

Abnormal Cytology in HIV-Positive Women Referred for Colposcopy: An Analysis of Cytology-Colposcopy-Histology Correlation.

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Abstract

Context: HIV/AIDS is thought to facilitate the development of cervical neoplasia. Concern has been expressed about the efficiency of standard screening and treatment procedures in HIV/AIDS patients.

Objective; The objective of the study was to examine the performance of standard modalities of cervical cancer screening and management in Human Immunodeficiency Virus (HIV) positive women.

Method: A retrospective review of case records of HIV positive women referred to the colposcopy clinic of a tertiary referral centre in Cape Town, South Africa was done to correlate the cytologic referral findings with colposcopic evaluation and histological diagnosis of biopsy samples. Findings at subsequent follow-up examinations were also evaluated to assess efficacy of treatment or disease progression.

Result: A total of 77 patients, aged 20 to 55 with a mean age of 30.34 [SD: 6.86] years, constituted the study group. There was agreement between cytological and colposcopic findings in 53% and 69% of low-grade (LG) and high-grade (HG) squamous intraepithelial lesions (SIL) respectively. Only in 6% of patients did colposcopy find a higher-grade lesion than cytology. Histological samples were available for 58 of the 77 patients and the agreement between cytology and histology for HGSIL and LGSIL were 63.9% and 76.2% respectively. On follow-up for 3-24 (median: 8) months, 18% of LGSIL progressed to HGSIL, 63.6% remained stable and 18.2% regressed. Nearly 70% of patients with HGSIL remained lesion-free, 23% showed persistent disease and one patient progressed to invasive carcinoma during follow-up.

Conclusion: Standard modes of conservative management provide satisfactory results in the management of HIV seropositive women with abnormal Pap smears.

Key Words: HIV, Cytology, Colposcopy, Cervical Biopsy

Introduction

The association between Human Papilloma Virus (HPV), implicated in the aetiology of cervical cancer and Human Immunodeficiency Virus (HIV) is an interesting one. The prevalence of both viruses in a population is strongly related to sexual behavioural pattern. The immunodeficiency state, such as imposed by HIV on the individual, is also thought to facilitate the development of neoplasia^{1,2,3,4}. The 1993 Centres for Disease Control revised classification for HIV added moderate or severe cervical dysplasia as a "category B" defining condition and invasive cervical cancer as an Acquired Immune Deficiency Syndrome (AIDS) or "category C" defining condition⁵.

With the rising incidence of HIV/AIDS, there has been much concern about the appropriate modality of screening for cervical pre-cancer in this group of patients; following reports that invasive cervical carcinoma is of more advanced stage at presentation, with higher recurrence and death in HIV positive patients than in HIV negative patients⁶. Several reports have raised questions about the adequacy of cytology to accurately predict abnormal histology in this group of patients, citing unusually high false negative rates^{7,8}. Variations in exfoliation of cells or masking by coincident infection are reasons that have been adduced

for these high false negative rates. However other researchers did not verify this claim and found that colposcopic and histologic findings were reliably predicted by the cytologic smear^{9,10,11}.

The purpose of this study was to examine the correlation between cytology, colposcopy and histology using histology as the gold standard in the group of HIV seropositive patients referred for colposcopy on account of abnormal cytology reports, conduct a descriptive epidemiology of HIV positive patients with abnormal cervical cytology, and to examine disease progression and clinical outcome following standard conservative management.

Materials and Methods

The data for this study was obtained from the clinical records of HIV-positive women with abnormal cytology reports, referred to the colposcopy clinic of Groote Schuur Hospital, University of Cape Town, Republic of South Africa. The clinic serves as a referral centre, receiving referrals from secondary level and general

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practice health facilities within the Western Cape district.

Physicians who were neither blinded to the patients' referral cytology report nor her HIV status carried out colposcopic evaluation in the standard procedure. Biopsies were taken from most abnormal areas or the patient had treatment by *Large loop Excision of the Transformation Zone* (LLETZ) in a *see and treat* approach if a lesion was considered high grade and colposcopic examination was satisfactory. Where the examination was unsatisfactory or where there was marked discrepancy between cytologic and colposcopic assessment, the patients had either a cold-knife or hot-loop cone biopsy performed. Socio-demographic data relating to age, parity, and contraceptive use was collated.

The presence of evidence of Human Papilloma Virus (HPV) infection in cytological samples was noted if mentioned in the referral cytology report, otherwise it was regarded as absent. Serum CD4 counts were recorded if done at referral, otherwise the test was ordered on presentation at the colposcopy clinic.

Patients were followed up from records of subsequent attendance at clinic following the initial visit. Records of subsequent smears at follow up visits assessed disease progression. The colposcopic impression was recorded in preference where there was a disparity between follow-up cytology and colposcopy, except where follow-up histology report was available.

The results of cytologic referral were correlated with those of colposcopic evaluation and subsequent histological diagnosis of the biopsy samples. The Bethesda System¹² for reporting cytology was used. For ease of comparison, histologic reports of Cervical Intra-epithelial Neoplasia (CIN) are converted to corresponding grades of the Bethesda System. Findings at subsequent follow-up examinations were evaluated to assess efficacy of treatment or disease progression.

Results

A total of 77 cases of HIV positive patients were available for analysis. The mean age of the patients was 30.34 [SD: 6.86] years. The youngest patient was 20 years of age and the oldest was 55 years old. Patients were under the age of 30 were 53%, with the highest frequency occurring in the 25-29 year age group (39%). Fourteen (18.2%) of the patients were nulliparous. Majority of these patients (66.2%) practised contraception while 33.8% did not use any form of contraception. The most popular form of contraception in this group of patients was the injectable hormonal preparation, practised by 39 (50.7%) of the patients. Condom use was reported by 6 (4.6%) of the 77 patients reviewed.

Table 1:
Cytological Report Versus Colposcopic Impression

Cytology	Norm	Colposcopy			Total
		HPV	LSIL	HSIL	
ASCUS	0	0	1	0	1
LSIL	5	6	19	3	33
HSIL	2	5	6	29	42
Total	7	11	26	32	76

The referral cytology report was of the *High-Grade Squamous Intra-epithelial Lesion* (HSIL) category in 54.5% of cases while *Low-Grade Squamous Intra-epithelial Lesion* (LSIL) was reported in 44.2% cases. One case (1.3%) was referred because her cytology report showed *Atypical Squamous Cells of Unknown Significance* (ASCUS) on two occasions. The presence of features suggestive of Human Papillomavirus infection was reported in the 70.1% of the cytology reports.

The correlation between referral cytology and colposcopic findings is depicted in Table 1. Of the 42 cases reported as HSIL on cytology, the colposcopic impression was the same in 29 (69.1%) of the cases while 11 cases were thought to be of less severe degree of abnormality. Two cases were considered normal, which were, reported HSIL on cytology. Of the 34 cases reported as LSIL on cytology, colposcopic impression was in precise agreement in 18 (53%) cases, two cases were considered of higher degree abnormality, 6 were considered to depict HPV infection only, while 3 were considered normal. A colposcopic impression was not recorded for 1 of the cases.

Samples for histological diagnosis were available in 58 of the 77 cases reviewed, and a comparison of cytology report to subsequent histological diagnosis is shown in Table 2. Of the 42 cases with cytology report of HSIL, 36 biopsy specimens were available for histology, out of which 63.9% (23 of 36) were confirmed to be of high-grade disease (CIN II-III). Out of the cases reported on cytology as LSIL biopsies taken from 76.2% were confirmed to be low-grade lesions (CIN I) by histology. Only one of the 58 biopsy specimens had histological findings that were more severe than that suggested by cytology. The patient referred following two ASCUS reports had CIN I diagnosed on histology. Statistical performance characteristics for cytology compared to histology (when only HSIL is considered disease state and other grades considered disease free) are given below Table 2.

Table 3 shows a comparison of colposcopic impressions to the histological diagnoses. Again a high degree of correlation is observed with 65.5% and 72.7% agreement in diagnosis for HSIL and LSIL cases respectively.

Table 2 :
Cytological Versus Histological Diagnosis.

Cytology	Histology				Total
	Norm	HPV	LSIL	HSIL	
ASCUS	0	0	1	0	1
LSIL	3	1	16	1	21
HSIL	5	2	6	23	36
Total	8	3	23	24	58

*Sensitivity(Cytology) = 95.8%; Specificity = 61.8%;
Positive predictive value = 63.9% Negative Predictive Value = 95.5%
*(Disease = HSIL, No Disease = Norm, HPV, LSIL)

Table 3:
Colposcopic Impression Versus Histological Diagnosis.

Colposcopy	Histology				Total
	Normal	HPV	LSIL	HSIL	
Normal	1	0	0	0	1
HPV	0	1	3	2	6
LSIL	3	0	16	3	22
HSIL	4	2	4	19	29
Total	8	3	23	24	58

CD4 counts were available for 23 cases, out of which biopsy results were available for 15, which were analysed. Overall, the mean serum CD4 count was 271.3 +/-188.4/mm³ (mean +/- SD). The relation between CD4 serum level and *Squamous Intra-epithelial Lesion* (SIL) is shown in Table 4. The mean serum CD4 count was 292.0 +/- 298.3/mm³ in patients without histologically confirmed SIL and 266.2 +/-169.9/mm³ in patients with SIL. The mean serum CD4 count in LSIL and HSIL confirmed cases were 288.5 +/-199.5/mm³ and 243.8 +/-149.4/mm³ respectively. There was no statistically significant difference (Mann Whitney U test) between these groups.

Table 4:
CD4 Level and Squamous Intra-epithelial Lesion in 15 HIV-Positive Patients.

Abnormality (Histology) (per mm3)	No. of Patients	Mean Blood CD4 Count [SD]
None	3	292.0(+/-298.3)
LSIL	6	288.5(+/-199.9)
HSIL	6	243.8(+/-149.4)

Follow-up information was available for 54% (31 of 58) of cases that had histologic diagnosis. The median follow-up period was 8 months (range 3-24). Of 11 patients that had CIN I at initial histology, 63.6% remained stable, while 18.2% regressed. Another 18.2% (2 of 11) had CIN III at follow-up histology. One of these was treated with LLETZ and remained normal for the subsequent 9-month duration of follow-up. 69.2% (9 of 13) patients with high-grade (CIN II-III) disease

responded to treatment and remained disease free for the duration of follow up. 23% showed evidence of persistent disease. One patient was diagnosed squamous cell carcinoma when seen after eight months. Follow up was uneventful for 7 patients who had normal or HPV histologic diagnosis.

Discussion

Several authors have shown that HIV infected women have a higher prevalence of genital HPV infection and cervical intra-epithelial lesions, the severity of the genital abnormality increasing in relation to the degree of immune depression^{4,13,14,15}. Our results indicate that standard modalities of screening and treatment as applicable to the general at risk population may suffice for HIV/AIDS positive women. The study population however is of such small magnitude as may make any real differences undetectable

There was good correlation between the cytologic referral, colposcopic impression and subsequent histologic diagnosis. Only one patient had a histologic diagnosis more severe than predicted by cytology. Since the study deals with a group of patients in whom all cytological reports were abnormal, performance characteristics of cytology were computed in which only patients with high-grade disease (CIN II-III) on histology were regarded as disease positive, and other histological diagnoses as disease negative. Using this criterion, sensitivity and specificity values for cytology of 95.8% and 61.8% respectively were obtained and thus concluded that abnormal cytology accurately predicts the degree of cervical disease in this cohort of patients. This finding is very similar to that of Adachi *et al*⁹ who in a prospective study of 25 sero-positive women with abnormal smears found only one whose histological diagnosis was more severe than predicted by cytology. The results however contrast with others who have reported poor performance of cytology in the presence of HIV infection. Fruchter *et al*¹⁶ found cytologic results to be less severe than histologic results in HIV-infected women. Maiman *et al*⁷ also reported a poor predictive value of normal cytologic results. We note that our study did not evaluate patients whose smear reports were normal and our population represents a cohort with a very high likelihood of disease.

Our findings confirms, as has been established in the general population by some studies, that age is a major determinant in degree of severity of cervical disease. This appears from this study to hold true for HIV positive patients also: 37% of patients aged over 30 years have high-grade disease as opposed to only 26.3% of patients below the age of 30 years. Fruchter *et al* however found no association between age and disease

severity in HIV positive patients, finding that a majority of younger women had high-grade disease and supporting the hypothesis that HIV infection enhances disease progression. Severity of HIV infection, as assessed by the level of depression of the CD4 count, made no statistically significant difference to the severity of cervical disease.

Follow up records showed that standard methods of care were adequate in the treatment of intraepithelial cervical lesions in HIV infected women, as revealed by the high cure rate and lack of recurrence. Only 18% (2 of 11) patients with low-grade disease showed disease progression at follow up. 69% of cases with high-grade disease had normal findings at re-evaluation, indicating efficacy of treatment. One patient though, who had CIN III diagnosed by punch biopsy specimen was found to have early invasive cancer when LLETZ was performed eight months later. It is possible that the focus of invasion was missed at the early biopsy. Maiman *et al*⁶, in a study of 37 women with cervical carcinoma reported that HIV sero-positive women were likely to have rapid disease progression, persistence of disease and recurrence following treatment. That study however did not examine HIV infected women with early intraepithelial neoplasia. A study by Wright *et al*¹⁷ reported a high persistence/recurrence rate of intraepithelial neoplasia in HIV infected women treated

by loop excision, persistence/recurrence rates increasing with HIV disease severity as, assessed by CD4 T lymphocyte counts.

The management of CIN in HIV seropositive women continues to generate a lot of debate with conflicting reports, based on differences in study designs and populations and methodology. We acknowledge the small size of our study population and the absence of a control group with which to compare results. The case for routine colposcopy for HIV positive patients as proposed by some authors may prove an impossible task especially for parts of the developing world with high HIV prevalence rates and lack of colposcopic services. The role of low technology cervical cancer screening methods such as Visual Inspection with Acetic acid (VIA) or Lugol's iodine (VILI) remains to be examined.

Our data suggests that cytology remains a useful tool in the diagnosis of cervical disease in this group of patients and standard modes of conservative management provide satisfactory results. Efforts should be geared towards improving access of these patients to existing standard efficient modalities of diagnosis and treatment of cervical intraepithelial lesions.

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