

## Persistent Müllerian duct syndrome diagnosed incidentally: A case report

Nazish Fatima, Zareen Kiran, Khalil Ullah Shabbir, Akhtar Ali Baloch

### Abstract

Persistent Müllerian Duct syndrome is a rare male disorder of sexual development. The phenotypically and genotypically male patient presents with female internal organs (i.e., uterus, cervix, fallopian tubes and upper part of vagina) due to deficiency of anti-müllerian hormone or insensitivity of tissues to Anti Müllerian Hormone.

We present a 19 year old male who came with complaint of right iliac fossa pain. He was investigated for acute appendicitis and on imaging, he was diagnosed to have bilateral cryptorchidism with rudimentary uterus. Computed tomography followed by pelvic ultrasonography was done which indicated two testes in abdomen and a soft tissue density structure, identified as a rudimentary uterus located posterior to the urinary bladder. CT scan findings were further confirmed by magnetic resonance imaging pelvis. A trial of stepwise orchidopexy followed by orchidectomy with removal of rudimentary uterus was performed laparoscopically. Additionally, he was counselled for long term sex hormone replacement and reproductive failure in future.

**Keywords:** Cryptorchidism, rudimentary uterus, anti-müllerian hormone, Müllerian duct derivatives, differences in sex development, ultrasonography.

**DOI:** <https://doi.org/10.47391/JPMA.9172>

**Submission completion date:** 02-02-2023

**Acceptance date:** 17-06-2023

### Introduction

Persistent Müllerian Duct syndrome (PMDS) is a genetic disorder with an autosomal recessive inheritance. The incidence of PMDS is not very common, with only 200 cases having been reported to date.<sup>1</sup> PMDS is a diagnostic challenge because of the complex presentation and anatomic variability. It is typically diagnosed late because of the absence of specific clinical features. Children with cryptorchidism or inguinal hernia are usually suspected cases, whereas adults present with infertility or azoospermia/ oligospermia.<sup>2</sup> The Sertoli cells are the main source of anti-müllerian hormone (AMH), and they begin to produce AMH (Anti-müllerian hormone) during 7 weeks

of gestation, which leads to regression of Müllerian duct (MD), followed by trans-abdominal descent of testes to the deep inguinal rings and into the scrotum. In patients with PMDS, due to deficiency of AMH or defective AMH type-II receptors, MD structures persist.<sup>3</sup> This leads to undescended testes (UDT) because of attachment of fallopian ducts to the testes that prevent them from descending normally. Mostly impalpable UDT present on one side with either an inguinal hernia or palpable UDT on the other side (unilateral cryptorchidism). Bilateral palpable UDT can present in few patients (bilateral cryptorchidism) and can rarely present with bilateral impalpable UDT or transverse testicular ectopia.<sup>4</sup>

The basic pathophysiology behind PMDs is mutation in AMH gene or AMHR2 (anti-müllerian hormone receptor-II) gene, which provides instruction for production of protein for AMH and AMH receptor type 2, respectively. In a normal male, these two proteins work together to regress the Müllerian duct and its derivatives, but in PMDS, mutations in AMH and AMHR2 genes produce nonfunctional proteins, with persistence of the Müllerian duct structure. On the basis of genetic mutations PMDS is categorized into type-1 PMDS- which is caused by mutations in AMH gene and accounts for around 45% of cases- and type-2 PMDS -with mutations in AMHR2 gene occurring in 40% of cases, whereas, 15% of cases do not show any mutations on AMH or AMHR2 genes, and the genes involved are still unidentified in these cases.<sup>5</sup>

We present a case of an incidental discovery of a rudimentary uterus with bilateral cryptorchidism, with challenging management issues related to sexual well-being, infertility and risk of malignant transformation. Failing early surgical correction, gonadectomy must be offered to prevent malignancy. Malignant transformation is as likely as the presence of abdominal testes in an otherwise normal man. In this case we describe a sequential prognostic evaluation and treatment in a patient with PMDS.

### Case presentation

A 19-year old male, university student, was referred to the endocrine clinic at National Institute of Diabetes and Endocrinology, Dow University of Health Sciences, Karachi from a local hospital due to incidental finding of bilateral undescended testes and a soft tissue density structure seen

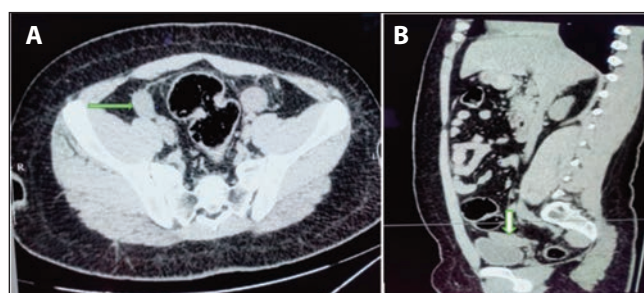
Dow University of Health Sciences, Karachi, Pakistan.

**Correspondence:** Nazish Fatima. e-mail: [nazzishfatima@gmail.com](mailto:nazzishfatima@gmail.com)

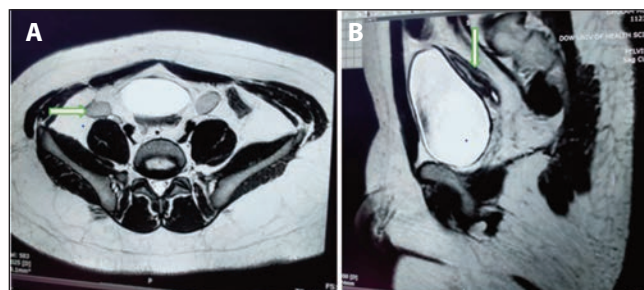
ORCID ID. 0000-0002-1624-8727

**Table-1:** Baseline laboratory investigations.

Investigations	Results	Reference range
Haemoglobin	13.6 gm/dl	13-17 gm/dl
Total leukocyte count	10.0x 10 <sup>9</sup> /L	4-10 x 10 <sup>9</sup> /L
Platelet count	437x 10 <sup>9</sup> /L	150-400x 10 <sup>9</sup> /L
Serum Sodium	140 mEq/L	136-146 mEq/L
Serum Potassium	4.4 mEq/L	3.5-5.1 mEq/L
Serum Chloride	107 mEq/L	98-107 mEq/L
Serum Bicarbonate	22 mEq/L	23-29 mEq/L
HbA1C	5.63 %	<5.7%
Triglycerides	184 mg/dl	<150 mg/dl
Serum Cholesterol	150 mg/dl	<200 mg/dl
LDL Cholesterol	110 mg/dl	<100 mg/dl
HDL Cholesterol	38 mg/dl	40-60 mg/dl



**Figure-1:** CT scan of abdomen and pelvis showing bilateral undescended testes (A) and rudimentary uterus (B).



**Figure-2:** MRI pelvis with contrast. (A) A well-defined oval-shaped homogeneously enhancing structures identified in bilateral iliac fossa anterior to iliac vessels representing undescended testes. Right sided testis measured 3.0 x 1.6 cm and the left sided testis measured 2.8 x 1.4 cm. (B) A tubular structure with signal characteristics and zonal anatomy resembling uterus is identified posterior to urinary bladder extending inferiorly up to right seminal vesicles.

posterior to urinary bladder, which was likely to be a rudimentary uterus.

He had complained of pain in the right iliac fossa for 3 weeks. He visited a general practitioner and workup was done for suspected acute appendicitis. Past history was unremarkable, the patient had normal intelligence and developmental history, and he was not taking any regular medicine. The parent's marriage was consanguineous, and there was no family history of any infertility or DSD. He was stable on examination, with a pulse of 84 beats per minute, blood pressure of 130/82 mmHg, height of 167cm and

**Table-2:** Hormonal work up for difference in sex development (DSD).

Investigations	Results	Reference range
Serum Testosterone	11.4 nmol/L	9-34 nmol/L
TSH	2.04 uIU/ml	0.4-4.2 uIU/ml
FSH	23.13 mIU/ml	1.4-15.4 mIU/ml
LH	19.89 mIU/ml	1.2-7.8 mIU/ml
Serum Prolactin	12.03 ng/ml	3-14.7 ng/ml
ACTH	48.6 pg/ml	<85 pg/ml
Serum Cortisol	13.95 ug/dl	5-23 ug/dl
Serum Oestradiol	17.43 pg/ml	10-50 pg/ml
Anti-Mullerian Hormone level	11.95 ng/ml	0.7-19 ng/ml

Karyotyping showed 46XY chromosome. TSH: Thyroid Stimulating Hormone. FSH: Follicular Stimulating Hormone. LH: Leutinising Hormone ACTH: Adrenocorticotrophic Hormone.

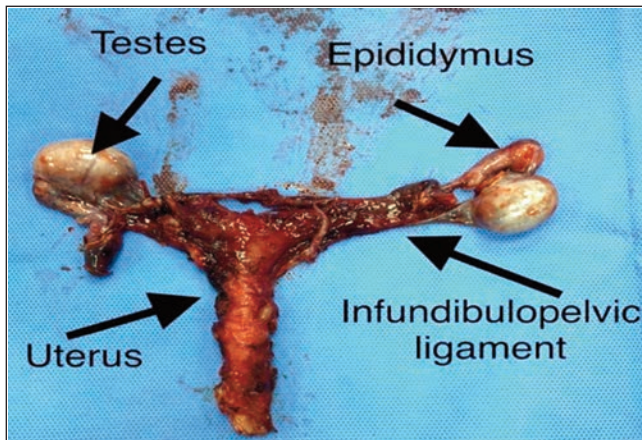
weight of 85kg and a body mass index (BMI) of 30.5 kg/m<sup>2</sup>. Regarding his secondary sexual characteristics, he had sparse facial, pubic and axillary hair with partial masculine features. Genital examination showed absence of both testes in the scrotum. Stretched penile length was 2.5 cm. A comprehensive systemic examination was unremarkable. Ultrasonography followed by computed tomography (CT) scan of the pelvis was done, and the patient was referred to the endocrine OPD because of abnormal findings on these investigations. His baseline workup is shown in Table 1.

He also had semen analysis performed which showed azoospermia. Ultrasonography along with CT-scan of abdomen and pelvis (Figure-1) showed well defined enhancing areas in lower abdomen which appeared to be undescended testes. Soft tissue density structure was seen posterior to urinary bladder and was likely to be a rudimentary uterus.

Magnetic resonance imaging (MRI) (Figure-2) was performed to further confirm the USG and CT scan findings.

Based on these incidental imaging findings, and signs of hypogonadism a clinical impression of differences in sex development (DSD) was made and further investigations were done, as shown in Table 2.

A decision was made to do exploratory laparotomy with bilateral orchidectomy and hysterectomy. Patient was thoroughly explained the diagnosis and need of surgery. Consent was also taken for removal of rudimentary uterus and testes. Diagnostic laparoscopy showed immobile testes and rudimentary uterus behind the urinary bladder. However, a trial of extension to the vas deferens within the spermatic cord was given to preserve testicular tissue through orchidopexy. But because of unsuccessful extension of vas deferens after 2 months, the patient was finally counselled for removal of undescended testes. He underwent a second laparoscopy with bilateral gonadectomy and total excision of uterus. He had an



**Figure-3:** Specimen showing testes, epididymis, uterus and infundibulo-pelvic ligament.

uneventful post-operative period. On gross examination, the removed specimens were found to be the uterus, testes and epididymis, infundibulo-pelvic ligament, with right sided testis measuring 2.6 x 1.4 cm and the left sided measured 2.2 x 1.2 cm. (Figure-3) No ovarian tissue was appreciated in the specimen. The histopathology from the testes sample further confirmed that the uterus and testes were without evidence of malignancy. Patient was followed up by endocrine and urology services after 2 weeks of surgery. He has not had any urological symptoms relating to the Müllerian structure, such as urinary tract infection or urinary incontinence, and he was started on testosterone replacement therapy. He continued his studies after 3 weeks of surgery. Psychiatric evaluation was also done regarding issues of future infertility and long term hormonal therapy.

## Discussion

There are two anatomic variants of PMDS, with 80-90% of cases presenting with unilateral cryptorchidism and contralateral inguinal hernia. This variant is further categorized into two types: hernia uteri inguinalis and crossed testicular ectopia.<sup>6,7</sup> Hernia uteri inguinalis is characterized by descended testes and herniation of uterus and fallopian tube of ipsilateral side into inguinal canal, whereas crossed testicular ectopia manifests as herniation of both testes, uterus and both fallopian tubes.<sup>6,7</sup> The second variant is found in only 10-20% and is depicted as bilateral cryptorchidism with testes fixed to round ligaments in an ' ovarian position.<sup>7</sup> If the Müllerian structures are fixed, testicular descent may be difficult, however if uterus and fallopian tubes are mobile, they may descend with testes during testicular movement through inguinal canal.<sup>6,7</sup> In our case there was bilateral cryptorchidism and rudimentary uterus. In view of the immobile Müllerian structures, our case probably fell into the second variant of PMDS.

The testes are mostly histologically normal in patients with PMDS, except for the changes that occur due to cryptorchidism in longstanding cases, while the risk of malignant transformation is 18%, which is somewhat equivalent to intra-abdominal testes in a normal male. Prior studies have reported cases of embryonal carcinoma, yolk sac tumours, and teratomas in patients with PMDS.<sup>3,8-10</sup> There are also case reports of malignant potential of müllerian remnants; like clear cell carcinoma arising from uterine remnant.<sup>11</sup>

Infertility is inevitable in most patients with PMDS,<sup>6,10,12</sup> with few reported cases of paternity, 13 with 11% revealed in one study.<sup>13</sup> Non descent of testes, abnormality in epididymis with its separation from testes, and dysplastic changes of testes are the likely causes of infertility.<sup>14,15</sup>

To the best of our knowledge, the definitive approach to PMDS has not been specified. However, recent studies have demonstrated some effective outcomes with laparoscopic approach.<sup>16</sup> The main aim of treatment is to preserve patient's fertility<sup>17,18</sup> and to prevent malignant transformation of ectopic testicular tissue. On incidental finding of Müllerian remnants (MR) during surgery, a gonadal biopsy is usually done prior to excision, with re-exploration and definitive surgery usually done after genetic (where available) and hormonal confirmation.<sup>18</sup> The damage to germ cells of convoluted seminiferous tubules begins at 1 year of age and becomes permanent after 2 years of age. Therefore orchidopexy is required at 2 years of age.<sup>19</sup> If early orchidopexy is not possible because of late diagnosis of condition then bilateral orchidectomy, with or without removal of MR remnants should be done.<sup>20</sup> Resection of Müllerian remnants (MR) is controversial with few authors agreeing for resection due to probability of malignant transformation, recurrent urinary tract infection and haematuria. However, others disagree with resection and emphasize on preservation of Müllerian remnants (MR) to protect the blood supply of testes and vas deferens.<sup>21</sup>

Treatment with hormone replacement will improve the sexual well-being of such patients who underwent bilateral gonadectomy, however, a multidisciplinary team with a urologist and psychologist is required to address issues related to infertility and malignant changes in the gonads. Genetic testing can help in early diagnosis of this condition but is not available in our setup.

## Conclusion

We present a case of bilateral cryptorchidism associated with rudimentary uterus, which was discovered incidentally. Treatment aims to correct cryptorchidism and ensure timely appropriate scrotal placement of testes in the scrotum. Failing early surgical correction as in our case,

gonadectomy must be offered to prevent malignancy. Moreover, laparoscopic surgery can be considered for diagnosis and treatment in PMDS patients. Genetic counselling is needed in patients with PMDS, if there is parental consanguinity.

**Acknowledgments:** The authors wish to thank the department and laboratory staff of National Institute of Diabetes and Endocrinology, Karachi who provided full cooperation in performing investigational procedure and supporting patient care.

**Ethics approval and consent to participate:** Informed consent was obtained from the patient to participate in publication of his clinical and laboratory data. Confidentiality was preserved.

**Consent for publication:** Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

**Disclaimer:** None.

**Conflict of Interest:** None.

**Funding Sources:** None.

## References

- Brunello FG, Rey RA. AMH and AMHR2 Involvement in Congenital Disorders of Sex Development. *Sex Dev* 2021; 138-46.
- Shalaby MM, Kurkar A, Zazour MA, Faddan AA, Khalil M, Abdelhafez MF. The management of the persistent Müllerian duct syndrome. *Arab J Urol* 2014; 12: 239-44.
- Barad AK, Bharath NM, Narayana V, Raja VO, Jambula PR. Persistent Mullerian Duct Syndrome with Embryonal Cell Carcinoma along with Ectopic Cross Fused Kidney. *J Clin Diagn Res* 2016; 10: PD07-8.
- Kaul A, Srivastava KN, Rehman SM, Goel V, Yadav V. Persistent Müllerian duct syndrome with transverse testicular ectopia presenting as an incarcerated inguinal hernia. *Hernia* 2011; 15: 701-4.
- Mullen RD, Ontiveros AE, Moses MM, Behringer RR. AMH and AMHR2 mutations: A spectrum of reproductive phenotypes across vertebrate species. *Dev Biol* 2019; 455: 1-9.
- Dekker HM, de Jong I, Sanders J, Wolf R. Persistent Mullerian duct syndrome. *Radiographics* 2003; 23: 309-13.
- Clemente A, Macchi V, Berretta M, Morra A. Female form of persistent müllerian duct syndrome: MDCT findings. *Clin Imaging* 2008; 32: 314-7.
- Manassero F, Cuttano MG, Morelli G, Salintri G, Spurio M, Selli C. Mixed germ cell tumor after bilateral orchidopexy in persistent müllerian duct syndrome with transverse testicular ectopia. *Urol Int* 2004; 73 :81-3.
- Aboutorabi R, Feiz zadeh B, Rajabian R. Gynecomastia secondary to choriocarcinoma in a man with persistant Mullerian duct. *Int J Endocrinol Metab* 2005; 3: 140-2.
- Wu HC, Chen JH, Lu HF, Shen WC. Persistent Mullerian duct syndrome with seminoma: CT findings. *AJR Am J Roentgenol* 2000; 174: 102-4.
- Shinmura Y, Yokoi T, Tsutsui Y. A case of clear cell adenocarcinoma of the müllerian duct in persistent müllerian duct syndrome: the first reported case. *Am J Surg Pathol* 2002; 26: 1231-4.
- Shamim M. Persistent Mullerian duct syndrome with transverse testicular ectopia presenting in an irreducible recurrent inguinal hernia. *J Pak Med Assoc* 2007; 57: 421-3.
- Picard J-Y, Cate RL, Racine C, Josso N. The persistent Müllerian duct syndrome: an update based upon a personal experience of 157 cases. *Sex Dev* 2017; 11: 109-25.
- Josso N, Belville C, Di Clemente N, Picard JY. AMH and AMH receptor defects in persistent Müllerian duct syndrome. *Hum Reprod Update* 2005; 11: 351-6.
- Berkmen F. Persistent müllerian duct syndrome with or without transverse testicular ectopia and testis tumours. *Br J Urol* 1997; 79: 122-6.
- Raicevic M, Saxena AK. Laparoscopic management of Müllerian duct remnants in the paediatric age: evidence and outcome analysis. *J Minim Access Surg* 2018; 14: 95-8.
- Patil V, Muktinaini S, Patil R, Verma A. Persistent müllerian duct syndrome: a case report. *Indian J Surg* 2013; 75(Suppl 1): s460-2.
- Wang S, Jiang D, Li Z. Research progress of persistent Müllerian duct syndrome. *Chin J Pediatr Surg* 2016; 37: 73-6.
- Shao F, Mao Q, Yang H, Hou L. Persistent Mullerian duct syndrome: A report of two cases and literature review. *Chin J Pediatr Surg* 2011; 32: 468-70.
- Altincik A, Karaca F, Onay H. Persistent Müllerian duct syndrome: A novel mutation in the Anti-Müllerian Hormone gene. *Hormones (Athens)* 2017; 16: 205-8.
- Ren X, Wu D, Gong C. Persistent Müllerian duct syndrome: A case report and review. *Exp Ther Med* 2017; 14: 5779-84.