Comparison of clinical, histological, and virological symptoms of HPV in HIV-1 infected men and immunocompetent subjects

Olivier Aynaud, Dominique Piron, Renzo Barrasso, Jean-Dominique Poveda

Objective: We assessed the clinical, histological, and virological features of anogenital human papillomavirus (HPV) infection, according to their immune status in HIV-1 infected men, referred for an anogenital examination or treatment, in comparison with immunocompetent patients.

Methods: The study population comprised 33 HIV-1 infected heterosexual or homosexual men and 38 HIV negative men seen in a screening and treatment centre for anogenital HPV infections. All patients were examined with a colposcope. Biopsies were carried out on all subjects with anogenital lesions for histological studies and HPV detection by Southern blot.

Results: The HIV infected patients had a balanopreputial HPV infection in 70%, anal in 30%, and urethral in 37%, while HIV negative patients had balanopreputial lesion in 72%, anal in 26%, and urethral in 16%. Diffuse anogenital lesions were present in 33% of the HIV infected cases and in 10.5% of HIV negative cases (p<0.02). Among the HIV infected patients, the genital HPV lesions were condylomatous in 67.5% of the cases and dysplastic in 57%. HIV negative patients had condylomatous lesions in 86% of the cases and dysplastic in 14%. The condylomatous lesions of HIV infected patients had a low grade malignant histological aspect in 36% of the cases and high grade histological criteria were found in 22% of the dysplasias. Oncogenic HPV were detected more frequently in HIV infected patients (35%† 12%) and more than one HPV type was found in 21.5% of cases. Neither the anogenital diffusion of the HPV lesions nor their morphological, histological, and virological features differed significantly in patient with CD4 cell counts > or < 200 × 10⁶/l. In contrast, patients with CD4 cell counts < 50 × 10⁶/l had a higher risk of several types of HPVs and of developing a diffuse anogenital infection.

Conclusion: HIV-1 infected patients had an increased frequency of high grade anogenital dysplastic lesions and a higher frequency of HPV infection with multiple and diffuse sites of involvement. These characteristics of HPV infection were independent of the patients' immune status up to CD4 cell counts > 50 × 10⁶/l but showed an increased risk when the CD4 cell count was < 50 × 10⁶/l. The higher frequency of diffuse anogenital infections among HIV infected men calls for rapid treatment, laser or surgery, given the association of histological features of intraepithelial neoplasia and the presence of multiple HPV infection sites which may be the consequence of immune disturbances, most of which are transmissible potentially oncogenic HPVs.

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Keywords: HIV; human papillomavirus; squamous cell carcinoma; anogenital neoplasm

Introduction

Human papillomaviruses (HPV) cause benign and preneoplastic anogenital lesions which are associated with HPVs 6, 11, and 42 (most condyloma acuminata and flat condyloma), or HPVs 16, 18, 31, 33, 35, and 39 (most preneoplastic lesions).1 It has been shown that immunodeficiency, whatever its cause, is associated with an increased frequency of HPV infection, suggesting that the expression of HPV may be modulated by host immune status.2 In addition, HIV positive homosexual men with anal HPV infection appear to be at an increased risk of developing anorectal precancer.3 Thus, HPV associated lesions should be screened and the aim of this study was to determine the clinical, histological, and virological characteristics of HPVs in HIV-1 infected homosexual or heterosexual men attending an HPV screening centre for diagnosis or treatment, according to their immune status.

Patients and methods

Over 6 months, 27 HIV-1 infected men (17 heterosexual, 16 homosexual) and 38 HIV negative men (26 heterosexual, 12 homosexual) were referred for diagnosis or treatment of anogenital HPV infection, to our centre for laser treatment of recalcitrant lesions. All patients had cryotherapy and/or podophyllotoxin for at least 3 weeks. All patients underwent anopeniscopy with a colposcope (Zeiss OPMI99) before and after application of 5% acetic acid. Urethral lesions were detected during colposcopy with a Hartmann speculum visualising the first 20 mm of the urethra.4 Anuscopy was also performed during colposcopy. The clinical aspects of HPV infection are now well defined: exophytic lesions (condyloma acuminata, papulae) or macular/endophytic lesions (flat condyloma), and preneoplastic lesions (leucoplasic, erythroplastic, or pigmented).5
All morphologically different HPV anogenital lesions were biopsied: 37 lesions in 27 HIV infected patients and 43 lesions among 38 HIV-negative. Specimens were fixed in Carnoy for histological studies and cultured in Eagle’s medium for virological analysis by means of molecular hybridisation (Southern blot). The biopsied HPV lesions were classified histologically as condylomatous or intraepithelial neoplasia (IN). The degree of intraepithelial neoplasia (grades I to III/in situ carcinoma) was judged on the degree of atypical cellular aspects and their topography within the epithelium as for cervical intraepithelial neoplasia.

DETECTION OF HPV

All specimens for this study, HPV DNA sequences were detected at the Pasteur Institute by means of molecular hybridisation (Southern blot) with probes specific for HPV 6, 11, 42, 16, 18, 33, 31, 35, and 39, also permitting the detection of HPV related viruses.

STATISTICAL METHODS

Associations between variables were examined by \( \chi^2 \) test for categorical variables. Odds ratio (OR) are presented for each risk factor and corresponding exact 95% confidence intervals (CI) were calculated. A p value < 0.05 was considered significant.

**Results**

The mean age of the men was 32 (range 23–45 years). In the HIV infected group, the mean rate of CD4 was 175 × 10⁶/l. Nine patients had CD4 cell counts > 200 × 10⁶/l, of whom three had counts > 400 × 10⁶/l, while 18 had CD4 cell counts < 200 × 10⁶/l, and six with counts < 50 × 10⁶/l. In the HIV negative group the mean rate of CD4 was 986 × 10⁶/l (range 615–1714 × 10⁶/l).

Among the 27 HIV infected patients with clinical HPV lesions, 16 (59.3%) already had these lesions diagnosed before serological diagnosis of HIV infection, in two cases (7.4%) they were diagnosed at the same time as HIV seropositivity, while in nine cases (33.3%) the HPV lesions appeared after serological diagnosis (range 40 months).

The HPV lesions were balanopreputial in 46 cases (71%), anal in 18 (28%), and urethral in 16 (25%). In five cases (8%) the urethral lesions were not associated with HPV lesions at other sites. Their location according to sexual habits and HIV status is shown in table 1. HIV infected patients had two to three locations (urethral-preputial, urethral-anal, anal-urethral-preputial) in eight cases (30%) and HIV negative in five cases (13%), but the number of location of HPV lesions is independent of seropositivity (p < 0.10, OR = 2.77; 95% CI = 0.82–9.39) as well as of sexual behaviour (homo/bisexual 12% and heterosexual 25%, OR < 0.20, 95% CI = 0.63–9.46). However, a diffuse infection (total area > 4 cm²) was present in nine HIV infected cases (33%) and four HIV negative cases (10.5%) (p < 0.02, OR = 4.25; 95% CI = 1.22–14.8).

The clinical aspect was suggestive of condylomata in 60 cases (75%) and preneoplastic lesions in 22 cases (27.5%). HIV infected patients more often had clinically preneoplastic

### Table 1: Comparison of clinical, histological, and virological aspects of anogenital HPV infection in HIV-1 infected men and immunocompetent subjects

<table>
<thead>
<tr>
<th>Anogenital location of HPV lesions</th>
<th>No of cases</th>
<th>Balanopreputial (%)</th>
<th>Urethral (%)</th>
<th>Anal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV+</td>
<td>27</td>
<td>19 (70)</td>
<td>10 (37)</td>
<td>8 (30)</td>
</tr>
<tr>
<td>HIV−</td>
<td>38</td>
<td>27 (72)</td>
<td>6 (16)</td>
<td>10 (26)</td>
</tr>
</tbody>
</table>

**Sexual habits:**

- Homosexual: 13/12 (63/33) for HIV+ and HIV−, respectively.
- Heterosexual: 14/26 (93/39) for HIV+ and HIV−, respectively.

**Clinical aspect:**

- Condylomata: 23/32 (94/62) for HIV+ and HIV−, respectively.
- Dysplasia: 2/3 (6/9) for HIV+ and HIV−, respectively.
- Erythroplasias: 5/4 (25/20) for HIV+ and HIV−, respectively.
- Leucoplasia: 7/3 (30/12) for HIV+ and HIV−, respectively.

**Histological aspect:**

- Number of lesions: 37/43 for HIV+ and HIV−, respectively.
- Condyloma: 25/35 (71/28) for HIV+ and HIV−, respectively.
- Grade I neoplasia: 13/6 (88/12) for HIV+ and HIV−, respectively.
- Grade II-III in situ: 8/2 (40/10) for HIV+ and HIV−, respectively.

**Virological findings genotype SBH:**

- HPV 6/11: 23/31 (74/26) for HIV+ and HIV−, respectively.
- HPV 42: 2/3 (67/33) for HIV+ and HIV−, respectively.
- HPV 16: 10/4 (75/25) for HIV+ and HIV−, respectively.
- HPV 18: 1/1 (50/50) for HIV+ and HIV−, respectively.
- HPV 31/33/35/39: 4/4 (100/0) for HIV+ and HIV−, respectively.
- HPV X: 4/4 (100/0) for HIV+ and HIV−, respectively.

HIV+ = HIV infected; HIV− = negative; SBH = Southern blot hybridisation.

*Ano-urethro-preputial lesion in 1 case, ano-preputial lesion in one case.
†Condylomata + grade I intraepithelial neoplasia in nine cases.
‡Several types of HPV: co-infection in the same lesions: HPV 6+X in one case, HPV 6+16 in four cases, HPV 6+18 in one case, HPV 6+31 in one case, HPV 6+16+33+35 in one case; HPV in different lesion from the same patient: HPV 6 and 39, HPV 6 and X, HPV 6+16 and X.

HISTOLOGICAL EXAMINATION

All morphologically different HPV anogenital lesions were biopsied: 37 lesions in 27 HIV infected patients and 43 lesions among 38 HIV negative. Specimens were fixed in Carnoy for histological studies and cultured in Eagle’s medium for virological analysis by means of molecular hybridisation (Southern blot). The biopsied HPV lesions were classified histologically as condylomatous or intraepithelial neoplasia (IN). The degree of intraepithelial neoplasia (grades I to III/in situ carcinoma) was judged on the degree of atypical cellular aspects and their topography within the epithelium as for cervical intraepithelial neoplasia.

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lesions (52% v 21%, p < 0.01) alone or associated with condyloma. Among HIV infected, in six cases (26%) the condyloma acuminata were hyperkeratinised and in four cases (11%) several clinical aspects were observed (exophytic + leucoplastic, exophytic + erthroplastic, leucoplasic + erthroplastic).

Histology confirmed, among HIV infected patients, the intraepithelial neoplasias (IN) were low grade (IN I) in 13 cases (35%), and associated with a condyloma in nine cases (two anal, five preputial, and two urethral lesions). The risk of presenting high grade lesions was increased in HIV infected patients (22% v 5%, OR = 5.65; 95%CI = 1.31–25.3).

The 80 biopsy specimens were analysed virologically (table 1). Southern blot revealed HPV DNA sequences of type 6/11 in 34 cases (42.5%) and potentially oncogenic HPVs were detected in 18 cases (22.5%) with a frequency (67.5%) and potentially oncogenic HPVs were detected in 18 cases (22.5%) with a frequency of 78% HPV 16. Oncogenic HPVs were detected more often in the lesions of HIV infected subjects (35% v 12%, p <0.02). Among HIV infected subjects a co-infection with several HPVs in the same lesion was discovered in seven cases (9%). In three cases (8.5%) we observed several types of HPVs in different lesions from the same patient. HPVs 31, 33, 35, and 39 were detected in patients with CD4 cell counts < 200 × 10^6/l.

Diffuse infection, high grade intranepithelial lesions, oncocogenic HPVs, and several types of HPV DNA were related to the CD4 cell counts, only < 50 × 10^6/l in HIV positive patients (table 2).

**Discussion**

In this study, among HIV infected patients, 33% developed HPV lesions 36 to 48 months after becoming seropositive. Most (78%) of the patients who developed HPV lesions after the diagnosis of HIV infection had CD4 cell counts < 200 × 10^6/l, 57% of whom had counts < 50 × 10^6/l. Since genital HPV infection is sexually transmitted, the presence of these HPV lesions after the diagnosis of HIV infection in patients, most of whom are immunodepressed, points to a latent HPV infection reactivated by the immunodepression, more than to a recent sexual transmission signalling the non-use of condoms.

Clinical screening for HPV lesions in the anogenital sphere must also include both metapenonsis (non-invasive) and anuscopy, regardless of sexual behaviour. However, HIV positive increases the frequency of multiple location of HPV lesions, urethroperpituition in homo/bisexual men and only urethral in heterosexual men.

Among HIV infected patients, the exophytic condylomatous lesions were frequently associated with low grade intraepithelial neoplasia (33%) and oncogenic HPVs (26%), suggesting that the onset of oncogenic HPV associated lesions is facilitated by immunodeficiency. In the same way, the increase of high grade intraepithelial neoplasia (IN II-III/in situ) (22%) and of a higher frequency (15%) of HPV types 31, 33, 35, and 39 among the HIV positive patients suggests the involvement of immunological cofactors in the development of certain lesions of HPV. HIV facilitates either the activation of recently acquired HPVs or the reactivation of latent infection, or both.

Potential oncogenic HPVs associated intraepithelial neoplasia and several types of HPV was statistically more frequent in patients with CD4 cell counts < 50 × 10^6/l. The absence of a significant difference between patients with CD4 cell counts > and < 200 × 10^6/l in terms of clinical, histological, and virological signs of HPV infection does not predispose to a wider diffusion of HPV infections or the type of viral DNA among HIV seropositive patients.

Table 2  Correlation among clinical, histological, and virological findings and immune status in HIV-1 men infected

<table>
<thead>
<tr>
<th>No of cases</th>
<th>CD4 &gt;200 9 (33)</th>
<th>200&gt; CD4 &lt;50 12 (45)</th>
<th>CD4 &lt;50 6 (22)</th>
<th>Grade ratio</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse condylomatosis</td>
<td>9</td>
<td>2 (22)</td>
<td>3 (25)</td>
<td>4 (66)</td>
<td>OR = 2.23 (NS) OR = 6.4 (p&lt;0.05)</td>
</tr>
<tr>
<td>High grade lesions</td>
<td>8</td>
<td>2 (22)</td>
<td>3 (25)</td>
<td>3 (50)</td>
<td>OR = 1.75 (NS) OR = 3.7 (NS)</td>
</tr>
<tr>
<td>Oncogenic HPV</td>
<td>13</td>
<td>4 (44)</td>
<td>5 (41)</td>
<td>4 (66)</td>
<td>OR = 1.25 (NS) OR = 2.7 (NS)</td>
</tr>
<tr>
<td>Several types of HPV</td>
<td>10</td>
<td>2 (22)</td>
<td>4 (35)</td>
<td>4 (66)</td>
<td>OR = 0.8 (NS) OR = 5 (p&lt;0.05)</td>
</tr>
</tbody>
</table>

OR = odd ratio between the patients with CD4 cell counts > and <200×10^6/l.
OR = odd ratio between the patients with CD4 cell counts > and <50×10^6/l.

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