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Case report: Comprehensive evaluation and management of male infertility with complete AZFC microdeletion and undescended testicle

Niyazi Emre Turgut [a], Mehmet Murad Basar [b,*]

[a] NESTA Clinic, Istanbul, Turkiye
[b] Private Practice, Istanbul, Turkiye

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ABSTRACT

This case report presents a 31-year-old male patient with primary infertility, a unilaterally undescended testicle, and a complete AZFc microdeletion. Despite failed attempts at testicular sperm extraction, the patient underwent successful microscopic testicular sperm extraction and subsequent viable sperm extraction, leading to successful fertilization through intracytoplasmic sperm injection (ICSI). The report underscores the potential for successful ICSI in male infertility cases with complex genetic and reproductive issues, highlighting the importance of comprehensive genetic evaluation and individualized reproductive techniques in managing male infertility associated with undescended testicle and genetic anomalies.

1. Introduction

Undescended testicle, a prevalent congenital anomaly in men, occurs in approximately 3 % of term male infants and in 33 % of preterm male infants, with 30–35 % of the cases being unilateral and 58–60 % bilateral.[1,2]. Two primary concerns associated with undescended testicles are infertility and an increased risk of testicular cancer development. Although testicular cancer is believed to result from tissue degeneration due to elevated temperatures, infertility can result from the combination of multiple factors, including concomitant endocrine anomalies, anatomical factors, environmental influences, and genetic disorders.[2,3].

Genes located on the long arm of the Y chromosome play a crucial role in the process of normal spermatogenesis. Any complete or partial deficiencies in these regions can lead to a range of sperm production disorders, from azoospermia to oligoasthenoteratozoospermia.[4–6]. In recent years, there have been reports of testicular descent anomalies occurring alongside Y chromosome anomalies. However, the co-occurrence of these two conditions is exceedingly rare.[7,8].

Variations in the staining pattern and size of structural heterochromatin regions of chromosomes among individuals are referred to as heteromorphism. This condition is frequently observed in the pericentric regions of chromosomes 1, 9, and 16, as well as in the distal portion of the long arm of the Y chromosome. Heteromorphism refers to the variations of the normal karyotype, distinguished by tandemly organized, repetitive satellite DNA sequences that appear to lack protein-coding potential. Nevertheless, conflicting findings exist regarding the clinical implications of heteromorphism, as well as differing perspectives on its role in male infertility.[9,10].

This case report presents a patient with a complete AZFc microdeletion, unilateral undescended testicle, and male genetic polymorphism.

2. Case report

A 31-year-old male patient presented to our clinic with primary infertility. He had undergone an orchiopexy to correct right cryptorchidism at age two, which was followed by hydrocele aspiration six months later. His semen analysis indicated azoospermia. In 2012, testicular sperm extraction was attempted, but was unsuccessful. A testicular biopsy sample obtained later revealed Sertoli cell-only syndrome.

The patient sought additional evaluation at our medical center in 2021. Subsequent semen analysis revealed azoospermia, with no spermatogenetic cells detected upon examination with an inverted microscope. The patient's serum hormone values were as follows: follicle-stimulating hormone, 26.34 IU/L; luteinizing hormone, 6.01 IU/L; total testosterone, 4.05 ng/mL; estradiol, 27.53 pg/mL; prolactin, 36.1 ng/mL; and inhibin B, 22.1 pg/mL. At this stage, a genetic evaluation was performed on the patient for the first time. This test revealed that the patient had a karyotype of 46, XY, with additional findings of qh+,

* Corresponding author. Tesvikiye Mahallesi Hakkı Yeten Caddesi, Terrace Fulya Center-2, 8th Floor Internal Number:40, Sisli/Istanbul, Turkiye.
E-mail address: muradbasar66@hotmail.com (M.M. Basar).

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14pstk+, 21pstk+, and a complete AZFc microdeletion. Subsequently, the patient was given comprehensive information regarding the microscopic testicular sperm extraction (micro-TESE) procedure, and he was advised that intracytoplasmic sperm injection (ICSI) would be pursued if viable sperm were obtained.

In April 2022, the patient underwent an initial micro-TESE procedure under general anesthesia. The surgical intervention involved a midline scrotal incision to access the left testis, which was anatomically positioned at birth. Upon longitudinal opening of the tunica albuginea, heterogeneous seminiferous tubules were observed, with a few dilated tubules intermixed with thin fibrotic tubules. A total of twenty tubules were collected from this side. Since no sperm were detected during the operation, the same procedure was applied to the right testicle. The seminiferous tubules appeared thin and fibrotic, with no dilated tubules observed. A total of 10 tissue samples were collected from the right side, yielding no sperm during the initial investigation.

Following the PSS procedure on the testicular tissue in the andrology laboratory, a total of two motile and 17 immotile amorphous spermatozoa were observed in the left testicular tissue samples. Consequently, ovum pick-up and ICSI procedures were scheduled. Ten oocytes were retrieved during the ovum pick-up procedure, and eight mature oocytes were identified and utilized for the ICSI procedure. Five oocytes were successfully fertilized. On the third day, one grade I and two grade II embryos were observed. By the fifth day, one 4AA and one early blastocyst stage embryos were cryopreserved. Two months later, two embryos were transferred in the frozen embryo transfer cycle, but pregnancy did not ensue.

In July 2022, the patient requested a re-evaluation. Serum hormone levels were as follows: follicle-stimulating hormone, 36.64 IU/L; luteinizing hormone, 13.24 IU/L; testosterone, 3.24 ng/ml; estradiol, 23.54 pg/ml; and prolactin, 25.98 ng/mL. The patient was thoroughly informed about all potential risks and options and willingly consented to undergo a repeat micro-TESE. Before this procedure, human chorionic gonadotropin was started at a dose of 250 U/week and continued for six months.

In April 2023, the couple began a new in vitro fertilization (IVF) procedure, and the third micro-TESE was performed. During this procedure, a total of 45 tubules were retrieved from the left side. Although no sperm were initially observed during the preliminary investigation, the following concentration procedures revealed the presence of three motile and 15 immotile spermatozoa in the andrology laboratory. A total of 12 oocytes were retrieved, and ICSI was performed on six of them. Subsequently, four oocytes were successfully fertilized. On the third day, one grade I and two grade II embryos were obtained. A fresh embryo transfer procedure was planned, during which two embryos were implanted. This resulted in the formation of a single sac, and at the 40th week, a healthy female infant weighing 3660 g was born.

3. Discussion

The role of Y chromosome microdeletions in the development of cryptorchidism remains a topic of debate. One study detected a high rate of Y microdeletions in 40 cases of unilateral cryptorchidism, suggesting a potential link to testicular descent anomalies.[7]. In contrast, another study of similar size found no Y chromosome microdeletions in any of the undescended testicle cases.[11]. Similarly, a study involving 20 young male individuals with concurrent hypospadias and cryptorchidism, in which etiological factors related to steroidogenesis were excluded, revealed the absence of Y chromosome microdeletions in all patients.[12]. Furthermore, Kunej et al..[3]. noted a lower frequency of Y chromosome microdeletions in cryptorchid cases compared to other infertile patients. A separate study conducted in Turkey evaluating 64 cases of single or bilateral undescended testicles found no Y chromosome abnormalities in any patient.[13].

It is important to note that while Y chromosome microdeletions are not directly associated with cryptorchidism, they may be present in cases of cryptorchidism. Therefore, genetic testing, including peripheral karyotyping and Y chromosome microdeletion testing, is advisable for these patients. Foresta et al.[7] discovered a heightened incidence of Y chromosome anomalies in severe infertile cases with unilateral cryptorchidism (27.5 %), such as azoospermia or severe oligoasthenoteratozoospermia. They proposed that, although the Y chromosome might not directly cause testicular descent anomalies, it could be linked to testicular damage and impaired spermatogenesis in these cases. Adding to this, Ferlin et al.[8] suggested that Y chromosome microdeletions did not directly cause descent anomalies. However, they posited that the testicular damage resulting from these anomalies could potentially hinder the testicle's response to the descent-controlling mechanisms.

It is currently unclear whether there is a relationship between chromosome heteromorphism and infertility or unsuccessful IVF attempts. Some studies have suggested that chromosome polymorphisms are linked to infertility and recurrent miscarriages, while others have reported that these anomalies are not associated with the results of IVF.[8,10,14,15]. Although there have been few reported cases of simultaneous Y chromosome variations with Y-chromosomal microdeletions, it has been suggested that Y chromosome heteromorphism does not directly affect sperm count.[16]. Previous research has shown that Y chromosomes do not significantly contribute to the occurrence of undescended testicles. Additionally, reports suggest that genetic polymorphism does not affect spermatogenesis. Studies involving mice have suggested that various gene mutations may play a role in the testicular descent process, and that these mutations have a location-specific effect. In most cases, the mechanism of action operates through the steroidogenesis pathway.[17,18]. However, our current understanding of this subject in humans is limited.

There are numerous factors that can impact male infertility. In 20–30 % of men presenting with infertility, no cause is identified, and these cases are considered idiopathic male infertility. While a single etiological factor is observed in 50 % of the remaining cases, two different etiological factors are present in 30 % of the cases, and two or more factors are found in 20 %.[2].

4. Conclusion

As in our case, genetic evaluation must be performed even if there is a known factor causing infertility, such as undescended testicles in an azoospermic man. This condition should also be considered in cases of azoospermia due to radiotherapy or chemotherapy. The combination of these three factors does not affect the indication of micro-TESE in patients and does not alter the possibility of sperm retrieval.

CRediT authorship contribution statement

Niyazi Emre Turgut: Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Mehmet Murad Basar:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

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