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Review

Intra-epithelial and Invasive Cervical Neoplasia During HIV Infection

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Patients affected by human immunodeficiency virus (HIV) infection present an elevated risk of developing cancer. In the last 10 years, the relationship between human papilloma virus (HPV) infection and female cervical intra-epithelial neoplasia (CIN) has been established. Several studies have described an increased prevalence of both cervical HPV infection and CIN among HIV-positive women compared to HIV-negative ones. A high recurrence rate of CIN after standard treatment has been noted in HIV-infected women and the severity of these lesions seems to be inversely correlated to immune function. Taking into account these data, the Centers for Disease Control (CDC) since 1993 have included invasive cervical carcinoma among the AIDS-defining conditions. Once cervical cancer develops in HIV-positive women, the disease may be aggressive and less responsive to treatment. A primary means by which HIV infection may influence the pathogenesis of HPV-associated cervical pathology is by molecular interaction between HIV and HPV genes. Although these have not been well defined, an upregulation of HPV *E6* and *E7* genes expression by HIV proteins (such as tat) has been postulated by some authors. Cervical cytology appears to be adequate as a screening tool for the cervical intra-epithelial neoplasia in HIV-positive women, but the high recurrence rate and multifocality of this disease reinforces the need for careful evaluation and follow-up of the entire anogenital tract in these women. Probably in the next few years, cervical tumours will represent one of the most frequent complications of HIV infection, a part of progression through AIDS. This points to a need for greater interdisciplinary co-operation for a best disease definition and for the development of effective prevention measures. Copyright © 1996 Elsevier Science Ltd

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INTRODUCTION

FIFTEEN YEARS have passed since the first notification of an Acquired Immunodeficiency Syndrome (AIDS) case, and this illness has spread worldwide, with a larger increase in the number of cases expected in the next few years. The World Health Organization (WHO) estimates that approximately 13 million people worldwide have already been infected with the Human Immunodeficiency Virus (HIV) since the beginning of the epidemic; approximately 3 million of these have already developed AIDS, a syndrome that has become an important cause of death in many urban areas, especially for people between the age 20 and 40 years [1].

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In Italy, more than 31 076 cases of AIDS have been notified to the AIDS Operative center (COA) of the Istituto Superiore di Sanità (ISS) since June 1985, and the number of cases registered each year is constantly increasing. Recent surveillance trends indicate that AIDS morbidity and mortality are increasing among women in countries where heterosexual transmission predominates. In Italy, in the last few years, the percentage of women infected with HIV has progressively increased, from 18.5% in 1989 to 22.5% in 1994. The increase in the absolute number of cases highlights the importance of these data—from 1989 to 1994, there was an increase of over 100%, from 453 to 952 [2].

According to the Centers of Disease Control (CDC) in Atlanta, Georgia, U.S.A., in a HIV-infected person, AIDS is defined by a series of conditions: opportunistic infections

(OI), central nervous system (CNS) pathologies, and tumours such as Kaposi's sarcoma (KS), primitive CNS non-Hodkgin's lymphomas (NHL) and B-cell lymphomas with unfavourable histology [3].

The increasing incidence of cervical intra-epithelial neoplasms (CIN) of the lower genital tract in HIV-infected women [4–12] has recently induced the CDC to include invasive cervical carcinoma among the AIDS defining conditions, even in the absence of a significant statistical increase. Two factors have determined the inclusion of the invasive instead of the intra-epithelial cancer: (1) the need for overcoming difficulties in diagnosing dysplasias when multiple infections of the genital tract are present, as usually occurs in HIV-infected women; (2) the need for all HIV-infected women to undergo a gynaecological screening [13].

The modification of the immune system which occurs during HIV infection seems to play an important role in the pathogenesis of HIV-associated tumours [14–18]. In immunodepressed subjects, oncogenic viruses, which often coexist with HIV in the same host (i.e. EBV (Epstein–Barr virus), HPV (Human Papilloma virus), HSV (Herpes Simplex virus), HBV (Hepatitis B virus) etc.) can infect specific target cells and cause polyclonal proliferation. Various factors, including molecular and/or cytogenetic events, could modify the infected cell's DNA resulting in growth advantages. In this setting, oncogenic activation, growth factor production, and increased resistance to cytotoxic actions of T-cells, could lead to the development of transformed clones [19].

A common feature of most HIV-associated tumours is a typical clinical presentation. These neoplasms generally have an aggressive evolution, with a poor response to conventional therapies (successfully employed to treat the same tumours rising in immunocompetent hosts) and an unfavourable prognosis [20, 21]. In fact, in such tumours, the conventional prognostic factors, such as histology and disease stage, are replaced by HIV-dependent criteria such as immune deficiency degree and HIV infection stage, which influence the course and the natural history of the disease. The main problems of the HIV-associated tumours are represented by a short median survival, by a high incidence of opportunistic infections during chemotherapy and a reduced haematological tolerance to conventional doses of chemotherapy.

Natural history of the preneoplastic and neoplastic lesions of the uterine cervix in the general population

In the general population, the role of oncogenic sexually transmitted viruses in the pathogenesis of intra-epithelial and invasive cervical neoplasms is still being defined. Among them, HPV is considered the aetiological agent of condylomata and of most dysplastic and neoplastic lesions of the lower female genital tract. One study suggests that women with HPV infections are at least ten times more likely to develop cervical cancer than those without the infection [81]. Other studies have focused on the role of specific oncogenic types. HPV types 6 and 11, considered low-risk or non-oncogenic HPV, are closely related to the development of condylomatous and low-grade, squamous intra-epithelial lesions (mild dysplasias or CIN1; SIL1 according to the Bethesda System of Classification) [25]. HPV types 16 and 18, considered high-risk or oncogenic HPV, are linked to high-grade intra-epithelial lesions (moderate dysplasias or CIN2 and severe dysplasias or CIN3/carcinoma *in situ*; SIL2) as well as to SIL1 and invasive carcinoma [26, 27]. These lesions are frequently multifocal because the entire squamous epithelium of the lower female genital tract can easily be infected by HPV ('field effect') [82].

Known risk factors for the development of cervical dysplasias and carcinomas are sexual behaviour, including early sexual intercourse, a large number of sexual partners [23, 30, 31] and smoking. These factors favour HPV infection by modifying the epithelium through direct mutagenic action or a depression of the local cell-mediated immunity affecting the Langerhans' cell number [32].

Since there is a large discrepancy between cervical cancer (1%) and HPV infection prevalence (10–20%), it is considered that other cofactors interfere with the development and progression of viral-induced lesions; i.e. sociodemographic factors, including age, ethnicity, low educational attainment and poverty.

Modification of the immune system plays an important role in this disease [33–35]. In fact, it has been reported that there is a higher frequency and biological aggressiveness of lesions during pregnancy, in patients treated with immunosuppressive therapy for organ transplants, and in women treated with antiblastic therapy [36–39]. Recent studies in the literature show that an HIV-infected woman is 4.9 times more likely to develop cervical cancer than a woman without HIV and that the progression of cervical cancer is especially rapid in women with AIDS [40–44, 71, 82, 83]. However, currently, there are no data that indicate an increasing incidence of cervical invasive carcinomas among HIV-positive women. The relationship between HIV-HPV genital dysplasia is complex and not well known. In particular, which aspect of pathogenesis has the most important role in HPV-associated cervical neoplasms occurring in HIV-infected women still has to be defined, i.e. HIV-induced immune depression or the known HPV risk factors. The sexual behaviour and smoking risk factors associated with HPV are also frequently found in women with a high risk for HIV infection.

HPV-HIV CO-INFECTION

Epidemiology

According to recent epidemiological studies, there are currently around 3 million HIV-infected women worldwide: in the U.S.A. there are 80 000, a number that is rising every year by 30% [45].

Several studies have shown an increasing incidence of cytological and/or histological HPV-related abnormalities in the lower genital tract of HIV-infected women compared to HIV-negative women [44, 46–49, 51, 52].

HPV-HIV co-infection is not an unexpected event since both viruses are transmitted by sexual intercourse. Currently, it is unclear if the high incidence of HPV-related genital lesions in HIV-positive women is a consequence of the HPV-infection increasing frequency and repetition.

In HIV-infected women, the prevalence of HPV infection varies according to the presence of symptomatic HIV infection. Three studies, in which different techniques were used to diagnose HPV infection, demonstrated that its prevalence in North America was similar in HIV-negative women and

in those with asymptomatic HIV infection (20 versus 27%) [49, 53, 54], while the prevalence in women with symptomatic HIV infection was 79% [49, 53–56].

In the study conducted by Wright and associates, HIV-infected women with a CD4 count < 500/mm^3 had a higher prevalence of HPV infection (59%) compared to those with a CD4 count > 500/mm^3 (40%) ($P = 0.008$), demonstrating that the prevalence in HIV-infected women seems to be inversely correlated to the degree of immunodeficiency [57].

Furthermore, several studies have shown that, in HIV-infected women, HPV lesions can progress more rapidly and can regress more slowly than in HIV-negative women [58–61]. This is thought to be related to the HIV-associated immunodeficiency [57, 59].

The role of specific HPV types in the development of anogenital tumours in HIV-infected women has not been evaluated extensively in HIV-negative women. It has been found that HPV types 16, 18, 31, 33, 35, 45 and 51 as well as other less frequent types (i.e. HPV types 39, 40, 52 and 56) are associated with high-grade CIN and also with invasive cervical carcinoma [62–64]. One study, carried out in New York City on 192 HIV-infected women and 187 HIV-negative controls, using techniques such as PCR, found that the total HPV infection prevalence was 52% and 22%, respectively, while the HPV type 18 prevalence was 29% and 7%, respectively ($P < 0.001$) [57].

Molecular interactions

In recent studies, data have been reported on the capacity of the HIV gene (*tat*) to modulate heterologous promotor gene expression, with consequent activation of co-infecting pathogenic agents (i.e. viruses). The biological value of a possible interaction between HIV and HPV is founded in observations that HIV does not only infect haematopoietic system cells expressing the CD4 receptor, but also cells that could be infected by HPV, such as Langerhans' cells, M cells, rectal and genital mucosa dendritic cells, and colon epithelial cells. *In vitro* studies on the molecular interaction between HIV and HPV have been reported by Vernon and associates [65] and Tornesello and associates [66]. These authors demonstrated that tat protein is able to induce the expression of *E6* and *E7* early transforming HPV genes, through LCR-regulating region stimulation. This finding suggests that tat protein has an additive action in the HPV-induced neoplastic progression [65–67]

UTERINE CERVIX NEOPLASMS DURING HIV INFECTION

Intra-epithelial neoplasms

Uterine cervical intra-epithelial neoplasms associated with HPV infection are more frequent and severe in HIV-infected women than in HIV-negative women [43, 49, 50, 53, 68, 70]. In a meta-analysis of five epidemiological studies, published between 1986 and 1990, Mandelblatt and associates reported that the risk of developing a CIN was five times higher in HIV-positive compared with HIV-negative women with the same risk factors for CIN [71]. As reported above, HIV-induced immunodepression seems to have an important role in the pathogenesis of these neoplasms.

According to several studies in the literature, there is a close correlation between risk and severity of cervical dysplasia on one side and HIV-induced immunodepression on the other. In a study conducted on 135 HIV-positive women in New York and Chicago, CIN prevalence was 45% for women with a CD4 count < 400 cell/mm^3, and 26% for women with CD4 > 400/mm^3. No other risk factor for CIN development (such as age and HIV transmission modality) were statistically significant for cervical lesion prevalence [48].

In a study by Maiman, patients with CIN had a CD4 count significantly lower than women without dysplasia (221/mm^3 versus 408/mm^3; $P < 0.05$) [70]. Similarly, Johnson found a higher incidence of CIN in women with a CD4 count < 200/mm^3 compared to those with CD4 count > 200/mm^3. This finding was closely associated with a higher prevalence of HPV infection, particularly type 18, in women with higher immunodepression [51].

In the study of Conti and associates, which considered only HIV-positive subjects, CIN1 and CIN2–3 frequency increased with the stage of HIV infection and was higher in women with lower CD4 values [47]. For example, compared with women with CD4 values > 500, the odds ratio (OR) of CIN1 and CIN2–3 was 3.6 and 5.4, respectively, for those with CD4 values < 500 [47].

A correlation between immunodepression and severity of cervical dysplasia has been confirmed by other authors. Spinillo and associates recently documented a significantly lower CD4 count among patients with CIN3 when compared with those with CIN1 and -2 (CD4 count = 257/mm^3 versus 402–345/mm^3, respectively, $P = 0.04$) [72]. In this study, Langerhans' cell count in CIN lesions of HIV-seropositive women was associated both with the severity of CIN and with the number of circulating T-cells, and was reduced independently by co-existing HPV infection, suggesting a direct HIV action on cervical immunity [72]. In contrast, in a single institution's study conducted on 51 HIV-positive patients at fertile age, Sopracordevole and associates [84] did not find any correlation between SIL presence, its severity, and absolute CD4 levels as published by Tweddel and colleagues in 1994 [73]. In the study by Sopracordevole and colleagues, risk factors for HPV-related genital lesions were well represented in the examined patients, but the authors found the same SIL prevalence in HIV-positive and in HIV-negative women, suggesting that the expression of the HPV-related genital lesions is a complex process in which the classic risk factors for genital SIL play an important role, with the role of HIV to be defined further. Based on these results, it can be inferred that, if HIV does not have a determinant role in the expression of HPV, a decrease in the prevalence of cervical SIL in HIV-positive women should be seen, according to the spread of HIV infection to women with lower risk factors for HPV-related genital lesions.

Several studies have shown that cytology alone seems to be less reliable for diagnosis of a CIN in HIV-positive women than in the general population. False negative results occurred in a recent study conducted by Koutsky and associates on 241 HIV-positive women with a normal cytological examination, who underwent gynaecological screening every 4 months by colposcopy and HPV research performed with molecular techniques, such as PCR. In this cohort, after 24 months follow-up, 28% of HIV-positive women developed CIN compared to 3% of HIV-negative

women [74]. In the Maiman series, a CIN diagnosis occurred in 41% of cases with normal Pap smears, with colposcopy and biopsy [70]. False negative Pap test results have been documented most of all during vaginal infections by *Neisseria Gonorrhoeae, Chlamidia, Herpes Simplex, Candida* and *Trichomonas vaginalis*, all organisms frequently seen in HIV-infected persons. In comparing colposcopy to Pap smear, it has been suggested that this examination should be performed routinely for gynaecological screening of HIV-infected women [75].

HIV-related cervical lesions are typically wide and multifocal when they develop in the lower genital tract [40, 77]. There is not much information on the natural history of these lesions in the literature, and what is known is controversial. In the Maiman series of 17 HIV-positive and 11 HIV-negative women, all affected by CIN, the recurrence rates were significantly higher among HIV-positive women compared to HIV-negative women after standard treatment (39% versus 9%, respectively; $P < 0.01$). A second major finding in this study was the relationship between immune status and recurrent CIN. HIV-positive patients with CD4 counts < 500/mm^3 were at extremely high risk of developing recurrent disease (recurrence rate = 46%), whereas women with counts > 500/mm^3 had recurrence rates of only 18%, about twice that of HIV-negative patients [78].

These results have been confirmed in a recent study by Fruchter and associates [85]: among 127 HIV-infected CIN patients, 62% developed recurrent CIN compared with 18% of 193 HIV-infected CIN patients. Recurrent rates reached 87% in 41 HIV-infected women with CD4 counts less than 200 cells/mm^3, and progression to higher-grade neoplasia, including one invasive cancer, occurred by 36 months in 25% of HIV-infected and in 2% of HIV-negative women. The recurrence rate for HIV-negative patients was 18%.

In the Spinillo series, after a median follow-up of 12 months, the recurrence rate was 14% in a group of women treated with conisation (10 cases) and diathermic loop (4 cases), a value significantly higher when compared to the general population [52]. Klein and colleagues reported only three cases of persistent disease in a group of 28 HIV-positive women with CIN compared with 11 HIV-negative women with the same disease (median follow-up 12 months; range 4–32) [79].

In a recent study by Adachi and colleagues, the HIV-related CIN (treated with standard therapy = conisation) recurrence rates were not different from that of the HIV-negative population. These authors suggest that treatment inadequacy can sometimes be responsible for an apparent higher biological aggressiveness of the disease in HIV-positive women. Also characteristic of this series was a high rate of disease persistance and multifocality, both conditions seen with increased HPV infection in these women [80].

Even if it is not possible to exclude the role of inadequate treatment, some discrepancies seen in different series, as Maiman suggests, could be subordinate to the non-correlation between recurrence risk and HIV-related immunodepression. It is noteworthy that cryotherapy or diathermic loop treatment are associated with a greater failure rate, as has already been documented in HIV-negative patients with iatrogenic immunodepression [76, 77, 82]. The impact of antiretroviral therapy on the development and progression of intra-epithelial cervical neoplasia (CIN) is still to be defined. The only report in the literature comes from Maiman and associates [70], who found no notable difference in the severity of cervical dysplasia between women treated with (16/32) and without AZT. According to the authors these data are not conclusive because the two patient groups (treated and not treated) were not homogeneous for immunodepression status.

In conclusion, HPV infection-associated CIN is significantly increased in HIV-infected women. There is a high correlation between CIN and severity of dysplasia on one side and HIV-induced immunodepression on the other. Other cofactors besides immunodepression also play important roles in disease pathogenesis, including a possibly molecular interaction between HPV and HIV. The natural history of the disease is controversial and the optimal treatment still to be defined. Close monitoring and repeated ablative and excisional therapies may prevent the development of invasive cancer.

Invasive carcinoma

Uterine cervix invasive carcinoma has been recently included among AIDS-defining conditions, even though it has not significantly increased in the HIV-positive female population, contrary to what happens for other tumours such as KS and NHL. However, as previously mentioned, in this way, CDC in Atlanta highlights the need for careful surveillance because of a significant increase in preneoplastic lesions and survival improvement among HIV-infected people in the last decade. Hence, the incidence of invasive cervical cancer is expected to increase over time due to the fact that HIV-infected women will survive long enough to exceed the latency time of these tumours.

The natural history of HIV-related cervical cancer is currently unknown. Data reported in the literature are poor and all confirm that, as in other AIDS-related malignant lesions, patients with invasive cervical carcinoma have a more advanced disease stage and, controlling for stage, a poorer prognosis than HIV-negative patients. Most works reported in the literature are case reports.

In an American series by Maiman, 16 of 84 (19%) patients with invasive cervical carcinoma were HIV-seropositive, of which 14 (85%) were asymptomatic for HIV infection according to current CDC definitions. The median CD4 count (360/mm^3) was not particularly compromised. Almost 70% (11/16) of HIV-seropositive patients were stage III–IV compared with 28%(19/68) in the seronegative group ($P = 0.01$). After standard treatment (surgery and/or radiotherapy; radiotherapy and/or chemotherapy) no evaluable HIV-seropositive patients with clinically advanced disease were recurrence-free. This result was significantly different from the uninfected group with advanced disease, in which 17 out of 35 (49%) patients had recurrence ($P < 0.01$). Disease-free survival (DFS) and overall survival (OS) in both groups were, respectively, 15% and 5% versus 50% and 30% ($P = 0.01$) [78]. In a smaller Italian series, only 1/6 patients (17%) was AIDS affected at the time of cervical cancer diagnosis. The median CD4 count was not particularly compromised (317/mm^3, range 130–486). Advanced disease was present at the time of pathological staging in all 6 patients. After radiotherapy alone (4 cases) or surgery followed by chemotherapy (2 cases), only 2

patients were alive and disease-free, after a median follow-up of 24 months [50]. Multifocality of cancer lesions in the lower genital tract, aberrant metastatic spread (psoas muscles, clitoris and meningeal involvement) and a poor response to conventional treatment represent the main features mentioned in the various case reports.

The lack of published reports does not allow a detailed definition of the natural history and prognostic factors for cervical cancer in HIV-infected women. With these reservations, this carcinoma seems to arise more frequently in the early phase of HIV-induced immunodepression compared with other HIV-related cancers such as NHL. High prevalence of advanced disease state and the unfavourable prognosis after conventional treatment suggest the involvement of other cofactors in the pathogenesis and in the natural history of the disease. As reported by recent epidemiological studies, HIV infection is increasing among the female population, and probably in the new few years cervical tumours will represent one of the more frequent complications of this infection, apart from progression through AIDS. This points to a need for a greater interdisciplinary co-operation to properly define the disease and to develop effective preventative measures. Currently, this may only be possible within co-operative multicentric groups, such as the GICAT.

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