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Case report *Medical research*

Male form of persistent mullerian duct– A case report

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ABSTRACT

Persistent Müllerian duct syndrome (PMDS) is a developmental disorder. The males suffering from this disorder also bear uterus and fallopian tube which belong to the female reproductive system. During the development of fetus a structure known as the Mullerian or the Para mesonephric duct gives rise to the uterus and the fallopian tube. Generally, Mullerian duct degenerates in males during the early development, however if this persist it leads to PMDS. Affected males although have the normal genotype (46, XY) and normal external male genitalia.

Males with persistent Müllerian duct syndrome usually present with undescended testes (cryptorchidism) or inguinal hernias. The uterus and fallopian tubes are usually discovered when surgery is performed to treat these conditions.

PMDS (PMDS) is usually an accidental finding either during orchipexy or during routine inguinal hernia repair in male patients. It is caused by a defect in the mullerian inhibiting substance system. PMDS is a rare disorder; however, the prevalence of the condition is unknown. The authors report a case of an 11year old male child with PMDS and bilateral undescended testis.

Key Words: PMDS, Mullerian Duct, Orchipexy, Cryptorchid testes.

INTRODUCTION

Persistent Mullerian Duct Syndrome is a rare form of male developmental disorder .It is inherited in an autosomal recessive pattern that indicates both copies of the gene in each cell have undergone mutations. Therefore, the parents of an individual with an autosomal recessive condition typically do not show any signs and symptoms of the condition. Intersexual disorders have always been a primary concern for the clinicians with regards to their diagnosis, treatment and sex of rearing. These intersexual disorders are majorly classified as the disorders which are associated with the normal phenotype or the normal chromosomal constitution and those with the abnormal chromosomal constitution. PMDS is a form of male intersex caused by a defect in the mullerian inhibiting substance (MIS) system. Patients are phenotypically male and usually present with unilateral or bilateral crypt orchid testes and an inguinal hernia into which prolapses an infantile uterus and fallopian tubes. Familial cases have been reported with a probability of sex-limited autosomal recessive or X-linked recessive inheritance. An incidence of PMDS in identical twins has also been

reported. PMDS is often misdiagnosed due to a lack of familiarity with the condition. We report our case to stress the association of this condition with most undescended testis. A review of the literature showed only about 20 case reports from India including familial cases[1]. In, PMDS usually the testes and the female reproductive organs can be found to be situated in different positions. It is rare that both the testes remain undescended known as the bilateral cryptorchidism. Unilateral descent of testis into the scrotal sac is commonly observed. The uterus however is found in the pelvic cavity. Hernia uteri inguinalis occurs when the descended testis pulls the fallopian tube and the uterus into the track through which it has descended. In other cases, the undescended testis from the other side of the body is also pulled into the same track, forming an inguinal hernia. This condition, called transverse testicular ectopia, is common in people with PMDS. The PMDS may also present some of the other symptoms such as infertility, blood in semen and sometimes may lead to carcinoma if the undescended testes are left untreated. Most people with persistent Müllerian duct syndrome have mutations in the AMH gene or the AMHR2gene. The AMH gene is located on the short (p) arm of chromosome 19 at position 13.3. The AMH gene provides instructions for making a protein called anti-Müllerian hormone (AMH). During development of male fetuses, the AMH protein is produced and released (secreted) by cells of the testes. The secreted protein attaches (binds) to its receptor, which is found on the surface of Müllerian duct cells. The Müllerian duct, found in both male and female fetuses, is the precursor to the female reproductive organs. Binding of the AMH protein to its receptor induces self-destruction (apoptosis) of the Müllerian duct cells. As a result, the Müllerian duct breaks down (regresses) in males. In females, who do not produce the AMH protein during fetal development, the Müllerian duct becomes the uterus and fallopian tubes. Mutations in the AMH and AMHR2 genes lead to nonfunctional proteins that cannot signal for regression of the Müllerian duct. As a result of these mutations, the Müllerian duct persists and goes on to form a uterus and fallopian tubes. Approximately 45 percent of cases of persistent Müllerian duct syndrome are caused by mutations in the AMH gene and are called persistent Müllerian duct syndrome type 1. Approximately 40 percent of cases are caused by mutations in the AMHR2 gene and are called persistent Müllerian duct syndrome type 2. In the remaining 15 percent of cases, no mutations in the AMH and AMHR2 genes have been identified, and the genes involved in causing the condition are unknown.

CASE REPORT

An 11 year old boy was presented with the case of bilateral undescended testis. On chromosomal analysis the patient presented with a normal phenotype representing (46 XY) male. The ultrasonography evaluation revealed that the scrotal sacs were bilaterally empty, undescended testis was on the left side was observed as an oval isoechoic structure measuring about 14x 7 mm found lying deep to the deep inguinal ring however the testis on the right side could not be visualized. The patient was then advised for an orchiopexy operation. During orchiopexy, rudimentary uterus and fallopian tubes were also observed indicating that the patient suffered from the Persistent Mullerian Duct Syndrome. His FSH, LH and testosterone levels were all found to be in the normal range.

FIGURES

Fig 1: Figure depicting the empty scrotal sacs.

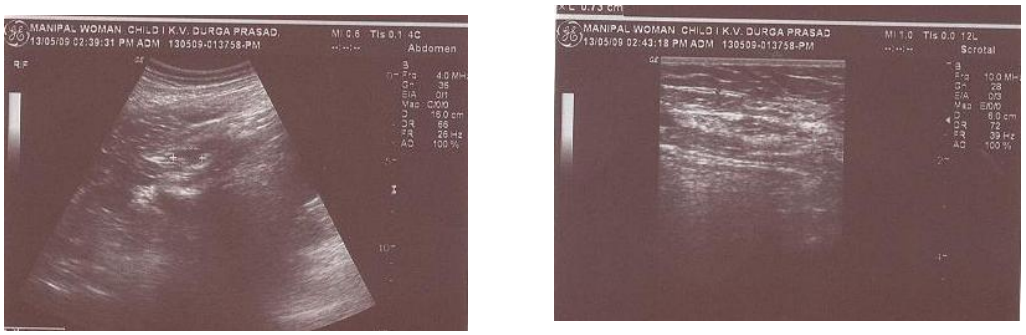

Fig 2: Ultrasound of the abdominal cavity showing undescended testis.

DISCUSSION

PMDS is a rare form of male pseudo hermaphroditism characterized by the presence of mullerian duct structures in 46 XY phenotypic males. It is caused by a defect in the Mullerian Inhibiting Substance system. The MIS is a large glycoprotein that sertoli cells produce early in fetal life. The gene responsible for the substance is on chromosome 19. MIS is also known as anti-mullerian hormone. MIS is a homodimeric glycoprotein linked by disulfide bonds with a molecular weight of 140 kD, belonging to the transforming growth factor-β (TGFβ) superfamily2. MIS is expressed in fetal and prepubertal Sertoli cells and causes degeneration of the Müllerian ducts. Mutation of the MIS gene or the MIS receptor type II in human males leads to persistent Müllerian duct syndrome (PMDS) 3. The primary function of MIS is to cause regression of the mullerian (paramesonephric) ducts in the male fetus. MIS is first secreted in effective amounts at 56-62 days after fertilization, and the process of mullerian regression is normally completed by about Day 77, after which the mullerian tissue is no longer sensitive to MIS. Another important function of MIS is to initiate testicular descent, principally by its postulated regulatory control over the gubernaculum testis4, 5. These two functions of the MIS explain the clinical findings. Once the gonads are formed, the pivotal event in male sexual differentiation is expression of the SRY gene (sex determining region of the Y chromosome). SRY is necessary and sufficient to initiate the male development cascade of PMDS6. SRY encodes a high-mobility group (HMG) box-transcription factor and, similar to other HMG-transcription factors, binds preferentially to a consensus DNA sequence and causes DNA bending7. The physiological target genes for SRY/Sry remain unknown, but potential candidates including Sox9, SF-1, DMRT1, GATA-4, Dhh, andtestatin, are up-regulated during testicular differentiation. SRY/Sry triggers differentiation of the supporting cell lineage into Sertoli cells8. After the differentiation of gonads into testes, the masculinization of the embryo is promoted by the sufficient secretion of the testicular hormones. The male phenotype relies on the secretion of three testicular hormones: MIS, testosterone, and Insl3. Evidence suggests that MIS causes regression indirectly through its effects on mesenchymal cells surrounding the Müllerian ducts. The MIS type II receptor is expressed in the mesenchyme cells surrounding the Müllerian ducts during the period of sex determination and Müllerian duct regression. Indeed, MIS has no effect on isolated epithelial cells9. In addition to Müllerian duct regression and androgen-dependent virilization of the urogenital system, transfer of the male gonad from its site of origin at the urogenital ridge, opposed to the kidney, into the scrotum is yet another critical event in male sexual differentiation. In humans, failure of complete testicular descent into the scrotum (cryptorchidism) is one of the most frequent congenital abnormalities involving 3% of male births. At 1 yr. of age, 1% of infants still have undescended testes. Cryptorchidism is a clinical issue for two reasons. First, spermatogenesis requires a lower temperature present in the scrotum. Untreated cryptorchidism can lead to infertility. In addition, cryptorchidism is associated with an increased risk of testicular tumors .The genital mesentery, composed of the cranial suspensory ligaments (CSL) and the caudally positioned gubernaculum, connects the gonads to the abdominal wall. In mice, sexually

dimorphic development of the genital mesentery is responsible for the sexually dimorphic position of mature testes and ovaries. In the female embryo, development of the CSL but not of the gubernaculum maintains the ovaries at the original position of the gonads. In contrast, in the male embryo, regression of the CSL and the outgrowth and subsequent regression and inversion of the gubernaculum mediates transfer of the testes into the scrotum10. Clinically, PMDS cases are divided into three categories. Majority (60-70%) with bilateral intra-abdominal testis in apposition analogous to ovaries, smaller group (20-30%) with one testis in the scrotum associated contralateral inguinal hernia whose contents are testis, uterus and tubes (classical presentation of hernia uteri inguinale) Smallest group (10%) where both the testes are located in the Same hernia sac along with the mullerian structures (transverse testicular ectopia-TTE) Manjunath et al. reported two cases of PMDS (familial), one with bilateral intra-abdominal testes and the other having hernia uteri inguinale with TTE which was similar to the present case5. However, in the present case no dysplastic changes or malignancy were observed. However, Berkmen11 reported three cases with PMDS associated with testicular malignancy: Two cases were of testicular seminoma and the remaining one case showed both testicular seminoma and teratoma. Compared with a normally descended testis, the cryptorchid testis has a 7-35% increased risk of developing a malignant tumor, especially seminoma. Moreover, the risk of developing a malignancy is greater in an abdominal than in an inguinal testis. Seminoma is the most common histological type in cryptorchid patients or in PMDS. The diagnosis of PMDS is made incidentally during surgical exploration for cryptorchidism or herniorraphy as the mullerian remnants are not palpable on abdominal, rectal or scrotal examination. Intraoperative methods of diagnosis, especially the gonadal biopsy, can be performed to rule out mixed gonadal dysgenesis and developing malignancy [9]. Mixed gonadal dysgenesis is a disorder associated with an abnormal sex chromosome constitution, characterized by ambiguous genitalia with unilateral testis and a streak gonad contralaterally, with persistence of mullerian duct structures on the side of the streak[3]. Another clinical presentation is that of crossed testicular ectopia or transverse testicular ectopia. It is usually seen to be associated with PMDS. It is a rare congenital anomaly in which both the gonads migrate toward the same hemiscrotum6.

CONCLUSION

PMDS has an autosomal recessive inheritance. Screening of siblings and second-degree relatives is necessary. Although ultrasonography and magnetic resonance imaging are reported to play a role in locating the mullerian remnants, laparoscopy has a distinctive advantage in diagnosing PMDS. Familiarity of the operating surgeon with this disease condition would increase the chances of correctly diagnosing and appropriately dealing with the mullerian remnants. In cases of unilateral, bilateral and cryptorchidism with or without inguinal hernia as in the present case, the possibility of PMDS should be sought in mind by the pediatric surgeon to prevent further complications such as infertility and malignant changes.

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