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Case Report

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A Rare Presentation of Chimerism (46, XX/ 46, XY), Y (q11.221) Microdeletion Persistent Mullerian Duct Syndrome; A Case Report

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Abstract

The persistent Mullerian duct syndrome (PMDS), classically known as hernia uteri inguinale, genetically and phenotypically male subjects develop female internal organs (uterus and Fallopian tubes). Diagnosis is established when Mullerian duct structures are discovered either during ultrasonography for localization of undescended testis, during surgical exploration for cryptorchidism or hernia repair. The presence of both 46, XX and 46, XY cell lines in a person is known as either chimerism or mosaicism. We reported on a 3- year old child (reared as male) born to consanguineous couple presented with bilateral undescended testis. He underwent the work up, diagnosis and management of PMDS. The patient was karyotyped using the GTG-banding technique and 50 metaphase spreads were counted and analyzed using (FISH). The report revealed two cell lines with chimeric 78% male and 22% female Karyotype (46, XX/ 46, XY) with Y (q11.221) microdeletion. The child was under follow up 3 months and 6 months interval with clinical, USG study and color Doppler scrotal US after surgery. The Patients with such pathology should be studied carefully and parents should be genetically counselled. Suspected future fertility of the patient need to be kept in mind and ethical counselling before performing the definitive surgery is essential to prevent future litigation.

Keywords: Chimerism; Microdeletion; Persistent; Mullerian; Duct

Introduction

The persistent Mullerian duct syndrome (PMDS), classically known as hernia uteri inguinale, is a rarely reported disorder of sexual development (DSD). In this condition, genetically and phenotypically male subjects develop female internal organs (uterus and Fallopian tubes) due to a deficiency in the anti-Mullerian hormone (AMH) produced by Sertoli cells, or its type II receptor (AMHR-II), and it has an autosomal recessive mode of inheritance [1]. Anatomically PMDS is divided into three categories. Patients suffering from PMDS present with cryptorchidism, inguinal hernia, and infertility [2]. Diagnosis is established when Mullerian duct structures are discovered either during ultrasonography for localization of undescended testis, during surgical exploration for cryptorchidism or hernia repair. The presence of both 46, XX and 46, XY cell lines in a person is known as either chimerism or mosaicism. Chimerism results from the amalgamation of two different zygotes in a single embryo, whereas mosaicism results from a mitotic error in a single zygote. The phenotypic spectrum of 46, XX/46, XY chimeric patients is variable [3]. It ranges from normal male or female genitalia to different degrees of ambiguous genitalia [4]. A considerable percentage of all reported PMDS cases were found to have a malignant transformation of their Mullerian structures. Accordingly, all such structures should be removed whenever possible to eliminate the risk of malignancy and to save the patient a lifelong follow-up [5]. The co-existence of PMDS and transverse testicular ectopia in a patient of chimeric Karyotype (46XY/46XX) is a unique genetic association. Here, we report on a new case of chimerism (46, XX/46, XY) PMDS variety, female type with bilateral cryptorchid testis, uterus and Fallopian tubes.

Ethics statement

Written informed consent was obtained from the patients' parent who participated and managed in this report for publication of both cases and any accompanying images. The scientific and health

committee in our Health directorate office approved this publication.

Case Report

A 3- year old child (reared as male) born to consanguineous couple presented with bilateral undescended testis. On clinical examination, the patient had normal phallus, stretched penile length (SPL) 4.2 cm and bilateral testes were not palpable despite well-developed scrotum. A small mass in the right upper inguinal canal, it could not be reduced or pulled down into the scrotum easily. A clinical diagnosis of cryptorchidism with the indirect right inguinal hernia was made. His developmental milestones were normal and intelligence was average. There was no history of congenital and genetic diseases in their family. In ultrasonography USG, abdominal organs appeared normal, uterus was detected and ovary like structure could not be confirmed. Testis like structures were seen in the right upper inguinal canal and abdomen (near the first one) respectively. The first one measuring about 15.8x 7.3 mm, the abdomen one 14.6x 6.4 mm (figure 1). Magnetic Resonance Imaging MRI confirmed the USG findings. It showed a well-formed uterus and fallopian tubes alongside the urinary bladder and extending into the right inguinal region. Oval structures measuring 1.5 × 1 cm, and 1.3 x 1 cm with morphology and signal intensity consistent with testis were detected at the level of the right deep inguinal ring. The hormonal profiles were suggested, Serum level of testosterone (ST) was 11 nmol/L, luteinizing hormone (LH) 0.6 IU/ dL, follicular stimulating hormone (FSH) 0.1 IU/dL and Oestradiol 3 pmol/L. The human chorionic gonadotropin (HCG) stimulation test was performed (724 ng/dL), which was suggestive of functional testicular tissue. Anti-Mullerian hormone (AMH) was <0.01 ng/ml, reconfirmation, was quite undetectable. Complete blood count, coagulation profile, liver function test, renal function test, and thyroid function test were normal. The patient was karyotyped by the standard conventional peripheral lymphocyte culture using the GTG-banding technique and 50 metaphase spreads were counted and analyzed using fluorescence in situ hybridization (FISH). The report revealed two cell lines with chimeric 78% male and 22% female Karyotype (46, XX/ 46, XY) with Y(q11.221) microdeletion at AZFa (AZoospermia Factor-a) location, (YSP9Y and DPY-DDX3Y) genes (figure 2, A-C). The condition was discussed with the parents when PMDS was the initial diagnosis and the patients arranged for surgery accordingly. Through the right inguinal skin crease incision, exploration and mobilization were done, uterus (Mullerian structures) split in the midline without damaging the vascularity of testes, it dissected away from the right, and left vas deferens. The vessels in the right and left broad ligaments were secured and the right and left Fallopian tube and gubernaculum were ligated and cut. A Gross uterus measured 5×4×4 cm with each tube measuring 6.5 cm (figure 3, A-B). A Prader orchidometer was enrolled to measure the testicular volume at the time of the orchidopexy [6]. Both gonads (testis) were biopsied, the testes brought separately into scrotum and orchidopexy were done. The biopsy report was suggestive of normal testicular tissue (No ovarian stroma or primordial follicles were identified). The report of uterine and fallopian structures submitted endometrium with small round glands and compact stroma with both the Fallopian tubes showing normal histology (figure 4, A-E). All these findings confirmed the diagnosis of PMDS. The child was under follow up 3 months and 6 months interval with clinical, USG study and color Doppler scrotal US. A good-sized right testicle in the scrotal sac was seen, the left one progressively atrophied.

Figure 1: Ultrasonography image, uterus was detected and ovary like structure could not be confirmed. Testis like structures were seen in the right upper inguinal canal (IT) and abdomen (AT) near the first one, respectively.

Figure 2: (A-C) fluorescence in situ hybridization report revealed. (A) Two cell lines with chimeric 78% male and 22% female Karyotype (46, XX/ 46, XY), (B and C) Y(q11.221) microdeletion at AZFa (A Zoospermia Factor-a) location, (YSP9Y and DPY-DDX3Y) genes.

Figure 3: (A-B): Operative images revealed (A) Uterus (U) (Mullerian structures) split in the midline without damaging the vascularity of testes, it dissected away from the right, and left testis (T) and vas deferens (arrowed). (B) The vessels in the right and left broad ligaments and mesosalpinx (MS) were secured and the right and left Fallopian tube (FT) and gubernaculum were ligated and cut with preservation of testis and vas deferens (V) (arrowed).

Figure 4: (A-E): histopathology images, (A and B) The report of uterine and fallopian structures submitted endometrium with small round glands and compact stroma. (B and C) Both the Fallopian tubes showing normal histology. (E) Normal testicular tissue (No ovarian stroma or primordial follicles were identified).

Discussion

The first report described the rare entity of transverse testicular ectopia (TTE) was submitted by Von Lenhossek in 1886 [7]. The association of TTE and PMDS announced by Jordan in 1895 [8]. In 1939, Nelson highlighted the association of inguinal hernia as hernia uteri inguinale [9]. Three anatomical classification was submitted in the literature; one, (male type) testis present in the scrotum or in the inguinal canal and can be brought into it by gentle traction, it presented in (60-70%) of PMDS, two, (male type) transverse testicular ectopia (20-30%), and three, (female type) bilateral cryptorchidism, testis present at ovarian position with respect to the uterus, which is fixed in the pelvis, (10-20%) [8]. Patient with PMDS have a normal male phenotype and are assigned to the male sex at birth. However, a thorough examination of the newborn shows genital abnormalities. True hermaphroditism was the closest differential diagnosis. Ultrasonography (USG), MRI, computerized tomography CT successfully detected the PMDS and the laparoscopy is by far the most accurate diagnostic method for the impalpable testis [9]. The usual molecular basis of the patients with the PMDS is 46, XY genetic males, with no chromosomal abnormalities and normal testosterone production and responsiveness. The condition is transmitted according to a recessive autosomal pattern and is due either to lack of production of AMH, secondary to a mutation of the AMH gene (was cloned in 1986; it is located on the tip of the short arm of chromosome 19, band p13.3), or to insensitivity of Mullerian ducts to AMH action, due to a mutation of the AMH receptor [10]. However, persistent Mullerian duct syndrome affects only males. Females with two mutated copies of the gene do not show signs and symptoms of the condition [9]. Accordingly, the Mullerian duct usually breaks down during early development in males, but it is retained in those with persistent Mullerian duct syndrome. In the vast majority of subjects, mutations are detected on both alleles; however, in exceptional cases, extensive searches yielded mutations on only one allele [11]. Authors' detected 38 different mutations of the AMH gene, representing 46% of the total number of families in literature survey, most are homozygous, due to the predominantly Mediterranean and Arab origin of the patients, populations with a high incidence of consanguinity [7]. This may give part of the explanation, as our patient is a product of Arab origin consanguineous couple. A chimera is an individual with two or more cell lines derived from different zygotes. The chimerism arises in utero from the combination of an XX zygote and an XY zygote (which otherwise would have developed into twins) into a single embryo [12]. It is not to be confused with mosaicism and hybridism, 46, XX/46, XY is sometimes associated with Intersex conditions such as ambiguous genitalia and hermaphroditism, but in many cases, phenotypically normal male or female development occurs [13]. In literature 46, XX/46, XY is an example of tetragametic chimerism because it requires 4 gametes, 2 sperm and two ova [14]. Two sperms from

the father fertilize two ova from the mother, one sperm contains an X chromosome; the other contains a Y chromosome. The result is that a zygote with an XY genotype and a zygote with an XX genotype are produced. Under normal circumstances, the two resulting zygotes would have gone on to become fraternal twins [15]. As individuals with 46, XX/46, XY possess both ovarian tissue and testicular tissue, depending on the individual, gonads (ovaries or testes) may function fully, partly or not at all [16]. At puberty, a mix of male and female characteristics may emerge. Some individuals will experience deepening of the voice and secondary hair development, while others may experience breast tissue development [17]. Authors reported in DSD individuals about 6.06% of patients showed 46, XX/46, XY Karyotype and in another study 0.1% patients referred to as male and karyotyping showed 46, XX/46, XY chromosomes [17,18]. Anatomically it refers to individuals who usually have a differentiated gonad on one side and a streak gonad or a streak testis on the other side. Few authors apply the term to patients who show testicular differentiation on both sides with bilateral streak testes or bilateral dysgenetic testes with karyotype 45X/46XY [19]. The rarity of our case was the presentation of the two testis and fallopian tubes in the right inguinal region. Other effects of persistent Mullerian duct syndrome may include the inability to father children (infertility) or blood in the semen (hematospermia) [20]. In addition, the undescended testes may break down (degenerate) or develop cancer if left untreated. A deletion analysis study of the Y chromosome has revealed three common deletions that are termed AZFa, AZFb, and AZFc with deletions linked to meiotic recombination errors in highly repetitive sequences within and adjacent to the deletion intervals [21,23]. The AZFa region appears to have the most severe outcome for spermatogenesis in men, consistently resulting in a complete absence of spermatogenic cells and a clinical diagnosis termed Sertoli-Cell Only (SCO) syndrome [24-26]. The karyogram in our patient may explain the future expectancy dealing with the susceptibility of infertility. For ethical consideration, the family informed about the all suspected sequel that this pathology might carry. The age of our patient, do not allow the fertility evaluation, but, considering the segment deleted in the Y-chromosome (q11.221), it is very likely that he will be infertile. The strict histological criterion necessary for the diagnosis of true hermaphroditism is ovotestis, that is, well-defined testicular elements like solid seminiferous tubules with immature Sertoli cells, few primitive germ cells, and ovarian stroma composed of numerous primordial or mature follicles containing primary oocytes [27]. It is important to differentiate the two conditions because it is necessary for gender assignment. In PMDS with mixed germ dysgenesis MGD, 30% of patients develop germ cell tumors like dysgerminoma, yolk sac tumor, embryonal carcinoma, and hence gonadectomy is necessary [28]. In our case, we removed the uterus and both fallopian streaks.

Conclusion

This is a rare presentation of chimerism (46, XX/ 46, XY), Yq11.221 microdeletion PMDS. The Patients with such pathology should be studied carefully and parents should be genetically counselled. Suspected future fertility of the patient need to be kept in mind and ethical counselling before performing the definitive surgery is essential to prevent future litigation. Awareness among the surgeons and the acknowledgements about the possible forms of PMDS helps to assign the frame of management during operation.

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Conflict of Interest

The authors declare that they have no competing interests.

Bibliography

1. Prakash N., *et al*. "Persistent Mullerian duct syndrome". *Indian Journal of Pathology and Microbiology* 52 (2009): 546-548.

2. Rehman A., *et al*. "Combined persistent Mullerian Duct Syndrome, Transverse Testicular Ectopia and Mosaic Klinefelter's Syndrome". *Journal of College of Physicians and Surgeons Pakistan* 18 (2008): 375-357.

3. Mansura Khan., *et al*. "A 46, XX / 46, XY mosaicism or chimerism diagnosed by Karyotyping". *Bangladesh Critical Care Journal* 6 (2018): 111-113.

4. Abdulrahman A Al-Bassam. "Persistent Mullerian duct syndrome associated with transverse testicular ectopia". *Annuals of Saudi Medicine* 17 (1997): 226-227.

5. Aruna N., *et al*. "46, XX/46, XY chimerism - a case report". *Journal of the Anatomical Society of India* 55 (2006): 24-26.

6. Prader A. "Testicular size: Assessment and clinical importance". *Triangle* 7 (1966): 240-243.

7. Vale´rie Malan., *et al*. "Prenatal diagnosis and normal outcome of a 46, XX/46, XY chimera: A Case Report". *Human Reproduction* 22 (2007): 1037-1041.

8. Eric L Martin., *et al*. "Persistent Mullerian duct syndrome with transverse testicular ectopia and spermatogenesis". *Journal of Urology* 147 (1997): 1615-1617.

9. Faure E., *et al*. "Mutant isoforms of the anti-Müllerian hormone type II receptor are not expressed at the cell membrane". *Journal of Biological Chemistry* 271 (1996): 30571-30585.

10. Clemente A., *et al*. "Female form of persistent mullerian duct syndrome: MDCT findings". *Clinical Imaging* 32 (2008): 314-317.

11. Josso N and di Clemente N. "Transduction pathway of anti-Mullerian hormone, a sex-specific member of the TGF-b family". *Trends in Endocrinology and Metabolism* 14 (2003): 91-97.

12. Cate RL., *et al*. "Isolation of the bovine and human genes for Mullerian inhibiting substance and expression of the human gene in animal cells". *Cell* 45 (1986): 685-698.

13. Cohen-Haguenauer O., *et al*. "Mapping of the gene for anti-Mullerian hormone to the short arm of human chromosome 19". *Cytogenetic and Genome Research* 44 (1987): 2-6.

14. Nathalie Josso., *et al*. "AMH and AMH receptor defects in persistent Mullerian duct syndrome". *Human Reproduction Update* 11 (2005): 351-356.

15. Fitzgerald PH., *et al*. "A true hermaphrodite dispermic chimera with 46, XX and 46, XY karyotypes". *Clinical Genetics* 15 (1979): 89-96.

16. Schoenle E. "46, XX/46, XY chimerism in a phenotypically normal man". *Human Genetics* 64 (1983): 86-89.

17. Malan V., *et al*. "Prenatal diagnosis and outcome of a 46, XX/46, XY chimera: a case report". *Human Reproduction* 22 (2007): 1037-1041.

18. Zhen-Guo MI and Xiao-Feng Y. "Karyotypic analysis of intersexuality in Chinese from Taiyuan Asian". *Journal of Andrology* 2 (2000): 155-157.

19. Duarte AC., *et al*. "Cytogenetics of Genetic Counseling Patients in Pelotas, Rio Grande do Sul, Brazil". *The Genetics and Molecular Research Journal* 3 (2004): 303-308.

20. Renu D., *et al*. "Persistent Mullerian duct syndrome". *Indian Journal of Radiology Imaging* 20 (2010): 72-74.

21. Scully RE., *et al*. "Atlas of Tumor Pathology: Tumors of the Ovary, Maldeveloped Gonads, Fallopian Tube, and Broad Ligament, 3rd Series". *Armed Forces Institute of Pathology:* Washington, DC (1998): 399-408.

22. Blackless M., *et al*. "How sexually dimorphic are we? Review and synthesis". *American Journal of Human Biology* 12 (2000): 151-166.

23. Vogt PH. "Genomic heterogeneity and instability of the AZF locus on the human Y-chromosome". *Molecular and Cellular Endocrinology* 224 (2004): 1-9.

24. Kuroda-Kawaguchi T., *et al*. "The AZFc region of the Y chromosome features massive palindromes and uniform recurrent deletions in infertile men". *Nature Genetics* 29 (2001): 279-286.

25. Skaletsky H., *et al*. "The male-specific region of the human Y chromosome is a mosaic of discrete sequence classes". *Nature* 423 (2003): 825-837.

26. Blagosklonova O., *et al*. "AZFa deletions in Sertoli cell-only syndrome: a retrospective study". *Molecular Human Reproduction* 6 (2000): 795-799.

27. Foresta C., *et al*. "Deletion and expression analysis of AZFa genes on the human Y chromosome revealed a major role for DBY in male infertility". *Human Molecular Genetics* 9 (2000): 1161-1169.

28. Foresta C., *et al*. "Role of the AZFa candidate genes in male infertility". *Journal of Endocrinological Investigation* 23 (2000): 646-651.