Acta Clin Croat 2024; 63:828-833
doi: 10.20471/acc.2024.63.03-04.47

Case Report

A MAN WITH UTERINE LEIOMYOMA AS PART OF PERSISTENT MÜLLERIAN DUCT SYNDROME – A CASE REPORT AND REVIEW OF THE LITERATURE

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SUMMARY – We present a clinical case of a 59-year-old man, father of two children, who complained of irritative voiding of the bladder. An unknown retrovesical structure was detected by ultrasound and computed tomography, and was surgically removed later. Histopathologic analysis reported uterine tissue with a leiomyoma, thus the diagnosis of persistent müllerian duct syndrome (PMDS) was established. It is a rare disorder characterized by the appearance of müllerian derivatives (fallopian tubes, uterus, and upper two-thirds of vagina) in males with normally developed external and internal genitalia. Patients usually present with cryptorchidism and inguinal hernia. Irritative voiding has not yet been described as the main symptom of PMDS. The major complications of the disorder are infertility, testicular tumorigenesis, and malignant transformation of müllerian structures. To the best of our knowledge, in addition to our case, only one case of PMDS with uterine leiomyoma has been described in the literature so far.

Keywords: *Persistent müllerian duct syndrome; Leiomyoma; Uterus; Fertility; Lower urinary tract symptoms*

Introduction

Persistent müllerian duct syndrome (PMDS) is a rare type of disorder of sexual development, in which derivatives of müllerian ducts are present in a completely virilized individuals (46,XY karyotype) with the usual external and internal male genitalia[1]. In reported cases, patients presented with female genital organs (uterus, cervix, fallopian tubes, and upper two-thirds of vagina) in various degrees of development. A case where irritating voiding symptoms led to detection of a retrovesical mass extruding into the bladder wall is described.

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Received July 24, 2023, accepted September 20, 2023

Case Report

A 59-year-old male presented to our urology department complaining of dull pelvic pain accompanied by frequency, nocturia, urgency, and precipitancy. There was no history of fever or dysuria, and his urine sample

showed no signs of urinary tract infection (UTI). Digitorectal examination revealed a normal-sized prostate without pathologic findings. External genitalia were morphologically normal without visible or palpable alterations; the patient had no history of cryptorchidism, and is father of two children. He scored 15 points (moderately symptomatic) on the International Prostate Symptom Score (I-PSS) questionnaire but he experienced only irritating symptoms without a history of any obstructive symptoms. Routine ultrasound (US) showed a retrovesical mass measuring 10x6x7 cm and pressing on the posterior wall of the bladder. A computed tomography scan followed and confirmed the US finding, more precisely, an intrapelvic mass located between the bladder and the rectum. The patient was offered surgery to remove the mass.

Intraoperatively, a partly encapsulated, firm mass measuring 11x6x7 cm was found between the bladder and the rectum impressing itself toward the posterior bladder wall. It was easily dissected from the surrounding structures as it did not appear to infiltrate the bladder or the rectum. Considering the clear border between the bladder and the tumor, bladder origin was excluded. No signs of neovascularization were found and intraoperative bleeding was minimal. The surgeon's overall impression was that it had been a benign tumor. The postoperative period was uneventful and the patient fully recovered. His I-PSS score postoperatively was 0.

The cut surface of the tumor was whorled, gray-white, with a central cavity measuring 3.5 cm in diameter (Fig. 1). Histologically, part of the sample was an oval tumor composed of uniform smooth muscle bundles showing positive immunohistochemical reaction to smooth muscle actin and desmin, and a proliferation index measured by Ki67 was up to 1% (Fig. 2A). The central cavity contained dilated glandular formations lined by regular columnar epithelium (Fig. 2B), showing a positive reaction to cytokeratin 7 (CK7), estrogen receptor (ER) and progesterone receptor (PR) (Fig. 2C, D). Mitoses or atypia were not observed. These findings matched the lining of the

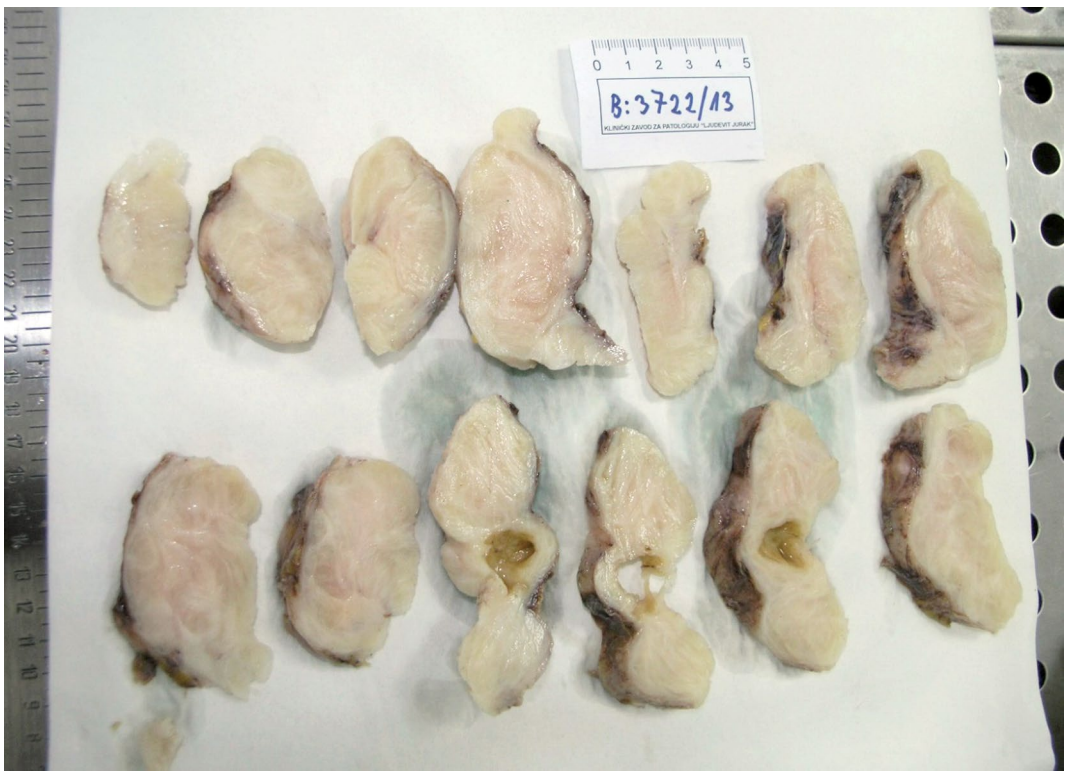

Fig. 1. Macroscopic view of surgical material: whorled, gray-white cut surface, with a central cystic cavity.

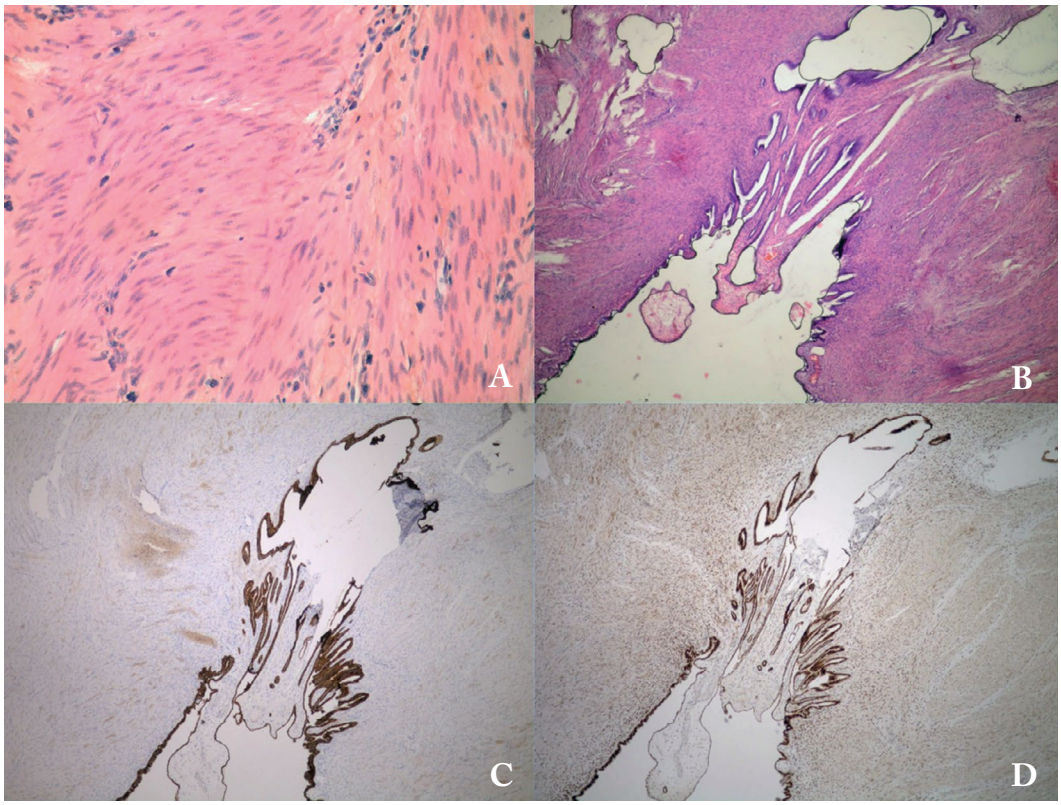

Fig. 2. Histologically, the sample is composed of (A) leiomyoma with bundles of uniform smooth muscle cells (HE, X400); (B) muscular wall with central cavity lined by regular columnar epithelium (HE, X100); (C) epithelium showing positive reaction to cytokeratin 7 (CK7, X40); and (D) estrogen receptor (ER, X40).

endometrium and fallopian tubes. In the rest of the sample, areas corresponding to the wall of the uterus (myometrium) were found. Findings were histopathologically described as a uterine leiomyoma and possible remnants of the uterus with fallopian tubes.

Discussion

Persistent müllerian duct syndrome is characterized by the appearance of female genital inner organs arising from müllerian ducts (fallopian tubes, uterus, upper part of vagina) in individuals with 46,XY karyotype and fully developed male external and internal genital organs, and it represents a rare type of male pseudohermaphroditism[1]. In around 90% of cases, mutations of the *AMH* (anti-müllerian hormone) or *AMHR2* (AMH receptor type 2) genes can be found, while the remaining cases are caused by other hitherto undiscovered molecular changes (idiopathic PMDS)[2]. AMH protein, also known as müllerian inhibiting substance (MIS), is member of the TGF-β family of growth factors and is encoded by a gene located on chromosome 19p13.3. AMHR2 is a unique receptor for AMH, encoded by a gene located on chromosome 12q13.13[3]. The signaling pathway triggered by the activation of AMHR2 ultimately leads to the activation of genes involved in apoptosis and epithelial-mesenchymal transition, processes that are responsible for regression of the müllerian ducts[2]. After differentiation of the testes in the 7th week of embryonic development, the secretion of AMH from the Sertoli cells begins, which leads to regression of the müllerian ducts by the 10th week[3]. At least 72 pathogenic alleles of the *AMH* and at least 78 pathogenic alleles of the *AMHR2* are known, and it has been proven that inactivating mutations of *AMH*

or *AMHR2* in males cause the absence of regression of the müllerian ducts[2–4]. PMDS is inherited in an autosomal recessive manner but several papers have been published about possible X-linked inheritance[2,5]. The frequency of *AMH* and *AMHR2* mutations is higher in consanguineous families[2].

The exact incidence of PMDS is not known but it is considered a very rare disorder. The first case was described in 1895. Based on a review by Picard *et al.* in 2017, about 240 cases had been reported by the year 2017[2]. According to our knowledge and literature search, at least 72 articles were published in the 2017-2022 period, with at least 130 patients diagnosed with PMDS.

Clinically, PMDS is most often (60%-70% of cases) manifested as bilateral cryptorchidism[2,4]. The attachment of the testes to müllerian derivatives and the broad ligament prevent them from normal descending toward the scrotum[2,6,7]. In 20%-30% of cases, one testicle is located in the abdomen and another one in the inguinal canal, together with müllerian remnants. This condition is known as hernia uteri inguinalis, i.e., unilateral cryptorchidism with contralateral inguinal hernia. Sometimes both testicles are located in the same hemiscrotum, along with müllerian derivatives, a condition known as transverse testicular ectopia[2,4]. In some cases, hematuria is the dominant symptom and patients may feel pain or discomfort in the abdomen or pelvis[6,7]. So far, no correlation between phenotype and *AMH/AMHR2* genotype has been observed[2]. Our patient presented with irritative voiding symptoms, which are part of lower urinary tract symptoms (LUTS). LUTS include frequency, urge incontinence, nocturia, storage, incomplete voiding, hesitancy, poor stream and postmicturition symptoms, and can significantly reduce the men's quality of life, as well as point to serious pathology of the urogenital tract. Although extravesical masses have been reported to cause such symptoms, they are rare and commonly affect women[8,9].

The most important complications of PMDS are infertility, testicular tumors, and malignant transformation of müllerian remnants[2,4]. Although the majority of patients are infertile, about ten cases of fertile patients diagnosed with PMDS have been described in the literature, including our patient who is father of two children[10–16]. It is considered that the prerequisites for proper fertility are normal anatomy of excretory ducts and at least one properly descended testicle. For this reason, it is desirable to perform orchidopexy at an early age, where the main surgical challenges are preservation of the excretory ducts and arterial supply of the testicles during their separation from müllerian derivatives[2]. The estimated risk of testicular tumors in PMDS is up to 33%, compared to around 18% in men with cryptorchidism without PMDS, and the most frequent are seminomas[2,17–20]. Appearance of tumors originating from müllerian structures is expected according to some authors in up to about 8% of cases[1,4]. In our case, we found uterine leiomyoma that caused irritative voiding symptoms. To our knowledge based on the literature review, this is the first reported case of PMDS with irritating emptying of the bladder as the main clinical symptom. So far, 7 patients with uterine neoplasms have been described as part of PMDS; three cases of adenocarcinoma[5,7,21], one adenosarcoma[6], two multiple fibroids[1,4], and one case of leiomyoma[22]. The potential development of advanced malignant disease with fatal outcome[6,7] justifies surgical removal of müllerian remnants. However, there also are different opinions regarding the rarity of the mentioned pathology and intraoperative complications[5,6]. Our patient agreed with surgical removal of the mass. After four-year follow-up, he was well and without any symptoms.

Persistent müllerian duct syndrome is most often diagnosed incidentally during surgical interventions in the abdomen and pelvis[4,7]. However, in some cases, the diagnosis is missed even during surgery due to the doctor's very rare experience with this disorder. Recognition of müllerian structures using radiological methods, especially US, is very challenging and significantly depends on the experience of the radiologist[1,4]. Diagnostic laparoscopy, in addition to visualization, also offers the possibility of biopsy and is considered an excellent diagnostic method[1,4]. Determination of karyotype and genetic analysis to detect *AMH* or *AMHR2* mutations can significantly facilitate establishment of a correct diagnosis.

In conclusion, although irritative voiding symptoms are common in our practice and are generally associated with UTIs, bladder stones or various neurologic disorders, extravesical pressure should also be considered a cause. Therefore, despite its very rare

appearance, PMDS is a possible differential diagnosis. A positive family history of cryptorchidism, infertility and any consanguinity shall be elicited in the history. Surgical removal of the müllerian remnants should be considered in case of urinary tract symptoms, as well as due to possible malignant transformation. Furthermore, there is a greater risk of testicular tumorigenesis and therefore lifelong follow-up is necessary.

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Sažetak

BOLESNIK S UTERINIM LEJOMIOMOM U SPEKTRU SINDROMA PERZISTENTNIH MÜLLEROVIH VODOVA – PRIKAZ SLUČAJA I PREGLED LITERATURE

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U ovom izvještaju iz kliničke prakse opisujemo slučaj 59-godišnjeg muškarca, oca dvoje djece, s iritiranim pražnjenjem mokraćnog mjehura kao glavnom zdravstvenom tegobom. Metodama ultrazvuka i kompjutorizirane tomografije u retrovezikalnom je prostoru utvrđena nepoznata masa koja je potom kirurški uklonjena. Susljednom patohistološkom analizom zaključeno je kako se radi o urednom te djelomice lejomiomatoznom tkivu maternice, temeljem čega je postavljena dijagnoza sindroma perzistentnih Müllerovih vodova. Riječ je o rijetkom poremećaju spolnog razvoja koji je obilježen prisutnošću Müllerovih derivata (jajovodi, maternica i gornje dvije trećine rodnice) u osoba muškog spola s normalno razvijenim vanjskim i unutarnjim muškim spolnim organima. Bolesnici se najčešće prezentiraju kriptorhizmom i ingvinalnom hernijom. Dosad nisu opisani slučajevi s iritiranim pražnjenjem mjehura kao vodećim simptomom. Najvažnije komplikacije i klinički relevantne značajke ovog sindroma su neplodnost, veća učestalost tumora testisa te maligna transformacija Müllerovih struktura. Prema našim saznanjima, dosad je u literaturi opisan samo jedan slučaj lejomioma maternice u sklopu ovog sindroma.

Ključne riječi: *Sindrom perzistentnih müllerovih vodova; Lejomiom; Maternica; Plodnost; Simptomi donjeg mokraćnog trakta*