International Journal of Clinical and Diagnostic Pathology

ISSN (P): 2617-7226
ISSN (E): 2617-7234
www.patholjournal.com
2021; 4(3): 01-06
Received: 01-05-2021
Accepted: 03-06-2021

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Study of cervical cytological changes in HIV patients

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DOI: https://doi.org/10.33545/pathol.2021.v4.i3a.379

Abstract
Patients with HIV have an increased incidence of abnormal cervical cytological changes. This case-control study (30 cases, 30 controls) was aimed at demonstrating these findings. Both symptomatic and asymptomatic pre-menopausal women of 20-50 years were included in the study. Conventional Pap smears were taken and examined by cytopathologists. HIV cases had more incidence of abnormal cervical cytology (13 cases, 43.33%) than their sero-negative counterparts (5 cases, 16.67%).Out of the 13 cases, 2(6.66%) had LSIL and 1(3.33%) was with ASC-US, specific infections with coccobacilli, T. vaginalis and Candida was found in a total of 5 samples (16.67%) against only 1 t. vaginalis infection (3.33%) in the control group. Reparative changes (squamous metaplasia) was seen in 5 cases (16.67%) of the HIV positive group and in 2 cases (6.66%) in the control group. There was no case of malignancy in the HIV positive group, in contrast to the HIV negative control group which presented a single case of malignancy and another case of HSIL. The study showed that HIV infection was associated with an increased incidence of opportunistic infections along with dysplasias of the cervix. The cases with Dysplasia should be followed up to screen for malignant transformation.

Keywords: HIV, cervical cytology, pap smears

Introduction

HIV (human immunodeficiency virus) is one of the most dreaded infections today. First recognized in 1980s, its spread throughout the world has been alarming - 2.1 million Indians currently living with HIV [1].

India's first HIV case was detected in sex workers in Chennai, in 1986 [2]. The number has risen steadily - quick rate of spread coupled with vast numbers affected, has made research in this field important. Between 2010 and 2017, new infections declined by 27%. AIDS-related deaths fell by 56% [3]. Adult HIV prevalence in India has undergone a steady decline from 0.38% in 2001-03 to 0.22% in 2017 [4]. NACO data states India having 87.58 thousand new HIV cases in 2017.

HIV weakens the immune system, increasing infection susceptibility. Cervical intraepithelial lesions have a more aggressive course in HIV-seropositive than HIV-seronegative women [5]. HIV+ve women have a higher risk of Human Papilloma Virus (HPV) infections, which can cause cervical cell changes (Dysplasia or neoplasia) leading to cancer [6]. This can be detected by Pap smear cytology screening - an effective and reliable technique which has reduced the number of cervical cancer deaths by early detection of the pre-cancerous lesions.

Various studies have shown that HIV positive women, especially with CD4 counts < 200 have more infections from high risk HPV [7. 8, 9, 10]. Studies have also reported that Highly Active Anti-Retroviral therapy (HAART) seems to be associated with the regression of Cervical Intraepithelial Neoplasia (CIN) [9, 11]. In India, HPV testing has reduced the number of deaths from invasive cervical carcinoma [12].

Study findings have suggested that HIV-induced immunosuppression exacerbates HPV-mediated cervical cytological abnormalities [13] and risk of HPV infection dramatically increases with declining CD4 count [14]. Michelle *et al.* [15] reiterated the necessity for careful evaluation and follow-up of HIV-infected women given the higher frequency of infections.

A study concluded that Anti-retroviral therapy (ART) use bears no association with HPV incidence [16]; whereas another study found ART reduced HPV 16 and 18 incidences by 72% [17]. One study comparing effective ART (defined as reducing HIV VL by >90% or to undetectable), to no treatment found that effective ART decreased incidence of any HPV by 36% but the impact on HR HPV incidence was statistically insignificant [18].

Aim

1) To study the cervical cytological changes in HIV affected individuals.
2) To study the differences between HIV infected and non-infected individuals with respect to cervical changes.

Material and Methods

The study was a hospital-based study on patients who routinely attended the Gynecology Clinic. Both symptomatic and asymptomatic HIV patients were included. Informed consent was taken after explaining the full procedure and Pap smears were obtained.

This was a case-control study, with 30 sero-positive cases and 30 controls. The objective was to check the incidence of cervical cytologic abnormalities between HIV-positive and HIV-negative patients. Pre-menopausal women of 20-50 years were included.

Conventional Pap smears were taken and examined from the vagina, cervix (Squamo-columnar junction) and ulcerated skin lesions (if any) by Ayer's spatula after exposing the cervix with a Simms or Cusco's speculum. The material obtained was smeared on glass slides and fixed using 95% ethanol. On examination, slides which were normal or showed inflammatory changes were reported as class-I in Bethesda system of classification. Slides showing some abnormal changes in cellular pattern were scrutinized and further classified.

According to 2001 Bethesda System, the Pap smears can be classified as

1. Negative for intraepithelial lesion or malignancy (NILM)
2. Other
3. Epithelial cell abnormalities

In NILM, cells manifest reactive morphologic changes in response to different traumatic insults - infection, inflammation and radiation. Reparative processes, radiation, atrophy and intra-uterine contraceptive devices are examples of entities that induce cellular changes that may mimic intra-epithelial lesions or even cancer. Severe reactive/reparative changes are difficult to distinguish from neoplastic changes and such interpretations have lower reproducibility than classic repair [19]. It is important to recognize benign reactive features in order to avoid over and false positive interpretations. Reparative changes are easier to recognize on LBP, yielding less false positives than conventional smears [20].

Only exfoliated, intact endometrial cells should be reported under the "Other" category. Direct sampling over lower uterine segment/abraded stromal cells / histiocytes, when present alone should not be reported under this category.

In epithelial cell abnormalities, the atypical squamous cells are recognized as:

1. Small cells with a high N:C ratio or "atypical metaplasia", nuclear membrane irregularity, hyper-chromasia and chromatin irregularity favor High Grade Squamous Intraepithelial Lesion (HSIL) over benign metaplasia.
2. Crowded sheets/hyperchromatic cell groups, dense cytoplasm, and polygonal cells with distinct cell borders favor squamous over endocervical cells. This cell pattern includes a broad differential from normal (atrophy, endometrial cells) to neoplastic (endocervical adenocarcinoma, HSIL or HSIL involving glands) changes.
3. Atypical cells in atrophy, following radiation, poorly preserved endometrial cells/histiocytes and IUD may show cellular changes similar to HSIL.

These come under atypical squamous cells, Cannot Exclude High-Grade Squamous Intraepithelial Lesion (ASC-H).

Atypical squamous cells of Undetermined Significance (ASC-US), involves non-inflammatory changes in squamous cells with mature superficial/intermediate type cytoplasm. Nuclear enlargement is approximately 2.5 to 3 times that of normal intermediate squamous nucleus, but chromatin is normal. Nucleomegaly may be seen but contour is smooth.

In Squamous Intraepithelial Lesions (SIL), nuclear changes may include enlargement with hyperchromasia/pyknosis, chromatin smudging and membrane irregularity. Cytoplasmic changes - peri nuclear halo, peripheral thickening of the cytoplasm / cytoplasmic orangeophilia and rounding of cellular contours.

Epithelial cell abnormalities involve Atypical Glandular cells (AGC). These include:

a) Atypical endocervical cells, NOS—Cells with significant nuclear enlargement/crowding, hyperchromasia, loss of mucin and polarity.
b) Atypical Endocervical cells, Favor Neoplastic—cellular strips and rosettes with elongated overlapping nuclei, moderately coarse chromatin and hyperchromasia. The peripheral border may be "feathered" with protruding nuclei, in contrast to smooth border of typical glandular fragments.
c) Atypical Endometrial Cells— small cell groups with slight nucleomegaly and variable nucleoli and hyperchromasia.
   Endocervical Adenocarcinoma (In Situ and Invasive) — high grade endocervical neoplastic lesion - cytologically demonstrates nucleomegaly, hyperchromasia, stratification and mitotic activity.
d) Endometrial Adenocarcinoma — cytologic features directly related to histological grade of tumor - well differentiated cases: malignant cells with minimal atypia, poorly differentiated tumors being obviously malignant.
e) Extrauterine Adenocarcinoma- clean background and cytologic features not characteristic of uterine/cervical tumors should raise the possibility of metastasis [21].

Statistical analysis

For statistical analysis, the cytological findings were coded into 4 groups as follows:

1	Normal study
2	Inflammatory Non-specific
3	Infective
4	Pre-malignant /malignant lesions

Spearman rank-order correlation test was performed to assess if there was any correlation between the CD4 counts in HIV positive cases and their cytological findings and Chi-square test done to detect significant difference between cases and controls.

Since the actual numbers of patients in each cytological subgroup were too few in both HIV positive and HIV negative categories, only 2 groups were considered in each category. The subgroups were:

1. Abnormal cytology (13 in HIV positive, 5 in HIV

negative group)
2. Normal/ non-specific cytology (17 in HIV positive, 23 in HIV negative group)

Results

HIV cases had more incidence of abnormal cervical cytology (13 cases, 43.33%) than their sero-negative counterparts (5 cases, 16.67%). 2/13 had LSIL and one had ASC-US, specific infections with coccobacilli, T. vaginalis and Candida was found in five samples against one T. vaginalis infection in control group. Reparative changes (squamous metaplasia) were seen in five cases in the HIV positive group and in two cases in the control group. There was no case of malignancy in the HIV positive group. HIV negative control group had a single case of malignancy and another case of HSIL (table 1).

2/30 sero-positive cases with low CD4 counts (87 and 54). One with CD4 count 87 had HPV infection. Clinically, both presented with fever. The HPV infected case also complained of white discharge per-vaginum.

One sero-positive case had ASC-US. (CD4 count: 186). The patient presented with fever and itching per-vaginum.

Five sero-positive patients presented with specific infections with bacteria and fungi. Two showed infection with coccobacilli, two Candidiasis and one T. vaginalis. In both cases of bacterial infection, the CD4 range was below 250 (226 and 105) and patients had fever and WDPV. Candidiasis cases had counts of 112 and 291 and presented with intense itching and WDPV, one having chronic diarrhoea, while T. vaginalis case had a count of 142, clinical presentation was that of itching per-vaginum and dysuria.

Five cases were found to have Inflammatory Smear with Squamous Metaplasia, with the CD4 counts being 298, 70, 154, 133 and 430 i.e within the range of 70-430. 3/5 had generalized weakness, 2/5 had persistent fever and dysuria and one had chronic diarrhoea.

The highest numbers of cases, were those of non-specific inflammatory smears with a total of 13. The CD4 counts of these ranged from 146-297. Among the HIV+ cases, four had normal cervical cytology with CD4 values ranging from 100-540.

The CD4 counts of HIV+ cases ranged from 54-540; the case with 54 showing LSIL and that with 540 having normal cervical cytology. A CD4 count < 200 was diagnosed as AIDS. Normal CD4 count ranges from 500-1200. There were 15 patients with AIDS in this study.

AIDS patients showed more cervical cytological abnormalities. 9/ 15 cases showed some degree of metaplasia, dysplasia or infection. Three showed inflammatory smears with squamous metaplastic changes. The remaining six had non-pecific inflammatory changes. AIDS affected individuals showed more predisposition to opportunistic infections.

Nine cases belonged to the age-group 35-39. The CD4 counts ranged from 100-540; five had non-specific inflammatory smear, two normal cervical cytology, one Coccobacillary infection and one T. vaginalis infection. Age-groups 25-29 and 30-34 had a total of seven patients in each group. The CD4 counts of 25-29 group ranged from 54-268 with one case of LSIL, one of Inflammatory smear with squamous metaplasia and one with ASC-US. One had normal cervical cytology and the rest had non-specific inflammatory smears. The CD4 counts of patients of age-group 30-34 years ranged from 70-211. Two had inflammatory smears with squmaous metaplasia, one had LSIL with HPV infection, one showed candidiasis, one had normal cervical cytology, 1 specific coccobacillary infection and the rest were with non-specific inflammatory smears. The 40-44-year age group had six cases. Six showed inflammatory smears with squamous metaplasia, one Candidiasis and the rest had non-specific inflammatory smears. 20-24 age-group had one case with non-specific inflammatory smear (CD4 count=146). No malignant cases were found in the HIV+ group.

Among controls aged 24-52years, maximum cases reported were of non-specific inflammatory smears (25 cases). Two cases had Inflammatory smears with squamous metaplasia (Ages=45, 46 years), one case of ASC-H (Age=52 years), one of HSIL and specific infection with T. vaginalis and one case positive for malignancy (Age=35 years).

Table 1: Cytological findings and CD4 counts of HIV positive patients

Age (years)	CD4 count (millimoles/litre)	Diagnosis
38	320	NS
35	226	Sp inf-coccobacilli
36	297	Infl sm ns
40	291	Sp inf candidiasis
39	386	Infl sm ns
43	298	Infl sm with sq met
22	146	Infl sm ns
30	87	LSIL-HPV
25	152	Infl sm ns
33	100	NS
30	70	Infl sm with sq met
35	540	NS
30	105	Sp inf-coccobacilli
28	54	LSIL
32	211	Infl sm ns
28	186	Infl sm ns
33	112	Sp inf candida
35	380	Infl sm ns
27	468	NS
25	154	Infl sm with sq met
35	164	Infl sm ns
25	159	Infl sm ns
30	133	Infl sm with sq met
40	430	Infl sm with sq met
45	302	Infl sm ns
40	204	Infl sm ns
25	186	ASC-US
38	142	Sp inf-T.vaginalis
35	338	Infl sm ns
40	294	Infl sm ns

NS=Normal study
Infl sm with sq met=Inflammatory smear with squamous metaplasia
Infl sm ns=Inflammatory smear non-specific
SP INF=Specific infection
LSIL=Low grade squamous intraepithelial lesion
ASC-US=Atypical squamous cells of undetermined significance

Spearman rank correlation test revealed that CD4 counts showed a significant negative correlation with the degree of cytological abnormality ($r = -0.378$, $p=0.039$).

The difference between cases and controls was statistically significant ($p<0.05$) according to chi square test.

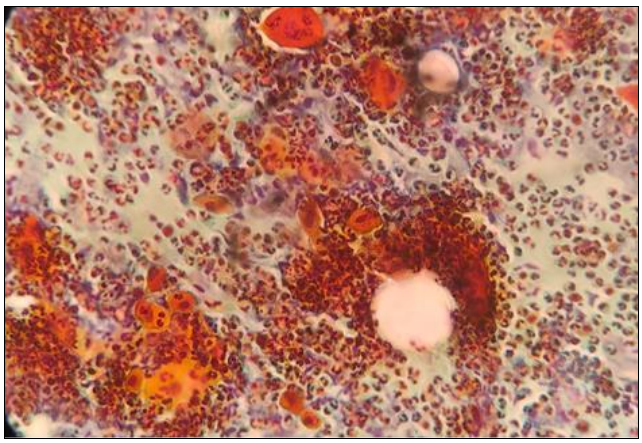

Fig 1: HSIL x400

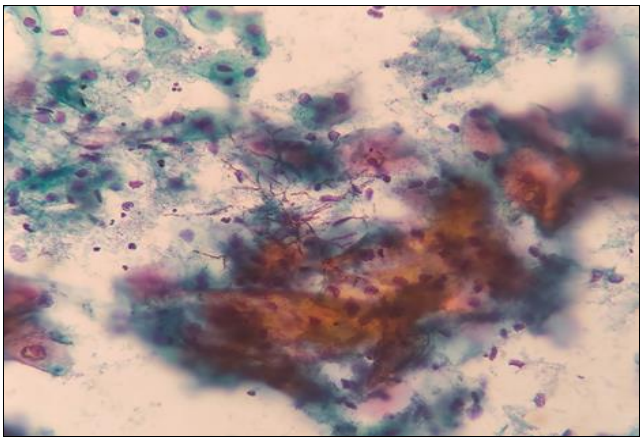

Fig 2: Candidiasis x400

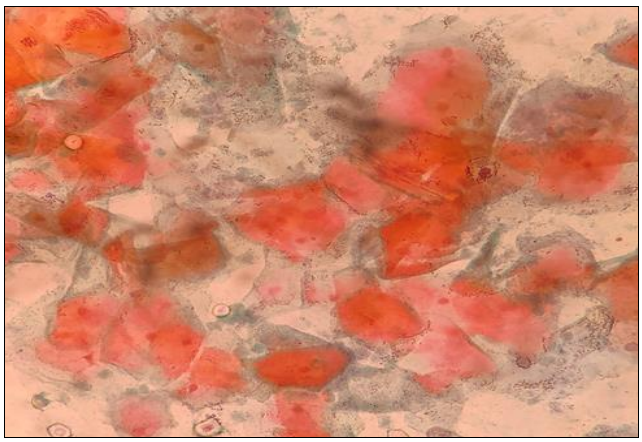

Fig 3: Bacterial Vaginosis x400

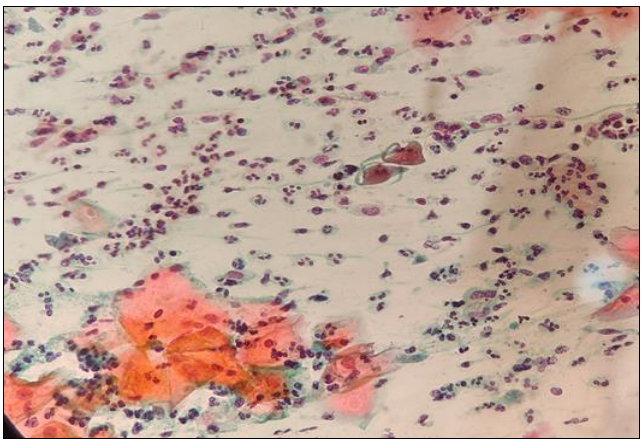

Fig 4: Trichomoniasis x400

Discussion

HIV is a global Pandemic with >38 million positive people across the globe in 2019. South-East Asia region, with 11 member states, has an estimated 3.5 million people living with HIV [22].

Now into its fourth decade, India's epidemic is marked by heterogeneity. A trend to shift from the highest risk group (commercial sex workers, homosexual men, drug abusers) to the Bridge population (clients of sex workers, STD patients, migrant population, population in conflict areas and partners of drug abusers); and then to the general population is seen [23]. This trend indicates that HIV infection spreads from individuals practicing high risk behavior, with an increasing number of housewives with single partners gradually accounting for large proportion of infections [24].

HIV causes progressive immune suppression of affected individuals targeting T-Helper cells leading to decreased CD4 counts. CD4 count < 200 is diagnostic of AIDS [25]. Screening of CD4 counts is an effective way to check the progression of HIV and treatment response.

HIV infection and other STIs increase the transmission of HIV by approximately three to five-fold [26, 27]. Vaginal candidiasis may occur earlier and may serve as an early marker of HIV infection in women [28].

Globally, cervical cancer is the fourth most common cancer in women with approximately 5,70,000 cases and 3,11,000 deaths in 2018 [29]. However, in 42 low-resource countries, it was the most common cancer in women [30]. Pap smear is the most commonly used test for diagnosis of cytological abnormalities of the cervix. Before introduction of Pap test, carcinoma of cervix was a leading cause of cancer death in women. Deaths have reduced by up to 99% in populations of women screened regularly [31].

The use of Pap smears to test a group of HIV-infected women, both pregnant and non-pregnant, showed a high incidence of LSIL, but a low incidence of the high-grade variety [6]. Various studies also show that the risk for CIN is 4-5 times higher in HIV infected than HIV non-infected women and girls [32, 33]. HIV+ women have higher risk for cervical cancer than HIV-negative women [7, 34].

This study was conducted with a total of 30 HIV+ cases and 30 controls. Cervical cytological abnormalities were found in 13 cases - two of LSIL, one case of ASC-US, two cases of Coccobacillary infection, two of candidiasis, one case of T. vaginalis and five of inflammatory smear with squamous metaplasia. Majority of the cases had non-specific inflammation of the cervix (13 cases), with four having no cytological abnormalities.

The controls had a majority of non-specific inflammatory smears (25 cases), considerably more than that in HIV patients. However cervical cytological abnormalities were found in only 5 as opposed to 13 in the HIV positive group. This is in accordance with the established fact that HIV positive individuals tend to have more opportunistic infections, metaplasia and dysplasia than in their sero-negative counterparts. The control group had 2 inflammatory smears with squamous metaplasia against 5 in the HIV+ cases and one ASC-H case. There were no such cases in the HIV positive samples, except for one showing ASC-US. Both groups showed T. vaginalis infection (1 in each group) but the one in the control group also showed HSIL. The HIV positive group had 2 cases of LISL, with one having HPV infection. This finding was in contrast to the ones in control group where there were no such cases. The control group however showed 1 case of malignancy,

but sero-positive group showed none. This finding is considerably different from other case studies which show a high risk of cervical carcinoma in HIV positive patients. [35] The prevalence of cervical dysplastic lesions present at colposcopic/bioptic examination was found to be 3.2 times greater in HIV+ve women than in HIV-ve women (38% v/s 12%, $p<0.001$) and that of lesions of a higher degree 7 times greater [35]. In this study, patients who were positive presented more severe dysplastic lesions, a higher frequency of HPV-derived lesions and inflammatory pictures as compared to non-HIV+ women. Correlation between high incidence of dysplastic cervical lesions and advanced stage of immune depression was observed.

Although this study did not show any sample positive for malignancy in the HIV+ve group, it did demonstrate a correlation between high incidence of dysplastic cervical lesions and advanced stage of immune depression, with both cases of LSIL in patients with a CD4 count of less than 100, well in accordance with the earlier studies. Various studies also establish a link between cervical dysplasia and HIV infections.

Studies have shown a positive correlation between HIV viral load, CD4+ count, and opportunistic infections, as well as the incidence of various malignancies. Of 82 cases of cervical dysplasia, 33 (40.24%) were mild (CIN I), 47 (57.32%) were either moderate or severe (CIN II–III) dysplasia, and two demonstrated invasive squamous cell carcinoma (2.44%). A significant difference was found when comparing either HIV plasma VL or CD4+ T-cell counts with the presence of cervical dysplasia on biopsy ($P < 0.005$) [36]. This study showed a correlation between HIV infection and cervical dysplasia as well as opportunistic infections with 16.67% of cases showing opportunistic infections, 16.67% with squamous metaplasia, 6.66% with LISL and 3.33% with ASC-US, both being considerably higher than in the control group of sero-negative cases. Hence it is in accordance with the established fact that HIV infection predisposes to various cervical cytologic abnormalities. Absence of a malignant case in the HIV positive group is a limitation of the study, although HPV infection was seen. Presence of malignancy in the control group may be because of use of hospital controls as opposed to general population.

Conclusion

The primary aim of this study was to study the cervical cytologic changes in HIV positive patients, which has been accomplished. The secondary objective which was to study the differences between HIV infected and non-infected individuals with respect to cervical changes, which can still be worked upon further especially with respect to establishing a relationship between HIV infection and malignancy.

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