

Combined Persistent Mullerian Duct Syndrome, Transverse Testicular Ectopia and Mosaic Klinefelter's Syndrome

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ABSTRACT

Persistent Mullerian Duct Syndrome (PMDS), a rare form of male pseudohermaphroditism, is characterized by the persistence of Mullerian duct structures (uterus, fallopian tubes and upper two-thirds of vagina) in otherwise normally-virilized males (Karyotype 46XY). Patients suffering from PMDS present with cryptorchidism, inguinal hernia and infertility. Diagnosis is established when Mullerian duct structures are discovered either during ultrasonography for localization of undescended testis(s), during surgical exploration for cryptorchidism or herniorrhaphy (hernii uteri inguinalis). Presence of both testes on one side of the scrotum is known as Transverse Testicular Ectopia (TTE). Co-existence of PMDS and transverse testicular ectopia in a patient of mosaic Klinefelter's syndrome (Karyotype 46XY/47XXY) is a unique genetic association.

Key words: *Persistent Mullerian duct syndrome. Male pseudohermaphroditism. Transverse testicular ectopia. Mosaicism. Klinefelter's syndrome.*

INTRODUCTION

Persistent Mullerian Duct Syndrome (PMDS), a rare disorder of male sexual differentiation, is characterized by the persistence of Mullerian duct derivatives (uterus, fallopian tubes and upper two-thirds of vagina) in a phenotypically and genotypically male (Karyotype 46XY). Since the first description by Nilson in 1939 as "hernii uteri inguinalis," only about 150 cases of PMDS have been reported worldwide.¹ Normally, men possess Wolffian duct structures while women possess Mullerian duct structures. Individuals suffering from PMDS possess both the Mullerian and Wolffian ducts structures. Presence of Mullerian duct structures in the hernial sac of male patient is also known as hernii uteri inguinalis.

Presence of both testes on one side of the scrotum is known as Transverse Testicular Ectopia (TTE). It is rare to find combination of persistent Mullerian duct syndrome and transverse testicular ectopia in one patient. It is extremely rare to find persistent Mullerian duct syndrome and transverse testicular ectopia in a patient of Klinefelter's syndrome (47XXY)² and even

rarer to find these in association with mosaic Klinefelter's syndrome (46XY/47XXY).

The aim of reporting this interesting case is to create its awareness among the healthcare professionals and to highlight pathophysiological, morphological and clinical features of this rare clinical entity along with its management.

CASE REPORT

A 58 years old male presented with an irreducible right inguinal hernia of two years duration with no other abdominal or urinary complaints. Although married with normal sexual life for the last 40 years, he was issueless. Due to absence of sexual dysfunction, he never intended to get investigated for his infertility. He had a brother and a sister; both married with children.

Phenotypically, he was a tall muscular man with well-developed secondary sex characters. He was bald with moustache, beard and well-developed bodily, axillary and pubic, male-pattern hair distribution. Systemic and abdominal examinations were unremarkable. Digital anorectal examination revealed normal sized prostate. Inguinoscrotal examination showed a fully-developed penis. Left hemiscrotum was undeveloped and empty while a large irreducible inguinoscrotal hernia was present on right side. Routine laboratory investigations, ECG and chest x-rays were within normal range.

He was operated upon through right inguinal incision under spinal anaesthesia. The hernia sac contained an adult-sized uterus, fallopian tubes, broad ligament, vas deferentia and atrophic testes (Figure 1). Total Inguinal Hysterectomy (TIH), bilateral salpingectomies, bilateral

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orchietomies and mesh hernioplasty were performed through the same incision (Figure 2).

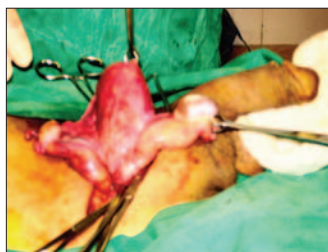


Figure 1: Peroperative view showing uterus, fallopian tubes, testes and penis.

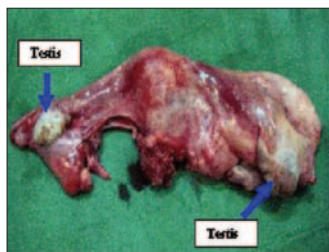


Figure 2: Resected specimen showing uterus, cervix, fallopian tubes and testes.

Histological examination of the resected specimen revealed uterus composed of well-formed myometrium with atrophic endometrial and cervical glands. Testicular histology showed seminiferous tubules lined with germinal epithelium. Evidence of spermatogenesis and Leydig cell hyperplasia was present at few places (Figure 3 a, b and c). Postoperative hormonal assay showed testosterone value of 21.1 ng/ml, estrogen 39 pg/ml and progesterone 0.3 ng/ml (reference normal values are 212 ng/ml, <56 pg/ml and <0.6 ng/ml respectively). Chromosomal analysis (karyotyping) revealed a mosaic Klinefelter's syndrome (46XY/47XXY). Postoperative ultrasonography and MRI of abdomen and pelvis demonstrated normal kidneys, urinary bladder, prostate and seminal vesicles. Excretory urography displayed normally functioning kidneys.

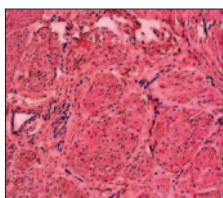


Figure 3 (a): Myometrium

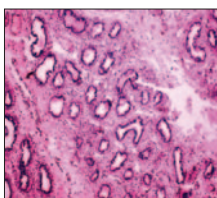


Figure 3 (b): Rudimentary cervical glands.

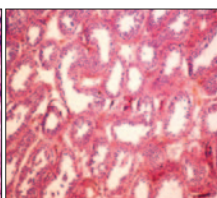


Figure 3 (c): Seminiferous tubules.

DISCUSSION

Persistent Mullerian duct syndrome (PMDS), a rare form of male pseudohermaphroditism, is characterized by the presence of Mullerian duct structures in phenotypically and genotypically males (46XY).³ It is a familial syndrome associated with autosomal recessive mode of inheritance.⁴ Embryologically, upto sixth week of intrauterine life, all the fetuses contain both the male (Wolffian) and female (Mullerian) genital ducts. After seventh week, in the male fetuses (46XY), the Mullerian ducts undergo regression mediated by Anti-Mullerian Hormone (AMH) while the Wolffian ducts continue to proliferate and differentiate into epididymides, vas deferentia and seminal vesicles under the effects of

testosterone released from Leydig's cells. AMH is a glycoprotein secreted by Sertoli's cells of the foetal testes. AMH, also known as Mullerian Inhibitory Substance (MIS), has two transmembrane receptors in the mesenchyme of fetal Mullerian ducts. Type-I receptors are non-specific while type-II AMH receptors are specific for its actions.⁵

Exact pathogenesis of PMDS is known in about 85% of the cases. PMDS is caused by either partial or complete deficiency of AMH secretion due to mutations of AMH gene -Type-I PMDS (45%) or by end-organ resistance to AMH actions secondary to mutations of gene of AMH-II receptors -Type-II PMDS Type (40%). In remaining 15% of the cases, the exact cause is unknown and probably unrelated to AMH physiology ("Idiopathic PMDS").⁶

There are two morphological forms of PMDS. Female form (10-20%) is characterized by the presence of bilateral cryptorchidism with no herniation of Mullerian duct structures and testes. Uterus and fallopian tubes are fixed in the pelvis and testes are embedded in the broad ligament. Male form (80-90%) is characterized by the presence of unilateral cryptorchidism with contralateral inguinal hernia containing the Mullerian structures and the testes. Male form is subdivided into two types. In type-I, hernia sac contains uterus, both fallopian tubes and both testes (hernii uteri inguinalis with TTE). This patient belonged to type-I. In type-II, hernia sac contains uterus, ipsilateral fallopian tube and ipsilateral testis (classic hernii uteri inguinalis).^{5,6}

Clinically, patients suffering from PMDS present during infancy, childhood or adulthood with cryptorchidism, inguinal hernia or infertility.¹⁻³ Mullerian duct derivatives are discovered unexpectedly during herniorrhaphy or surgical exploration for cryptorchidism. Occasionally, such patients may present with an intra-abdominal mass due to malignant transformation of undescended testes. Overall incidence of testicular tumorigenesis in patients with PMDS is about 18%, which is comparable to that of normal individuals with undescended testes.⁷ Various testicular tumours that have been reported in such patients include seminoma, teratoma, embryonal carcinoma, choriocarcinoma, mixed germ cell tumour, leiomyoma and adenocarcinoma of uterus.

Diagnosis of PMDS is established when Mullerian duct structures are discovered incidentally either during routine imaging for localization of undescended testes or surgical exploration for cryptorchidism or inguinal herniorrhaphy. Ultrasonography effectively depicts the presence of Mullerian derivatives in the male pelvis and accurately localizes the level of undescended testis, their malignant transformation and crossed testicular ectopia and, therefore, should routinely be requested in all cases of unilateral or bilateral cryptorchidism. Gadolinium-enhanced MRI⁸ is another excellent imaging modality for visualization of complex pelvic

anatomy. Multiplanar MRI can easily differentiate Mullerian structures from adjacent pelvic organs on the basis of signal intensity and morphological features. Currently, laparoscopy has emerged as an important modality for confirmation of diagnosis of PMDS and its management. Hormonal bioassay of testosterone, FSH and LH are routinely performed to substantiate the diagnosis of PMDS. Serum level of testosterone is decreased while those of FSH and LH are raised in the patients of PMDS. Measurement of serum AMH level by ELISA method during infancy and early childhood helps to differentiate the types of PMDS. Low or undetectable levels are found in type-I PMDS while normal or raised levels of AMH are found in type-II PMDS. Testicular biopsy and karyotyping are still the cornerstones for establishing diagnosis of PMDS.⁹

Management of PMDS is exclusively surgical. The main therapeutic objectives are preservation of testes, spermatogenesis and fertility and protection against testicular malignancies.¹⁰ Open or laparoscopic orchidopexy is a preferred surgical option in prepubertal patients. However, it should be performed with extreme degree of care and dexterity to avoid ischemic and traumatic gonadal damage. Removal of Mullerian duct structures is not advisable in the same sitting; rather these should be pushed back into the pelvis to be removed later by elective surgery. In transverse testicular ectopia, one testis is fixed in the ipsilateral subdartos pouch while the other in contralateral subdartos pouch across the median scrotal raphe (trans-septal approach).^{1,3} Total hysterectomy, bilateral salpingectomies and orchiectomies become imperative if testis could not be brought to a palpable position, testes are atrophic or there is strong suspicion of malignant transformation.¹⁰ However, before proceeding to such radical surgery, it is highly desirable that the patient and his family should be thoroughly counselled

about the diagnosis, the different surgical options and the need for long-term follow-up and androgen replacement therapy after orchiectomy. It is also recommended that an informed written consent should be obtained before surgery.

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