

Immunohistochemical expression of p53 and Ki 67 and its histopathological correlation in lesions of cervix

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Abstract

Introduction: Cervical lesions constitute one of the major health problems in Indian women accounting for major morbidity and mortality. To study p 53 and Ki 67 immunexpression in cervical lesions is an interesting area of research.

Aims: To study immunohistochemical expression of p53 and Ki 67 in lesions of cervix and its correlation with various histopathological diagnosis and assess their utility in segregating high risk cases and to explore its use as diagnostic tool in suspicious cases.

Materials and Methods: Retrospective and prospective study was undertaken in Department Of Pathology in our institute from 1st January 2014- January 2016.60 cervical biopsies with known histopathological diagnosis were randomly selected and stained for immunohistochemistry expression of p 53 and Ki 67 and results were correlated with various parameters. Data was analyzed using appropriate statistical tests .Age difference was examined using one way analysis of variance (ANOVA), chi square test is applied, and for quantitative data student [t] test is applied. P value is considered significant if p<0.05.

Results: 42.5% benign and 50 % of neoplastic cervical lesion had p53 positivity. For Ki 67, among chronic non specific cervicitis, a score of 2 and 3 was observed in 8 and 3 cases respectively. The chronic cervicitis cases with score 3 in retrospect had histomorphology suspicious of dysplasia but were inconclusive ,a high proliferative score helped us to objectify our findings and reclassified as 2 cases of CIN2 and 1 of CIN 3 respectively .These results were statistically significant (p<0.01). A single case of CIN 2 stained for Ki-67 had a score of 2 correlating with its histological diagnosis.

Conclusions: Ki 67 is a helpful marker to objectify cases with inconclusive histomorphological pattern and p53 may help segregate cases into high and low risk for follow up.

Keywords: Cervix, Immunohistochemistry, Ki 67, p53.

Key Messages: Lesions of cervix especially those which are pre neoplastic and dysplasia have to be followed up closely for possible conversion to neoplasia. Immunohistochemistry expression of p53 and Ki 67 may be considered as surrogate markers for segregating high risk cases and have diagnostic implications respectively.

Introduction

Cervical cancer is a major global public health problem. With 5,28,000 new cases every year, cervical cancer is the fourth most common cancer and cause of cancer death (2,66,000 deaths in 2012) in women worldwide accounting for 7.5% of all female cancer deaths. Almost nine out of 10(87%) of cervical cancer deaths occur in less developed countries and more than one fifth of all new cases are diagnosed in India. Cervical cancer is 2nd most common malignancy after breast carcinoma among Indians.¹ According to IARC estimates, mortality from cervical cancer is expected to witness a 79% increase from 74,118 deaths in 2002 to 132,745 deaths by 2025.²

This large scale morbidity and mortality due to cervical cancer is totally unwarranted not only because the definitive cause of cervical cancer is now known, but also because the disease takes a long time to develop after initial infection with high risk Human papilloma virus (HPV).³ Incidence of cervical cancer can be decreased by regular screening and treatment of precancerous lesions. Although Pap smear is central to screening, it has some limitations, most important being its limited sensitivity which is between 47-62% and the subjective interpretation of the results.⁴ Therefore, arises

the need for identification of specific biomarkers for to aid in screening and diagnosis to reduce diagnostic variability. Markers like p53 and Ki 67 may be of greater importance in low-grade CIN lesions showing high proliferative index. This will place the low-grade lesions in higher grade indicating the utility of proliferative markers in decision making for intervention.p53, Tumor protein P53, also known as p53-regulates the cell cycle and thus functions as a tumor suppressor, preventing cancer. Also, known as "the guardian of the genome" because of its role in conserving stability by preventing genome mutation -its expression in cervical lesions is an area of research & interest. Ki 67 is a proliferation marker that is confined to the parabasal cell layer of normal stratified squamous mucosa but shows expression in the stratified squamous epithelium in CIN lesions in correlation with the extent of disordered maturation.

Thus, immunohistochemical expression & its correlation with histopathological assessment of cervical lesions is an interesting & useful research proposition.

Materials and Methods

A retrospective and prospective study was undertaken in Department Of Pathology in our institute

from January 2014-jan 2016. A total of 60 cervical biopsies with known histopathological diagnosis were randomly selected and stained for immunohistochemistry expression of p 53 and Ki 67 on polylysine coated slides using BioGenX kits and results obtained were analysed and correlated with various parameters. Data was analyzed using appropriate statistical tests using software epi-info and SSPS .Age difference was examined using on way analysis of variance (ANOVA), chi square test is applied, and for quantitative data student [t] test is applied. P value is considered significant if $p < 0.05$, and highly significant if $p < 0.01$. For immunohistochemistry interpretation, Sections examined were assessed with

maximum positivity staining area examined under 40 x magnification.

Distinct brown nuclear staining was taken as positive.100 cells were counted and a count $>10\%$ was considered positive for p53.^{5,6} For Ki 67 , a score of 0, 1, 2 and 3 was assigned for 0%, 1-10%, 11-50%, 51% and more nuclear staining.^{7,8} Score 0-1 were regarded as low and 2-3 as high. Breast carcinoma was taken as positive control.

Results

A total of 28 benign and 32 malignant cervical lesions were evaluated. Distribution of cases for immunohistochemistry evaluation were as in Table 1.

Table 1: Distribution of cases for immunohistochemistry evaluation

| Histopathological Diagnosis (HPE) | IHC no. of cases |
|--|------------------|
| Chronic Cervicitis | 24 |
| Moderately Differentiated Squamous Cell Carcinoma(MDSCC) | 20 |
| Non Keratinizing Squamous Cell Carcinoma (NKSCC) | 7 |
| Well Differentiated Squamous Cell Carcinoma (WDSCC) | 2 |
| Poorly differentiated Squamous Cell Carcinoma (PDSCC) | 2 |
| Chronic Cervicitis With Dysplasia | 3 |
| Adeno Carcinoma | 1 |
| Cervial Intraepithelial Lesion 2 | 1 |
| Total | 60 |

In benign category, with respect to p53 immunohistochemistry expression ,among chronic non specific cervicitis, 41.66% (10) cases were p53 positive and only 33.33% i.e 1 out of 3 cases were positive among chronic cervicitis with dysplasia. One CIN case evaluated was positive for p53 expression. Overall, 42.5% benign lesion had p53 positivity.

For Ki 67 immunohistochemistry expression, among chronic non specific cervicitis, a score of 2 and 3 was observed in 8 and 3 cases respectively. Patients were candidates for regular follow up owing increased proliferative activity of lining epithelium of cervix and

increased chances of progression to pre and neoplastic lesions. The chronic cervicitis cases with score 3 in retrospect had histomorphology suspicious of dysplasia but were inconclusive, a high proliferative score helped us to objectify our findings and reclassified as 2 cases of CIN2 and 1 of CIN 3 respectively. Theses results were statistically significant ($p < 0.01$). A single case of CIN 2 stained for Ki-67 had a score of 2 correlating with its histological diagnosis .However, its use as an objective tool for diagnosis of CIN lesions require studies with larger sample size. In malignant group, following observations were made as in Table 2.

Table 2: p53 expression in malignant lesion of cervix

| Diagnosis | p53 present | p53 absent |
|---|-------------|------------|
| Moderately Differentiated Squamous Cell Carcinoma MDSCC(n=20) | 9 | 11 |
| Non Keratinising Squamous Cell Carcinoma NKSCC(n=7) | 6 | 1 |
| Poorly Differentiated Squamous Cell Carcinoma SCC(n=2) | 1 | 1 |
| Well Differentiated Squamous Cell Carcinoma WDSCC(n=3) | 0 | 2 |
| Adeno Carcinoma (Adeno Ca) (n=1) | 0 | 1 |

Thus, p53 was positive in 50% cases (16/32) of carcinoma cervix. Overall, p53 was positive in 41.66% cases of non neoplastic, 50% cases of both pre and neoplastic lesions of cervix. Taking broad subgroups of carcinoma cervix into consideration, p53 positivity was found significantly more for Non Keratinizing (6 cases, 92.9%) compared to Keratinizing Squamous Cell

carcinoma(10 cases, 73.9%) with p value=0.041($p < 0.05$).It was insignificant in comparison to adenocarcinoma with p value=0.44($p > 0.05$).

Among neoplastic category, Ki 67 scoring was done. Among carcinoma cervix cases, majority i.e 22 out of 32 cases had a score of < 2 .Mean Ki 67 scores for was 1.57

for Non Keratinizing squamous cell carcinoma compared to 1.10 for moderately differentiated carcinoma and 1 each for rest of histological variants.

Categorising into broad histological variants, The values were found to be significant statistically high for non keratinizing squamous cell carcinoma (1.57) compared with Keratinizing squamous cell carcinoma(1.08); p value = 0.009 (p<0.05). Mean Ki -67 score increased from 1.38 in non neoplastic cases to 1.5 in borderline category. Proliferation index dropped to 1.19 in neoplastic cases due to differentiation of tumor cells.

Age

The mean age for p53 expression positivity and negativity was 43.4 and 41.1 yrs in benign category. In malignant category, it was 48.1 and 44.9 yrs for positive and negativity respectively High ki 67 scores was

observed with mean age as 41.6 and 41.2 in benign and malignant group respectively.

Gravida

The mean gravida was 3.47 and 3.43 for p53 positivity and negativity respectively. Within benign and malignant category, mean gravida had insignificant difference in p53 positive cases on statistical analysis with p value as 0.086 and 0.48 respectively. Similar observations were made in Ki 67 expression, p value being statistically insignificant in benign (p=0.24) and malignant category(p=0.86).

FIGO staging and P53 expression

The following observations were made with respect to **FIGO staging** in cancer cervix cases and their p53 & Ki 67 immunoeexpression. (Table 3). No significant correlation was observed between FIGO staging with p53 (p=0.54) and Ki 67 (p=0.16).

Table 3: p 53 & Ki 67 expression with respect To FIGO staging

| Immunoexpression | FIGO early Stage | FIGO advanced Stage (IIB Onwards) |
|------------------|------------------|-----------------------------------|
| p53 Present | 2 | 14 |
| p 53 Absent | 1 | 15 |
| Low Ki 67 score | 1 | 21 |
| High Ki 67 score | 2 | 8 |

Correlation OF p53 with KI 67 expression

Mean Ki 67 scores were correlated in broad categories of cervical lesions with p53 expression. The correlation was insignificant in pre neoplastic and neoplastic group with p value being 0.99 and 0.11 respectively (p>0.05). However, in non neoplastic group, significantly high mean Ki 67 score was observed with p53 expression with p value=0.0017(p<0.05). Overall, mean Ki 67 score was 1.68 ± 0.86 in case of p53 positivity and 0.94± 0.88 in

absence of p53 expression .On statistical analysis, Mean Ki 67 score was significantly high in p53 positive cases with p value=0.002(p<0.05).

Discussion

We compared present study of cervical p53 expression with other similar studies and observations were as in Table 4.

Table 4: Comparitve analysis of expression of p53 in cervical lesions

| Study | No. of cases | p53 Positivity (SCC) | AdenoCa |
|--------------------------------|--------------|-------------------------|---------------------------------------|
| Holm R ⁹ 1993 | 237 | 62% | 11% |
| Cardillo MR ¹⁰ 1993 | 65 | 35%-WDSCC 32.5%PDSCC | nil |
| Bosari S ¹¹ 1993 | 92 | 74% | - |
| MD Jeffers ¹² 1994 | 57 | - | - |
| Cheah Pl ¹³ 2002 | 281 | 70% | - |
| S rajaram ¹⁴ 2006 | 30 | 50% | - |
| Florina V. ¹⁵ 2009 | 26 | 53.86% | - |
| Madhumita ¹⁶ 2012 | 36 | 45.4% | Stage III and IV maximum positivity |
| S. Shukla ¹⁷ 2014 | 35 | 50% | 42.1% |
| Present study 2015 | 60 | 50% | 100% (n=1).Normal epithelium-(41.66%) |

While Malisic¹⁸ & Oliveira¹⁹ could not establish any correlation in cervical cancers, Türkçüoğlu I²⁰ observed that p53 increased proportionally to the grade of CIN and cancers. Thus, it helps decide a neoplastic lesion but the absence of p53 does not exclude neoplasia similar to present study.

While observations were similar to other studies in carcinoma cases, it was in contrast to those in Holm R,⁹ Cardillo,¹⁰ S Rajaram¹⁴ which had nil in normal epithelium. We had 41.66% positivity like those found by MD Jeffers¹² And Bosari S.¹¹

p53 expression in benign lesions underlines a careful approach. The unexpected finding of p53 immunoreactive cells in inflammatory lesions, though possibly related to an increased proliferation rate of the basal cell compartment, requires further study and underlines the need for a careful approach to p53 immunocytochemistry.

We had a single case of CIN 2 which was positive for p53 expression while dysplastic epithelium cases showed 33% cases as positive. Most studies had a large number of specimens under consideration along with a longer time period. Expression was increased in carcinoma compared with normal squamous epithelium. The highest expression was seen in dysplasias and invasive carcinomas. p53 correlation with FIGO staging was not significant in our study similar to Mega Tiber P.²¹

With regards to Ki 67. immunohistochemical expression Al Saleh²² & A. E. G. Godoy²³ found Ki 67 expression confined to the parabasal and basal layers of normal and metaplastic epithelium and increased with increasing grades of cervical lesions similar to present study. In consensus with Ancuta,²⁴ though HPV correlation was not included, mean Ki score increased from benign to dysplasia spectrum in present study as well.

Fatemeh Sari Aslani²⁵ reviewed and re-classified 77 cervical biopsies, originally diagnosed as 31 non-CIN, and 46 CIN, as 54 non-CIN, and 23 CIN. He recommended Ki67 as complementary tests for differentiating between dysplastic and non-dysplastic lesions .In present study also, 3 cases of chronic cervicitis with non conclusive features of dysplasia were reclassified as CIN on the basis of proliferation in upper epithelium of cervix similar to present study with 3 cases of chronic cervicitis with debatable histological features were classified as CIN.

McCluggage and colleagues²⁶ also found that Ki 67 staining level increased with the grade of CIN lesions while we stained only one CIN cases, its Ki 67 index correlated with its histology. Thus, Ki 67 expression may be considered as a confirmatory marker for CIN diagnosis. However, our sample size was too small to conclude the same.

Anju et al²⁷ showed that Ki 67 staining levels increased with the progression of lesion from normal through increasing grades of dysplasia to invasive

carcinoma .In present study, though level increased from non neoplastic to pre neoplastic spectrum, it decreased in carcinoma cases probably due to differentiation of tumor cells.

Garzetti et al²⁸ and Anju et al²⁷ suggested that Ki 67 is a sensitive biological indicator of progression independent of age and menopausal status and can be used as an independent prognostic factor to determine the progression and biological behavior of cervical neoplasia especially when HPV infection is missing.

However, in present study we did not follow up carcinoma patients due to time constraints, we did find variable Ki 67 expression in different histological subtypes of carcinoma as well as variable expression among different patients with same subtype and this conclusion by Anju et al²⁷ and Garzetti et al²⁸ seems plausible and more long term studies may be undertaken in present scenario to study the same.

Recently, it was found that in patients with high risk HPV the viral load (detected by hybrid capture II method) is positively correlated with the expression of Ki 67 and CIN grade.²⁰ Though we did not assess the viral load, Ki 67 expression was particularly found to be increased in cases with more risk factors for cervical cancers.

Milana Panjkoviæ²⁹ studied Ki 67 in squamous intraepithelial lesions and a statistically significant relation between proliferative activity, distribution of Ki-67 positive cells, and CIN grade and could be a tool to identify women who are at higher risk for progression and/or recurrence of cervical squamous precancerous lesions. In present study also, we observed increased expression in women with more risk factors for cancer and presenting with chronic cervicitis. Ki 67 index may act as a tool for segregating women requiring more regular follow up than others.

Florina V¹⁵ and K. Gupta³⁰ observed Ki-67 positivity in more than in present study probably because we encounter cases in later stages in our setting compared to others.

Florina V.¹⁵ observed that Ki-67, showed better correlation with cancer progression than p53. This observation could be useful in clinical practice in order to identify those patients requiring more aggressive treatment even in present setting where mean Ki score was higher in p53 positive patients and may be selected as a candidates requiring more aggressive treatment.

Our overall observations were similar to views expressed by Yim³¹ that Ki- 67 is normally expressed in the parabasal cells of mature cervical squamous epithelium and presence of Ki 67 positive nuclei in the upper two thirds of cervical squamous epithelium helpful in differentiation of non neoplastic lesions that mimic cancer and may enhance the diagnostic accuracy to detect high grade CIN.

Conclusion

We concluded that though p53 expression was not diagnostic of carcinoma cases, though its expression may support the diagnosis of dysplasia and carcinoma. It may relate with increased progression to aggressive course and poor prognosis and more long term follow up of patients with larger study group is recommended.

Also, the non neoplastic cases having p53 expression may be considered high risk owing to mutation status and should be followed up more regularly than others. This may help in using the resources more efficiently and help in resource scarce settings like ours. In view of diagnostic significance of Ki 67 in difficult to assess lesions, we strongly recommend Ki 67 immunohistochemistry expression to segregate cervical lesions especially in high risk group.

We infer that p53 and Ki 67 immunostaining will prove helpful in segregating cases of cervical lesions requiring more regular follow up as well as help in objectifying the histomorphological diagnosis prone to interobserver variability and discordance.

Future steps are to evaluate the clinical importance of these findings with a greater population regarding the histological changes in cervical lesion, which could be detected earlier if females at higher risk are examined at shorter intervals. Large scale screening programs for target populations should be organized to reduce the long term morbidity, mortality and socioeconomic burden related with cervical lesions.

Also, increasing literacy rate, personnel hygiene, socioeconomic strata, use of contraceptive measures to reduce parity will be highly instrumental in tackling the current and future burden of cervical cancers.

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