

## CASE REPORT

# Squamous Cell Carcinoma of the Vulva in a Patient with Androgen Insensitivity Syndrome

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The first case of squamous cell carcinoma of the vulva in a patient with androgen insensitivity syndrome is described. © 1990 Academic Press, Inc.

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### INTRODUCTION

The complete form of androgen insensitivity syndrome (testicular feminization) occurs in a 46,XY karyotype with a mutant X-linked recessive gene that is responsible for the androgen intracellular receptor [1]. An individual with androgen insensitivity syndrome is a male pseudohermaphrodite. Phenotypic characterizations include scanty or absent axillary and pubic hair, slight vulvar hair, a rudimentary or absent vagina, euchooidal structure, and breasts with small nipples and pale areolae.

Cancers, in association with androgen insensitivity syndrome, have been thoroughly investigated. Neoplasms arising from the gonads and the neovagina have been reported. The following is the first report of squamous cell carcinoma of the vulva in a patient with androgen insensitivity syndrome.

### CASE REPORT

A 47-year-old patient with androgen insensitivity syndrome presented to the University of Michigan gynecology clinic with complaints of vaginal burning and discomfort. She had not undergone a Papanicolaou smear for approximately 6 years. A "hernia repair" on the right side had been performed at age 5 at an outside hospital. A 5 × 3 × 1.5-cm mass was removed from the right inguinal area. Microscopic analysis revealed loose connective tissue with a lining of endothelial cells. The tissue was arranged in formations resembling embryonic testicular tissue.

She presented to the gynecology clinic initially at age 22 with a 4.0-cm mass in the left groin, persistent amenorrhea, and a vaginal canal with a depth of 1.5 cm. Physical examination revealed normal breast development. There was a lack of axillary and pubic hair. No pelvic organs were palpated on rectal examination. A buccal smear revealed a negative six chromatin pattern consistent with a 46,XY karyotype. A 24-hr gonadotropin was 54.0 Mouse Uterine Units (normal, 6.0-48.0 Mouse Uterine Units). The 24-hr 17-ketosteroids were 6.5 mg (normal male values, 3.5-15.0 mg; normal female values, 2.5-8.5 mg). The 24-hr 17-hydroxysteroids were 3.8 mg (normal, 5.0-10.0 mg). Testicular feminization was diagnosed.

The patient's family history was significant for a sister with androgen insensitivity syndrome who presented at age 19 with persistent amenorrhea and vaginal agenesis requiring vaginal reconstruction.

At age 22, the patient underwent a split-thickness skin graft vaginoplasty and excision of the left groin mass. Pathological examination revealed testicular tissue with marked interstitial cell hyperplasia, tubular sclerosis, and aspermatogenesis with preservation of Sertoli cells.

At age 47, the patient presented with complaints of a clear vaginal discharge and vaginal burning for over 4 months. Physical examination revealed a 3.0 × 3.0-cm indurated, friable lesion on the medial aspect of the right vulva, extending into the neovagina and distal urethra. Groin nodes were clinically negative. A vulvar biopsy was performed, revealing invasive keratinizing squamous cell carcinoma. Preoperative evaluation included a normal chest X ray, pelvic ultrasound, and lymphangiogram. This lesion was classified as a stage III (T3N0M0) carcinoma of the vulva.

The patient underwent a radical vulvectomy, bilateral

groin lymph node dissection, and a partial resection of the neovagina and distal urethra. A bilateral pelvic lymph node dissection was performed since the neovagina also was involved. A moderately differentiated invasive squamous cell carcinoma of the vulva was identified. All of the groin and pelvic lymph nodes were negative for neoplasm. No angiolymphatic invasion was present and the surgical margins were clear. Blot hybridization methods were used to screen for the presence of human papillomavirus (HPV) [2]. No detectable HPV DNA sequences were found in the excised tissue screened for HPV types 6, 11, 16, 18, and 31. The patient's postoperative course was without complications.

## DISCUSSION

The male pseudohermaphrodite is a phenotypic female with an XY karyotype and testicular gonads. Androgen insensitivity syndrome is the most common form of male pseudohermaphroditism. Approximately two-thirds of the androgen insensitivity syndrome cases are familial [3]. About one-half of the male children of an individual with this genetic abnormality are affected [4]. The frequency of androgen insensitivity syndrome is estimated to vary from 1 in 20,000 to 1 in 64,000 male births. Ten percent of all cases of primary amenorrhea are secondary to androgen insensitivity syndrome [5].

In patients with androgen insensitivity syndrome, there is an increased incidence of malignant germ cell neoplasms developing after puberty in the gonads. Gonadal neoplasms reported in association with androgen insensitivity syndrome include seminomas [6,7], gonadblastomas [8], malignant teratomas [6,9], embryonal cell carcinomas [9,10], testicular tubular adenomas or Sertoli cell tumors [7,11], "alveolar carcinomas" [6], dysgerminomas, arrhenoblastomas [12], and heman-gioendotheliomas [13]. The risk of neoplasia is low before age 25 [12]. The usual recommendation is to leave the gonads in place in patients with androgen insensitivity syndrome until puberty is completed, to allow normal sexual maturation. The patient is started on hormonal replacement therapy following surgery. An investigation to evaluate carcinomatous changes in patients prior to puberty was performed by Müller and Skakkebaek. Intratubular neoplasia was found in the testicles of two prepubertal (youngest age, 2 months) and one pubertal patient out of 12 with the androgen insensitivity syndrome. It is notable that all three of these patients with intratubular neoplasia had incomplete androgen insensitivity syndrome. Müller and Skakkebaek recommend testicular biopsy in all patients with androgen insensitivity syndrome as soon as the syndrome is diagnosed. If carcinoma *in situ* is found, immediate orchidectomy

is indicated. They recommend a repeat biopsy at puberty if orchidectomy is not performed [14]. Hurt *et al.* describe a 14-year-old girl with complete androgen insensitivity syndrome who was found to have a left abdominopelvic mass consistent with a seminoma. A right adnexal mass was an immature testis that contained foci of intratubular seminoma. Two suspicious lymph nodes were sampled and found to contain metastatic disease. Their review of the literature found three other teenagers with androgen insensitivity syndrome who developed gonadal malignancies [15]. These studies suggest the need to reevaluate the postponement of prophylactic gonadectomy until pubertal growth and feminization are completed.

Although these patients are at risk for developing gonadal neoplasms, malignancies arising in the lower genital tract are unusual. Duckler, in 1972, reported a moderately differentiated squamous cell carcinoma that developed in the neovagina of a patient with a "presumed" androgen insensitivity syndrome [16]. The patient presented with vaginal bleeding from an artificial vagina created at age 17. The patient was phenotypically female with a complete loss of axillary hair, clitoral hypertrophy, and absence of a vagina. Urinary steroids, chromatin blood types, plasma levels of 17-ketosteroids, and chromosomal analysis were not obtained. At laparotomy no internal female genitalia were present. The right side contained a normal testicle and the left side had a spermatocele. She was diagnosed with squamous cell carcinoma of the vagina and rectum 19 years following a vaginal reconstruction which used a split-thickness skin graft taken from the lateral aspect of the thigh.

The present case demonstrates that malignancies may also involve the vulva. It is interesting to note that this malignancy occurred approximately 20 years before the mean age for invasive squamous cell carcinoma of the vulva. In addition, the patient's past medical history was not significant for diabetes mellitus, obesity, granulomatous disease, or hypertension, which are findings often associated with patients who have carcinoma of the vulva. Another finding noted in conjunction with carcinoma of the vulva is the presence of human papilloma virus [17]. As was previously mentioned, no HPV DNA sequences were detected when the tissue was examined for HPV types 6, 11, 16, 18, and 31.

Did the vaginal reconstruction 25 years earlier play a role in the development of the carcinoma? There is a possibility that the squamous cell carcinoma arose in the neovaginal graft and spread to the vulva, although it is rarer for tumor to spread in this manner. In truth, the cause of the squamous cell carcinoma in this patient is unknown. The above case emphasizes that continued surveillance and gynecologic care are indicated for these individuals.

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