Case Report

Testosterone-induced “Virilization” of Mesonephric Duct Remnants and Cervical Squamous Epithelium in Female-to-Male Transgenders: A Report of 3 Cases

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Summary: Mesonephric ducts regress in genotypic females, leaving behind few remnants. These vestigial structures are often recognized in the mesosalpinx and paracervical regions. We report here 3 cases of female-to-male transgenders who underwent hysterectomy following testosterone treatment. Both female and male genital structures were identified on histologic examination. Although the morphologic appearances of the specimens were unremarkable, histologically 1 case revealed a well-formed fallopian tube as well as an epididymis and 2 cases showed prostate glands to be present in the cervical squamous epithelium. Key Words: Wolffian duct—Mesonephric duct—Transgender—Female-to-male—Fallopian tube—Epididymis—Cervix—Prostate.

The embryonic human genital tract consists of a pair of mesonephric and paramesonephric ducts, also known as wolffian and müllerian ducts, respectively. After sex determination, in males, testosterone secreted by the leydig cells and anti-müllerian hormone from sertoli cells, induce differentiation of the mesonephric ducts into male genital ducts and regression of the paramesonephric ducts, respectively. Conversely, the absence of anti-müllerian hormone and testosterone leads to paramesonephric duct differentiation into oviducts, uterus, and upper vagina (1). During routine histologic examination of hysterectomies, the mesonephric remnants are usually identified at paraovarian and paracervical locations.

Sex identity disorder is a relatively rare condition, with reported worldwide incidence of 1 per 120,000 for female-to-male (FTM) transgenders (2). The number of transgender individuals living in United States in 2010 was estimated to be ~89,667 (3). Sex identity disorder is a condition of abnormal sex development in which there is a psychological perception of self as masculine or feminine that is incongruent with one’s natal sex. A FTM transgender, to acquire male secondary sex characteristics, undergoes sex steroid therapy with androgens followed by hysterectomy, bilateral salpingo-oophorectomy (BSO), and mastectomy. The goal of testosterone treatment is to induce virilization, manifested by male-pattern body hair growth and physical contours, together with cessation of menstruation. This clinical setting of exogenous androgen exposure provides an opportunity to study the effects of exogenous androgens on the female genitourinary tract, including the mesonephric remnants. There are few reports describing the histologic alterations in the genital tract after long-term testosterone exposure in FTM transgenders.

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We report new histologic findings in the genital tract of 3 FTM transgender patients who underwent sex reassignment surgery. These findings contribute to the existing limited knowledge of the histologic changes seen in female genital organs in this setting.

**CASE PRESENTATIONS**

**Clinical History**

**Case 1**

A 28-yr-old FTM transgender underwent laparoscopic total hysterectomy (TLH) and BSO for menstrual cramps and severe abdominal pain. He received injectable testosterone (0.3–0.5 mg) for 3 yr.

**Case 2**

A 34-yr-old FTM transgender underwent TLH and BSO for sex reassignment and definitive management of painful menstrual periods and pelvic pain. The patient had undergone FTM chest reconstruction and he received testosterone treatment (60 mg, subcutaneous and intramuscular) for 3 yr.

**Case 3**

An 18-yr-old FTM transgender underwent TLH and BSO. He received intramuscular testosterone (1 mL of 200 mg/mL testosterone cypionate) q2wk for 2 yr and depot Leuprolide acetate (Lupron), before taking testosterone for many years.

**Pathologic Findings**

**Case 1**

The uterus weighed 89 g. The ectocervix measured 3.0 cm in diameter, displayed 1.2 cm external os and 3.0 cm long endocervical canal. Uterine corpus revealed 4.3\(^2\)2.8 cm endometrial cavity with thin (0.2 cm) endometrium and 1.8-cm thick myometrium. Grossly unremarkable right and left fallopian tubes with attached fimbria measured 0.8 cm in largest diameter and 8.3 and 8.0 cm in length, respectively. Ovaries measured 3.2 \(\times\) 2.9 \(\times\) 1.8 cm (left) and 3.7 \(\times\) 3.2 \(\times\) 1.3 cm (right). Ovarian surfaces were smooth. Multiple bilateral cortical cysts measuring up to 0.8 cm were present.

**Microscopy:** The endometrium showed weakly proliferative endometrial glands. The cervix and bilateral fallopian tubes were histologically unremarkable. Multiple ovarian follicular cysts with hemorrhage were present. The left paratubal mesonephric remnants showed hyperplastic changes (Fig. 1). A simple low cuboidal epithelium was replaced by a pseudostratified columnar epithelium. The closely apposed tubules showed rigid-appearing dilated lumens with scant acellular amorphous material. The presence of a thin peritubular smooth muscle layer was also noted. Sterocilia were present at the luminal border of the epithelium. The overall morphologic features were highly reminiscent of an epididymis. No testicular tissue was identified.

**Case 2**

The uterus, weighing 93 g, and cervix were grossly unremarkable with a 3.2 \(\times\) 3.0 cm ectocervix, a 1.5 cm slit-like external os, and a 3.5 cm long endocervical canal. The uterine corpus revealed 2 subserosal leiomyomas, thin endometrium (<0.1 mm) and 2.0-cm thick unremarkable myometrium. Grossly unremarkable right and left fallopian tubes with attached fimbria measured 0.7 and 0.6 cm in largest diameter and 10.0 and 9.5 cm in length, respectively. Ovaries measured 2.2 \(\times\) 2.0 \(\times\) 1.3 cm (left) and 3.0 \(\times\) 2.0 \(\times\) 2.0 cm (right). Ovarian surfaces were smooth. Multiple bilateral cortical cysts measuring up to 1.0 cm were present.

**Microscopy:** Histologic examination of the cervix was remarkable for the presence of distinct gland-forming epithelial islands within the cervical squamous epithelium (Fig. 2). The acini were lined by a single layer of cuboidal to low columnar cells with moderate to abundant foamy to finely vacuolated cytoplasm and basally located small round nuclei with fine, evenly dispersed chromatin. On step sectioning, the lumens of some of these glands appeared to open onto the epithelial surface, suggesting a tubulo-acinar architecture. The entire cervical tissue was examined microscopically. Glands involved the cervical squamous epithelium circumferentially, extending from the squamo-columnar junction to a point adjacent to the vaginal resection margin. The immunohistochemical staining pattern of the glands differed from the cervical squamous or endocervical cells. Glandular cells were negative for cytokeratin 7 and cytokeratin 20 but diffusely and strongly positive for prostate-specific antigen (PSA), all consistent with a prostatic immunophenotype. Transitional cell metaplasia was present. Endometrial glands showed weakly proliferative changes. The fallopian tubes were histologically unremarkable. Mesonephric remnants with cuboidal epithelium lining were present; unlike first case, no testosterone-induced
histologic changes were noted. Ovarian cystic follicles were present.

Case 3
The uterus weighed 35 g. The ectocervix measured 2.3 cm in diameter, displayed 0.7 cm oval external os, and 2.7 cm long endocervical canal. Uterine corpus revealed 2.3 × 1.8 cm endometrial cavity with thin (0.2 cm) endometrium and 1.2-cm thick myometrium. Grossly unremarkable right and left fallopian tubes with attached fimbria measured 0.5 and 0.6 cm in largest diameter and 7.2 and 6.4 cm in length, respectively. Ovaries measured 2.0 × 1.3 × 0.9 cm (left) and 2.7 × 1.4 × 0.7 cm (right). Ovarian surfaces were smooth. Multiple bilateral cortical cysts measuring up to 0.5 cm were present.

Microscopy: The cervical squamous epithelium was atrophic, and extensive transitional cell metaplasia was present. Intraepithelial glandular inclusions reminiscent of prostate-type acini, similar to case 2, were identified in the cervical squamous epithelium. These acini were present only within the squamous epithelium, extending from the squamo-columnar junction to the vaginal cuff resection margins. Immunohistochemical staining confirmed the prostatic phenotype (cytokeratin 7 and 20 negative, and PSA positive). PSA immunostaining was limited to the intraepithelial acinar structures. No PSA staining was identified in the endocervical columnar epithelium proximal to the squamo-columnar junction (Fig. 3). Endometrium was weakly proliferative. Multiple cystic follicles were present in both ovaries. Adnexal mesonephric remnants showed cuboidal epithelium, with no histologic changes suggesting virilization.

DISCUSSION
Examination of the sex reassignment surgical specimens of FTM transgenders receiving exogenous
hormones will probably unveil novel histologic findings in gynecological pathology. Pathologists should encounter more and more of these specimens in the near future as several states have removed ban on exclusion of insurance coverage for this operative procedures.

Our first case showed unequivocal histologic features of epididymis-like tissue in a left paratubal location. A similar alteration was not identified on the contralateral side. No prostate-type glands were identified in the cervix of this case. This phenomenon of mesonephric duct differentiation/virilization is most likely related to exogenous testosterone exposure. Interestingly, “virilization” of the mesonephric ducts mimicking epididymis, in response to circulating androgens, has been reported in female tammar wallabies (4). We did not encounter any report of this phenomenon in humans in the published English literature. In a report of 51 cases of mesonephric hyperplasia in the uterine cervix, the authors suggested that so-called “endometrioid metaplasia,” identified in 10%–27% cases, might actually represent epididymal differentiation (5). The authors did not elaborate on the histologic features that favored an epididymal over an endometrioid phenotype.

To our knowledge, this is the first report of testosterone-induced prostate-type glandular metaplasia within the cervical squamous epithelium. Larrazá-Hernández et al. (6) first described prostate tissue in the uterine cervical stroma of a gravida 2, para 2, 38-yr-old female, who had undergone a loop electrosurgical excision. The patient had no history of virilization or any clinical findings of hermaphroditism. The authors proffered a metaplastic versus a developmental anomaly as the 2 possible theories of origin of prostate tissue in an otherwise normal female. However, in the absence of mesonephric remnants in the examined tissue, the authors favored

FIG. 2. Prostate-type glands involving the cervical squamous epithelium in case 2 (A–E). Glands are located at the base of the atrophic squamous epithelium (A, 20×), some gland lumens extend to and open onto the surface (B, 40×). Glandular epithelium is cytokeratin 20 negative (C; IHC, 40×), cytokeratin 7 negative (D; IHC, 40×) and PSA positive (E; IHC, 40×).
a developmental anomaly (6). Two other case series describe the finding of prostate tissue in cervical stroma (7,8). The authors designated this phenomenon as “ectopic” prostate tissue. Kim et al. (9) reported transitional cell metaplasia and prostate glands in the cervix and vagina of a 23-yr-old patient with androgenital syndrome. Authors did not explicitly describe an intraepithelial location of the prostate-type glands; however, one of the figures (Fig. 1) in that report shows histologic features similar to the 2 cases being reported here (cases 2 and 3). A case report of prostatic adenocarcinoma associated with untreated congenital adrenal hyperplasia in a 62-yr-old genotypically female pseudohermaphrodite has also been reported (10). The testosterone level of this patient was noted to be elevated (263 ng/dL; normal female 30–75 ng/dL, normal male 270–1000 ng/dL) and the authors concluded that the prostate adenocarcinoma probably arose from periurethral Skene’s glands, in a setting of persistently high testosterone (10). Interestingly FTM transgenders, even without testosterone treatment, are known to show hormonal changes and symptoms of polycystic ovarian syndrome, increased androgens, and nonclassical congenital adrenal hyperplasia. These symptoms include acne, hirsutism, obesity, and menstrual abnormalities (11). We did not encounter any report of prostate carcinomas in FTM transsexuals.

In contrast to previously published reports where prostate tissue was identified in the cervical stroma of normal females without any history of hormonal abnormality and labeled as “ectopic,” our finding of prostate glands in the cervical squamous epithelium of FTM transgenders exposed to testosterone suggests an alternative etiopathogenesis, in a distinct clinical setting. So-called “ectopic prostate tissue” is typically described as “large duct like” and usually contains squamous metaplasia. Prostatic tissue in the cervix of FTM transgenders comprises of small

FIG. 3. Inclusion-type glands present in the cervical squamous epithelium in case 3 (A–D). Glands extending from squamo-columnar junction (B) to near the vaginal cuff (C; H&E, 40 ). The glands are PSA positive (D; IHC, 40 )
prostate acini limited to cervical epithelium. No squamous differentiation is identified in these smaller prostate acini. No cervical mesonephric remnants were identified and prostate glands were identified involving cervical tissue circumferentially. We propose that prostate glands can arise in the cervical epithelium as a metaplastic process secondary to testosterone exposure. Interestingly, using immunohistochemistry, Kim et al. (9) reported androgen receptor expression in the prostate tissue of the cervix. Prostate tissue in the cervical stroma, described in earlier case series, may have an ectopic origin. Larraza-Hernandez et al. (6) admitted that a developmental anomaly is most plausible, but incomplete, explanation. It is also possible that the prostate glands in these cases arose from the surface epithelium, similar to our cases, and eventually were disconnected from the surface and became embedded in the cervical stroma.

Cervical squamous epithelial atrophy with transitional metaplasia was identified in 2 studies of 32 and 28 FTM transgenders undergoing hysterectomy after testosterone treatment (12,13). In the largest published study of hysterectomy and BSO specimens from 112 FTM transsexuals minimal cervical changes were identified. The authors reported endocervical glandular hyperplasia in 24 and polycystic ovarian disease (PCOD)-like ovarian changes in 89 (79.5%) cases (14). Interestingly, no prostatic metaplasia of cervical squamous epithelium or hyperplastic mesonephric remnants was identified in these reports. Studies reporting the histologic changes in the müllerian organs of FTM transgenders undergoing sex reassignment surgery have largely focused on the ovarian changes. Cystic follicles, reminiscent of PCOD, were reported in 1 study (15). Unequivocal changes of PCOD were not found in another similar study (16). All 3 cases in our series showed cystic follicles.

In conclusion, we report novel histologic findings of mesonephric remnants showing epididymal differentiation and prostate-type glands within the cervical squamous epithelium of FTM transgenders. Prostate gland location supports a metaplastic theory of origin, especially in a setting of exogenous testosterone exposure. The current report documents these findings and serves as a reference for future work by other investigators.

REFERENCES