

Human Papillomavirus— Associated Vulvar Verrucous Carcinoma in a 20-Year-Old with an Intact Hymen A Case Report

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A 20-year-old woman with vulvar verrucous carcinoma, the youngest such patient reported to date, had human papillomavirus DNA 6/11 identified with an in situ hybridization technique. In addition to her youth, the patient was unusual in that she had an intact hymen. Although she denied having engaged in sexual activity, venereal transmission of the virus may have occurred without vaginal penetration.

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0024-7758/91/3603-0213/\$1.50/0 © The Journal of Reproductive Medicine, Inc.
Journal of Reproductive Medicine

Introduction

Vulvar verrucous carcinoma is a distinct variant of squamous cell carcinoma and is remarkable for its histologic similarity to benign condyloma acuminatum and its low metastatic potential. Fifty-eight cases have been reported, generally involving older women.¹⁻¹⁰ Human papillomavirus (HPV) DNA, types 6 and 11, has been identified in several of these tumors.¹¹⁻¹⁴ The youngest previously reported patient with this lesion was 21 years of age.⁶ This report documents the case of a 20-year-old woman with vulvar verrucous carcinoma positive for HPV 6/11 on *in situ* hybridization. The presence of an intact hymen strongly suggested that venereal transmission of HPV occurred without vaginal penetration.

Case Report

A 20-year-old, Hispanic woman, para 0, presented to the Brady-Green Gynecology Clinic of the University of Texas Health Science Center at San Antonio. The patient was accompanied by her mother, who complained that her daughter "smelled." On physical examination large, fungating, foul-smelling masses were found. These polypoid masses were attached to each of the labia major over broad bases (Figure 1). No other condylomatous lesions were present over the vulvar or perineal area. The inguinal lymph nodes were not palpably enlarged. A biopsy of one of the masses showed condylomatous changes; in conjunction with the clinical findings, the diagnosis of verrucous carcinoma was suggested. On questioning, the patient admitted that the lesions had been growing during the previous year but denied having engaged in any sexual activity.

Wide local excision of both lesions was performed. During surgery an intact hymen was found; it had to be incised to facilitate examination of the vaginal canal and uterine cervix. The vagina and cervix were free of gross abnormalities.

Laboratory Studies

Tissues were fixed in 10% neutral buffered formalin and processed to hematoxylin-and-eosin slides with standard techniques. Immunoperoxidase staining for polyclonal human papillomavirus antigen (Dako Corporation, Carpinteria, CA, dilution 1:200) and DNA *in situ* hybridization techniques for HPV types 6/11 and 16 (Enzo Diagnostics, Inc., New York, NY) were performed according to the manufacturers' specifications. The Enzo DNA probe detects HPV 6 (and closely related HPV 11) as well as HPV 16 with a high degree of specificity (98%).



Figure 1
The exophytic and bilateral tumors. Although they appear to have broad bases, they were attached by pedicles of <math><1.5\text{ cm}</math> each.

Pathologic Findings

Each labial tumor formed a cauliflowerlike mass. The left one measured $6 \times 6 \times 3$ cm and the right, $8 \times 7 \times 7$ cm. Each tumor was pedunculated and attached to a small base of skin measuring no greater than 1.5 cm. The outer surface had a nodular, gray-white appearance. On sectioning, broad-based bulbs of white tissue were seen burrowing into the fibrous stalk of the polypoid masses (Figure 2). Microscopically a broad, pushing front of condylomalike epithelium encroached on the underlying fibrous stroma (Figure 3A). Focal koilocytotic atypia was present, but there was no evidence of nuclear anaplasia in numerous sections (Figure 3B). Immunoperoxidase staining for HPV antigen was negative, but DNA probes demonstrated *in situ* hybridization for HPV 6/11, while *in situ* hybridization for HPV 16 was negative (Figure 3C). The surgical margins were negative.

Discussion

The term *verrucous carcinoma* was first applied in 1948 to large, condylomalike lesions of the oral cavity that were locally aggressive but rarely metastasized.¹⁵ Subsequently, similar tumors were reported to have occurred in the larynx, scrotum, penis, rectum and bladder. In 1966 Kraus and Perez-Mesa reported the

first cases to involve the female genital tract (vagina and vulva).⁸ By early 1989, 111 cases of verrucous carcinoma involving the vulva, vagina and cervix had been reported. The 58 vulvar tumors affected patients ranging in age from 21 to 89 (average, 56).³⁻⁵ The largest vulvar mass measured 15 cm in diameter. In our patient, as in one-quarter of the reported cases, the lesions were bilateral.

It is generally agreed that wide local excision is the optimum therapy for this lesion. Cryosurgery and electrocoagulation for condylomas usually are followed by recurrence. Radical surgery is thought to be unnecessary by most because of the low probability of metastases. Verrucous carcinoma may coexist with an invasive squamous carcinoma of the usual type and thereby acquire definite metastatic potential. Metastases of verrucous carcinoma reported in the older literature may have originated from such composite tumors.^{4,7}

The etiology of verrucous carcinoma is uncertain, but the frequent association of the lesion with genital warts and other venereal diseases suggests a sexually transmitted agent. HPV particles and HPV DNA, as in condyloma acuminatum, have been identified in these tumors.^{4,11-14} Hybridization studies have

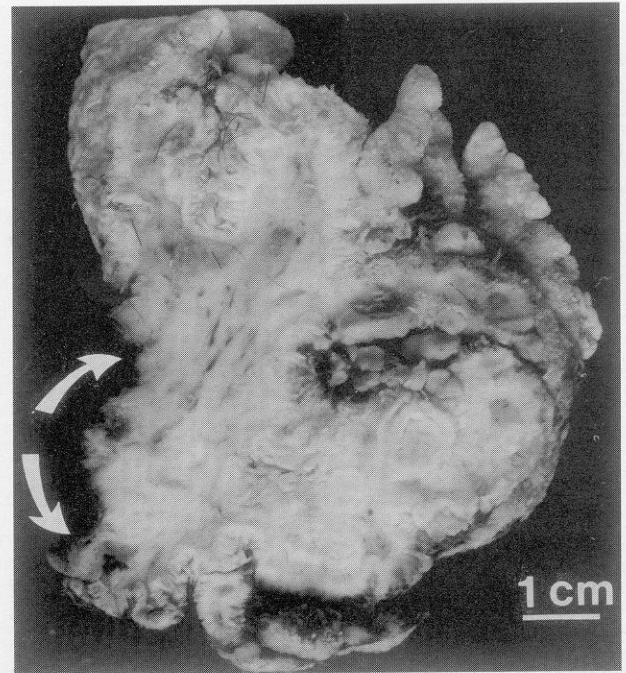


Figure 2
The smooth, fibrous surface of the cut surface. Note the invasive bulbs of epithelium extending deeply into the stalk. The arrows indicate the location of the base of the polypoid lesion.

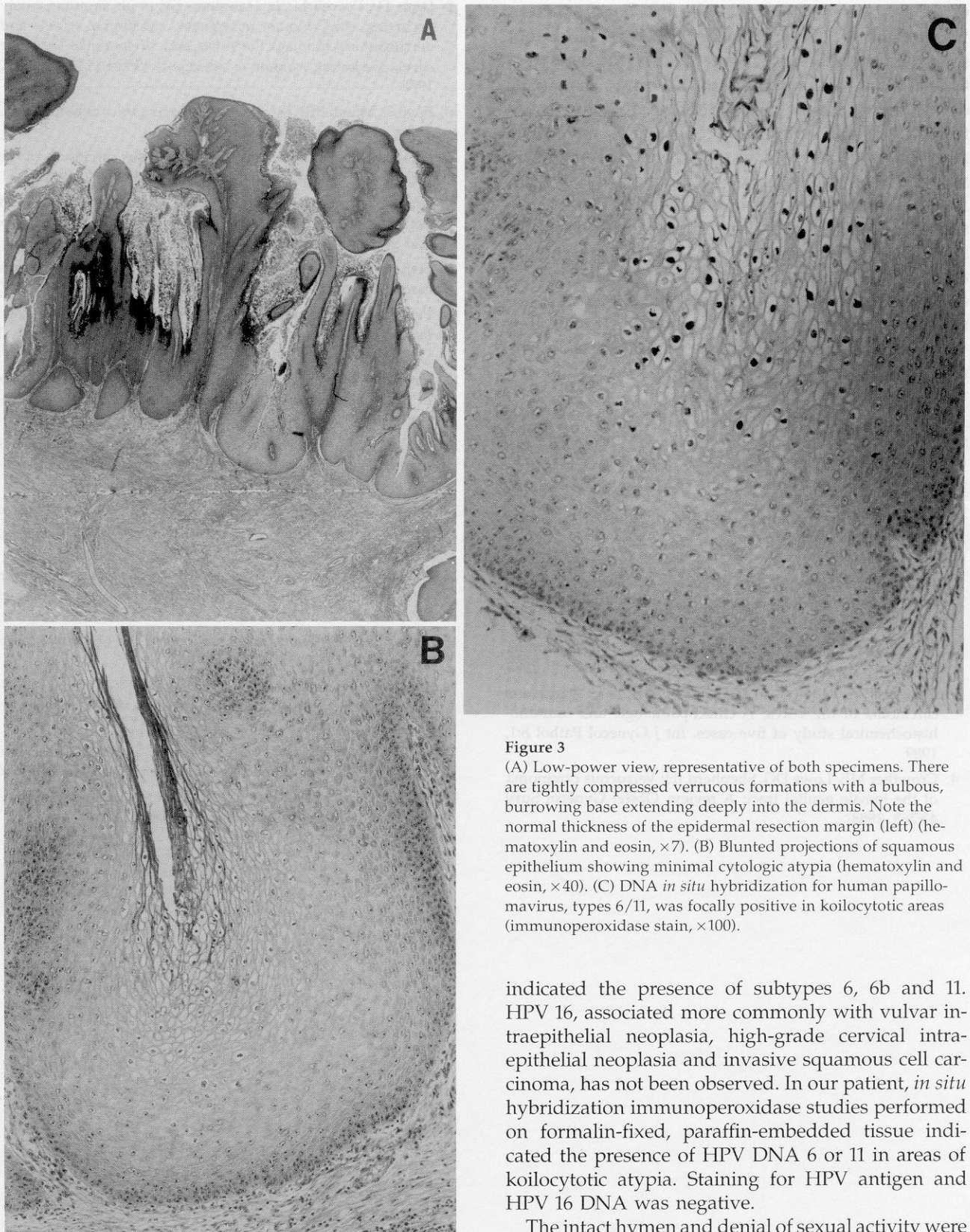


Figure 3

(A) Low-power view, representative of both specimens. There are tightly compressed verrucous formations with a bulbous, burrowing base extending deeply into the dermis. Note the normal thickness of the epidermal resection margin (left) (hematoxylin and eosin, $\times 7$). (B) Blunted projections of squamous epithelium showing minimal cytologic atypia (hematoxylin and eosin, $\times 40$). (C) DNA *in situ* hybridization for human papillomavirus, types 6/11, was focally positive in koilocytotic areas (immunoperoxidase stain, $\times 100$).

indicated the presence of subtypes 6, 6b and 11. HPV 16, associated more commonly with vulvar intraepithelial neoplasia, high-grade cervical intraepithelial neoplasia and invasive squamous cell carcinoma, has not been observed. In our patient, *in situ* hybridization immunoperoxidase studies performed on formalin-fixed, paraffin-embedded tissue indicated the presence of HPV DNA 6 or 11 in areas of koilocytotic atypia. Staining for HPV antigen and HPV 16 DNA was negative.

The intact hymen and denial of sexual activity were

unusual features of our case. The fact that the patient was brought to the clinic by her mother and did not seek medical attention spontaneously for her large, foul-smelling lesions suggests a strong pattern of denial. HPV can be transmitted in a nonvenereal fashion,^{16,17} and congenital condylomas have been reported to occur even in a newborn infant whose mother had genital warts.¹⁸ In the majority of cases, however, a sexual mode of transmission can be presumed. In our patient, nonvenereal transmission of HPV may have occurred. However, the presence of an intact hymen suggests that sexual contact short of actual vaginal penetration could have been responsible for transfer of the virus if it had been transmitted venereally. Whatever the route of transmission, the role of the virus in the genesis of verrucous carcinoma remains unclear.

Acknowledgments

D. Craig Allred, M.D., assisted with the immunohistochemical staining. Phred Petersen and Lester Rosebock provided photographic assistance.

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