46.

Austin J In Vitro Fertili - Volume 2 Issue 1 - 2015
ISSN : 2471-0628 | www.austinpublishinggroup.com
Ghirelli-Filho et al. © All rights are reserved

Citation: Lopes LS, Pane CEV and Ghirelli-Filho M. 47, Xyykaryotype Associated with Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Mutation in an Infertile Man Presenting with Obstructive Azoospermia: Spermal Retrieval and *In Vitro* Fertilization Feasibility with Preimplantation Genetic Diagnosis. Austin J In Vitro Fertili. 2015;2(1): 1015.