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Case Report

Persistence of Müllerian Derivatives in an Adult Male

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Abstract

Persistent Müllerian duct syndrome (PMDS) is a rare congenital abnormality that leads to male disorders of sexual development (DSD) due to the persistence of Müllerian duct derivatives in otherwise normally virilized male patients with a normal karyotype. It is usually diagnosed in the early years of life at the time of surgery for cryptorchidism or repair of an inguinal hernia. Cases of affected adult males have been reported as well. We report a rare case of PMDS in a middle-aged (47-year-old) infertile male who was referred to the endocrine clinic for the evaluation of primary infertility. A high index of suspicion needs to diagnose such conditions as early treatment is necessary to preserve fertility and to reduce the occurrence of neoplastic transformation in remnant Müllerian structures.

Keywords: Anti-Müllerian hormone/Müllerian-inhibiting factor, cryptorchidism, persistent Müllerian duct syndrome, primary infertility, Disorders of sexual development (DSD)

Introduction

Persistent Müllerian duct syndrome (PMDS) is a rare condition of internal male disorders of sexual development (DSD), which is characterized by the presence of Müllerian duct structures (i.e., a uterus, cervix, fallopian tubes, and the upper two-thirds of a vagina) and a cryptorchid testis or testes in a phenotypically and genetically (46, XY) male patient. PMDS results from a failure in the synthesis or release of the Müllerian-inhibiting factor (MIF)/anti-Müllerian hormone (AMH) or the failure of the end organ to respond to MIF. PMDS is often delayed or misdiagnosed due to a lack of familiarity with the condition. We report our case with PMDS, who presented with bilateral undescended testis and infertility to enhance the chances of correctly diagnosing and appropriately dealing with the Mullerian remnants.

Case Report

A 47-year-old phenotypically well-developed male presented to our clinic with primary infertility for 13 years. There was no history of decreased libido, shaving frequency or erectile dysfunction.

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The patient's surgical history includes bilateral herniorrhaphy at the age of 18 years. The patient reported that he had a family history of a brother with undescended testicles (UDTs). On examination, the secondary sex characters were found to be well developed. Local physical examination revealed normal phallus with no palpable testis bilaterally. Laboratory data showed high follicle-stimulating hormone and luteinizing hormone levels and low testosterone levels with azoospermia. Chromosome analysis revealed a normal male karyotype of 46, XY.

Ultrasonography of the genitalia [Figure 1] showed an empty scrotal sac bilaterally , as well as an empty inguinal area bilaterally, with no evidence of the testicular tissue. Magnetic resonance imaging of the abdomen and pelvis [Figure 2a-d] showed a rudimentary uterus with an endometrial component connected to dilated seminal vesicles. Bilateral UDTs and a normal appearance of the prostate gland were also apparent. With a presumed diagnosis of bilateral cryptorchidism, an exploratory laparotomy was performed. Intraoperative findings were UDTs in addition to a uterus, vagina, and fallopian tubes. Subsequently, bilateral orchiopexy with resection of the uterus and fallopian tubes was performed. Histopathological analysis showed atrophic uterus with an unremarkable myometrial wall and normal fallopian tubes. Cylindrical tubules with columnar epithelium and a thick muscular wall, in keeping with male genital organs, favored vas deferens fibrosis and calcification. In view of the patient's clinical presentation, intraoperative findings, and histological features, a diagnosis of PMDS was considered. Furthermore, genetic testing was offered to the patient and family, but they declined.

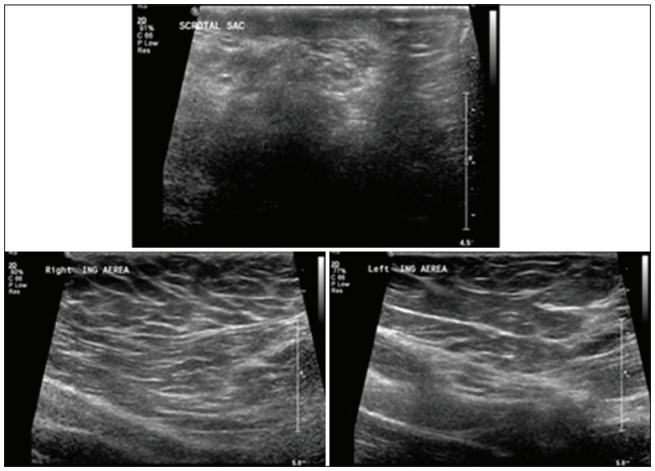

Figure 1: Ultrasonography images showing an empty scrotal sac and empty inguinal areas, bilaterally

Discussion

PMDS was first described by Nilson[1] in 1939 as a rare disorder with <300 cases described in the literature so far.[2] PMDS patients undergo normal development of the external genitalia and secondary sexual characteristics with the presence of Müllerian duct structures (fallopian tubes, uterus, and a proximal vagina). PMDS patients are usually infertile due to the absence of spermatozoa, as seen during semen analysis, but there have only been a few reported cases of fertility.

In a human fetus, the Müllerian and Wolffian ducts are both present at 7 weeks of gestation. In a male fetus, the testis differentiates by the end of the 7th gestational week. Normal sex differentiation is controlled by testosterone, dihydrotestosterone,

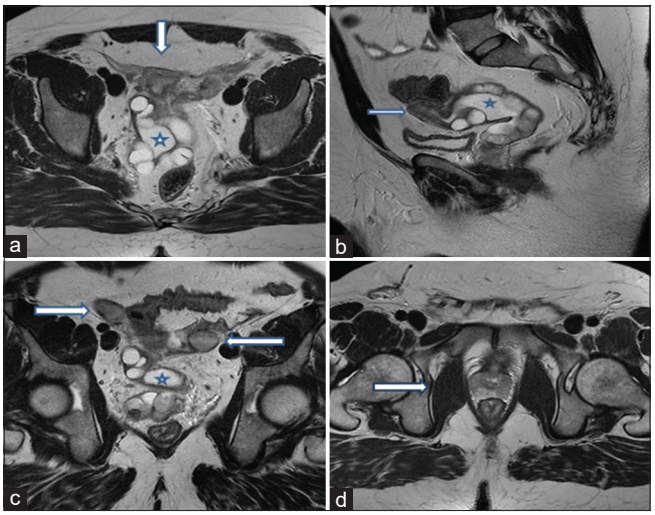

Figure 2: Magnetic resonance imaging of the pelvis showing various structures: (a) Sagittal T2-weighted magnetic resonance image. The arrowhead shows a rudimentary uterus with an endometrial component; the endometrial cavity is connected to the dilated seminal vesicles (represented by the star in the image). (b) Sagittal and axial T2-weighted magnetic resonance imaging; the arrowhead shows a rudimentary uterus with an endometrial component; the endometrial cavity is connected to the dilated seminal vesicles (represented by the star on the image). (c) Axial T2-weighted pelvic magnetic resonance imaging: The arrowhead shows a normal appearance of the prostate gland. (d) Coronal T2-weighted pelvic magnetic resonance imaging: The arrowheads point to the bilateral undescended testicles. The star shows a dilated seminal vesicle

and MIF. Sertoli cells secrete MIF, which leads to regression of the Müllerian ducts. Testosterone has a direct effect on the Wolffian ducts, and it promotes their differentiation into the epididymis, vas deferens, and seminal vesicles. Dihydrotestosterone induces male differentiation of the external genitalia.[3] PMDS patients have both Wolffian and Müllerian duct structures due to a deficiency in MIF.

PMDS is thought to result from a deficiency of MIF or from MIF receptor defects. The MIF gene has been located to the short arm of chromosome 19, and the gene of the receptor is located on the long arm of chromosome 12.[4,5] In the absence of the MIF gene, the Müllerian duct differentiates into the upper part of the vagina, uterus, and fallopian tube in males. It is likely that these remnant Müllerian structures produce cryptorchidism by hindering the normal testicular descent mechanism.

There are two anatomical variants of PMDS: The male type and the female type. The male type is most common, which accounts for 80%–90% of cases. The male form of PMDS has two types. The first form is known as hernia uteri inguinalis, which is usually characterized by a descended testis, as well as herniation of the ipsilateral uterus and the fallopian tube into the inguinal canal, whereas the second form – crossed testicular ectopia – is characterized by herniation of both testes, the entire uterus, and both fallopian tubes.[6,7]

The female form is described in only 10%–20% of cases and is characterized by bilateral cryptorchidism and no hernia. The testes are fixed within the round ligaments in an "ovarian position."[6,8] The uterus is fixed within the pelvis.[6,7] The mobility of the Müllerian structures is an important factor that determines a patient's clinical presentation.[6,7] If the uterus and fallopian tubes are mobile, they may descend into the inguinal canal during testicular descent. On the other hand, if the Müllerian structures are relatively immobile, testicular descent may be affected, resulting in testicular ectopia.[6,7] PMDS can occur sporadically, or it may be inherited, likely through a sex-linked autosomal recessive or X-linked recessive inheritance pattern.[9,10]

The mean age of onset of PMDS is considerably variable that usually becomes apparent during infancy or early childhood, but adult cases have also been reported.

Differential diagnosis of PMDS includes mixed gonadal dysgenesis (MGD) and Morris syndrome due to Androgen Insensitivity Syndrome (AIS).[11] In MGD cases, patients have the residual Mullerian duct structures and vague external genitalia, and the karyotype is usually 45, XO/46, XY mosaic type, whereas in AIS, the phenotype ranges from normal female external genitalia in the complete form to normal male external genitalia associated with infertility and/or gynecomastia in the mild form and karyotype is 46, XY.[12,13] Therefore, it is necessary to obtain both a karyotype and sex hormone levels to verify both genetic sex and the existence of functional testicular tissue.

As is the case for undescended testes in general, the gonads of these patients are at an increased risk of malignant transformation. Our patient did not show evidence of malignancy. There have been case reports of embryonal carcinoma, seminoma, yolk sac tumor, and teratoma in patients with PMDS.[14] The overall incidence of malignant change has been found to be 18%, which is similar to the rate reported for otherwise intra-abdominal testis.[15]

The measurement of serum AMH level helps to diagnose and differentiate the types of PMDS but was not done in our patient as the karyotyping and testicular biopsy are the cornerstones for establishing the diagnosis of PMDS.[16] The main therapeutic considerations for PMDS offer the potential for fertility, as well as for the prevention of malignant change. Surgical management is geared toward preserving fertility and performing orchiopexy to retrieve the testis and position it in the scrotum. Testosterone replacement is required for those undergoing orchiectomies or those with low levels of testosterone to prevent lifelong complications. In the present case, our patient made a good recovery. Postoperative semen analysis gave the same results of azoospermia. Testosterone replacement therapy was initiated, and the patient demonstrated optimal clinical and biochemical responses.

Conclusion

In the event of bilateral cryptorchidism associated

with a hernia, as in our case, a high index of suspicion of PMDS should be kept in mind. Early treatment is necessary to reduce the likelihood of – and to foresee complications associated with – infertility and neoplastic transformation.[17]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Authors' contributions

All authors contributed to the care of the patient, drafting of the case report, revision, and approval of its final version.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Compliance with ethical principles

No prior ethical approval is required for single case reports. However, the patient provided consent for publication as stated above.

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