Cervical-vaginal disease in HIV immunosuppressed patients: management and present screening programme

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Summary

The aim of this study was to evaluate the rate of the cervical intraepithelial neoplasia (L-SIL and H-SIL) in HIV-positive patients using cytological, colposcopic and histological examinations. The correlations between these cervical lesions, the role of HPV and the clinical and immunological aspects of HIV infection and inflammatory cervical-vaginal disease were studied. We believe that HPV infection and preneoplastic and/or neoplastic lesions occur more often in immunodepressed HIV-positive patients, and that on the grounds of the high risk of precancerous lesions in this population and the low sensibility of the Pap test, it is advisable to perform a colposcopic examination to discover early lesions that must undergo a specific biopsy.

Key words: Colposcopic examination; Pap test; HIV infection; HPV infection; Cervical-vaginal disease; Immunological state.

Introduction

The preoncogenetic and oncogenetic role of HPV in producing cancer of the lower female genital tract, alone or together with other well-known factors, is common knowledge. According to the WHO in 1999 HIV patients numbered 34 million [1]. In 2004 HIV infection was discovered in 40 million patients [2]; half of these were female. In spite of this increase, there has been a significant improvement in the quality and length of life for HIV patients in at least the Western countries of the world [3]. This is due to the potent retroviral therapy (HAART) together with better treatments for opportunitic infections. Various authors have reported a higher rate of human papillomavirus (HPV) infection and HPV-related preneoplastic lesions and neoplasias in HIV-(human immunodeficiency virus) seropositive women than in HIV-seronegative women [4]. The HIV-HPV relationship is not completely well known.

We report several hypotheses regarding the role of HIV in producing pre- or neoplastic lesions in patients with HPV infections of the lower genital tract [5, 6]. The hypothetical mechanisms are:

1) Alteration of the synthesis of cytokines (IL4) due to a Th1-Th2 shift caused by HIV infection with the breakdown of cellular-mediated immunity (Figure 1) [7].

2) Reduction of Langheran's cells and macrophages, consequently decreased synthesis and modulation of natural killer (NK) and local cellular activity, mediates immunodeficiency (Figure 1).

3) Local invasion of CD4/CD8 and local functional deficit.

4) Enhancer effect of the HIV TAT gene on open reading frame (ORF) E6-E7 of HPV with a high oncogenic power (HPV 16-18).

This effect produces the inactivation of p53 and alteration of the protoncogene-oncogene suppressor relationship. Consequently there is activation of the first and suppression of the second.

General and local immunodeficiency together with the HIV/HPV relationship could influence the natural course of HIV infection and could produce an oncogenic virus with a great number of viral cells and consequently a smaller viral positivity on cytological examination [8]. The aim of this study was to evaluate the rate of cervical intraepithelial neoplasia (L-SIL and H-SIL) in HIV-positive patients using cytological, colposcopic and histological examinations. The correlations between cervical lesions and the clinical and immunological aspects of HIV infection and inflammatory cervical vaginal disease were studied. In order to do an accurate follow-up, HPV DNA testing by polymerase chain reaction (PCR) was done in HPV-positive women to evaluate the oncological risk. Another study will explain the results of the last examination.

Materials and Methods

The study was carried out between December 2001 and January 2004 at in Colposcopic Center for the evaluation of cervical vaginal disease of the Gynaecological and Obstetrics Department together with the Infections Disease Department and the Center of Anatomopathology and Histology of S. Salvatore Hospital, L'Aquila.

Fifty-eight HPV-positive women with HIV infection diagnosed using the Elisa test and confirmed by Western blot analysis were enrolled in the study. HIV-positive women underwent an accurate anamnesis and gynaecological, vulvoscopic and colposcopic examinations together with a pap smear and a specific colposcopic biopsy in cases of suspicious lesions. The aim of the anamnesis was to determine the stage of the disease according to the Centers for Disease Control (CDC) classification (1993) [8] form of the infection, association with STD

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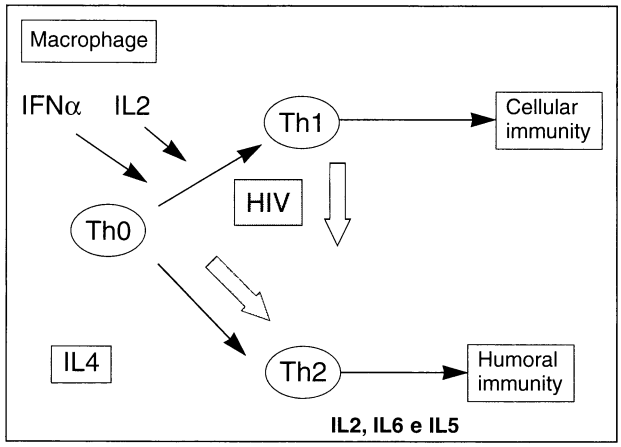

Figure 1. — Immune antiviral reaction (hypothetical role of HIV).

(sexual trasmitted disease), sexual use, smoking, use of drugs (especially IV), use of contraceptives and the kind of antiviral therapy.

HIV-positive women underwent a pap smear in a specific region of the cervix (GSC) always using a cytobrush. The cytological specimens were analysed by a histopathologist who was blinded to the serological stage of the HIV-positive women who were classified according to the Bethesda System (2002) [9]. The colposcopic reports (Zeiss plus colposcope) were classified according to the International Classification (IFCPC) [10].

All patients underwent HPV DNA testing by HYBRID-CAPTURE II (VIKA PAP© Digene Diagnostics) and were stratified into two groups: high cancerous risk according to the various viral types and also low risk.

In our study the value of CD4/CD8 T-lymphocytes and viral presence were considered to evaluate the degree of immunodeficiency. HIV-infected women who did not undergo therapy were observed during the period December 2003 to December 2004 and enrolled in a specific follow-up programme.

Results

Women who were participating in the study, subject to written consent, averaged 32 years old (range 21 to 45 years). The patients were stratified into two groups of 29 women (50%). The first group included AIDS patients with A_3, B_3, C_1, C_2 and C_3 stages and the second one (no AIDS patients) included HIV-infected patients with an initial or intermediate stage of HIV infection (A_1, A_2, B_1 and B_2 phases). Table 1 show the epidemiological data with regard to specific risk factors in cervical intraepithelial precancerous lesions. Table 2 shows the

Table 1. — *Epidemiology: 58 patients.*

Age	32 (21-54 aa)
First menstruation	12.2 ± 1.8
No. of partners	6 ± 6.2
Beginning sexual activity	13.4 ± 2.6
Drug dependence	24 patients
Blood transfusion	12 patients
Tabagism	44 patients < 10 (6 patients - 13.6%) 10-20 (22 patients - 50%) > 20 (16 patients 36.4%)
Contraception	None of 38 (65.5%), 14 E.P. (24.1%), 4 C (6.9%), 2 IUD (3.5%)

E.P. = estrogen/progesterone; C = condoms.

Table 2. — *Classification of HIV-infected population (CDC, 1993).*

CD4 count	A Asymptomatic HIV infection LAS	B Symptomatic different from A and B	C AIDS
1) > 500/mm³	A_1	B_1	C_1
2) 200-499/mm³	A_2	B_2	C_2
3) < 200/mm³	A_3	B_3	C_3

subdivision of the population according to the CDC classification. In our study heterosexual transmission was the most important modality of infection, 30 of the 58 patients (51%), with the second form of contagion being IV drug use in 18 cases (31%). In seven cases (12%) infection was produced by both previous modalities of infection. Blood haemotransfusion was responsible for infection in 5% of the cases (3 cases). Among the 58 patients, 38 (65%) reported no use of contraception, 14 (24%) use of oral contraceptives and only four (6.8%) the use of condoms (Figure 2).

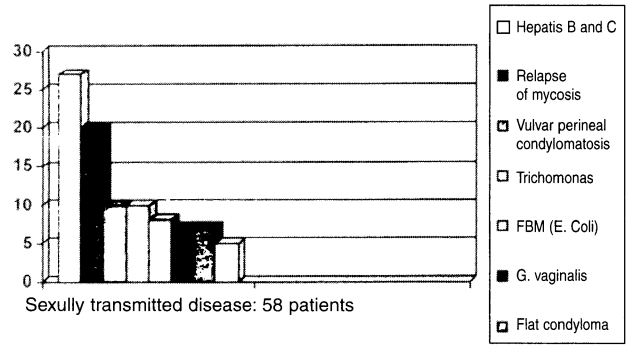

Figure 2. — Sexually transmitted disease (STD): 58 HIV patients.

Only 52 patients (89%) reported sexually trasmitted diseases. The most frequent pathologies were Hepatitis B and C, various stages of HPV condylomatosis infections, Trichomonas vaginalis infections, Gardnerella vaginalis and relapse of mycosis. Host infection was more frequent than Trichomonas and Gardnerella because of a modification of the vaginal enviroment, with regard to local cellular mediate immunity and to the flora in HIV-positive patients. Results of the specific colposcopic biopsy (BMC) are shown in Table 3. Forty-six patients underwent BMC because 12 women (20.6%) were completely negative except for one case of $ANTZ_{G1}$ diagnosed under colposcopic vision (12x). Among 19 cases with negative pap test results, the histology revealed ten negative conditions, three cases of VEC (viral cytopathic effect) and six of L-SIL. In seven cases of ASCUS (12%) pap test results, the histology showed one negative case, two cases of VEC (koilocytosis) and one H-

Table 3. — *Histological results: 58 HIV-positive patients.*

Histology	Cases	%
Negative	12	21
VEC (viral cytopathic effect)	6	10
L-SIL	19	33
H-SIL	16	27
Microinvasive neoplasia IA_1	3	5
L-SIL-$VAIN_2$	1	2
H-SIL-$VAIN_3$	1	2
Total	58	100

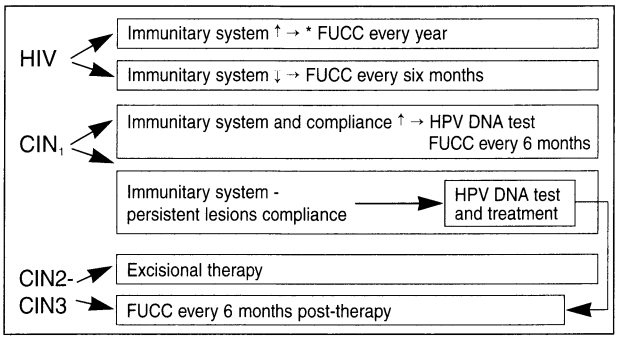

Figure 3. — HIV-positive patient management - diagnostic and therapeutic itinerary.

SIL. Among 11 L-SIL patients (18.9%) diagnosed using the pap test, histology reported one negative, one koilocytosis, nine LSIL (considering LSIL together with $VAIN_2$).

Among 19 HSIL patients (32.7%) diagnosed using the pap test, histology showed one koilocitosis, one LSIL, 15 HSIL (considering the case in association with $VAIN_3$), and three cases of cancer. The correlation between histology and colposcopy shows almost total agreement between histology and colposcopy (Table 5). In detail, colposcopy revealed 12 negative reports and 46 positives ones (79%); among the positive cases 23 were light alterations and 23 were serious illness. On the grounds of these data the correlation between histology and colposcopy seems to be very near to 100%. Table 6 shows the correlation between preneoplastic lesions and the immunological status of the patients (CD4 mm^3 count < 200, between 200-499, > 500). The data show a prevalence of precancerous lesions of low and high grade (LSIL, HSIL, cervical microinvasive cancer, $VAIN_2$ - $VAIN_3$) in HIV-positive patients with a CD4 count < 500/μl and in detail in 19 cases with CD4 count < 200/μl, and in 12 cases with the same count between 200-499/μl. In the group of patients with a CD4 count > 500/μl only seven LSIL and two HSIL cases were diagnosed. Therefore, excluding the negative cases and the three microinvasive cancers ($1A_1$ according to FIGO) that underwent excisional therapy, all the other cases underwent HPV typing. The results of this typing can be seen in Table 7.

Table 4. — *Histology vs pap test.*

Histology	Cytology Negative	Cytology ASCUS	Cytology L-SIL	Cytology H-SIL
Negative	10	1	1	
VEC	3	2	1	
L-SIL	6	4	8+1*	1
H-SIL		1	1	14+1°
Microinvasive neoplasia IA_1				3
Total (100%)	19 (32.7)	8 (13.9%)	11+1 (20.7%)	18+1 (32.7%)

Table 5. — *Correlation between histology and colposcopy.*

Histology	Cytology NTZ	Cytology ANTZ G_1	Cytology ANTZ G_2
Negative	11	1	–
HPV-VCE	1	5	–
L-SIL	–	15+2*	4
H-SIL	–	3	13
Microinvasive neoplasia	–	–	3
Total (100%)	12 (20.6%)	24+2 (45%)	20 (34.4%)

Table 6. — *Correlation between histology and immunological state: 58 HIV-positive patients*

Histological reports	Class based on CD4 count < 200/μl	Class on the ground of CD4 account 200-499/μl	Class on the ground of CD4 account > 500/μl
Negative	–	4	8
HPV	–	2	4
L-SIL	4	8	7
H-SIL	10	4	2
Microinvasive neoplasia	3	–	–
L-SIL-$VAIN_2$	1	–	–
H-SIL-$VAIN_3$	1	–	–
Total	19 (32.7%)	18 (31%)	21 (36.3%)

Table 7. — *Colpocytology and viral typing (Hybrid Capture II): 43 HIV-positive patients.*

Viral typing 6 cases (10%)		Viral typing 19 cases (32.7%)		Viral typing 16 cases (27%)		Viral typing 1 case (1.7%)		Viral typing 1 case (1.7%)	
HPV/coilocytosis		L-SIL		H-SIL		L-SIL-$VAIN_2$		L-SIL-$VAIN_3$	
H-risk	L-risk	H-risk	L-risk	H-risk	L-risk	H-risk	L-risk	H-risk	L-risk
2 (33%)	4 (66%)	15 (79%)	4 (21%)	14 (87%)	2 (13%)	1 (100%)	–	1 (100%)	–

H = high; L = low.

Discussion and Conclusions

According to our data we can say that:

– a clear correlation was not found between the age of patients and presence and seriousness of cervical lesions which can be discovered in young women with HIV;

– the high incidence of STD (Candida, Trichomonas, Gardnerella, Clamydia trachomatis) could be the cause of the high percentage of negative pap tests (32.7% in our study);

– on these grounds it could be advisable to do a pap test only after resolution (using specific therapy) of cervicovaginal inflammatory disease.

In accordance with other authors [9, 10] we believe that HPV infection with preneoplastic and/or neoplastic lesions occurs more often in immunodepressed HIV-positive patients [12].

This could be due to the co-infection of high-risk HPV types or/and to quick progression (slow usually) of dysplastic disease in HIV-positive patients in comparison with HIV patients with an intact immune system. A statistically significant difference between the three groups was found:

– there was a high prevalence of lesions, mostly severe, in patients with a low count of CD4 (200-499) and for the most part if the CD4 count was < 200 mm^3;

– the Atlanta guidelines [11, 12] for precocious diagnoses of cervical cancer in HIV-positive patients reported that the pap test should be the first examination and that colposcopy together with a specific biopsy should be made only if there is positive cytology at least HSIL.

We, on the contrary, believe that on the grounds of the high-risk of precancerous lesions in this population and the low sensibility of the pap test, it is advisable to perform a colposcopic examination (Figure 3). Consequently, the number of pap tests could be reduced and it may be possible to detect early lesions that need to be submitted to a specific biospy.

Therefore complete control of cervical conditions could be obtained as well as and the most appropriate therapeutical management (HPV DNA test – conservative therapy – excissional surgical therapy).

In screening and evaluation of the cervical "status", we believe that the management of HIV-positive patients should not be redtricted. Many factors such us the clinical condition of the

patient, immunological defects, compliance of the patients, the high frequency of relapses post-therapy and the effect of the antiretroviral therapy should be considered. A multidisciplinary approach (physicians of contagious disease, anatomopathologists and oncological gynaecologists) is very important.

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