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MIXED GONADAL DYSGENESIS WITH AN UNUSUAL "INVERTED" Y CHROMOSOME

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Abstract

Mixed gonadal dysgenesis is a rare disorder of sex development associated with sex chromosome aneuploidy and mosaicism of the Y chromosome. It is characterized by a unilateral non-palpable (usually intra-abdominal) testis, a contralateral streak gonad and persistent mullerian structures. The clinical presentation can vary from a typical male to female phenotype including all degrees of cryptorchidism, labial fusion, clitoromegaly, epispadias and hypospadias. It is the second most common cause of ambiguous genitalia in the neonatal period. We report a case of Mixed Gonadal Dysgenesis with an inverted Y chromosome.

Key words: disorders of sex development, mixed gonadal dysgenesis, inverted Y chromosome, mosaicism

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INTRODUCTION

The term Mixed Gonadal Dysgenesis (MGD) was first coined by Sohval in 1963 and first reported in 1975 by Zah and associates [1]. It is an intersex condition characterized by a unilateral testis (often intra abdominal), contralateral streak gonad and persistent mullerian structures along with varying degrees of inadequate masculinization [1]. Most of the patients with MGD have a 45XO/46XY karyotype which probably results due to anaphase lag during mitosis [1].

The nomenclature of intersex conditions was changed to the term "Disorder of sex development (DSD)" in the Chicago Consensus on Management of Intersex Disorders in 2005 [2]. The congenital conditions under DSD are classified into sex chromosome DSD, 46XX DSD and 46XY DSD [2]. The cases with testicular dysgenesis and 45XO/46XY karyotype have been termed as Mixed Gonadal Dysgenesis (MGD) as per the Chicago Consensus [2]. This study reports a rare association of Inverted Y chromosome in a patient with Mixed Gonadal Dysgenesis (MGD).

CASE REPORT

A 2 yr 6 month male child presented with an empty right hemiscrotum and passing urine from the undersurface of penis since birth. On examination, he had right-sided non palpable testis and penoscrotal hypospadias. The stretched penile length was 3.5 cm and there was no chordee. The left testis was normal and present in a well developed left hemiscrotum (fig. 1). On Ultrasonography, the right testis was not localized and the left testis in the left hemiscrotum measured 1.9x1.3x0.8 cm. A uterus of size 2x0.9x0.8 cm could be seen but bilateral ovaries were not visualized. Karyotyping revealed mosaicism 45X/ 47XY inv(Y) /46X inv (Y) (fig. 2).

On HCG stimulation test, there was a significant rise in the testosterone level (Basal level 0.01 ng/ml; post HCG stimulation level 1.43 ng/ml)

At diagnostic laparoscopy (fig. 3), the vas and vessels were seen passing through the left internal inguinal ring. The right internal inguinal ring was closed. A hypoplastic uterus was present. Fallopian tube with an atrophic gonad-like structure could be seen below the fimbrial end on the right side. Right gonadectomy was done. On histopathology (fig. 4), tubular structures resembling ductuli deferentes were seen. The patient underwent staged hypospadias repair.

DISCUSSION

Sexual differentiation is a dynamic and sequential process [1]. As per the Jost paradigm, there are three stages in the fetal sex development [1, 2]:

I. Undifferentiated stage – identical primitive structures develop in XY and XX embryos.

II. Gonadal differentiation – into testis and ovaries.

III. Differentiation of the internal and external genitalia.

Gonadal dysgenesis results in the defective embryonic development of the gonads, which can be divided into complete or pure XY gonadal dysgenesis, incomplete or partial gonadal dysgenesis and mixed gonadal dysgenesis [2].

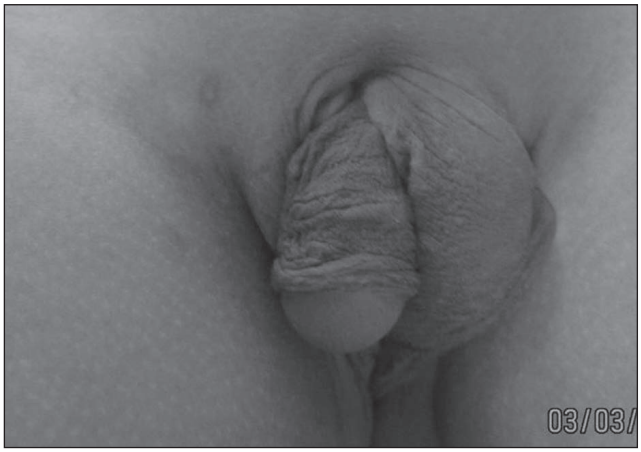

Fig. 1.

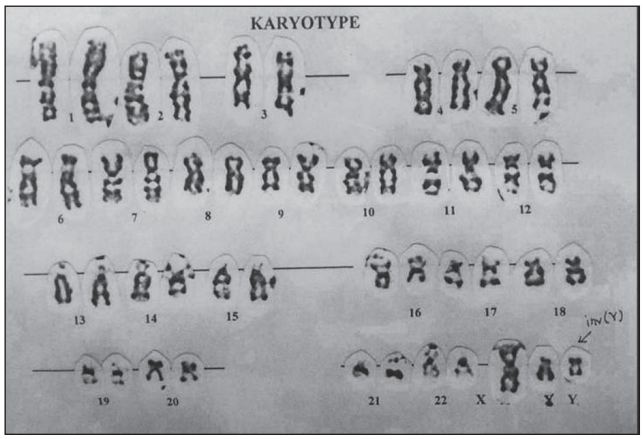

Fig. 2.

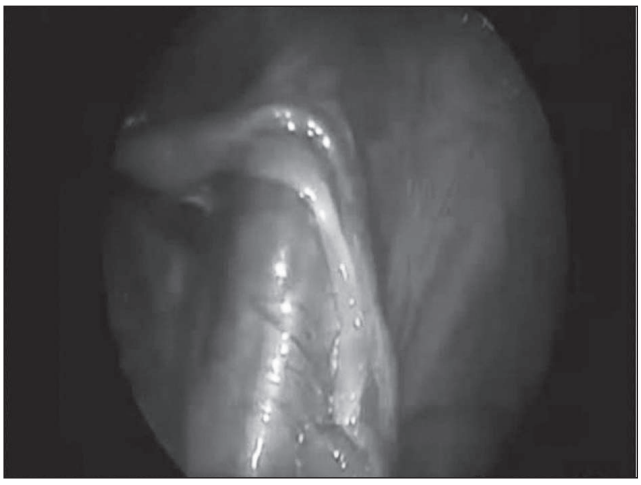

Fig. 3.

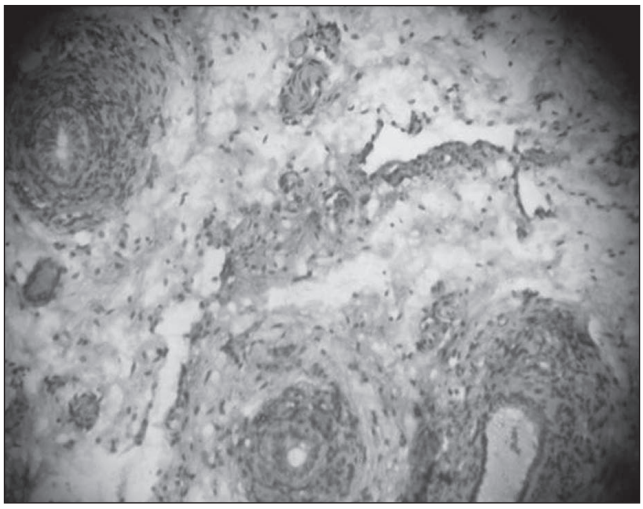

Fig. 4.

Mixed gonadal dysgenesis (MGD) is a disorder of sexual differentiation. It has a sporadic inheritance pattern [2]. It is characterized by a unilateral testis (often intra abdominal), contralateral streak gonad and persistent mullerian structures along with varying degrees of inadequate masculinization. It is the second most common cause of ambiguous genitalia in neonatal period. Although characterized by various karyotypes, 45XO/46XY mosaicism is most common, occurring in 35% of patients [3]. The phenotype of the gonads and the external genitalia depends on the proportion of monosomic cells. The presence of 45X cell lines is frequently associated with Y chromosome rearrangements (commonly dicentric and ring Y chromosomes), which may also have an impact on the phenotype. The gonadal tissue of these patients with 45XO/46XY, normal or structurally abnormal Y depends on the frequency of cell-lines present in their genome [4]. The incidence of inverted Y chromosome in the general population is 0.6 – 1 per 1,000 male births [4]. Inverted Y chromosome runs in families. There has been no evidence regarding the inverted Y chromosome associated with reproductive disadvantage or any phenotypic expression (Bernstein et al, 1986) [4]. However, infertility is the rule in MGD.

The patients present with ambiguous genitalia in the neonatal period. Gender assignment becomes difficult in such neonates. This is because the phenotype of MGD with mosaicism is less well characterized [5].The external genitalia vary from typical male to female configuration including all degrees of cryptorchidism, labial fusion, clitoromegaly, epispadias and hypospadias [3]. Thus, their phenotype can vary from females with Turner's syndrome, new-borns with ambiguous genitalia and the normal male [5]. Internally, the uterus is often rudimentary, but may be normal [3]. A testis is often present in one enlarged labia and a streak gonad containing ovarian tissue without oocytes is present on the opposite side [3]. Though usually raised as males, these patients usually have an absence

or an altered course of pubertal development associated with a final short stature and impaired fertility [5].

Ultrasound (USG) is the first imaging modality, followed by genitography and Magnetic Resonance Imaging (MRI) [3]. The uterus is easily identified on USG as it is relatively enlarged under the effect of maternal hormones [3]. With uterus been identified, the differential diagnosis becomes a virilized female, an MGD or less likely, an ovotesticular DSD (true hermaphrodite) [3]. The presence, location, echotexture of the gonads can also be assessed on USG which may be completely or partially atrophic. Malignancy should be suspected in cases of asymmetric gonadal enlargement and if secondary sexual characteristics develop in the child other than at puberty [3]. MGD is associated with an increased incidence of gonadoblastoma at 15 years (20% incidence) and at 26 years (75% incidence) [3].

Genitography demonstrates the relationship of the urethra with a possible vagina and uterine cavity. The level of communication between the urethra and vagina is demonstrated which is important for planning reconstruction. MRI, if available, allows better morphological evaluation of the mullerian duct structures, the gonads and any developing phallus [3].

Management is based on sex assignment taking into consideration the genital appearance, surgical options (both cosmetic and functional), need for lifelong replacement therapy, potential for fertility and views of the family [2, 6]. This requires a multidisciplinary approach and psychosocial involvement [2]. There is controversy regarding testosterone therapy in these patients [2].

The risk of malignancy in the streak gonad is increased to 70% by the third decade [2]. So, annual testicular ultrasound from age 10 year onwards and follow-up ultrasound and biopsy until age 20 is recommended [2]. Patients need screening for Wilms' tumour as there is increased risk of Wilms' tumour with MGD.

CONCLUSION

Multidisciplinary management should be favoured in cases of obvious ambiguous genitalia, allowing informed decisions for sex assignment and planning of procedures. Surgical reconstruction of genital status should be performed in due course. The possibility of growth hormone treatment needs to be discussed if short stature is found.

Clinical and psychological outcomes depend on the quality of care and level of support provided. Mixed Gonadal Dysgenesis can be a difficult condition for the families to accept. However, individualized management, gender assignment, appropriate gonadectomy, lifelong replacement therapy, psychosexual therapy and screening for malignancy are the key points in the management.

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