

Prostatic adenocarcinoma in a patient with persistent Müllerian duct syndrome

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Abstract

The embryonal male sexual differentiation is driven by testosterone, and Anti-Müllerian hormone (AMH). AMH is responsible for regression of Müllerian ducts in a genetically male fetus. Mutations inactivating AMH or its receptors are responsible for persistent Müllerian duct syndrome (PMDS) in virilized 46, XY males. PMDS is a rare genetic disorder affecting males, with less than 300 cases described in literature. The syndrome is usually recognized early in life with patients present with bilateral undescended testicles, and often decreased testosterone production by Leydig cells later in life. The role of testosterone in the development and progression of prostate cancer is well established, and men with low circulating free testosterone are expected to have a lower risk of developing prostate cancer. Indeed, 2 cases of prostate cancer in patients with PMDS have previously been described. Herein, we are reporting the third of prostate cancer in patient with PMDS.

Keywords: Müllerian duct malformation, persistent Müllerian duct syndrome, prostate adenocarcinoma

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INTRODUCTION

Male sexual differentiation is driven by the presence of testosterone, and anti-Müllerian hormone (AMH).^[1] AMH is a large glycoprotein that belongs to the transforming growth factor-P and is produced by Sertoli cells early in fetal life. The gene responsible for AMH is located on chromosome 19.^[1,2] If the fetus has XY (male) chromosomes, the testes will produce AMH and the Müllerian ducts will disappear. Then, testosterone produced in the testes will promote the development of the male reproductive system. AMH is first secreted in effective

amounts in the 8th week after conception, and the process of Müllerian duct regression is normally completed by about the end of the 11th week, as the Müllerian tissue will become insensitive to AMH.^[3,4]

Persistent Müllerian duct syndrome (PMDS) is a form of disorder of sexual differentiation caused by a defect in the coding of AMH or its receptors. Patients are phenotypically male and usually present with unilateral or bilateral cryptorchid testes.^[4,5] The testes can be located anywhere from the retroperitoneum to the scrotum; cryptorchidism and transverse testicular ectopia have been associated

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with this condition.^[5] Internal genitalia, however, consist of structures that are derived from the persistence of the Müllerian ducts, i.e., fallopian tubes, uterus, cervix, and upper vagina.^[6,7] Familial cases have been reported with a probability of sex-limited autosomal recessive or X-linked recessive inheritance. An incidence of PMDS in identical twins has also been reported.^[6,8]

The role of testosterone in prostate cancer is well established, and men with low circulating free testosterone may have a lower risk of prostate cancer than the rest of the population.^[1] Cryptorchidism and diminished testosterone levels in postpubertal life in patients with PMDS play a protective role against prostate cancer.^[7,9,10]

Herein, we present the case of a patient with PMDS who presented with prostatic adenocarcinoma. Previously, only two cases of prostate cancer have been reported in the English literature.^[1]

CASE REPORT

A 59-year-old phenotypic male was referred to our tertiary care center for treatment after he was newly diagnosed prostate cancer. He was seen by a community urologist for elevated prostate-specific antigen (PSA) of 13 ng/ml and a firm lobulated prostate upon rectal examination. The patient underwent ultrasound-guided prostate biopsy and that leads to the diagnosis of prostatic adenocarcinoma with Gleason score of 3 + 4 = 7 involving 30% of the submitted cores from the apex, and both prostatic lobes. He was classified as unfavorable intermediate risk according to the NCCN classification.^[11]

The patient was born with bilateral cryptorchidism, and bilateral inguinal orchiopexy was attempted at the age of 12. Unfortunately, the surgical procedure was successful in only bringing the right testicle to the right groin. However, the left testicle was not found. The patient did not follow up to have second-stage orchiopexy to bring the right testicle to the scrotum. He, eventually, had normal puberty and became sexually active but never fathered a child.

The patient had mild degree of lower urinary tract symptom with International Prostate Symptom Score of 11. Physical examination revealed atrophic empty scrotum with severe chordee. The right testicle was subcutaneous and palpable in the right groin. Bilateral inguinal scars were noticed. A firm nodular prostatic was identified upon rectal examination. No inguinal hernia was identified on physical examination.

Staging computerized axial tomographic (CT) scanning of the abdomen and pelvis revealed a uterus with bilateral fallopian tubes stemming out of the posterior aspect of the prostate. No lymph node enlargement was detected [Figure 1]. Subsequently, this patient was further evaluated with pelvic ultrasound which confirmed the presence of the uterus attached to the enlarged nodular prostate. The seminal vesicles and vas deferens were not identified on either of the former imaging. The CT scan confirmed the presence of both kidneys without agenesis, hypoplasia, parenchymal abnormalities, or collecting system anomalies. His bone scan was also negative for bony metastasis.

Given these findings, we performed hormonal assay of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, and testosterone and the results are displayed [Table 1]. The patient is genotypic male with karyotype of 46 XY without any mosaicism. The serum levels of testosterone and estrogen were within normal limits. The levels of LH and FSH were elevated which were deemed consistent with the history of cryptorchidism, and gonadal degeneration that resulted in failed feedback. The constellation of imaging and clinical data leads to establish the diagnosis of a PMDS in this patient.



Figure 1: Uterus superiorly (red arrow) and prostate inferiorly (white arrow) on the same midline sagittal image

Table 1: Serum levels of follicle-stimulating hormone, luteinizing hormone, estradiol, and testosterone

	Reference range	Preprocedure levels
FSH	1.0-12.0 IU/L	54.6 (H)
LH	0.5-11.0 IU/L	26.7 (H)
Estradiol	11-44 pg/mL	15
Testosterone	3.98-14.7 ng/dL	5.86

FSH: Follicle-stimulating hormone, LH: Luteinizing hormone

After long discussion with the patient about treatment option based on the NCCN guidelines, he elected to have surgical resection of the prostate and the Müllerian remains.^[1] Robotically assisted laparoscopic radical prostatectomy was performed along with hysterectomy, and bilateral pelvic lymph node dissection. The rationale to remove the Müllerian duct derivatives, i.e., uterus and fallopian tubes, was to prevent the occurrence of malignant degeneration reported in the literature.^[2,3] Besides, the uterus and prostate formed one block with the prostate with no clear tissue plane between them. The left testicle was not found in the expected locations. Rather, a uterus and bilateral fallopian tubes suspended to the pelvic wall through suspensory ligaments containing vascular pedicles were identified without any evidence of ovaries or testes within the abdomen.

The surgical technique

Five robotic trocars were utilized as follows: one trocar was placed at the level of the umbilicus to serve as camera trocar. Two trocars on each side were introduced, the far-right trocar was used for the assistance, and the rest were used to introduce the robotic instruments. The trocars were 8 cm apart of each other. Upon entering the abdomen, we were able to identify the uterus posterior to the bladder. We started by incising the broad ligament to free the uterus and the fallopian tubes. The uterus was dissected of the posterior aspect of the bladder all the way to its attachment to the prostate at the cervix. Lateral to the cervix, we identified the uterine vessels and transected them between two Hem-o-lok clips. The ureters were clearly identified under the uterine vessels passing to the bladder. Then, the bladder was dropped by opening the peritoneum lateral to the medial umbilical ligaments. The space of Retzius was developed, the endopelvic fascia was opened, and the puboprostatic ligaments were transected. The dorsal venous complex was suture ligated and transected. We, then, made an incision at the bladder neck to separate the prostate from the bladder. Instead of encountering the vas and seminal vesicles, we encountered the cervix. We separated the prostate from the rectum, and the prostatic pedicle was transected establishing wide excision. The prostatic apex was freed, and the urethra was transected. The uterus was removed *en bloc* with the prostate. Bilateral pelvic lymphadenectomy was also performed. The bladder neck was subsequently anastomosed to the urethral stump over a 20-French Foley catheter.

Surgical pathology of the prostatic mass demonstrated an acinar adenocarcinoma. Gleason score was 7 (3 + 4), grade group 2 with 60% prostatic, left bladder neck with extracapsular invasion to the apex, bladder neck, and the

cervix. The surgical resection margins were negative. One of the 18 resected right pelvic lymph nodes was positive for a 3-mm metastatic deposit. None of the 14 resected left pelvic lymph nodes were positive for metastatic disease.

In addition, a review of the surgical pathology for urogenital structures removed showed a uterus with identifiable rudimentary endometrium and stroma and a focal small leiomyoma with calcification. Bilateral fallopian tubes were identified in the pathology specimen as well. Although not identified intraoperatively, seminal vesicles were readily identified within the endocervix and communicated with prostatic urethra. The endocervical tissue was present adjacent to the prostatic tissue. Interestingly, the cervical os was communicating with the urethra, an established finding from case reports in the literature.^[3] Similarly, bilateral vas deferens were not identified intraoperatively but were readily identified in the pathology specimen adjacent to the uterus. No testicular tissue was identifiable on pathology. Figures 2 and 3 show the histopathology and gross specimens of the resected tissue.

Finally, the catheter was removed on postoperative day 9, and the patient achieved nadir PSA of <0.1 ng/mL. Due to the involvement of one lymph node, decision was made to undergo androgen deprivation therapy and that was achieved surgically by removing the right inguinal subcutaneous testicle. His testosterone dropped after the surgical castration to <50 mg/dL.

DISCUSSION

PMDS is an extremely rare genetic condition of genotypic males with <300 cases described in the literature.^[3,4] These patients can have normal-appearing external male genitalia (normal phallus and scrotal skin). However, it is common for the patient to have bilateral or unilateral cryptorchidism. Bilateral or unilateral inguinal hernias, with or without testicular ectopia, are quite common findings.^[5] The hallmark of internal genitalia phenotype is persistence of derivatives of the Müllerian ducts (fallopian tubes, uterus, cervix, and upper vagina) that normally regress in males under the influence of androgens (mainly testosterone) and AMH. The testes are developed normally however can be located anywhere from the retroperitoneum to the scrotum. PMDS usually results from mutations resulting in the deficiency or defect of AMH or, occasionally, defect in the AMH receptors. PMDS is caused by genetic defects hallmarked by the deletion of the gene encoding the AMH or its receptors that is usually inherited as an autosomal recessive trait.^[3-5,8] Of note, it has previously been reported in literature Wolffian duct derivatives abnormalities, such

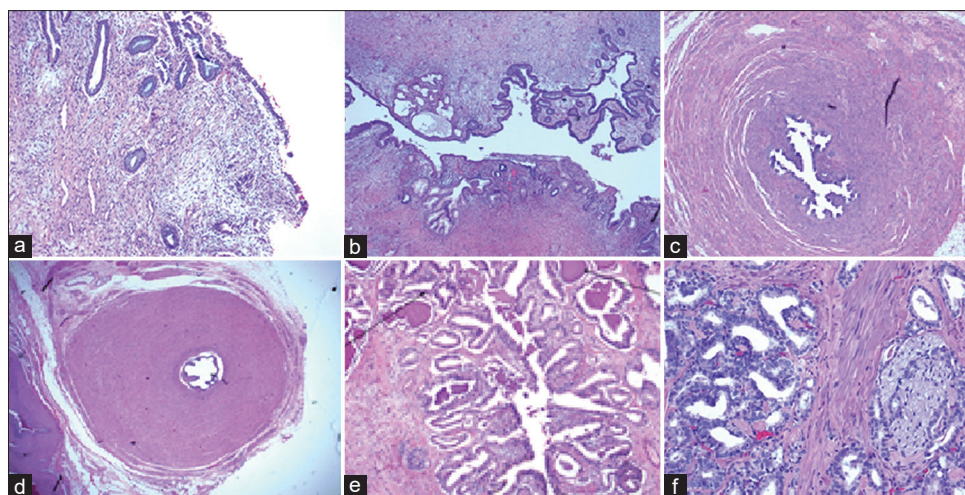


Figure 2: Histopathology showing endometrium with stroma in uterus (a), cervical canal (b), fallopian tube (c), vas deferens (d), seminal vesicle (e), and prostatic carcinoma (f)

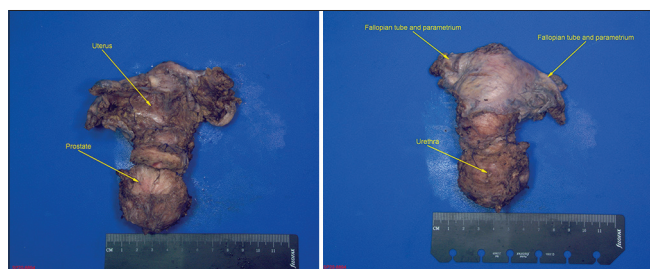


Figure 3: Gross specimen demonstrates *en bloc* resected prostate and cervix inferiorly, and uterus with fallopian tubes superiorly

as opening of vas deferens into the superior vagina, and narrowing or absence of Wolffian duct derivatives.^[3] Interestingly, the seminal vesicles were embedded in the endocervical canal in this case and the Müllerian derivatives are in close proximity to the prostate, seminal vesicles, and vas deferens as evidenced on histopathological examination. The condition is important to recognize in early childhood to prevent worrisome complications of the PMDS such as infertility and malignant transformation of the gonads or Müllerian derivatives.^[2,4,8] Early correction of cryptorchidism and resection of the derivatives of Müllerian duct address the risk of malignant transformation. The management is usually complex and surgical resection requires expertise due to the proximity of derivatives of Wolffian and Müllerian duct and their delicacy.^[7] This case demonstrates the role of imaging in identifying the abnormalities and providing valuable information toward the surgical planning.^[6,7,9]

The association of prostatic cancer with PMDS is quite rare as only two cases of prostate cancer among PMDS patient have been reported in the literature so far.^[10,12] This case represents the third case of prostate cancer among a patient with underlying PMDS. We demonstrate radiological-pathological correlation for this case for

an opportunity to further the existing knowledge of this extremely rare medical diagnosis. Finally, we also demonstrate that surgical management for removal of Müllerian duct derivatives can safely be performed with minimally invasive technique if prior planning is done based upon imaging findings.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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