

# A Rare Cause of Male Infertility: Mixed Gonadal Dysgenesis

CASE REPORT

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## ABSTRACT

Infertility is a significant health problem that affects many couples in the reproductive age range globally. While only the male factor is responsible for 20%-30% of cases of infertility, contributing to a further 20%. We aimed to describe a rare cause of male infertility, a male patient with 45,X/46,XY mosaic chromosome structure. The patient presented to our endocrinology department due to infertility. Phenotypically, the patient appeared as a normal male with normal development of the penis and secondary sex characteristics. Both testicles were small in the scrotum. Azoospermia was detected in the spectrogram. The patient underwent testicular sperm extraction using microdissection, but spermatozoa were not found in either of the testicles. In the cytogenetic and molecular cytogenetic examination of the patient's peripheral blood, the chromosome structure was reported as a 45,X[22]/46,XY[8] mosaic karyotype, and Y microdeletion. 45,X/46,XY, sometimes called mixed gonadal dysgenesis, affects hormonal balance, gonadal development, growth, and fertility, and presents a wide range of clinical manifestations. Similar to our case, these patients may have an entirely male phenotype. Even when the patient exhibits phenotypical normal male characteristics, karyotype anomalies should always be considered when evaluating the infertility associated with azoospermia.

**Keywords:** 45,X/46,XY, mosaicism, mixed gonadal dysgenesis, infertility

## Introduction

Infertility is defined as the inability of couples to conceive after at least 12 months of regular unprotected sexual intercourse. It is a significant health problem that affects 8%-12% of couples who are in the reproductive age range globally. While the male factor is responsible for 20%-30% of infertility cases, an additional 20% contribute to this phenomenon.<sup>1</sup>

Male infertility can be caused by a wide range of factors, including genetic abnormalities, lifestyle choices, diseases, and drugs. Genetic causes account for at least 15% of male infertility. These factors can affect spermatogenic quantitative-qualitative defects, ductal obstruction or dysfunction, and hypothalamic-pituitary axis disturbances.<sup>2</sup> Genetic causes include chromosomal anomalies (numerical or structural), Y chromosome deletions, and autosomal gene mutations. In the general community, karyotype anomalies affect 0.4% of people. The prevalence of genetic anomalies in male infertility is associated with sperm count. Among men with azoospermia, genetic anomalies can be detected in up to 25% (15% karyotype anomaly), with this frequency progressively decreasing as sperm count increases.<sup>3</sup>

The first genetic test that should be performed on patients with quantitative spermatogenic abnormalities is karyotyping (also known as chromosomal analysis). The most frequently detected chromosomal abnormality in karyotyping is Klinefelter syndrome and its variants (47,XXY and mosaics 46,XY/47,XXY). 45,X/46,XY mosaicism is detected less frequently in karyotyping.

Y chromosome microdeletion analysis is another genetic test that should be performed in patients with oligo-azoospermia. Genes on the long arm of the Y chromosome (Yq) are essential for normal spermatogenesis. The azoospermia factor (AZF) region microdeletions are divided into AZFa, AZFb, and AZFc in Yq, the most often seen Y microdeletions. Apart from these, AZFd, an overlapping region of AZFb and AZFc, has been defined. It is not expected to obtain sperm from patients who have complete AZFa and AZFb deletions of the Y chromosome, even with testicular sperm extraction. Genes of the short arm of the Y chromosome (Yp), like SRY (sex-determining region on the Y chromosome) and ZFY, are associated with testis determination during embryogenesis.<sup>2,3</sup>

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In this report, we aim to describe a male patient with 45,X/46,XY mosaic chromosome structure, known as mixed gonadal dysgenesis (MGD), and Y microdeletions, who applied to our Endocrinology Department due to infertility. Written informed consent was obtained from the patient.

### Case Presentation

A 31-year-old male presented to our Endocrinology Department due to infertility. He and his spouse had attempted pregnancy for 13 years. In his sexual history, erection, ejaculation, libido, and frequency of sexual intercourse were normal. His medical history was normal, with no recorded events affecting spermatogenesis such as urogenital or systemic infection, trauma, or torsion, except varicocele surgery. He had no chronic illnesses, was not taking prescription drugs or herbal remedies. There was no data regarding infertility from the time of varicocele surgery until his admission to our hospital.

Phenotypically, the patient appeared as a normal male. His height was 173 cm, weight was 66 kg, and BMI was 22.3 kg/m<sup>2</sup>. There were no abnormalities detected in the clinical examination of the genitals. He had normal secondary sex characteristics and normal development of the penis. Ultrasound examination of the testicles revealed no abnormalities except for the small volume of both testicles. Right and left testicular volumes were 8 mL and 10 mL, respectively. No pathology was detected in the patient's pelvic imaging.

The patient's laboratory test data on admission with reference ranges of our hospital laboratory were as follows: FSH 30 U/L (1.27-19.26), LH 11 U/L (1.24-8.62), total testosterone 4.25 µg/L (1.75-7.81), dehydroepiandrosterone sulfate 240 µg/dL (106-464), 11-deoxycortisol 0.58 ng/mL (0.43-7.56), and 17-OH progesterone 1.413 µg/L (0.2-2.3). Azoospermia was detected in the spectrogram. The patient was referred to the Genetic Department for karyotyping and Y microdeletion screening for AZF, SRY, and ZFY. A 45,X[22]/46,XY[8] mosaic karyotype was detected using fluorescence in situ hybridization analysis at 550 band resolution. AZFb (SY127, SY130, SY131, and SY134), AZFc (SY157, SY254, and SY255), and AZFd (SY152, SY153) microdeletions were detected by multiplex polymerase chain reaction using specific primers.

Mixed gonadal dysgenesis was considered in the patient with these findings. Testicular sperm extraction with microdissection was applied to the patient, but spermatozoa were not detected in either testicle.

### Discussion

The 45,X/46,XY karyotype, sometimes called MGD, is a rare chromosomal abnormality of about 1.5 per 10 000 newborns. Mixed gonadal

dysgenesis originates from a late anaphase lag during mitosis in the zygote, even though interchromosomal rearrangement and, as a result, Y chromosomal abnormalities occasionally occur. The time of Y or Y derivative chromosomal loss determines the rate of mosaicism. This condition may occur with a wide clinical presentation in both genders as it affects hormonal balance, gonadal development, growth, and fertility based on the distribution and percentage of the abnormality in important fetal tissues.<sup>4-6</sup>

A karyotype of 45,X/46,XY may lead to disorders of sexual differentiation with heterogeneous phenotypes, varying from Turner-like females to those with genital ambiguity, to phenotypically normal males with oligo-azoospermia. Mullerian ducts or Wolffian ducts can be found as internal ducts. Gonads may be present as normal testicles or streak gonads. Short stature is one of the phenotypic features that can be seen in these patients. If diagnosed early, they may benefit from growth hormone therapy.<sup>5,6</sup>

Gonadal sex differentiation and phenotype have been linked to Y chromosomal material in the cell line colonizing the primitive gonadal ridge.<sup>7</sup> The percentage of mosaicism in peripheral blood cells and clinical manifestations were found to be unrelated. This also holds for mosaic males who have Y chromosomal structural defects.<sup>8</sup>

In a few studies of the hormone levels of patients with 45,X/46,XY, both genders have been described as having high gonadotropin levels, and male patients have low-normal testosterone levels.<sup>4,6,7,9</sup> Our patient's laboratory test results were consistent with the literature.

Patients with MGD are more likely to develop gonadoblastoma and in situ germ cell neoplasia. It further depends on the patient's age, location of the gonad, and genetic predisposition. Conflicting data exists regarding the connection between this elevated risk and the clinical phenotype. While some studies have reported a high risk of neoplasia in patients with a female phenotype, some studies have reported a higher risk in patients with ambiguous genitalia.<sup>6,10</sup>

All patients with 45,X/46,XY karyotypes should be evaluated for malignancy, irrespective of phenotype. Early investigation and individualized care, including prophylactic gonadectomy, are advised due to the higher risk of gonadal malignancies.<sup>5,10,11</sup> Bilateral gonadectomy is advised for patients raised as female. Hormone production and fertility potential should be evaluated for patients reared as males. Prophylactic gonadectomy is recommended for male patients with streak gonads that contain Y chromosomal material in which hormone production and fertility are not expected. Gonadal biopsies should be considered to exclude the presence of germ cell neoplasia in situ or gonadoblastoma in patients who have not undergone prophylactic gonadectomy. It has been stated in the literature that gonadal malignancy rates in patients with MGD are 15%-20%. Moreover, it increases to 46% at the age of 40.<sup>10-14</sup> Our patient was referred to be evaluated for gonadectomy due to his malignant potential.

### Conclusion

45,X/46,XY mosaicism, a rare chromosomal anomaly, has a wide clinical presentation affecting hormonal balance, gonadal development, growth, and fertility. These patients may appear to have a completely male phenotype with oligo-azoospermia, as observed in our case. Endocrinological evaluation is important before urological invasive procedures are performed in patients admitted due to infertility. One

### MAIN POINTS

- 45,X/46,XY mosaicism, known as mixed gonadal dysgenesis, is a rare cause of infertility.
- 45,X/46,XY mosaicism causes may lead to disorders of sexual differentiation with variable phenotypes ranging from Turner-like females to those with genital ambiguity to phenotypically normal males with oligo-azoospermia.
- All patients with a karyotype of 45,X/46,XY should be assessed for malignancy due to higher risk of developing gonadoblastoma and in situ germ cell neoplasia.

of the first tests to be performed after detecting hypergonadotropic hypogonadism is karyotype analysis and Y microdeletion. From this perspective, a multidisciplinary approach becomes important in terms of the patient's genetic, urological, and endocrinological evaluation.

**Informed Consent:** Written informed consent was obtained from the patient who agreed to take part in the study.

**Peer-review:** Externally peer-reviewed.

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