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CASE REPORT

AMHR2 mutation in persistent Müllerian duct syndrome: A case of transverse testicular ectopia

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Abstract

Backgroud: Persistent Müllerian duct syndrome (PMDS) is a rare condition characterized by the persistence of Müllerian duct structures in genotypic and phenotypic males.

Case Presentation: We present the case of a 4-month-old male with PMDS who presented with transverse testicular ectopia. The patient underwent diagnostic laparoscopic orchiopexy with preservation of the Müllerian structures to maintain future fertility options. Due to the abnormal appearance of the testes, a biopsy revealed normal testis tissue without any ovarian tissue. Genetic testing identified a unique mutation in each copy of the *AMHR2* gene: c.322A>C and c.658G>C. Neither mutation has been previously reported.

Conclusion: This case highlights the importance of considering PMDS in male infants presenting with transverse testicular ectopia. Early recognition and fertility-preserving surgical management are essential, and novel genetic variants continue to expand the mutational spectrum of *AMHR2*-related PMDS.

KEYWORDS

AMH/AMHR2 mutation, fertility preservation, laparoscopic orchiopexy, persistent Müllerian duct syndrome (PMDS), transverse testicular ectopia

1 | INTRODUCTION

Müllerian structures or paramesonephric ducts typically develop into the uterus, cervix, fallopian tubes, and upper two-thirds of the vagina in 46, XX individuals. In 46, XY individuals, anti-Müllerian hormone (AMH), a TGF-β protein produced by the sertoli cells, is essential for the regression of Müllerian structures during male fetal development. Mutations in the AMH gene or AMH receptor type 2 (AMHR2) are responsible for persistent Müllerian duct syndrome (PMDS) in otherwise normally virilised 46, XY males[1]. AMH and AMHR2 signal through two distinct serine/threonine receptors, type 1 and type 2, that phosphorylate cytoplasmic effectors[2]. Mutations of both conditions are transmitted through an autosomal recessive pattern and are symptomatic only in males[3]. PMDS usually presents in one of three ways: unilateral cryptorchidism with contralateral hernia, bilateral cryptorchidism, or transverse testicular ectopia[1]. Affected individuals are otherwise normally virilized, undergo normal male puberty; and may be fertile if at least one testis can be palpated or replaced into the scrotum with intact excretory ducts[3]. After PMDS diagnosis, early orchiopexy is typically recommened to preserve fertility while preserving endogenous hormone secretion[4]. Annual imaging and

Abbreviations: AMH, anti-Müllerian hormone; AMHR2, anti-Müllerian hormone receptor 2; CT, computed tomography; DSD, disorders of sexual differentiation; MRI, magnetic resonance imaging; PMDS, persistent Müllerian duct syndrome; XX, denoting female chromosomes; XY, denoting male chromosomes.

follow-up surveillance may be indicated depending on the time of diagnosis.

2 | CASE REPORT

A 4-month-old male was presented with a left undescended testis. He was born at 38 weeks via C-section, and all prenatal ultrasounds were normal. The genitourinary physical examination revealed a circumcised phallus, glanular hypospadias with a 3–4 mm ventrally displaced meatus accompanied by a distal pit, 90° counterclockwise penile torsion, and midshaft penoscrotal webbing. The left hemiscrotum was devoid of palpable structures, while the right hemiscrotum contained two palpable testes. Additionally, a right communicating hydrocele was identified. A scrotal ultrasound (Figure 1A,B) confirmed an empty left hemiscrotum and a right hemiscrotum with two testes. The testes' dimensions were 1.5 cm × 0.7 cm × 1 cm (volume: 0.6 mL) and 1.4 cm × 0.7 cm × 1.1 cm (volume: 0.6 mL), respectively. To determine whether the spermatic cords were individual or branched from a single side, a pelvic magnetic resonance imaging (MRI) was conducted (Figure 1C,D). The MRI results illustrated crossed testicular ectopia, with both testes located in the right hemiscrotum, each having a distinct spermatic cord.

He was scheduled for diagnostic laparoscopic orchiopexy, circumcision, correction of penile torsion, and scrotoplasty. Diagnostic laparoscopy revealed bilateral abnormal testes with cystic areas, raising concerns for ovotestes, and Müllerian duct remnants, including a rudimentary uterus and fallopian tubes, as depicted in Figure 2A,B. The left vas deferens, spermatic artery, and vein traversed from the left internal ring to the right internal ring. The ectopic left testis, situated at the right internal inguinal ring, resembled a peeping testis. Closer inspection of the testis revealed cystic/fatty structures at the poles, indicating potential ovotestis. The left ectopic testis, when grasped at the right internal inguinal ring, could not be moved across the abdomen to the opposite inguinal canal. With this maneuver, the right testis moved into the abdomen. A tube-like structure emanated from this testis, bearing resemblance to a remnant fallopian tube. Similarly, cystic/fatty tissues were observed on the poles of the right testis. Situated

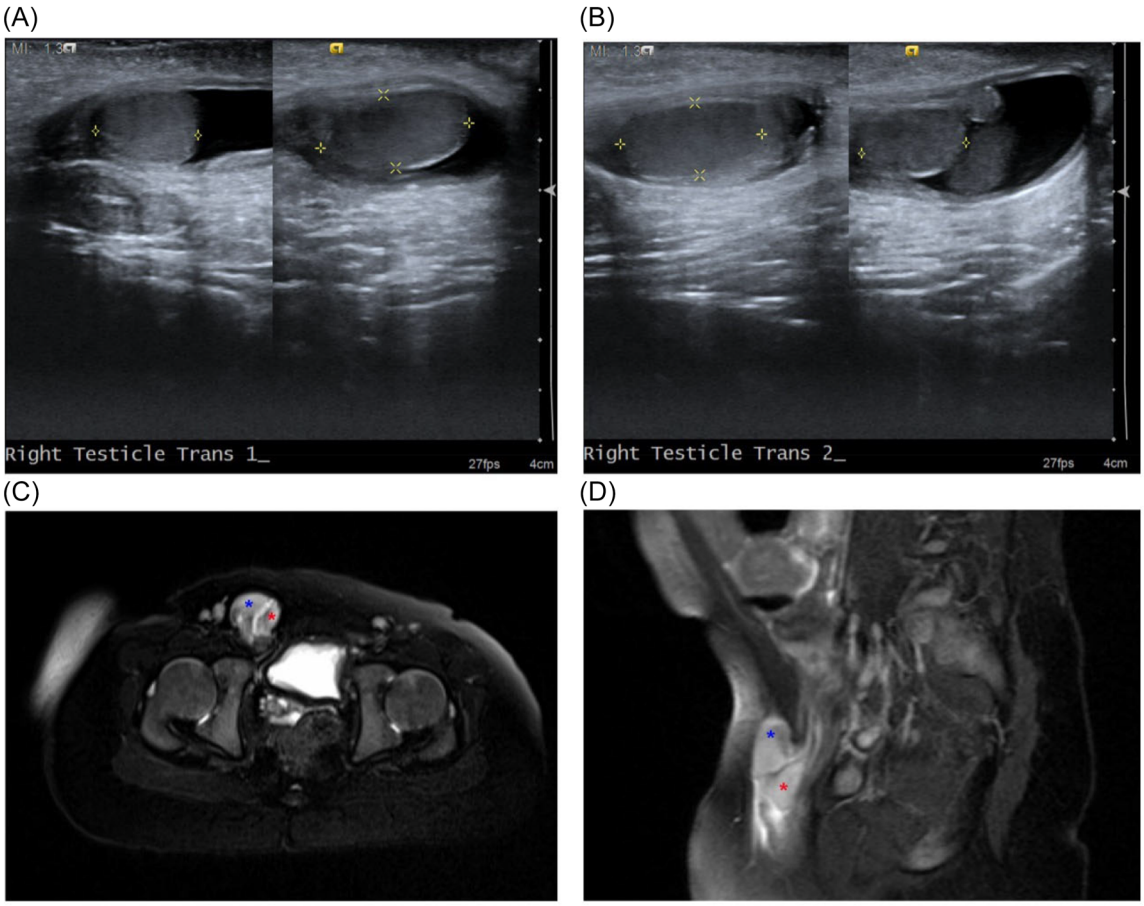

FIGURE 1 Preoperative scrotal ultrasound and Pelvic MRI without contrast. (A) Transcrotal ultrasound of testicle 1 in the right hemiscrotum; (B) transcrotal ultrasound of testicle 2 in the right hemiscrotum; (C) pelvic MRI axial view; (D) pelvic MRI sagittal view. The blue star represents testicle 1 and the red star represents testicle 2. MRI, magnetic resonance imaging.

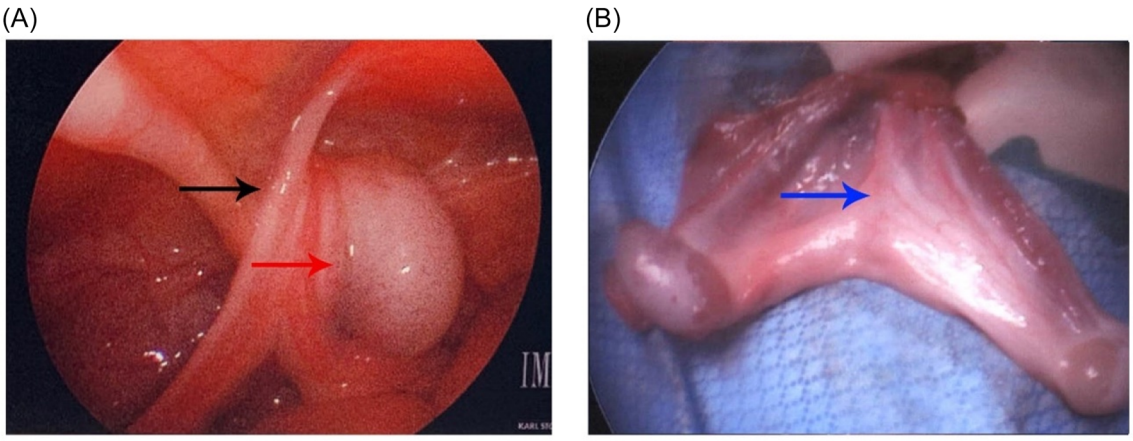

FIGURE 2 Intraoperative picture during laparoscopic exploration. (A) The testes and the vas deferens at the right internal ring; (B) the rudimentary Müllerian structure is consistent with undeveloped Fallopian tubes and uterus. The black arrow represents the vas deferens; the red arrow represents the testis; the blue arrow represents the rudimentary uterus.

between the testes was another triangular structure believed to be a rudimentary uterus.

After discussing the findings with the family, a biopsy of the polar cystic/fatty testis tissues was conducted. Due to uncertainty about the structure between the two testes and in the interest of preserving potential future fertility, the rudimentary Müllerian structures were preserved. Both testes, with cords intact, were relocated to the scrotum via the right inguinal canal, and the left testis was positioned in the left hemiscrotum through the scrotal septum using an arm of the uterus/fallopian tube/vas deferens. The processus vaginalis was meticulously dissected off the cord structures and subsequently closed. Post-op biopsy results of the testes confirmed normal testis tissue, absence of ovarian tissue, and no malignancy, effectively ruling out other disorders of sexual differentiation (DSD). The diagnosis was persistent Müllerian duct syndrome (PMDS) combined with transverse testicular ectopia.

The post-op course progressed smoothly. His karyotype was determined to be 46, XY, and the CGH array appeared normal. Subsequent genetic testing of *AMH* and *AMHR2* disclosed two abnormal *AMHR2* variants: c.322A>C and c.658G>C. Genetic testing was done through Invitae with a targeted panel and the transcript from Invitae is included in Supporting Information. Familial genetic testing indicated that the father carried the c.658 G>C mutation, while the mother had the c.322A>C mutation. After counseling the parents about the consistent testicular malignancy risk, the low malignancy risk associated with the Müllerian structures, and potential fertility complications resulting from Müllerian duct removal in PMDS, the family opted for annual follow-ups and observation in the urology office, forgoing further surgical interventions.

3 | DISCUSSION

PMDS is a rare disorder of sexual development caused by mutations in the anti-Müllerian hormone gene *AMH* or anti-Müllerian hormone receptor gene *AMHR2*. AMH is coded by a 5-exon gene which is 2.8 kb long and located on the short arm of chromosome 19 (19p13.3)[5]. On the other hand, *AMHR2* encodes the primary AMH receptor that binds AMH and activates the phosphorylation of R-Smad protein, leading to translocation of R-Smad/Smad4 complex in the nucleolus and represses the transcription of the target genes including *Wnt4* or *5A* or others. These factors stabilize β-catenin, which associates with T-cell factor/lymphocyte enhancer factor 1 to facilitate the apoptosis of Müllerian duct epithelium[6]. Also, *Wnt4* gene was known to antagonize the testis-determining factor play a concerted role in both the control of female development and the prevention of testes formation. Overall, AMH/AMHR2 function as one of the factor to suppress the female sex phenotype and development of Müllerian duct.

PMDS is characterized by persistence of Müllerian derivatives, uterus, and Fallopian tubes in otherwise normal 46, XY subjects. Patients with PMDS presented with different clinical characteristics depending on the degree of mobility of the persistent Müllerian derivatives[7]. If the Müllerian derivatives are fixed in the pelvis, the testes attached to the uterus will be retained in a high intra-abdominal "ovarian-like" position. If one or both testes descends into the inguinal canal or scrotum, the Müllerian derivatives can be dragged into the same canal[8]. "Hernia ureteri inguinale" is diagnosed when one testis, the uterus, and Fallopian tube are contained within the hernia sac. Transverse testicular ectopia is not uncommon: both testes and the Müllerian derivatives are contained in the same hernia sac with or without testicular fusion[9]. Picard et al.

reviewed 151 patients with PMDS: 29 (19.2%) patients presented with unilateral cryptorchidism, 89 (58.9%) patients presented with bilateral cryptorchidism, and 33 (21.8%) patients presented with transverse testicular ectopia[10]. Also, 32% of patients reported having hernia uteri inguinale. Abnormalities of the Wolffian duct structure are common in PMDS. These include a blind, narrow, or absent vas deferens, an abnormal ejaculatory duct, and abnormal epididymides[11]. In our case, the patient presented with a unilateral undescended testis and was found to have hernia uteri inguinalie with transverse testicular ectopia.

The Müllerian duct structures are variable in PMDS. Often the Müllerian duct structures can be easily detected in the hernia sac and are often atretic when compared to normal structures in genotypic/phenotypic 46 XX individuals. Sometimes, Müllerian duct structures may not be atretic or abnormal. In our case, the Müllerian duct structures were identified endoscopically in the right internal inguinal ring and were rudimentary and atretic.

As in our case, PMDS was diagnosed during the laparoscopic workup for cryptorchism. Patients with a family history of PMDS, unilateral cryptorchism with a contralateral hernia, or transverse testicular ectopia should raise clinical suspicion for PMDS[1,12]. Ultrasound can be the initial test to confirm the testicular position and content of the hernia sac, but may not be able to detect Müllerian structures. MRI is often used to delineate the pelvic organs and the complex structures in PMDS, which are difficult to detect on ultrasound or CT. Other congenital abnormalities associated with PMDS include intestinal atresia[13], Hirschsprung's disease[14], horseshoe kidney[15], mental deficiency, prematurity, or small for gestational age syndrome.

Infertility is the most common complication in PMDS patients. In Picard et al.'s case series, only 1 patient was able to father children among 157 cases[10]. However, only 24 patients in the series are older than 18 years. In their literature review, they found that 19% of PMDS patients were able to father children and all had at least one descended testicle. Natural fertility was rare and only possible when the patient presented with one or more descended testes as well as an intact excretory duct. In past series, infertility is common. Recent reports suggest that this may be due to excision of the Müllerian components. Since the Müllerian components share a blood supply with the Wolffian structures, excision of the Müllerian structures can devascularize the vas deferens. Some literature suggests that preserving the Müllerian structures is favored to preserve fertility because surgical excision poses a significant risk of vas deferens and testicular blood supply injury due to the vas deferens running close to or through the Müllerian remnants[1]. Fertility is rare but possible in PMDS if at least one testis is scrotal and its excretory ducts are intact[1].

Testicular malignancy is another common complication of PMDS. Although some authors believe that the risk of testicular malignancy in PMDS is not higher than that of cryptorchid patients[16], other studies suggest that these patients may have a higher risk. 33% of patients with PMDS developed malignant degeneration of the testicle[16]. The most common pathologies include seminoma, choriocarcinoma, mixed germ cell tumor, embryonal cell carcinoma, gonadoblastomas, or yolk sac tumor[17]. Early orchiopexy is recommended in patients with PMDS and regular follow-up with physical examination and/or ultrasound is indicated if orchiectomy was not performed. Malignant degeneration of the Müllerian derivatives is rare and can present as uterine leiomyoma or uterine adenocarcinoma[18,19]. Preservation of Müllerian structures favors fertility but requires lifelong surveillance for malignancy.

4 | CONCLUSION

PMDS is a congenital anomaly affecting the development of the male reproductive organs and is typically inherited in an autosomal recessive pattern. The most common genetic mutations are the *AMH* gene and the *AMHR2* gene. 88% of patients diagnosed with PMDS have an *AMH* or *AMHR2* gene mutation; the remaining cases are idiopathic[10]. Here, we report two distinct heterozygous *AMHR2* gene mutations, each in a different chromosome resulting in two unique non-functional AMHR2 receptor proteins: c.322A>C from the mother and c.658G>C from the father. These unique mutations resulting in PMDS have not been reported prior.

The management goal for PMDS is to restore or maintain fertility and prevent malignant transformation of the testes. The Müllerian structures in these patients are often intimately associated with the Wolffian structures required for normal male fertility. Any attempt to surgically remove the Müllerian organs will damage the vas deferens and their associated blood supplies. Surgical extirpation is only indicated when malignant degeneration is suspected or caused by Müllerian structure proliferation. In such cases, symptoms of pelvic discomfort, gross hematuria, or hematospermia would be diagnosed[20].

Orchiopexy should be performed in PMDS patients with the same rationale as cryptorchidism: decreasing the risk of malignancy, increasing the chance for fertility, and facilitating physical examination of the testicles. In our patient, we performed an intraoperative testicular biopsy to ensure the diagnosis, rule out malignancy, and rule out other DSD diagnoses. Then a transcrotal orchiopexy was performed without the removal of either the Wolffian or the Müllerian structures. Normally, orchiectomy only served as the last resort when malignancy was suspected or orchiopexy was not able to be performed. Regular follow-up with a urologist is

necessary to ensure fertility, normal hormonal function, as well as early detection and prevention of testicular malignant transformation.

AUTHOR CONTRIBUTIONS

Hangcheng Fu and Jeffrey T. White for case concept, manuscript writing, and design and study supervision. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data analyzed during this current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

Written informed consent was obtained from the patient for publication of this case and any accompanying images. Institutional review board (IRB) approval was not required for this single-patient case report.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.