

Anal and Penile Condylomas in HIV-negative and HIV-positive Men: Clinical, Histological and Virological Characteristics Correlated to Therapeutic Outcome

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Clinical, histological and HPV DNA hybridization findings were analyzed for 73 homosexual and 38 heterosexual men attending for anal warts; therapy results were evaluated retrospectively for 76 of these patients.

Concurrent anal and penile warts occurred most commonly in the heterosexual men ($p < 0.001$). While perianal warts were most common in heterosexuals ($p < 0.05$), intraanal warts were most common in homosexuals ($p < 0.001$). Altogether 23 homosexual men were HIV-infected; 13 HIV-positive men followed regarding therapeutic outcome were immunologically relatively intact with mean CD4 counts of 524/mm³. Of 136 biopsy specimens 70% revealed benign hyperplasia, 27% AIN I, 2% AIN II and none AIN III. Of ISH positive samples 94% contained HPV 6/11 and 6% HPV 16/18/31/33. Anal warts were cured after an average of 2.5 (mean 1-10) therapy sessions in 64% of heterosexual, in 84% of HIV-negative homosexual and in 62% of HIV-positive homosexual men.

The mean number of therapy sessions against anal warts was highest ($p < 0.001$) and the time for accomplishing cure for anal and penile warts was longest ($p < 0.001$) in the heterosexual study group. Key words: anogenital warts; therapy; HPV; *in situ hybridization*.

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Since the sexually transmitted nature of genital warts (condylomata acuminata; condylomas) was demonstrated in the 50's (1), the magnitude of the clinical problem has increased, representing a challenge, above all in STD and gynaecology clinics, but in urology and proctology units as well (2-6). Genitoanal warts are multifocal and currently subclassified into 1) acuminate, 2) papular, and 3) flat variants. More than one type are often seen in the individual patient (7, 8). They are predominantly induced by HPV types 6 and/or 11, commonly referred to as »low-risk« HPV types due to their rare association with malignant transformation. Sexually active individuals, however, are much more commonly afflicted with subclinical lesions induced by potentially oncogenic »high-risk« HPV types such as HPV 16, 18, 31 and 33. Oncogenic HPV types frequently give rise to intraepithelial neoplasia (IN), and the terms CIN, VAIN, VIN, PIN, PEIN and AIN are used when epithelial dysplasia engages the cervix, vagina, vulva, penis, perineum or the anus, respectively. Benign and dysplastic lesions often coexist (9, 10).

Whether benign condylomas represent a risk marker for IN is controversial, as the epidemiology of the conditions overlap

with regard to covarying risk factors such as sexual habits and the presence of other STDs. In immunologically competent patients, most dysplastic lesions regress spontaneously within some years, malignant progression occurring in a minority of cases when persistent lesions are concurrently influenced by various cocarcinogens (10-16).

Anal warts in males are mostly seen in homosexual men practising genito- and oro-anal sex (17) but are common in heterosexual men as well (4, 5, 18). As concurrent penile warts have been reported to occur more commonly in heterosexual compared to homosexual men (4), it has been postulated that other modes of transmission than penile-vaginal sex may also exist, such as digital autoinoculation from the penile warts and/or digitoanal transmission by the partner(s) during sexual interplay.

Multifocal occurrence both of penile and anal warts, however, may also indicate weak specific immune reactions against HPV in immunologically otherwise healthy individuals, including local depletion and functional alteration of Langerhans' cells (19-22) and/or some types of immunologically detrimental effects induced by yet unidentified HPV product(s) (22, 23). Multifocal occurrence and therapeutic recalcitrance may also occur late during HIV infection; an augmented risk of malignant transformation at this stage has been discussed (23-27).

The present investigation studied clinical presentation, prevalence of AIN and of HPV 6/11/16/18/31/33 as well as therapeutic outcome for anal and/or penile warts afflicting homosexual and heterosexual men.

MATERIAL AND METHODS

Patients

The study comprises 111 men representing a highly selected group of males who attended primarily for therapy of either previously untreated or therapeutically recalcitrant anal warts at the Department of Dermatovenereology at the Southern Hospital of Stockholm, Sweden, during a 19-month enrollment period 1986-7. Patients were selected among consecutive men who either self-attended the STD out-patient division, or who participated in a routine health screening program for homosexual men (»Venhälsan«) that comprised proctoscopy investigation. All patients were offered STD testing, including standard culture swabs for gonorrhoea and *Chlamydia trachomatis* infection, as well as serology tests for antibodies against *Treponema pallidum* and HIV. Patients were specifically interviewed with regard to sexual preference. Furthermore, data on duration of condylomata disease and number of previous therapy sessions were collected. Ethical committee application was not considered as a requirement, as the program for clinical management did not represent a deviation from already existing routine procedures, with the exception that condylomata biopsies were collected from all participants and stored at -70°C for subsequent investigations.

Clinical investigation

All men were sampled with standard culture procedures for the presence of *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Blood samples were drawn, subsequent to the patients' consent, for HIV infection, using ELISA testing for screening and Western blotting for confirmation in ELISA-positive cases, and for syphilis using standard Wasserman complement fixation procedures. In HIV-positive men CD4 counts were determined whenever patients gave their consent.

Throughout the 19 months' study period all patients were subjected to wart evaluation and to therapy, by one and the same investigator (GvK). Proctoscopy was performed as a routine at each clinic visit. The patients' warts were evaluated through colposcopic magnification and, when required for an optimal delineation of wart extension, with 5% acetic acid solution application as well.

Lesions were counted and depicted on a specially designed evaluation chart being used at each visit for a continuous monitoring of therapeutic results. Anal warts were grouped according to location, being *perianal* when occurring >1 cm laterally of the *anal verge*, or *intraanal* when occurring in the anal canal/on the dentate line of the rectum and not being easily accessible for inspection without the assistance of proctoscopy.

Warts were classified by appearance as *acuminate* (highly proliferative with prominent, finger-like surface projections), *papular* (easily identifiable exophytic warts being distinctively elevated over the surrounding undiseased epithelium but exhibiting a relatively smooth and sessile rounded surface texture) or as *flat* (exhibiting a visible/palpable epithelial undulation, often being better appreciable with colposcopic magnification when a wavy exterior associated with typical capillary »punctuation« was considered as the most reliable hallmark).

Histopathology and in situ HPV DNA analysis

A total of 136 biopsy specimens were collected, 128 from anal and another 8 from concurrent penile warts. Samples were frozen and stored at -70°C until being further processed for light microscopy and in situ HPV DNA analysis. Biopsies were analyzed at the Laboratory of Finnish Cancer Society, Department of Pathology, University of Kuopio, Finland (K.S.; S.S.).

Biopsies were thawed, fixed in 10% neutral formalin, and processed for light microscopy using hematoxylin and eosin staining. Lesions were analyzed by light microscopy using the criteria outlined previously for HPV influence, including commonly accepted criteria for any presence of AIN I, AIN II and AIN III (28, 29).

Whole genomic DNA probes of the HPV types 6, 11, 16, 18, 31 and 33 were ³⁵S-labelled and used for in situ DNA hybridization according to routine procedures applied at the time of the study initiation (30–32). The specimens were hybridized under conditions of high stringency for 50 h at 42°C in a humidified chamber (T_m (melting temperature) -17°C). After hybridization, the sections were placed in lightproof boxes for 4 days. Black autoradiography grains superimposed on the nuclei of epithelial cells indicated HPV DNA sequences in the lesions, as described previously (32).

Therapy

Among 111 men enrolled for clinical evaluation and biopsy sampling, 30 men did not comply with the proposal of returning to the clinical investigator for subsequent therapeutic measurements. A total of 81 men were included in the therapy protocol. Of these, a direct referral to the department of proctological surgery was required in 5 men due to extensive growth of intraanal warts. The remaining 76 men were treated as out-patients at least once at the STD clinic.

Favourable outcome of home treatment with 0.5% podophyllotoxin against penile warts has been reported elsewhere (5). Self treatment against perianal and/or penile warts with 0.5% podophyllotoxin as a cream formulation applied b.i.d. for 3 consecutive days was tried in 16 men as part of an open-labelled pilot project (Wartec®; Conpharm AB, Glunten, Uppsala, Sweden).

Surgical therapy was performed under local anaesthesia using lidocaine with adrenalin 1:200000 (Xylocain®; Astra, Södertälje, Sweden). Anxious patients were pretreated with EMLA cream® (Astra, Söder-

tälje, Sweden) for 10–15 min, and in a few instances premedication with 20–30 mg diazepam was required. Magnification with a colposcope (Zeiss) was used in all instances, and excision, diathermy and/or heat destruction was performed of 1–2 mm of colposcopically normal epidermis adjacent to individual warts. Perianal warts were mostly excised by lifting the lesions with a pair of toothed forceps, and by using fine-pointed slightly curved scissors. Intraanal warts were predominantly electrodesiccated through a transparent disposable proctoscope. In four cases warts were destructed with an infrared coagulator device (MBB-AT, MBB Angewandte Technologie, GmbH, Munich, Germany), using exposure time accounted for in detail elsewhere (33). The method has the advantage of destructing the warts with minimal risk of bleeding as well as avoiding heavy smoke development.

Follow-up investigations

Follow-up of therapeutic endeavour, based on a retrospective analysis of patient files, was possible in all of the 76 men submitted to out-patient therapy in the STD clinic. Efficacy evaluation was based on a confirmed wart cure being documented on clinical visits. Follow-up time refers to the number of months having elapsed since the last therapeutic session and the last visit to the clinic revealing a wart-free state. Therapeutic outcome was stratified according to the patients' sexual preference and their HIV status.

Statistical analysis

Yate's corrected chi-square test and Student's *t*-test for parametric data were used for analysis of differences.

RESULTS

Clinical evaluation

The mean age of the 111 men investigated by biopsy was 31.9 (range 17–68) years, 63% of patients being 20–35 years of age. None of them had gonorrhoea or chlamydia or had a positive syphilis test. Consent for HIV testing was obtained in 100 (90%) patients, of whom 23 homosexual men (21%) tested positive.

At presentation 25 of 38 heterosexual men (66%) presented with anal warts merely, and another 13 (34%) were concurrently afflicted with penile condylomas. During the study time, i.e. the time that elapsed between first attendance and clinically confirmed cure, 23 (92%) heterosexual men exhibited concurrent penile warts on some occasion. Of 73 homosexual men 69 (95%) presented exclusively with anal warts and only 4 (5%) were afflicted with penile condylomas throughout the study period. Thus, concurrent presence of anal and penile warts at some time during treatment was significantly less common ($p < 0.001$) in homosexual than in heterosexual men.

None of the men were afflicted with warts proximal of the dentate line of the rectum. Only one (3%) of the 38 heterosexual patients exhibited intraanal growth at the time of biopsy sampling, as opposed to 33 (45%) of 73 homosexual men, a highly significant difference ($p < 0.001$). Warts on the anal verge were equally common in both patient groups, afflicting 17 (45%) and 30 (41%) of the hetero- and homosexual men, respectively. Perianal warts, on the other hand, were more common ($p < 0.05$) in the heterosexual group, where they occurred in 16 (42%) compared to 16 (22%) of the homosexual men. HIV infection did not influence the distribution of warts (data not shown).

Warts had been present for < 6 months in 38%, for 6–12 months in 26% and at least for 1 year in another 37% of the patients. No differences were detected regarding the duration between HIV-positive and HIV-negative men. HIV-infected

Table I. Therapeutic outcome of anal warts as evaluated on retrospective follow-up

Population	N:o of men followed up	Mean age (range)	Follow-up time (months)	Number of men (%) completely cured of anal warts*	Number of surgical therapy sessions mean (range)	Months before cure** mean (range)
Heterosexual	25	28 (20-68)	7.3 (0-41)	16 (64%)	3.9 (1-10)	13.1 (0-49)
HIV-neg. homosexual	38	31 (20-48)	15.3 (0-57)	32 (84%)	1.9 (1-7)	5.5 (0-55)
HIV-pos. homosexual	13	35 (20-55)	28.6 (0-58)	8 (62%)	1.7 (1-3)	7.8 (0-42)
Total	76	30 (20-68)	14.9 (0-58)	56 (74%)	2.5 (1-10)	8.1 (0-55)

* As clinically confirmed at least once.

** Refers to time between first attendance and clinically confirmed cure.

men had been aware of their warts for < 6 months in 46% of cases, compared with 34% of HIV-negative men; corresponding figures for warts that had been present for at least 1 year were 32% and 40%, respectively. No differences in duration were detected with respect to sexual preference (data not shown).

A reliable history of previous therapy was obtained for 126 of the altogether 136 biopsied sites (93%). The majority, 94 (74%), had not received treatment, while 19 (15%) had been submitted to up to four therapy sessions, and 13 (10%) had been treated on at least five previous occasions (podophyllin, podophyllotoxin and/or various surgical procedures).

As evaluated by clinical appraisal, acuminate warts represented 87 (64%), papular warts 33 (24%), and flat lesions another 16 (12%) of the 136 biopsies. Wart morphology did not correlate to duration of condyloma disease, to the number of previous therapy sessions or to the HIV status of patients (data not shown).

Histopathology and HPV DNA analysis

Further details on light microscopy and virological findings have been presented in a previous publication (34). Of 136 biopsies 128 (84%) were taken from the anal warts, of which 90 (70%) exhibited benign hyperplasia merely. Another 35 (27%) and 3 (2%) of the biopsies revealed AIN I and AIN II, respectively, while no samples exhibited AIN III. Histopathological evaluation of lesional morphology was not uniformly in concurrence with that of clinical appraisal regarding classification into acuminate, papular and flat warts. These deviations have been accounted for in separate publications (7, 34). Among the 128 anal warts the presence of AIN I-II was most commonly detected in papular warts (57%; 8/14), compared to acuminate (28%; 27/95) or flat (16%; 3/19) lesions ($p < 0.05$).

HPV DNA in situ hybridization was successfully performed on 125 of the 128 anal biopsies (98%) and gave positive signals with the HPV 6, 11, 16, 18, 31 or 33 specific DNA probes in 109 cases (87%). HPV 6 and 11 were most commonly detected, comprising 62 (57%) and 40 (37%) of the positive cases, respectively. Only 7 (6%) of the biopsy specimens were associated with the remaining »high-risk« HPV types. No association was found between sexual preference and prevalence of the various HPV types; neither did the distribution of the various HPV types differ between HIV-negative and -positive men (data not shown). No correlation existed between the presence of AIN and HIV-negative versus HIV-positive status (34).

Therapy

Altogether 76 men were primarily treated in the STD out-patient clinic, but 15 men required additional assistance from either the proctology ($n=14$) or the urology ($n=1$) department at some time during therapeutic intervention. Podophyllotoxin cream applied b.i.d. for 1-2 3-day courses was given to 16 men afflicted with perianal warts. A complete cure was accomplished in one of them, while the other patients experienced a reduction in the numbers and size of the warts that was favourable for facilitating subsequent surgery. The test preparation of podophyllotoxin was tested only initially during the study. Surgery represented the predominant therapy. The infrared coagulator was used against anal warts in only 4 patients. The major drawback of the method was that the »window«-opening for infrared light energy transmission is standardized as circular areas of various sizes; we found that the window seldom fits adequately to completely cover warts of different sizes. Thus, most of the therapy against anal warts comprised conventional surgery using scissor excision/electrodesiccation.

Therapeutic outcome

The therapeutic outcome of anal warts for the 76 study patients (age mean 30, range 20-68 years) is summarized in Table I, accounting for 25 heterosexual and 38 homosexual HIV-negative men, as well as 13 HIV-infected homosexual men. The various subgroups of men with anal warts are compatible with regard to age. For 13 evaluable HIV-positive men, CD4 counts at entry were available for 8 of them, revealing a mean value of 524 (range 220-960)mm³.

The mean follow-up time for therapeutic evaluation among heterosexual men was 7.3 months (range 1-41) compared to 19.3 months (range 1-58) among the homosexual men. No statistical differences in therapeutic outcome for anal warts were detected between the various subgroups of men; a complete cure was accomplished in 64% of the heterosexual men, and in 84% and 62% of HIV-negative and -positive homosexual men, respectively (Table I). However, the average number of surgical sessions against anal warts was as high as 3.9 (range 1-10) in the heterosexual group, compared to only 1.9 (range 1-7) in HIV-negative homosexual men ($p < 0.001$). When penile warts were included, the higher number of surgical therapeutic sessions given in heterosexual men (mean 5.8) was even more pronounced ($p < 0.001$). As many as 29 (57%) of the homosexual

men were cured from their anal warts already after the first session, compared to 7 (28%) of the heterosexual men ($p < 0.05$). The time before cure of anal warts in the heterosexual group was 13.1 months compared to 5.5 and 7.8 months for the HIV-negative and HIV-positive homosexual men, respectively ($p < 0.05$). If also taking into account treatment for penile warts, the cure time for the heterosexual men was as long as 26.2 months, compared to only 5.5 months for the homosexual group ($p < 0.001$).

DISCUSSION

The mean age of our patients was 30 years, which is higher than the reported average age of 22–26 years for genital warts (1–3, 8). This probably reflects that one quarter of the men were enrolled due to long-lasting therapeutically recalcitrant lesions; one third of the men had carried their warts for more than 1 year. Also, many of the homosexual men were diagnosed through a routine health control programme, when they often were unaware of carrying anal warts. Thus, the selection factors in the present study may, in part, explain the relatively high number of therapy sessions and the long duration of therapeutic intervention in the heterosexual men.

A high frequency of concurrent penile and anal warts in heterosexual men and of intraanal warts in homosexual men may reflect differences in sexual practice. However, an alternative pathogenetic mechanism for multifocal affliction in the heterosexual patients includes that some type(s) of immunological tolerance might exist. A potentially injurious influence by some HPV-specific products has been postulated as a cause of weak local immune reactions in some condyloma patients, which could cause multifocal persistence of lesions in immunologically otherwise healthy individuals. Thus, partial depletion and morphological alterations of Langerhans' cells (20–22), as well as impaired HLA-DR and ICAM-1 associated antigen presenting capacity of infected keratinocytes (22–23), have repeatedly been demonstrated locally in persistent lesions. It has been postulated that specific viral proteins may mediate immunological suppression by inhibiting the IL-1 receptor and down-regulate the expression of MHC class molecules, being essential for the efficacy of cytotoxic cells in tumour surveillance (23).

The heterosexual men included in our study were all attending primarily because of anal warts. However, the conspicuously high rate of heterosexual males who also exhibited penile warts at some time during the follow-up period (23/25; 92%) is remarkable. Evidently, these men represent a rather biased population selection among heterosexual men afflicted with condylomas. The multifocal occurrence of warts and the high degree of therapeutic recalcitrance in these men, as shown by a longer duration of treatment and a higher number of therapeutic sessions than in the homosexual group of men, may very well be related to a relatively weak function of HPV-specific immunological surveillance mechanisms in this study population. The validity of the latter assumption is strengthened by the fact that intraanal warts, which are usually less easily accessible to surgical intervention, were less common in the heterosexual men.

Even in the HIV-infected homosexual men in our study, therapeutic outcome appeared to be more favourable than in the

heterosexual men (Table I). Thus, although HIV infection per se, is well known to infect and disturb not only Langerhans' cells but significant aspects of cell-mediated immunity in general as well (24, 25), HIV-associated immunological exhaustion represents a relatively late phenomenon during HIV disease. The HIV-infected men in our study were quite intact with respect to systemic cell-mediated immune surveillance, as measured by a mean CD4 quantity > 500 (range 220–960) mm^3 .

Although HPV DNA prevalence rates are generally somewhat higher in HIV-positive compared to in HIV-negative homosexual men, as evaluated by cytology sampling from the anal canal (25, 35–37), no significant association exists with HIV-seropositivity per se and frequency of dysplasia (38, 39). Development of HPV-associated AIN III is not significantly augmented in HIV-infected men during early HIV infection but tends to rise 2–5 years before AIDS diagnosis (25). Prior to the HIV epidemic, anal cancer was predominantly a disease of older women. Since the onset of the epidemic, however, the number of new cases of squamous cell anal cancer has increased more than seven-fold among single, never married men aged 20–49 years in the San Francisco Bay area compared to the period spanning 1973–1978 (25). The association with HPV is suggestive (35–38, 40). Using PCR methodology the frequency of HPV DNA detected in anal cancers has been as high as 78% (41). In a population-based case-control study, the HPV types 16, 18 and 31 were significantly associated with the development of anal cancer (42).

At the time of initiating the present study, we assumed that clinical investigation including colposcopic magnification, biopsy evaluation and carefully performed surgical intervention represent adequate measurements for preventing subsequent anal cancer development. In the light of more recent data, however, use of anoscopy/colposcopy and targeted biopsies have been repeatedly questioned as a primary reliable measurement for diagnosing precancerous lesions (25, 26, 36). It has been proposed that annual anal cytology rather should be considered more optimal for monitoring HIV-positive men, and this approach ought to be applied in patients exhibiting absolute CD4 counts below $200/\text{mm}^3$ (25, 37). Abnormal results, including atypia, should prompt additional anoscopy followed by one or more anoscopically-directed biopsies, regardless of the clinical appearance of the lesions.

Most clinicians tend to treat anal condyloma as well as AIN in HIV-positive individuals in the same manner as anal HPV lesions in HIV-negative individuals, i.e. with ablation of visually detectable diseased tissue (25, 43). Our results indicate that significant problems exist, entailing repeated and often long-lasting surgical intervention. Patients with concurrent penile warts appear to represent problem cases. Alternative therapy such as administration of antiviral and/or immunomodulatory substances, however, is not projected to become available in the near future.

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