CONDYLOMA ACUMINATUM: EPIDEMIOLOGICAL, CLINICAL AND THERAPEUTIC ASPECTS

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Condyloma acuminatum, CA or genital warts, are benign fibro-epithelial tumors with a predilection for moist environments, especially mucosal surfaces. This sexually transmitted disease (STD) is increasing rapidly in incidence. The lesions are associated with a number of human papillomavirus (HPV) types. Some HPV types are closely linked with genital (especially cervical) dysplasia and neoplasia. Treatment consists of such traditional modalities as podophyllin, cryotherapy or surgical excision and, more recently, administration of interferon (IFN).

ETIOLOGY

Condyloma acuminatum (CA) is known to be caused by a number of human papillomavirus (HPV) types: 6, 11, 16 and 18. Human papillomaviruses are members of the A genus of the family Papovaviridae and are non-enveloped viruses with icosahedral capsids and a double-stranded circular DNA genome of about 8,000 base pairs (50). A virus isolate is considered an independent HPV type if nucleic acid hybridization studies show less than 50% homology with known viral types (10). Since HPV has not been grown successfully in tissue culture, extensive in vitro studies of this virus have been impeded (43).

Viral DNA and protein production do not occur in the basal layer of the epidermis, but begin in the upper spinous layer (49). Final virus assembly occurs in the granular layer. Lesions induced by HPV most commonly produce the histopathologic phenomena of acanthosis and hyperplasia. In a recent investigation in Germany (34), four distinct HPV-associated anogenital epithelial lesions were distinguished clinically. Although these clinical presentations could not be correlated to specific histological patterns, three clinical forms were found to be associated with distinct HPV types. The first of these clinical forms was condylomatous lesions in which HPV-6 DNA and HPV-11 DNA were detected in 37 and 13 of 59 samples respectively. The HPV type of the other 9 condylomatous lesions remained unclassified. The second type of lesion was flat; HPV 6 and HPV 11 were associated with lesions of low epidermal atypia in 8 and 2 of 18 cases respectively. Six of the remaining lesions had severe atypia and were associated exclusively with HPV 16 and were referred to as Bowenoid papulosis. Pigmented papules were the third clinical presentation; HPV 16 was detected in 2 of 7 cases studied (Bowenoid papulosis). In 2 of the remaining pigmented lesions HPV 11 was detected. In the other 3 lesions neither

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HPV 6, 11 or 16 could be found. The fourth clinical presentation type described was condylomata plana, flat leukoplakia-like lesions. The HPV type in these lesions was not, however, described.

Another clinical presentation not described by these authors is the giant condyloma of Buschke-Löwenstein. These tumors have been associated with HPV-6 (6, 32).

**Epidemiology and Clinical Aspects**

Condyloma acuminatum is found most frequently in sexually active persons. Since CA has only been recognized as a separate venereal disease since 1954 (47), the epidemiology and incidence has not been as well studied as some other sexually transmitted diseases, STD. The average incubation period is 3 months (48) but, it ranges from 3 weeks to 8 months. The disease presents in females as verrucous lesions on the perineum, vaginal or vulvar mucosa, or as flat leukoplakic lesions on the cervix. Males have verrucous growths on the penis or less commonly on the scrotum. Both sexes can present with perianal, rectal, or inguinal lesions. Less common locations for CA include the urethra (17), bladder and ureters (38), and mouth (19, 21). In addition, we have treated two patients with biopsy-proven lesions on the cervix. Males have verrucous lesions on the urethra (17), bladder and ureters (38), and mouth (19, 21). In addition, we have treated two patients with biopsy-proven condyloma of the palpebral conjunctiva at the University of Alabama Hospitals in Birmingham. Condylomas are generally not the consequence of autoinoculation onto the general skin surface (45).

Condylomas may enlarge substantially during pregnancy, potentially complicating delivery, but usually regress after parturition (39). This observation may be due to hormonal changes and/or to altered immune competence. Patients with diabetes mellitus, hematological malignancies, exogenous immunosuppression because of organ transplantation and other conditions associated with depressed cellular immunity frequently develop large and rapidly growing CAs.

The incidence of CA in the United States is not available, but many reports suggest it is the third most common sexually transmitted disease (after gonorrhea and nongonococcal urethritis) (67). Data from the Centers for Disease Control show that there has been a 500% increase in the incidence of condyloma acuminatum from 1966 to 1981 (3), but some of this increase may be attributed to more accurate reporting. In a retrospective study of 746 patients treated for condyloma acuminatum in the Mayo Clinic from 1959 to 1978 (9), the mean annual incidence rate reached 106.5 per 100,000 population in the period 1975 to 1978. This rate is very similar to that of 103 per 100,000 population estimated in the Denver Metropolitan area (67), but more than twice the rate reported from England [48] (2) and Sweden [54] (63). In the Mayo Clinic study, the peak incidence for both sexes occurred between 20 to 24 years of age. Female patients contracted infection at a higher rate than male patients, which contrasts to other reports (67) showing males to be more commonly infected. While anal and perianal condyloma are reported to be 2.5 times more frequent in male patients than in females, male patients were less likely than females to have CA in multiple locations. Twenty-seven percent of the patients reported symptoms; itching (13%) and burning, pain, or tenderness (11%) were the most common. The incidence of recurrence was greater in male patients (30%) than in female patients (20%). A history of sexually transmitted diseases other than CA was present in 29% of the male patients and 71% of the female patients; concurrent diagnosis of other sexually transmitted diseases occurred in 7% and 31% of these patient populations, respectively. Racial differences in the incidence of CA cannot be ascertained as 98% of the patients were Caucasian.

A study of 49 women with CA at the University of Washington showed that patients reporting a history of CA had more sexual partners and were more likely to have a history of other sexually transmitted diseases than sex and age matched control patients without CA (14). There was no overall increased risk of CA among women who used oral contraceptives for less than 5 years. Women who had used oral contraceptives more than 5 years, however, had a relative risk of developing CA of 9.8. After adjustment was made for the number of sexual partners, history of other venereal diseases and duration of oral contraceptive use, the relative risk for development of CA was 3.7 in all smokers and 4.3 in women who had smoked for 3 years or more. It is notable that cigarette smoking (60) and long-term duration of oral contraceptive use (62) have also been frequently cited as risks factors for cervical neoplasia. Since HPV infections have been linked with cervical and other genital cancers (68), the risk factors of cigarette smoking and long-term oral contraceptive use may be associated with the transformation of benign CAs into malignant neoplasms. One possible explanation for this association is the depressed immune response reported in cigarette smokers (25) and in long-term users of oral contraceptives (46). Since race was not specified in the University of Washington study, racial differences in the incidence of CA cannot be determined.

The majority of patients enrolled in interferon treatment trials at the University of Alabama at Birmingham, UAB, have been recruited from the Jefferson County Department of Health. Most patients evaluated at this clinic are black, and males comprise the majority of patients with CA. Although not usually recognized by the patients as