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CASE REPORT

Persistent Müllerian Duct Syndrome: Fertility Challenge

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ABSTRACT

Persistent Müllerian duct syndrome (PMDS) is a rare, autosomal recessive disorder of sex development, of male pseudohermaphroditism, characterized by the persistence of Müllerian duct derivatives: uterus, fallopian tubes, and upper vagina. Mutations of the gene or the receptor of anti-Müllerian hormone (AMH) are responsible for clinical symptoms of PMDS, with subjects having a 46 XY karyotype and a male phenotype. We report the case of a 23-year-old male patient with bilateral undescended testes (UDT) and the surgical management as well as briefly the ethical principles behind the certain clinical decision. In conclusion, we suggest that such cases need a holistic approach with a multidisciplinary team as well as patient and health care professional education.

Keywords: Anti-Müllerian hormone, Autonomy, Beneficence, Hormones, Persistent Müllerian duct syndrome, Surgical management, Undescended testis.

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INTRODUCTION

Nilson in 1939 was the first one to describe the case of PMDS.[1] Until date, approximately 200 cases have been reported.

Persistent Müllerian duct syndrome is a rare, autosomal recessive disorder of sex development, of male pseudohermaphroditism, characterized by persistence of Müllerian duct derivatives: Uterus, fallopian tubes, and upper vagina. Müllerian structures do not regress either due to the absence of AMH or lack of response to it. Anti-Müllerian hormone induces Müllerian duct regression at around 7 weeks of gestation (Fig. 1).

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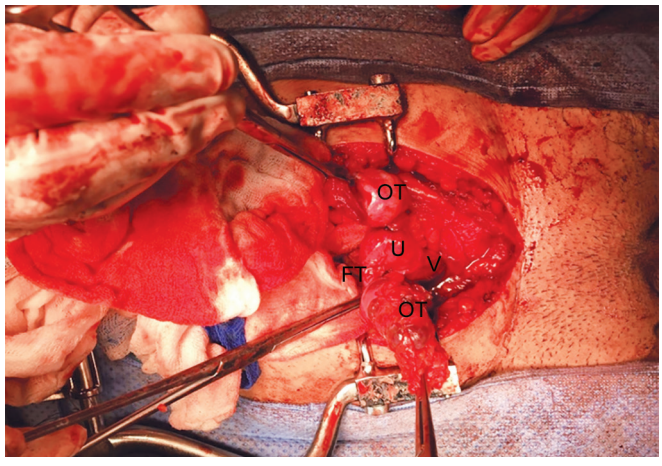

Fig. 1: Surgical management of PMDS. OT: Ovotestis; U: Uterus; V: Vagina

CASE REPORT

A 23-year-old male patient presented with a history of bilateral UDT. On physical examination, the patient was phenotypically male, with male pattern of external genitalia and secondary sexual characteristics. Scrotum was underdeveloped. Magnetic resonance imaging (MRI) revealed the presence of Müllerian structures (small uterus, underdeveloped vagina, and gonads).

Clinical laboratory findings: Karyotypically 46 XY male patient; azoospermia on semen analysis; high follicle stimulating and luteinizing hormone and normal testosterone.

Familial history indicated that his sibling passed away due to germ cell malignancy, had PMDS, and the same clinical presentation.

Surgical Management

Left testis was fixed near the anterior pelvic ring due to short spermatic cord. Orchiectomy of the right testicle and hysterectomy along with complete removal of other Müllerian structures were done. Left testicular biopsy, and right testicle, uterus, and other Müllerian structures were submitted for histopathology examination.

Tissue samples of right and left testes were also sent to *in vitro* fertilization (IVF) laboratory for processing and assessment.

Postsurgical Laboratory Findings

IVF Lab: No sperm or immature sperm cells identified after biopsy processing.

Table 1: Hormonal profile pre- and postsurgery

Hormones	*Presurgery*	*Postsurgery*	*Normal level*
Estrogen (E2) (pmol/L)	101	<18.4	28–156
Follicle-stimulating hormone (IU/L)	19.2	98.9	1.5–12.4
Luteinizing hormone (IU/L)	16	49.9	1.7–8.6
Testosterone (nmol/L)	18.38	0.909	9.9–27.8
Prolactin (µg/L)	22.88	17.3	4.1–18.4

Left testicular biopsy: Hyalinized seminiferous tubules with intratubular germ cell neoplasia (IGCN). No evidence of spermatogenesis.

Right testis, orchiectomy: Mixed germ cell-sex-cord stromal tumor with focal invasion and IGCN present.

Uterus: Benign endometrium and myometrium: Negative for malignancy.

Hormonal Profile

It can be noted that estrogen, testosterone and prolactin level dropped whereas the level of LH and FSH increased, due to the removal of the ovotestis (Table 1).

DISCUSSION

The production of AMH by immature Sertoli cells during the 8th and 9th weeks of male fetal life acts on its receptor in the Müllerian ducts to cause their regression through apoptosis and mesenchymal transformation.[2] Persistent Müllerian duct syndrome is an autosomal recessive congenital disorder characterized by the presence of Müllerian duct derivatives in a genetically male individual and classified as an intersex condition under 46 XY Disorder of Sexual Development (DSD) caused by a mutation in the AMH or AMH receptor genes.[3,4] Humans with defective AMH function normally have cryptorchidism, where the testes are often intra-abdominal and on an abnormally long gubernacular cord[5] as observed in our case, suggesting that AMH may have a role in testicular descent.

Anti-Müllerian hormone deficiency due to mutations in the AMH gene represents an early-onset fetal hypogonadism with Sertoli-cell specific dysfunction. Patients are normally virilized indicating normal Leydig cell function.[2] The endocrine profile of our patient indicates normal Leydig cell functioning as the testosterone level was in the normal range presurgery, and after orchiectomy, the level dropped below normal. Estrogen level was abnormally high presurgery, suggesting the presence of germ cell neoplasia and the level subsequently dropped below normal postsurgery.

It is estimated that the risk of germ cell tumor in untreated intra-abdominal UDT may be as high as 50%,[6] and this is evident from the histopathology report of our patient indicating the presence of germ cell neoplasia. Studies suggest that orchidopexy before the age of 10 to 11 years might eliminate the risk of testicular malignancy associated with cryptorchidism.[7]

Familial inheritance of PMDS is obvious in this case as the patient's male sibling passed away due to malignancy and had similar clinical presentation. In our opinion, screening of siblings and second-degree relatives due to the autosomal recessive inheritance nature of this condition is highly advisable.

The IVF report on testicular biopsy is obviously negative in this pathology. Fertility remains uncertain in cases of bilateral UDT. However, a recent study suggests that AMH may be a possible future treatment for stimulating germ cell development in cryptorchidism, which, however, needs further development and investigations.[8] Thus, along with study and stem cell research, this might be a hope to infertile patients. In our opinion, in cases of early diagnosis in early childhood or prepubertal stage where orchidopexy is performed, even if there is no anatomical connection between viable testes and the penis, there can be a possibility of retrieving sperm cells for intracytoplasmic injection.

On an ethical note, in the management of this case, physicians had to let go of the beneficence principle by respecting the patient's autonomy, despite all the risks explained to the patient. The urologists respected the autonomy of the patient by keeping the left testis intact (orchidopexy was performed instead of orchiectomy). We consider our patient as an independent moral agent with the right to choose what he wants.

On further follow-up postsurgery, the patient was advised for left orchiectomy due to the presence of the germ cell neoplasia. The patient was then placed on testosterone substitution requiring careful monitoring as well as good patient compliance.

CONCLUSION

Persistent Müllerian duct syndrome is an important differential diagnosis in males with bilateral cryptorchidism. As observed in our case, a positive family history of cryptorchidism, infertility, and consanguinity should be elicited in the clinical history. We advocate the use of MRI as the best imaging modality for such cases presurgery and postsurgery for follow-up. We recommend that in cases of abdominal cryptorchidism, bilateral orchiectomy be performed as well as excision of Müllerian structures due to high risk of neoplasia.

Management of patients with DSD, such as PMDS presents a unique challenge, both diagnostically and in terms of acute and long-term management requiring a

multidisciplinary team of medical and scientific experts including social workers and psychologists.

The unrealistic hope of our patient to keep one of the testes intact shows how individuals are psychologically burdened by culture to reproduce. In a country where consanguineous marriage is common, the occurrence of such DSD can be more prevalent and unnoticeable; currently, no relevant statistical data are available. We, thus, recommend that more efforts should be directed at educating and creating awareness among physicians, patients, and the public, in general.

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