Uterine Leiomyoma in a Man with Persistent Müllerian Duct Syndrome and Seminoma

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Male pseudohermaphroditism is the most diverse type of sexual disorder, in which the gonads have a 46-XY chromosomal pattern, but phenotypically there are variable degrees of feminization [5]. It has several causes including inborn errors of testosterone biosynthesis, Leydig cell aplasia or hypoplasia, androgen insensitivity syndrome, and persistent Müllerian duct structures (PMDS) [1]. PMDS is a rare syndrome due to failure of paracrine secretion of anti-Müllerian hormone (AMH), also called Müllerian inhibiting factor, by Sertoli cells or failure of the Müllerian ducts to respond to its secretion [2]. A genetic mutation of chromosome 19 seems to be implicated in this condition [2]. We present the case of a phenotypically normal man with fallopian tubes and a uterus along with testes and Wolffian duct derivates.

The syndrome was first described by Nilson in 1939 [1]. The condition is discovered at surgery prompted by cryptorchidism and/or inguinal hernia [1]. The existence of anti-Müllerian hormone was first suggested by the French scientist Alfred Jost in the 1940s but was isolated only in 1984 [2]. As shown by Jost's pioneering experiments almost 60 years ago, the testis has determinant importance in fetal sex differentiation via two independent pathways [2]: Leydig cells secrete androgens necessary for the masculinization of Wolffian ducts, the urogenital sinus and external genitalia, whereas Sertoli cells secrete AMH required for regression of Müllerian ducts. Subsequently, approximately 150 cases of PMDS have been reported, of which about 30 were reported to have PMDS with testicular neoplasm [3].

Uterine leiomyomas, commonly called uterine fibroids, are the most frequent benign neoplasia that develops within the muscular layer of the uterus in women [4]. Leiomyomas are the leading indication for hysterectomy among women in the United States [4]. These tumors are specific for women. This condition of uterine myoma is unlikely in males since it requires the presence of a uterus, which itself is necessary for growth of a myoma. This occurred in our case presented here, which was a combination of PMDS, testicular neoplasm (seminoma) and uterine leiomyoma.

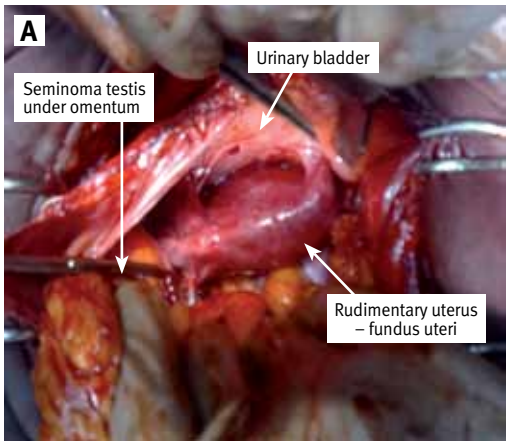
PATIENT DESCRIPTION

A 46 year old man presented after a few months of pain in the suprapubic region. He was married and the father of two children. He had undergone surgery as a child for cryptorchidism on both sides. During that operation the surgeon did not find the left testis and the presence of Müllerian derivatives had been overlooked. A clinical examination of the groin now showed an empty left scrotum with normal right testis and a normal phallus. Abdominal examination revealed an intraabdominal mass on the left of midline, which was not painful. The prostate gland was normal in size. The chest X-ray was normal. Ultrasonography of the abdomen showed a multilocular lower abdominal solid mass at the ventral side of the urinary bladder. Computed tomography examination of the abdomen revealed a multilocular tumor mass measuring 12 x 10 cm, localized to the left side of the pelvis, adjacent to the urinary bladder. The clinical suspicion of seminoma in the undescended and previously undiscovered abdominal testis was raised. The serum levels of tumor markers, namely alpha-fetoprotein and beta-human chorionic gonadotropin, were normal. The patient was taken for exploratory surgery [Figure A].

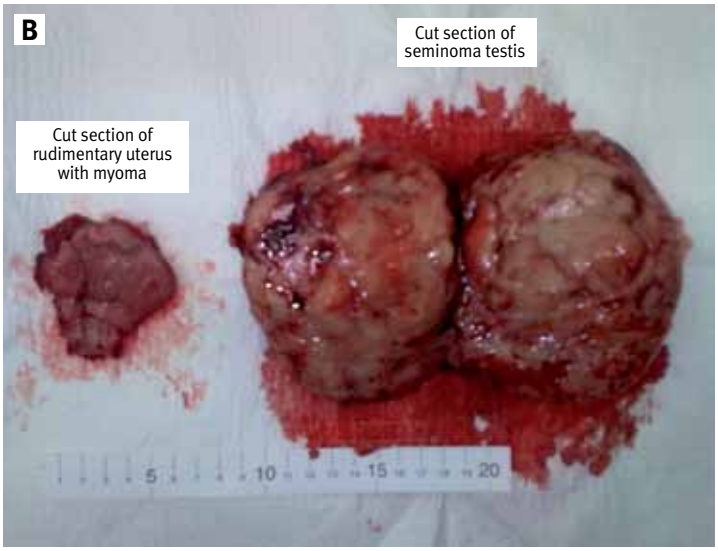
Subsequent laparotomy identified a mass, measuring 12 cm from the undescended left testis in the pelvis (frozen section showed testicular seminoma). The mass was supplied by the left spermatic vessels, with a vas deferens emptying to the right seminal vesicle and a round ligament arising from the mass. Next to the 12 cm testicular tumor was the unexpected finding of a rudimentary uterus with uterine body and cervix. The CT examination and ultrasonography performed earlier had shown no evidence of this. The uterus was attached to the testicular mass on the left and the bladder in front. The left round ligament of the uterus passed through the tumor (seminoma measuring 12 cm). Exploration did not disclose fallopian tubes, ovaries or vagina. An abdominal orchidectomy and hysterectomy was performed and the specimens were photographed and sent to the pathology department.

The gross pathological examination showed a predominantly solid grey-white, well-capsulated tumor measuring 13 x 10 x 6 cm. A cut section revealed multiloculated solid structure with slit-like spaces filled with clotted blood [Figure B]. Gross

[A] Initial finding of testicular seminoma on the left, under the omentum and next to a rudimentary uterus on the right. The rudimentary uterus is attached to the urinary bladder and parietal abdominal wall in front, without a developed uterovesical ligament, proper ovarian ligaments, uterine tubes or ovaries on both sides



[B] Cut section of uterus with leiomyoma submucosum and testicular tumor (seminoma)



examination of the uterus showed a uterine body and cervix measuring 6 x 5 x 1.5 cm. The cut section revealed an empty uterine cavity and small submucosal fibroid.

Microscopic evaluation of the solid tumor from the left testis showed a seminoma composed of large polyhedral tumor cells, separated by abundant fibrous stroma with lymphocystic infiltration, germinative areas and focal necrosis. Immunochemistry tests of the tumor cells showed 90% placental alkaline phosphatase and SD10 and no activity for vimentin, actin, desmin, alpha-fetoprotein and SD 34. No carcinogenic infiltration was found in the epididymis or spermatic cord. Microscopic evaluation of the uterus showed a normal uterine myometrium of 1.5 cm. The endometrium was atrophic and a submucosal leiomyoma with a diameter 0.7 cm was found. The cervical canal was short and had a blind end.

Based on preoperative, surgical and pathological findings, the diagnosis of persistent Mullerian duct syndrome with seminoma and leiomyoma was made. Peripheral blood chromosome analysis revealed a normal male karyotype 46XY. The postoperative course was uneventful and the patient subsequently underwent radiation and chemotherapy. At the last follow-up (July 2013), the patient was alive with no evidence of disease.

COMMENT

Persistent Müllerian duct syndrome is a form of internal male pseudohermaphroditism caused by deficiency of the anti-Müllerian hormone or failure of the Müllerian ducts to respond to its secretion [3,5]. PMDS patients are both karyotypically and phenotypically male, with normal development of secondary sex characteristics [3,5]. Until 2013, approximately 150 cases have been reported [3]. Our search of the literature demonstrated that in only 30 cases was some testicular neoplasm found (seminoma, yolk sac tumor, teratoma, embryonal carcinoma), and in only one case was both a uterine leiomyoma and seminoma found.

The exact cause of PMDS is not known. Renal development comprises three stages: pronephric, mesonephric and metanephric [2]. From the mesonephric ducts the internal genitalia develop [2]. At this stage the mesonephric ducts are called Wolffian ducts [2]. The paired paramesonephric ducts are the Müllerian ducts [2]. In a human fetus, both Müllerian and Wolffian ducts are present at 7 weeks of gestation [2]. Müllerian ducts and Wolffian ducts are the anlagen of the female and male reproductive tracts, respectively. In the XY fetus, the testis differentiates by the end of the 7th gestational week [1]. Leydig cells secrete testosterone, which drives Wolffian duct differentiation into epididymes, vasa deferentia and seminal vesicles acting through the androgen receptor [1]. In the anlagen of the external genitalia, testosterone is transformed by 5 α-reductase into dihydrotestosterone, a potent androgen that binds the androgen receptor to induce external virillization. Sertoli cells secrete AMH, which binds to a membrane receptor in Müllerian ducts and provokes their regression [1]. AMH is a member of the transforming growth factor-beta family of glycoprotein differentiation factors that include inhibin and activin [5]. PMDS patients develop both Wolffian and Müllerian structures due to a deficiency of AMH [5]. The gene responsible for AMH is localized on the short arm of chromosome 19 [5]. A defect in the AMH gene leads to the persistence of the uterus and the fallopian tube in the male

[5]. Mapping of this gene on an autosome implies an autosomal mode of inheritance for PMDS [5].

Two clinical variants of PMDS not genetically determined are possible [5]. The more common variant of PMDS (80% –90% of cases) is characterized by unilateral cryptorchidism and contralateral inguinal hernia [5]. In the rarer variant, patients may present with bilateral cryptorchidism where the uterus is in the pelvis and both testes are embedded in the broad ligament [5].

Distinguishing PMDS from other intersex disorders is critical [1]. A karyotype test and exact assessment of testicular response to chorionic gonadotropin stimulation are essential to verify both genetic sex and the existence of functional testicular tissue [1]. Testicular biopsy is necessary to complete the evaluation [1]. Measurement of the serum level of AMH is recommended [5]. Recognition of PMDS is important for prognosis. Ultrasonography initially, followed by magnetic resonance imaging are crucial in any patient with suspected PMDS [1]. The main therapeutic considerations are the potential for fertility and malignant changes [1]. Testicular tumors are not uncommon in patients with PMDS. It is well known that malformed structures have a greater than normal incidence of malignancy, which explains the increased incidence of neoplasia in cryptorchid testes whether or not they are surgically found in the scrotum [3]. The most common histology is seminoma. The overall incidence of malignant transformation in these gonads is 15%, which is similar to the rate in abdominal testis in normal men. Obviously, tumors arising from testis require surgical extirpation. However, since these patients are phenotypically normal males, the virilization potential should be preserved by primary or staged orchipexy of the unaffected testis.

Infertility is common, with absence of spermatozoa at semen analysis [3]. However, there have been a few reported cases of fertility, although proof of paternity was not established absolutely without a DNA test [3].

In most scientific publications on PMDS the presenting tumor arises from an undescended testis. We found only one publication on PMDS where myoma originated from the rudimentary uterus [1]. Uterine leiomyomas are benign neoplasms that arise from uterine smooth muscle. It is hypothesized that leiomyomas originate from somatic mutations of myometrial cells, resulting in progressive loss of growth regulation. The tumor is composed of genetically abnormal clones of cells derived from a single progenitor cell (in which the original mutation took place). Studies indicate that leiomyomas are monoclonal. Different rates of growth can reflect the different cytogenetic abnormalities present in individual tumors. Multiple myomas within the same uterus are not clinically related; each myoma arises independently [4]. If surgical specimens are serially sectioned, about 77% of women who undergo hysterectomy will have myomas, many of which are occult [4]. Overall, about 17% of the hysterectomies in the USA are performed for myomas [4]. The peak incidence for myomas requiring surgery occurs around age 45, approximately 8 cases per 1000 women each year [4].

There is no such statistic for men since a myoma in the uterus is predominantly a female disease. A uterine leiomyoma in men is an extremely rare condition. In fact, our literature search on PMDS yielded only one publication on uterine leiomyoma in males [1]. In our case the man with PMDS had a seminoma in the cryptorchid testis and submucosal uterine leiomyoma. We should not be surprised in the future when encountering a patient with PMDS to find not only a testicular tumor, but tumors and neoplasm in a rudimentary uterus and fallopian tubes.

The treatment of PMDS is exclusively surgical and aims to correct cryptorchidism if there are no tumors [1,3]. Removal of the uterus is not necessary, apart from the fact that it is usually difficult to bring the testes down to a normal position because the vasa deferentia are embedded in the mesosalpynx, lateral uterine wall and cervix [1,3]. In this context, careful dissection is required to avoid harming the excretory ducts [1]. Mobilization of the gonadal blood vessels may be necessary for completion of the orchiopexies [1]. Orchidectomy is only indicated for testis that cannot be mobilized to a palpable position [2]. Repair of the inguinal hernia must be performed if necessary [1]. Orchidectomy and/or total abdominal hysterectomy should be performed for any tumors found in the testis and/or uterus and fallopian tubes [3]. Testicular malignancy associated with this syndrome requires a staging and treatment policy similar to that for scrotal testicular tumors. In our case, surgical treatment consisted of orchidectomy and abdominal hysterectomy, followed by chemotherapy and radiotherapy, which led to good control of the disease.

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"I have always imagined that paradise will be a kind of library"

Jorge Luis Borges (1899-1986), Argentine short-story writer, essayist, poet and translator, and a key figure in Spanish literature