

Case Report

Clinicopathologic features of persistent mullerian duct syndrome complicated with seminoma: a case report and review of literatures

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Abstract: Persistent mullerian duct syndrome (PMDS) is a rare form of male pseudohermaphroditism characterized by the presence of a uterus and fallopian tubes owing to failure of mullerian duct regression, which was shown in a genetically and phenotypically normal male patient. PMDS can occur at any age, preoperative diagnosis of PMDS is quite difficult, as most of them were discovered incidentally during surgery before adolescence. The co-existence of PMDS with seminoma has been rarely reported in the literature. It is necessary for people to grasp knowledge to diagnose this rare case. Therefore, we report a case of PMDS complicated with seminoma. A 28-year-old-male who was made previous diagnosis of enorchia was found fallopian tubes and uterus during an exploratory laparotomy because of left abdominal pain.

Keywords: Persistent mullerian duct syndrome, AMH, seminoma

Introduction

Being a rare disorder of sexual development, PMDS was first mentioned by Nilson in 1939 [1]. Up to present, there have been only 200 cases reported in the literature worldwide. Among all reported cases, PMDS complicated with testicular cancer has been rarely reported. In this paper, in a case of PMDS complicated with seminoma, it is reported about the clinical characteristics and clinicopathologic features and reviewed literatures to explore the clinical pathology characteristics for the pathological diagnosis and differential diagnosis.

Case report

A 28-year-old Chinese man was diagnosed postoperatively as being a PMDS with a seminoma on the basis of finding fallopian tubes and uterus without ovarian tissue during an exploratory laparotomy for left abdominal pain without palpable mass. He was considered as enorchia previously. Physical examination on the patient revealed that a phenotypically male had normal external male genitalia. The testis was absent in the scrotum since birth, nor found in the inguinal region. He had normal secondary sexual characteristics with no gynaeco-

mastia. Although the patient had sexual life and ability to erect and ejaculate, he was childless. His brother and sister did not have similar medical history. Ultrasound revealed a substantial mass occupied in left lower abdomen (**Figure 1**). Previous diagnosis of enorchia was made. Suspecting of a malignant neoplasm involved in the undescended testis, an exploratory laparotomy was performed. During the operation, the left abnormal testis was found and another one at the right was absent, while tubae laciniatae and uterus were found in pelvic cavity, which were all excised. All the specimens were sent for histopathological examination. No obvious evidences indicated metastasis. Pathological examination of the excised specimen was reported as uterus and bilateral uterine tubes with histological findings of endometrium, cervix and left and right uterine tubes (**Figure 3A-C**). Karyotype analysis from peripheral blood resulted as 46XY (**Figure 2**).

Discussion

The pathogenesis of PMDS

The occurrence mechanism of hermaphroditism is unclear at present which is believed that

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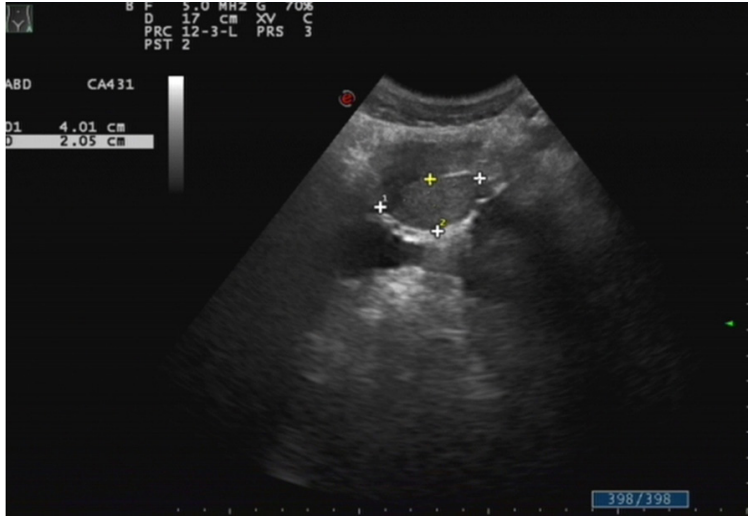


Figure 1. The abdominal ultrasound scan of the abdominal cavity showed that substantial low level echo mass occupied in left lower abdomen with the size of 4.01 cm × 2.05 cm (plus signs).

there is close correlation between chromosome, abnormal gonadal development and related endocrine disorders. In recent years, increasing investigations indicated that AMH, WT-1, SRY, SF-1, DAX-1, SOX-9 and other genes were involved in differentiation of two sexes, in the process of which any one of the above gene mutation, deletion or translocation can cause the abnormal sex differentiation and lead to the occurrence of the sexual abnormality [2].

Anti mullerian hormone (AMH) also called mullerian inhibiting factor (MIF) plays an important role in differentiation of reproductive organs in male fetuses. In a human fetus, the internal genital tract of fetus is composed of mullerian duct and wolf tube before sex determination; both of them coexist within 8 weeks. In male embryos, the immature Sertoli cells of the Leydig produce AMH which is responsible for the regression of the mullerian duct by the end of the 7th week. Then, testosterone promotes wolf tube is differentiated into vas deferens, epididymis and seminal vesicle after 2 weeks. In the female embryo, the mullerian duct is differentiated into the fallopian tube and uterus, while the wolf tube is degenerated [3]. The male with normal internal and external genital appear incomplete degradation of mullerian duct when the patient lacks AMH.

The gene is responsible for AMH located in the short arm of chromosome 19, p13.3 which plays a biological role through transmembrane

serine/threonine kinase receptor type II [4]. The deletion, insertion or mutation of AMH gene can affect its regulation, expression and translation, resulting in a lack of AMH. All kinds of factors that interrupt the process of the synthesis, secretion and function of AMH can lead to the occurrence of PMDS finally. The most common one is the mutation of AMH gene among these factors. A report about three brothers with PMDS in 1991 found that the mutation of the fifth exon of 2096th locus of the AMH gene resulted in the early termination of the translation [5].

PMDS has familial aggregation and genetic predisposition, which is an autosomal recessive disorder related to sex. In addition, there may be some factors that have not been noticed and confirmed, such as the failure of AMH action time, and the intrauterine environment during the embryonic period; these factors lead to the failure of mullerian duct of degeneration [6]. It was normal that AMH level and the expression of AMH gene occur in approximately half of the patients, the number of abnormal AMH receptor or insensitive AMH receptor may be another etiology of PMDS [7].

The classification of PMDS

According to the anatomical characteristics of the residual mullerian duct structure, PMDS is generally divided into 2 categories: the first kind (male form) accounts for 80% to 90% of cases, characterized by unilateral cryptorchidism with contralateral inguinal hernia. This kind can be further categorized into two hypotypes: the most common type is hernia uteri inguinalis, in which hernia content is undegraded uterus and ipsilateral fallopian tube. Another type is transverse testicular ectopia (TTE), which appears both testes in the same hernia sac with uterus and uterine tubes [4]. The second kind (female form) occupies only 10% to 20% of cases, characterized by bilateral cryptorchidism located in analogue positions of ovaries, with the uterus fixed in the pelvis bilateral,

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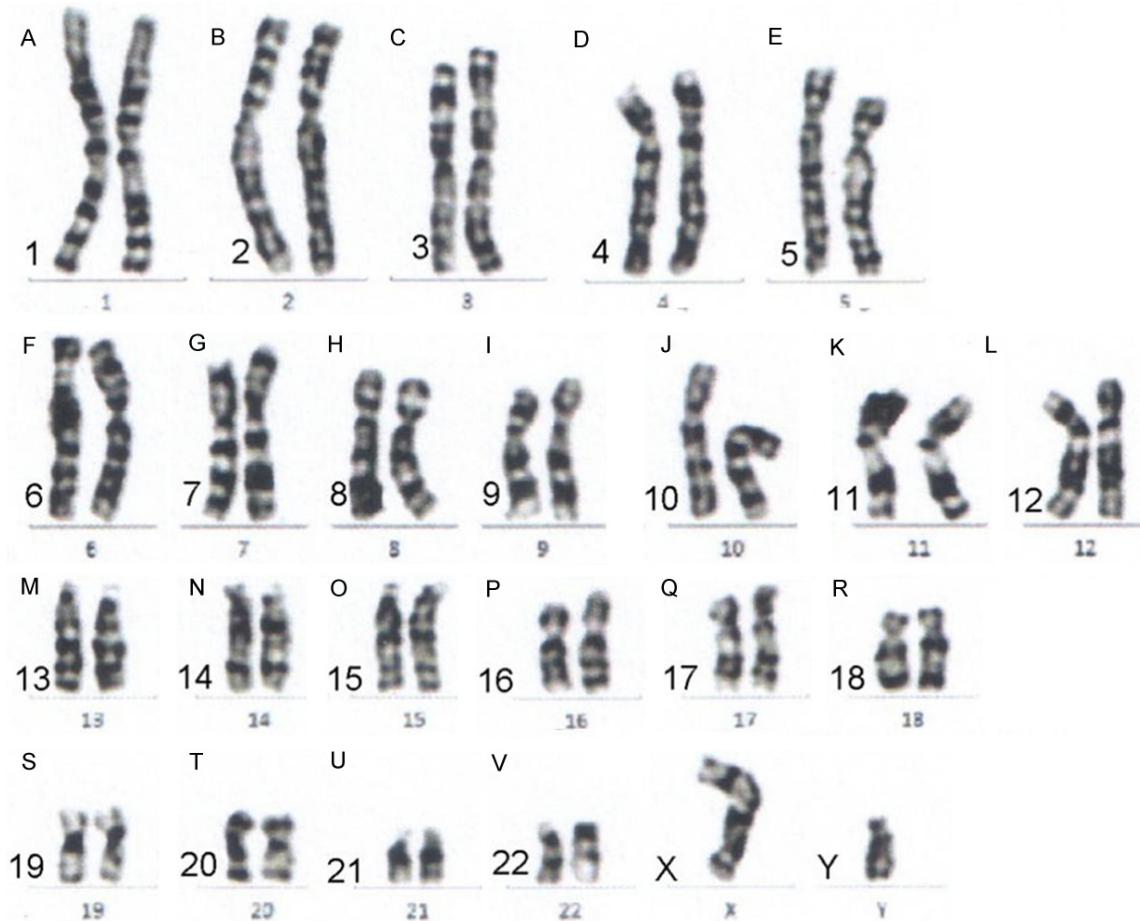


Figure 2. Chromosomal analysis result was 46XY karyotype. (A to V are autosomes, X and Y are sex chromosomes).

and both testes embedded in the round ligaments [4]; as in our case.

The clinical manifestation and diagnosis of PMDS

The secondary sexual characteristics of PMDS patients are normal and perform as male sexual psychological tendency and reproductive ability. Most of PMDS patients seek treatment for inguinal hernia, bilateral cryptorchidism, oligospermia and sterility or genital system tumor. The preoperative diagnosis of PMDS is quite difficult. CT, MRI, AMH hormone levels and laparoscopy may be helpful for diagnosis [8, 9]; and it is always discovered incidentally during surgery [10].

PMDS and seminoma

The relationship between PMDS and cryptorchidism or TTE is unclear. The mechanical

obstruction of the mullerian duct structure is considered to be a possible factor of preventing testis from descending into the scrotum. Increasing evidences revealed that the risk of developing a tumor of testis was greatly increased, which was 10 times higher in enorchia than the normal testis. Testicular tumours originating from an undescended testis is about 10% [11] and the relative risk of testicular neoplasm in cryptorchidism is 7.5% [12]. In patients with unrecognised intraabdominal testis, seminoma is more common than nonseminomatous germ cell tumor [13]. The incidence of testicular malignant transformation in the undescended testes of PMDS patients is estimated to be 5% to 18%, which is similar to the incidence of testicular carcinoma in abdominal testes in patients without PMDS [14]. No more than 17 cases that PMDS complicated with seminoma have been reported in the PubMed database since 1985 [15-30]. In this case,

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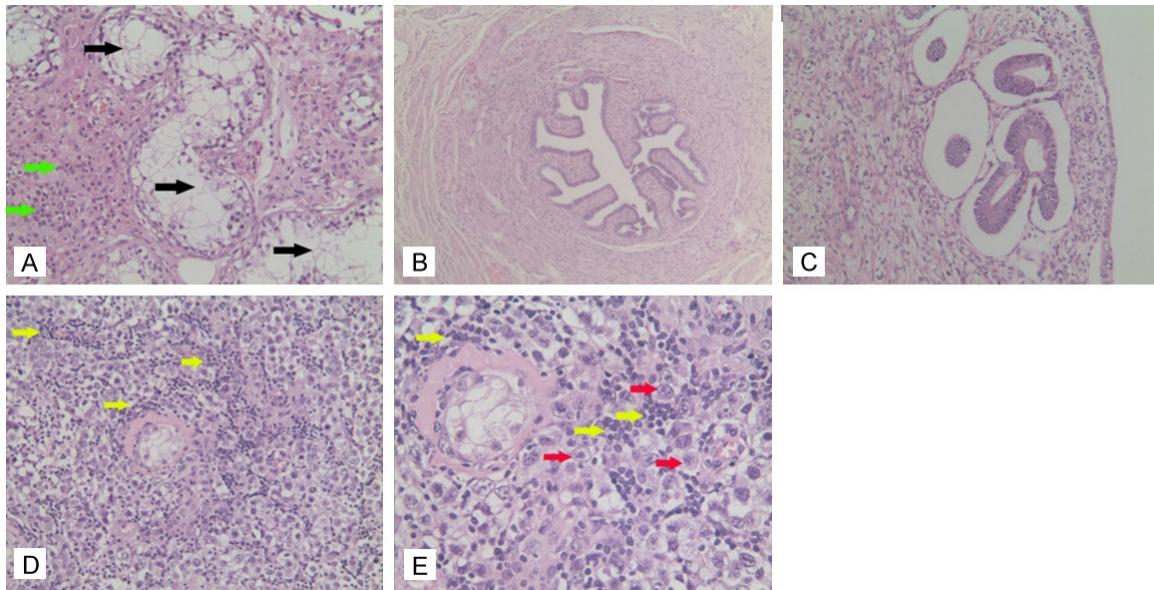


Figure 3. A. Pathological features of the left testis in patient with PMDS, which shows the dysplasia of seminiferous tubule (black arrows) and hyperplasia of Leydig's cell (green arrows) (original magnification $\times 200$). B. Pathological features of the fallopian tube (original magnification $\times 100$). C. Pathological features of the endometrium (original magnification $\times 200$). D, E. Pathological features of the seminoma. The picture partially showed the diffuse single heterotypic cell (red arrows). The tumor cells were large, with abundant transparent cytoplasm, coarse granular nuclei, deeply stained chromatin, and infiltration of substantial lymphocytes (yellow arrows) (original magnification $\times 200$, $\times 400$).

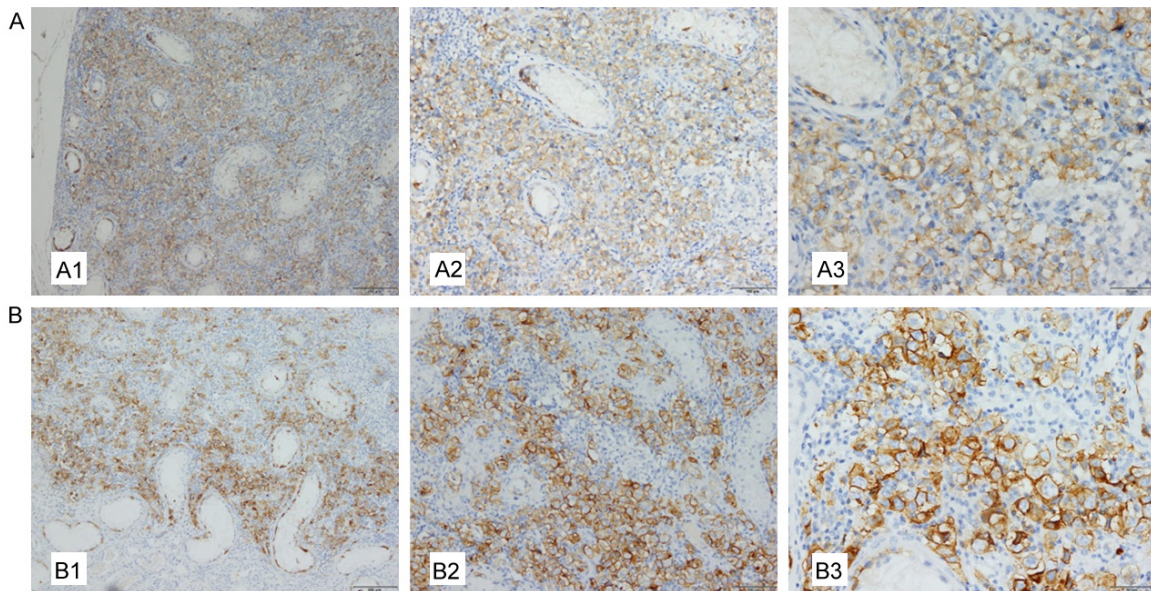


Figure 4. A1-A3. Seminoma of immunohistochemistry was positively express CD117. CD117 was highly expressed cytoplasm positive in the picture (original magnification $\times 100$, $\times 200$, $\times 400$). B1-B3. Seminoma of immunohistochemistry was positively express PLAP. PLAP was highly expressed membrane positive in the picture (original magnification $\times 100$, $\times 200$, $\times 400$).

besides that histology of the specimen revealed typical features of seminoma (**Figure 2D, 2E**), the immunohistochemical detection implicated

that PLAP and CD117 are positively while AFP (**Figure 4**), Vimentin, HCG, CK-LMW, Desmin, CD34 and CD30 are negative; the index of

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Ki-67 is 50%; all these indicators show the clear diagnosis of seminoma. With the research development of seminoma, more and more makers, such as *MAGEC2*, *CAG*, *CMTM2*, are applied in the early diagnosis of seminoma [31, 32].

The differential diagnosis of PMDS

It is critical to distinguish PMDS from other intersex disorders. Mixed gonadal dysgenesis (MGD) is the most important differential diagnosis in PMDS. In MGD cases, patients have the residual mullerian duct structures and vague external genitalia. But, the karyotype of MGD is usually 45, XO/46, XY mosaic type. Therefore, a karyotype and assessment of sex hormone levels are necessary to verify both genetic sex and the existence of functional testicular tissue.

The treatment of PMDS

At present, surgical treatment is the only effective treatment for PMDS. The main goal of surgical treatment is to deal with residual mullerian duct and ectopic testis. In order to prevent any malignant transformations and place the testes into a palpable position in the scrotum, early orchidopexy with removal of mullerian duct structures is recommended by most clinicians [33]. Vas deferens should be divided from the rudimentary uterus; and the blood supply of testis should be preserved before excision of mullerian duct structures. PMDS patients with intra-abdominal cryptorchidism have higher postoperative fertility before puberty. Cryptorchidism traction should be performed early in order to correct enorchia while exaeresis of hypogenetic testis is suitable for those cases of patients at over 2 years olds. The fertility rate is only about 14% for patients with intra-abdominal cryptorchidism after puberty, which have higher incidence of malignant transformations. Therefore, orchidectomy can be performed. One side of the testis should be retained in the cases of patients with bilateral cryptorchidism. PMDS patients with TTE, modified Omberdan technique is the most commonly described one that places the ectopic testis in the correct hemiscrotum through a window in the scrotal septum. Once malignant transformation had occurred, the treatment principle is the same as that of the common orchioncus. Seminoma is highly sensitive to

radiotherapy and chemotherapy; and its prognosis depends on clinical stages closely; the recurrence rates are 6%, 18% and 36% separately while the tumor size are <3 cm, 3~6 cm and >6 cm. In addition, blood and lymph metastasis is also the important factor involved in the prognosis of seminoma.

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Disclosure of conflict of interest

None.

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