Decision-making in pediatric persistent Mullerian duct syndrome

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We are reporting a case of an 18-month old male who presented with bilateral cryptorchidism. The patient underwent an explorative laparoscopy in which two gonads were identified in close proximity to the uterus and fallopian tubes. Biopsy of the gonads confirmed testicular tissue. Genetic analysis demonstrated a 46, XY male. Male external genitalia were appropriate for age with no evidence of female structures. Persistent Mullerian duct syndrome is extremely rare, with approximately 260 cases reported in the literature. Best practice for the extent of surgical management is still evolving as we gather data on long-term outcomes. *Ann Pediatr Surg* 14:24–26 © 2018 Annals of Pediatric Surgery.

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Introduction

Persistent Mullerian duct syndrome (PMDS) is a rare case of male pseudohermaphroditism. Patients have a 46, XY karyotype and are phenotypically male. However, internally they have remnant Mullerian structures, including uterus, fallopian tubes, and proximal vagina, which typically outflow into the prostatic urethra [1]. Approximately 260 cases have been reported [2]. It is commonly discovered in adulthood as an incidental finding during an inguinal hernia repair or orchiopexy for unilateral or bilateral cryptorchidism. Patients have normal male phenotype and undergo normal puberty with normal virilization; however, infertility is common [3].

Case presentation

An 18-month old male was referred to the pediatric surgery clinic for bilateral cryptorchidism. The patient had no significant medical or surgical history and no family history of cryptorchidism. On physical examination, the patient appeared healthy, well developed, well nourished, and of appropriate size and weight for age. Physical examination was unremarkable, except for an empty an scrotum bilaterally with no testes palpated in the scrotum or groin. No hernia was identified on either side. The patient was taken to the operating room for exploratory laparoscopy with possible orchiopexy. Two intra-abdominal testes were identified. Upon difficulty inserting the testes into the inguinal ring, closer investigation revealed that the testes were in communication through a midline structure. Because of poor visualization, testicle and the midline structure were brought to surface via a 3-cm lower quadrant excision. The testicle was embedded in a ligament and was attached to what appeared to be a uterus and fallopian tube (Figs 1 and 2). Testicular vessels were identified; however, vas deferens was not distinctly recognized. A biopsy of the testicle was taken for confirmation. Contents were placed back inside the pelvis and the operation was concluded. Pathologic evaluation of the gonadal tissue was consistent with testicular tissue with no evidence of ovarian tissue. The patient underwent a genotypic analysis, which revealed a normal 46, XY karyotype. The patient was diagnosed with PMDS.

Discussion

During embryologic development, the fetus contains both mesonephric (Wolffian) and paramesonephric (Mullerian) ducts. In a 46, XY male, the *SRY* gene on the Y chromosome produces testis-determining factor, which leads to the development of the testes. The testes are made of two compartments: seminiferous tubules, which enclose Sertoli cells, and interstitial tissue, which house Leydig cells [4]. Sertoli cells secrete anti-Mullerian hormone (AMH), also known as Mullerian inhibiting substance or factor, which suppresses the development of paramesonephric ducts, thereby inhibiting the formation of female internal structures, notably the uterus, fallopian tubes, and proximal vagina. Leydig cells secrete androgens that stimulate the development of mesonephric ducts, leading to the formation of male internal structures, including the seminal vesicles, epididymis, ejaculatory duct, and vas deferens. Androgens are converted to dihydrotestosterone to allow the urogenital sinus and genital tubercle to form the prostate and male external genitalia, respectively [5].

Female phenotype is the default phenotype, where even a 46, XY male will develop internal female structures if he has a defective *SRY* gene, Sertoli cells that fail to produce functional AMH, or have defective type II AMH receptors (AMH-IIR) [6]. In all, 85% of PMDS cases are due to a nonfunctional mutation in *AMH* or *AMH-IIR* gene that has autosomal recessive transmission. The remaining 15% of cases are idiopathic [7].

PMDS is typically discovered incidentally during an inguinal hernia repair or orchiopexy. Clinically, patients

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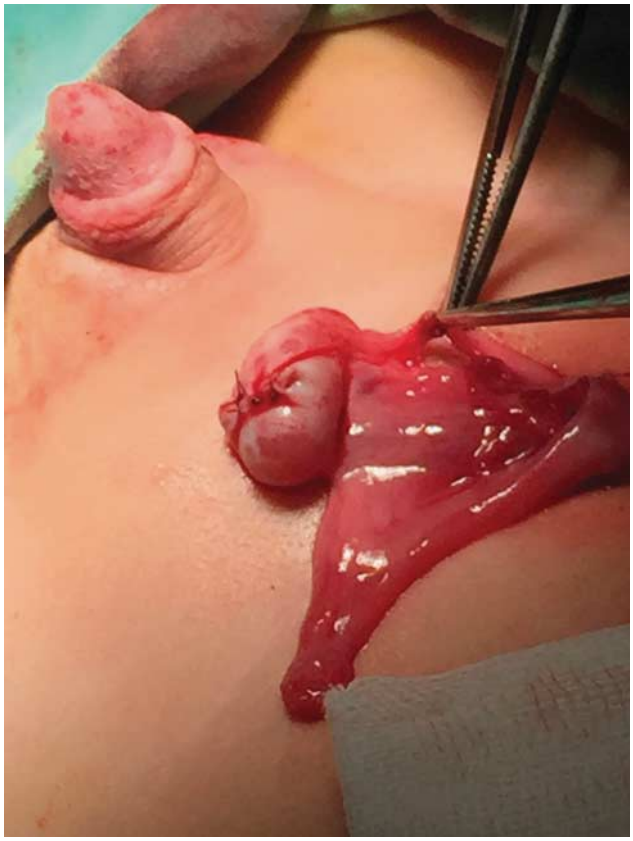
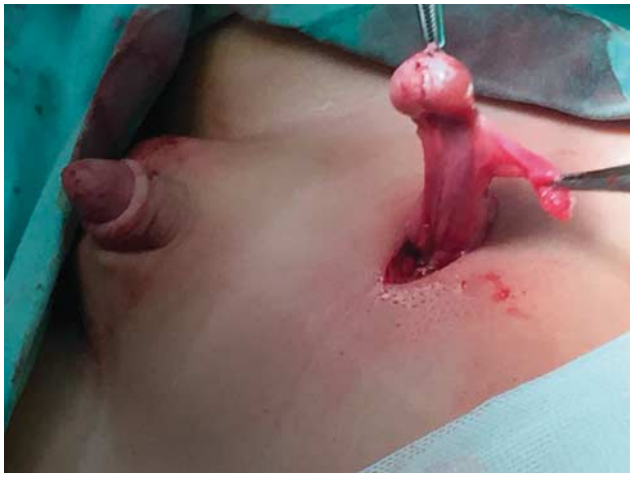
Fig. 1



Testicle embedded in a ligament and attached to what appears to be a uterus and fallopian tube. Clamp indicates testicular vessels.

Fig. 2



Testicle embedded in a ligament and attached to what appears to be a uterus and fallopian tube. Right clamp indicating the fallopian tube.

have normal growth and development without any external deficiencies. Upon identification, PMDS is divided into classes: *class A* (60–70%) – bilateral undescended testicles embedded in the broad ligament located in the area analogous to ovaries in a female; *class B* (20–30%) – unilateral undescended testicle with ipsilateral inguinal hernia that may contain the testis, uterus, and fallopian tubes (i.e. hernia uteri inguinale); and *class C* (10%) – involves transverse testicular ectopia with both testes in the same hernia sac along with Mullerian structures [8].

Management of the patient with PMDS is still under discussion. Depending on the age of diagnosis, orchiopexy or orchiectomy should be performed to help preserve fertility or eliminate the possibility of testicular malignancies, respectively. With regard to Mullerian structures, initially nonoperative management was favored because of difficulty in identifying the vas deferens, as many times it is found intimately adherent to lateral walls of the uterus or the fallopian tubes, and risk of damage to the vas deferens and testicular vesicles may lead to infertility and significant morbidity. In addition, it was believed that retention of Mullerian remnants was low risk [1]. However, 11 cases of advanced malignancies stemming from these remnants, even in the pediatric population, have been identified, many of which within the past two decades [2,8]. Furthermore, patients with PMDS are at a greater risk for Mullerian malignancy than testicular malignancy, resulting in increasing support for surgical intervention [9,10].

The majority of interventions have been staged, with stage 1 involving gonadal biopsy and hernia repair and stage 2 addressing the testes and Mullerian remnants. Of note, Manjunath *et al.* [8] argue that if the epididymis and vas deferens are present, this would unequivocally reveal that the gonads are testes, and a staged procedure is not needed as orchiopexy can be performed during initial exploration. This would eliminate the need for a biopsy and prevents insult to the blood–testes barrier and the possibility of forming antisperm antibodies, which would further decrease fertility [11]. Guerrier *et al.* [12] advocate bilateral proximal salpingectomies, leaving fimbriae with the epididymis, hysterectomy, and bilateral orchiopexy, if the testes are normal. If the testes are atrophic, orchiectomy should be performed. Risk of testicular malignancy in patients with PMDS is 5–18%, similar to that of patients with cryptorchidism [2]. Many patients present with neglected cryptorchidism (mean age 8.2 years in one study) and have short spermatic vessels, necessitating a staged Fowler–Stephens orchiopexy (FSO) [2]. However, dissection of Mullerian remnants would significantly risk damage to the deferential vessels, the remaining blood supply to the testes. Because of greater likelihood of testicular atrophy if FSO and Mullerian remnant excision are being done together, Shalaby *et al.* [2] advocate for leaving the Mullerian remnants in place whenever FSO is necessary and opt for long-term follow-up. Manjunath *et al.* [8] advocate for removal of remnants that can be safely removed, without risking damage to the vas deferens or testicular blood supply, and stripping/destroying the mucosa of the retained Mullerian remnants to reduce the risk of malignancy, which originate from the mucosa. Subsequently demonstrating that in patients where FSO is necessary, a midline splitting of the Mullerian remnants with obliteration of mucosa would allow for complete mobilization of both testes without risking damage to the vas deferens or testicular blood supply [8].

Conclusion

The treatment plan for our patient is to perform laparoscopic total abdominal hysterectomy with bilateral proximal salpingectomy and bilateral orchiopexy.

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Conflicts of interest

There are no conflicts of interest.

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