Clinical course of anogenital warts in men infected with human immunodeficiency virus

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SUMMARY Fifty four men with anogenital warts were studied; 22 had concurrent infection with the human immunodeficiency virus (HIV). The median duration of the warts before and after the start of treatment of seven HIV infected and 10 non-infected heterosexual men was similar. In homosexual men, however, the duration of the lesions in 15 HIV infected patients was greater before and after treatment than in 22 non-HIV infected men. As the median number of CD4⁺ cells in the peripheral blood was significantly lower in homosexual than heterosexual men infected with HIV, the difference in the course of anogenital warts in homosexual compared with heterosexual men may reflect different degrees of immunosuppression.

Anogenital warts caused by human papillomavirus (HPV) are common in patients who attend genitourinary medicine clinics and, in the absence of specific antiviral chemotherapy, can be difficult to eradicate. After variable periods, however, they usually regress, even if they have not been treated.¹ The immunological mechanisms that result in resolution of wart virus infection are largely unknown, but cell mediated immune responses are probably important.² Anogenital warts occur in about 40% of homosexual men infected with the human immunodeficiency virus (HIV),³ and, as HIV can produce pronounced impairment of cellular immunity, condylomata acuminata in men with HIV infection might be expected to have a somewhat protracted course. Surprisingly, few data on this aspect of HPV infection have been published. The aim of the present study was to learn something of the natural history of anogenital warts in men infected with HIV.

Patients and methods

PATIENTS

The study group comprised 54 men with anogenital warts who attended the department of genitourinary medicine of this hospital as "new" or "return new" patients in June to December 1984 and who were available for assessment in 1988. After October 1985,

when HIV antibody testing became available, and after counselling, each of these men had requested serological testing for HIV infection: 22 had antibody to HIV. At the initial clinic attendance we took a careful history from each patient, paying particular attention to the duration of his warts before the clinic visit. After undertaking a general physical examination, we inspected the genitalia and perianal region carefully and noted the location and extent of the warts. Whenever we found perianal condylomata acuminata, we undertook proctoscopy. We collected routinely the appropriate material for microbiological examination for sexually transmissible pathogens. Depending on the sites of the warts, patients were treated with podophyllin, cryotherapy, scissor excision, or electrocautery.

As far as possible, we reviewed patients at regular intervals, when we repeated the physical examination and noted the extent of the warts. We obtained blood at intervals from most patients who had antibody to HIV, to estimate the T cell subpopulation of peripheral blood lymphocytes and the serum immunoglobulin concentrations.

LABORATORY METHODS

Serum was screened for antibodies against HIV by competitive enzyme linked immunosorbent assays (Wellcome). Positive results were confirmed if samples reacted positively in a different assay of the antiglobulin type (Pasteur or Du Pont). A few serum samples required further investigation by immunoblotting.

The numbers of CD4⁺ and CD8⁺ cells in peripheral

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Table Summary of findings in 54 men with anogenital warts and biopsy specimens from 32 of them

Patient groups	No of patients in each group	Median (range) age of patients (years)	Location of warts		
			Sub-preputial only	Perianal/anal only	Both sites
<i>Homosexual men:</i>					
HIV infected	15	26 (21-41)	0	12	3
Non-HIV infected	22	23 (19-53)	0	20	2
<i>Heterosexual men:</i>					
HIV infected*	7	24 (22-32)	3	1	3
Non-HIV infected	10	22 (20-31)	0	7	3

*Each man infected through intravenous drug abuse.

blood were measured by flow cytofluorimetry, and serum immunoglobulin concentrations were estimated by radial immunodiffusion.

We obtained biopsy samples of the warts of 32 men, which were examined histologically. The type of infecting HPV was assessed by *in situ* hybridisation using probes HPV 6b, 11, 16, and 18.⁴

STATISTICAL METHODS

We used the Wilcoxon rank test to analyse the data.

Results

The table summarises the findings in the study groups. In each case, the warts were of the hyperplastic type.¹

CLINICAL COURSE OF ANOGENITAL WARTS

Heterosexual men

Of 17 heterosexual men available for assessment three years after the initial clinic attendance, seven had antibody to HIV, each having acquired his infection by sharing contaminated syringes and needles. Thirteen heterosexual men had perianal condylomata, but warts were not found within the anal canal. The differences between HIV infected and non-infected men in the median duration of the warts before treatment (9 v 3 months), the duration after the start of treatment (24 v 9 months), or the number of treatments required (10 v 5) were not significant.

Homosexual men

The median duration of anogenital warts before treatment was significantly higher ($p < 0.01$) in HIV infected men than in non-infected men. Similarly, the median duration of warts after the start of treatment (36 v 9.5 months) and the median number of treatments given (20 v 4) were significantly greater in men infected with HIV (in each case $p < 0.01$). Sixteen men (seven with and nine without antibodies to HIV) had condylomata of the anal canal, which were not treated other than by obtaining tissue by punch biopsy for

histological examination (data not shown). The median durations of these lesions were 36 months in HIV infected men and 14 months in non-infected men ($p < 0.05$), though the forms of treatment used for each group were similar.

Immunological variables

Data on the number of CD4⁺ cells in the peripheral blood and serum immunoglobulin concentrations were available in 14 HIV infected (nine homosexual and five heterosexual) men who attended during March 1988. The median number of CD4⁺ cells in blood from the homosexual men ($0.1 \times 10^9/l$, range 0.04-0.47) was significantly smaller than from the heterosexual men ($0.45 \times 10^9/l$, range 0.38-0.59) ($p < 0.02$). No significant differences were seen, however, in median serum IgG, IgA, or IgM concentrations in homosexual compared with heterosexual men (data not shown).

Type of HPV

Formalin fixed paraffin blocks were available for *in situ* hybridisation from 32 of the 54 patients, of which 23 (72%) gave positive results for HPV 6b/11. In addition to HPV 6b/11, HPV 18 was detected in two patients (both homosexual men with antibody to HIV) and HPV 16 in one (a homosexual man with no antibody to HIV).

Discussion

Although the precise immunological mechanisms that result in regression of anogenital warts are uncertain, as florid and recalcitrant lesions may occur in patients with defects of cellular immunity,² cell mediated immunity appears to play an important part. HIV is associated with the progressive impairment of cell mediated immunity,⁵ and warts in patients infected with HIV might be expected to have a prolonged course. The heterosexual men in our study, however, showed no significant difference in the median durations of warts before treatment, durations after the

Mean (range) duration of warts (months)		Median (range) No of treatments	No of biopsy specimens/No examined containing HPV types:		
Before treatment	After start of treatment		6b/11	16	18
12 (1-48)	36 (14-64)	20 (3-40)†	7/8	0/8	2/8
2 (1-12)	9.5 (2-24)	4 (1-27)‡	10/17	1/17	0/17
9 (2-24)	24 (15-36)	10 (1-20)§	0	0	0
3 (2-12)	9 (3-24)	5 (1-17)	6/7	0/7	0/7

†Five men treated by cryotherapy only, four with podophyllin only, five with both podophyllin and cryotherapy, and one by scissor excision under local anaesthesia.

‡Seven men treated with podophyllin only, six by cryotherapy only, six with both podophyllin and cryotherapy, and three by scissor excision.

§Three men treated by cryotherapy, three with podophyllin only, and one by scissor excision.

||Seven men treated with podophyllin only and three by cryotherapy.

start of treatment, or numbers of treatments given to HIV infected compared with non-infected men. The total number of patients, however, was small, and a larger series of patients would be required to confirm or refute these findings.

The homosexual men in our study showed a significant difference in the course of the warts between HIV infected and non-infected men. Although intra-anal warts are known to have a more protracted course, even in the absence of immunodeficiency,⁶ in our patients, the duration of perianal and anal warts was greater in men with antibody to HIV. This finding differed from that of von Krogh *et al*, who found that 32.1% of men with and 40.4% of men without antibody to HIV had anal warts for more than 12 months, a difference that was not significant.⁶ The duration of follow up of their patients was not stated, however, and more prolonged surveillance may have shown a significant difference between the two groups. Another factor that may explain the differences between our findings and those of von Krogh and the differences in durations of warts between our homosexual and heterosexual patients could be the degree of impairment of cell mediated immunity.

As the duration of HIV infection increases, there is a progressive reduction in the number of CD4⁺ cells in the peripheral blood and progressive impairment of cellular immunity.⁵ In our patients, the median number of CD4⁺ cells in the blood of HIV infected homosexual men was significantly lower than in heterosexuals. That may reflect differences in the duration of HIV infection or in exposure to antigenic stimuli such as spermatozoa. Thus the differences between our homosexual and heterosexual HIV infected patients in the course of anogenital warts may result from differences in degrees of impairment of cellular immunity.

Although intraepithelial carcinoma has been recorded in HIV infected men with anal warts,⁷ we did not find this in any of the biopsied lesions. Human

papillomavirus types 16 or 18, which are associated with genital tract malignancy,⁸ were detected by in situ hybridisation in warts from three of our patients, two of whom had antibody to HIV. Rüdinger *et al*, however, did not identify these types in perianal or anal warts from HIV infected men or women in Zürich.⁹ As HPV types 16 and 18 tend to be associated with non-condylomatous lesions,¹⁰ and as colposcopy of the anal canal was not undertaken, the prevalence may be higher than recorded in those two studies.

In conclusion, our data suggest that anogenital warts in HIV infected homosexual men run a protracted course, but anal malignancy appears to be uncommon. As HPV types associated with carcinomas of the anogenital regions can be identified in genital and anal condylomata, the perianal region and anal canal should be examined regularly to detect early neoplastic changes.

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