Cervical biopsy specimens and human papilloma virus positivity in patients with external genital warts

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Summary

Cervical biopsy specimens were taken from 16 women with external genital warts in order to diagnose concomitant cervical human papillomavirus (HPV) infection and cervical intraepithelial neoplasia (CIN) according to pathology. Positive HPV infection was detected 56% (9/16) of the patients. Among those patients 66% (6/9) had concurrent subclinical low-grade CIN lesions. One of those patients had a high-grade CIN lesion. It is concluded that cervical HPV infection was rather common in women with external genital warts and it is valuable to examine cervical HPV infection by biopsy to detect concomitant CIN.

Key words: Human papillomavirus; Cervical intraepithelial neoplasia.

Introduction

Clinical and subclinical human papillomavirus (HPV) infections are the most common sexually transmitted diseases today. Asymptomatic cervical HPV infection can be detected in 5%-40% of women of reproductive age [1]. HPV infection is a transient or intermittent phenomenon; only a small proportion of women positive for a given HPV are found to have the same type in subsequent specimens [2, 3]. Risk of subsequent cervical intraepithelial neoplasia (CIN) is proportional to the number of specimens testing positive for HPV, [4] which suggests that carcinogenic development results from persistent infections. It is now well established that HPV infection is the central causal factor in cervical cancer [5, 6]. Several research groups reported high coexistence of CIN lesions in patients with external genital warts [7, 8]. In this study cervical biopsy specimens were taken from 16 women with external genital warts in order to diagnose a concomitant cervical HPV infection.

Material and method

Sixteen women patients with external genital warts were recruited in the study. All of the patients had at least a four-year period with genital warts. The mean age of the patients was 34.8 ± 8.7 years. Patients had classic skin lesions of genital warts and in each case clinical diagnosis was confirmed histologically.

Colposcopically directed biopsy specimens were taken from the cervix of all patients. Biopsy specimens were fixed in 10% buffered formalin. Microscopically lesions displaying cellular disorientation, lack of cell polarity, and nuclear atypia were classified as CIN. Nuclear atypia was defined as nuclear pleomorphism, increase in nuclear/cytoplasmic ratio, and a coarse chromatin distribution. Lesions with features of CIN confined to the lower third of the epithelium were classified as low-grade CIN. Lesions with similar features above this limit were classified as high-grade CIN.

All biopsy specimens were stained immunohistochemically with the Biotin-Streptavidin Amplified (B-SA) method, which has polyclonal rabbit antipapilloma virus antikor (Biogenex) for a HPV antigen. Intranuclear or diffuse staining of two or more cells in superficial and granular layers was accepted as positive for HPV.

The control group was comprised of 20 patients with a mean age of approximately 39 years who had had a total abdominal hysterectomy for other disorders than cervical neoplasia.

Results

Nine of 16 patients with genital warts (56%) were positive for HPV immunohistochemically (Figure 1). Among those patients 66% (6/9) had concurrent subclinical low-grade CIN lesions. One of those patients had a high-grade CIN lesion. HPV was detected in 66% (4/6) of the low-grade and in one of the high-grade CIN lesions. Five of 16 patients with genital warts had other anogenital infec-

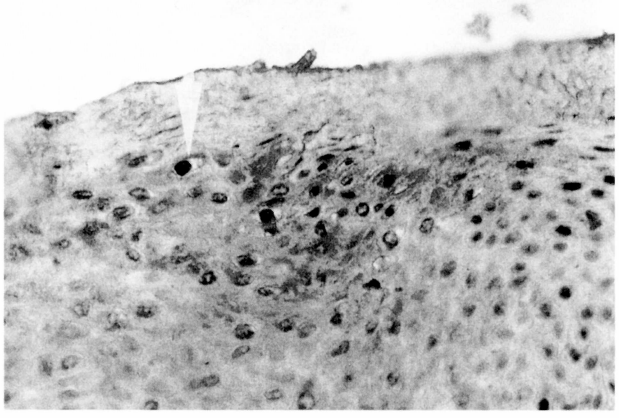

Figure 1. — HPV antikor with positive nuclear staining in a cervical biopsy specimen (immunperoxidase x160).

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tions, such as nonspecific urethritis, which was the most common. Four of the women with genital warts also had warts in the anal canal.

Three of the 20 control group patients were positive for HPV. Among those patients two had low-grade CIN lesions. HPV was detected in one of the low-grade CIN lesions. There were statistical differences between the two groups ($p < 0.05$) (Table 1).

Table 1. — *Cervical biopsy specimens and HPV positivity in patients with external genital warts and control group.*

	Patients n = 16	Control group n = 20	P
HPV	9 (9/16) 56%	3 (3/20) 15%	< 0.05
CIN low-grade	6 (6/9) 66%	2 (2/20) 10%	< 0.05
CIN high-grade	1 (1/9) 11%	-	< 0.05

Discussion

The thrust of epidemiological research in recent years has focused on the understanding of the role of risk factors that influence acquisition of persistent HPV infection or of coexisting factors that mediate progression in the continuum of lesion grades. The relative risks for the association between HPV infection and cervical neoplasia are of high magnitude. This high magnitude is greater than that for the association between smoking and lung cancer and is comparable only to that of the association between chronic hepatitis B and liver cancer, causal relations that are undisputable [9].

Approximately 1% of anogenital HPV infections result in clinically apparent warts which usually result in little physical discomfort but are psychologically distressing. Genital papilloma virus infection is in many patients a long lasting, relapsing disease for which no effective treatment is available. This fact and the association between the virus and cancer puts much stress on the afflicted patient [10].

Certain types of HPV are now recognized as the main cause of cervical cancer and its precursor lesions [10]. HPV infection of the uterine cervix is one of the most common sexually transmitted diseases [11], which is usually acquired around the time sexual activity begins. Consequently, cervical infections are frequently detectable among young women [12, 13]. Although the majority of infections are detectable only with molecular techniques, the most common cytopathologic manifestations of cervical HPV infection are low-grade CIN lesions, including koilocytotic atypia and flat condyloma. These lesions occur in the transformation zone of the cervix. They are characterized typically by cytoplasmic cavitation and nuclear atypia, cytopathic effects of a productive HPV infection [14].

Generally, pathologic changes and the molecular evidence of infection (HPV DNA detection) regress spontaneously with time [15], as do cutaneous warts caused by HPV types that infect nongenital skin. For yet unknown reasons, when the infection does not resolve, high-grade CIN lesions can develop and progress to cancer over a period of several years. HPV-associated genital warts in women has been reported as a risk factor for cervical neoplasia [7, 8, 16].

Several research groups reported a high coexistence of CIN lesions in patients with external genital warts [7, 8]. Song *et al.* reported a positive association between genital warts and CIN lesions in his study [7]. Peterson *et al.* reported a high frequency of human papilloma virus in normal appearing cervix and Pap-smear negative women who had external genital warts [8, 16]. In our study, we found a higher coexistence of CIN lesions in patients with external genital warts than the control group.

It is concluded that cervical HPV infection was rather common in women with external genital warts and it is valuable to examine cervical HPV infection by biopsy to detect concomitant CIN.

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