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Utility of P16/INK4a and Ki-67 in Preneoplasticand Neoplastic Lesions of Cervix

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ABSTRACT

Background and Objective: The currentstudy aimed at investigating the histomorphological spectrum of cervical intraepithelial and invasive lesions assessing the diagnostic significance of P16/INK4a and Ki-67 in such lesions, andcorrelatingP16/INK4a and Ki-67 immunoexpression with histologic type and grade.

Methods: A total of 60 cases were selectedcomprising 10 cases withchronic cervicitis, 29 cases withcervical intraepithelial neoplasia(CIN), and 21 cases withsquamous cell carcinoma. These cases were evaluated morphologically and immunohistochemically with P16 and Ki-67.

Results: There was no expression of P16 and Ki-67 in 10 (100%) cases withchronic cervicitis while in CIN, it was expressed in 25 (86.20%) cases and in carcinoma it was expressed in 20 (95.23%) cases. Ki-67 was expressed in 28 (96.55%) cases withCIN and in 100% of cases withcarcinoma.

Conclusion: Cervical carcinoma is a significant contributor to cancer-related morbidity and mortality worldwide. Identification of bio-markers in cervical neoplasia is necessary to distinguish CIN from other non-neoplastic cervical lesions to prevent under treatmentor overtreatment as the histomorphological features alone are not sufficient.Significant upregulation of P16, cyclin dependent kinase inhibitor, and Ki-67, a nuclear non-histone protein, was observed in carcinoma cervix and with the increasing severity of CINs. Correlation between grades of P16 and Ki-67 among cervical pre-neoplasia and neoplasia showed an increasing P16 expression with consistently increasing Ki-67 labelling index in the groups with theincreasing severity.

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Introduction

The cervix is one of the major organs of female genital tract and represents an important source of morbidity and mortality among females (1).Due to the availability of efficient screening methods to detect the pre-cancerous lesions, the incidence of carcinoma declined by two-thirdsin the past 40 years in the Western world (2). However, in the developingcountries such asIndia, it still remains the major cause of mortality (3).Some studies demonstrated an increased incidence of high-grade squamous intraepithelial lesions (HSIL) in young females subsequently followed by surgical interventions, and others considered these as more severe morphological manifestations of immature squamous epithelium due to human papillomavirus (HPV) infection. Therefore,overtreatment of these false positive lesions can affect future reproductive success and also hasemotional consequences, in addition to its economic impact on public health policy. Identification oftrue grade of cervical lesions, especially HSIL in the young females, is a challenge that may be helped by the use of biomarkers (4).

It is a long time that epidemiologic data implicatesthe role of HPV in cervical cancer with a particular

focus on high-risk HPV subtypes (5).Genomic integrations of these viral oncogenes can disrupt several cellular proteins resulting in their up-regulation. The two critical HPV oncoproteins involved in this integration are HPV E6 and E7 interacting with the tumor suppressor genes, p53 and pRb (retinoblastoma protein), respectively; andboth of them are key molecules in cell cycle control resulting in the up-regulation of another tumor suppressor gene P16/INK4a, which is a cyclin dependent kinase inhibitor (6).The overexpression of P16 is well established in cervical intraepithelial neoplasia and invasive cancer by many studies in recently(7-9), but till date there are only few reports from Indian literature, despite the fact that Indian females represent a major proportion of the affected population (10).

Ki-67 is a marker of non-histonic protein of cell proliferation and is expressed in all phases of cell cycle, except in G0. The interaction of E6 and E7 HPV DNA in the host cell disturbs the cell cycle expressing themselves by the abnormal expression of proteins including the Ki-67 (11).

The current study aimed at evaluating both P16 and Ki-67 as bio-markers in cervical intraepithelial neoplasia (CIN) and in invasive squamous cell carcinoma of cervix, and correlating the expression of these markers together in the cases with difficult interpretation, and helping in diagnosis and prognosis of cervical lesions.It ishoped that currentstudy improvestheunderstanding of the role of these molecules in the biology of cervical carcinogenesis.

Materials and methods

The current prospective study was conducted in the Department of Pathology, Postgraduate Institute of Medical Science, Rohtak, Haryana (India) from 2010 to 2012. The study was approved by the Ethical Committee of theinstitute. The studyincluded 50 cases withCIN and carcinoma cervix, and 10 caseswithbiopsies diagnosed as chronic cervicitis/inflammation induced dysplasia. The latter group served as control.

Brief clinical data were noted from case records, which included age, presentedsymptoms, address, and clinical diagnosis. All the cervical colposcopic specimens were subjected to careful and detailed gross examination;10% formalin fixed and paraffin embedded tissue sections from these specimens were used for microscopic study;4-5-µm thick sections were prepared and stained with hematoxylin and eosin (H&E) staining method for light microscopic examination and classified into benign and malignant lesions.

The cases of cervical pre-neoplasia were histologically graded by CIN classification as CIN I, II, and III (12).Immunohistostaining was performedsubsequently. The kits were obtained from BioGenex laboratories (Hyderabad, India) for P16 and from Dako laboratories for Ki-67. The applied antibodies were anti-P16/INK4a, mouse monoclonal antibody for P16, and MIB-1 for Ki-67. The staining was perfumedaccording to the manufacturer's protocol using peroxidase-antiperoxidase method.

Interpretation

brown color positivity (cytoplasmic/nuclear)

Expression and interpretation of p16 in cervical epithelium: Immunopositivity was considered when there was diffuse, intense, nuclear or cytoplasmic staining or both. Focal, moderate nuclear staining was also considered positive. Then, grading was performed for each case by the number of positive cells in different epithelial clusters as Grade 0, 1, 2, and 3, based on the number of positive cells, <1%, 1%-10%, 10%-50% and >50%, respectively (13).

Expression and interpretation of Ki-67 in cervical epithelium: For MIB-1, immunopositivity was considered when there was strong nuclear staining. Sincebasal staining was a normal finding, staining in the upper two-thirds of the epithelium was considered positive. Labelling indices (LI) were calculated for each case by evaluating the percentage positive nuclei and the cases were divided into four groups 0, I, II, and III, according to <1%, 1%-10%, 10%-20% and >20% positive nuclei, respectively (6).

The obtained results were statistically interpreted (mean, standard deviation, range, frequency distribution, percentages) withSPSS version 17.0. Where the data was qualitative, chi-square test was used to assess the association between these parameters.

P-value<0.05 was taken as significant (S) and <0.01 as highly significant (HS). Pearson's coefficient correlation was calculated. It hada value of 'r' between -1 and+1. The significance of correlation was evaluated using critical values table for Pearson's coefficient correlation (any value of r >0.273 irrespective of sign was significant with *P-value* ≤0.05).

Results

A total of 60 cases were selectedcomprising 10 cases withchronic cervicitis, 29 cases withCIN, and 21 cases withsquamous cell carcinoma (Table 1, Figure 1). The most common age groups included in the study were 36-40 and 41-45 yearsforming 21.66% of total. The mean age of the patients presentingwith chronic cervicitis was 48.8 ± 9.77 years. The mostcommon age group for CIN was 36-40 years, while 41-45 and 51-55 yearsfor carcinoma. Although there wasa positive correlation between age and the histopathological grade of the cervical lesion (CIN and carcinoma),it was statistically insignificant (*P* >0.05).

Table 1. Distribution of Cases of CIN According to Histopathological Grade

Diagnosis	No. of cases	Percentage
CIN I	8	27.58
CIN II	8	27.58
CIN III	13	44.8
Total	29	100

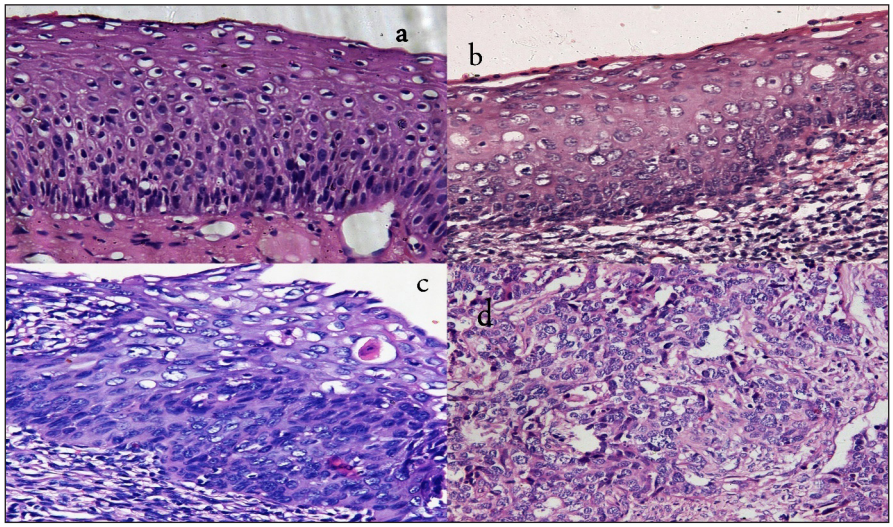

Figure 1. Photomicrographs showing- (a) CIN I, (b) CIN II, (c) CIN III & (d) carcinoma of cervix (H&E staining, 200X).

Sixcases withchronic cervicitis belonged to rural population and fourto urban population;fivecases withCIN I belonged to rural population and threeto urban population. In cases with CIN II,three cases were from rural population whereas fivefrom urban population;fourcases of CIN III were from rural population and ninefrom urban population. Amongst the cases with carcinoma, 17 belonged to rural population whereas fourbelonged to urban population. There was statistically significant difference in the residency of the patients withCIN and carcinoma indicated by *P-value* <0.05.

There was no expression of P16 in 10 (100%) cases withchronic cervicitis, while in the cases with CIN, it was expressed in 25 cases and in the cases with carcinoma it was expressed in 20 cases. There was statistically significant difference in the expression of P16 between chronic cervicitis, CIN, and carcinoma indicated by *P-value*<0.05. Four out of eightcases withCIN I showed grade II positivity, while onecase showed grade I and one caseabsent positivity. Out of the eight cases withCIN II, fivecases showed grade

II positivity, onecase showed absent positivity, one case grade I, and one case gradeIIIpositivity. Out of 13 cases withCIN III, 10 cases showed grade III positivity, while twocases showed grade II positivity and onecase showed absent positivity. There was statistically significant difference in the grades of P16 expression and histopathological grades of CIN indicated by *P-value* <0.05. Among the cases with carcinoma, maximum 18 cases showed grade III positivity and one case showed absent positivity, one case grade I and one case grade II positivity (Table 2, Figure 2).

Out of the 29 cases withCIN, 16 cases showed only nuclear positivity, three cases showed only cytoplasmic positivity, while sixcases showed both nuclear and cytoplasmic positivity. In the cases with carcinoma 11 cases showed both nuclear and cytoplasmic positivity while eightcases showed nuclear only and onecase showed only cytoplasmic positivity. As the histopathological grade of cervical lesion increased the staining of P16, it also increased from cytoplasmic to nuclear and to nucleocytoplasmic that was highly significant according to the *P-value*<0.01.

There was no expression of Ki-67 in 10 (100%) cases withchronic cervicitis, while in cases with CIN, it was expressed in 28 cases and in cases with carcinoma it was expressed in 100% of cases. The obtained data werestatistically significant (*P*<0.05) and showed positive association between the histological grade of cervical lesions and expression of Ki-67;fiveout of eightcases withCIN I showed LI I, while onecase showed LI II, one case LI III, and one case absent positivity. Out of eightcases withCIN II, fivecases showed LI II, twocases showed LI I, and onecase showed LI III. Out of 13 cases withCIN III, sevencases showed LI III, while sixcases showed LI II. The obtained data werestatistically highly significant (P<0.01);all cases withcarcinoma showed LI III (Table2, Figure 3).

The obtained data werestatistically significant (*P* <0.05) and showed positive correlation between the histopathological grade of cervical lesion, P16 grade, and Ki-67 LI.

Table 2. Corrlattion of P16 GRADE and Ki-67 Labelling Index with the Histopathological Grade of the Cervical Lesions

Cases	P 16 Grade					Ki-67 Labelling index				
	0	1	2	3	***value***	0	I	II	III	***P value***
Chronic cervicitis N=10	10	0	0	0		10	0	0	0	
CIN I N=8	2	2	4	0		1	5	1	1	
CIN II N=8	1	1	5	1	<0.05	0	2	5	1	<0.05
CIN III N=13	1	0	2	10		0	0	6	7	
Carcinoma N=21	1	1	1	18		0	0	0	21	

Pearson's coefficient for P16 grade = 0.693.
Pearson's coefficient for Ki-67 labelling index = 0.842.
P < 0.05.

ND-Not Done

Table 3. Comparison P16 and Ki-67 Immunoreactivity in Cervical Lesions by Different Authores with our study

S.N	STUDY	Correlation of P16 positivity with histologic grade	Correlation of Ki-67 positivity with histologic grade
1.	Klaes et al[5], 2001	Present	ND
2.	Murphy et al[9], 2004	Present	ND
3.	Aoyama et al[18], 2005	Present	Present
4.	Kalof et al[6], 2006	Present	ND
5.	Simionescu C et al[19], 2010	Present	Present
6.	Srivastava S[10], 2010	Present	Present
7.	Looi ML et al[20], 2011	Present	Present
8.	Present study	Present	Present

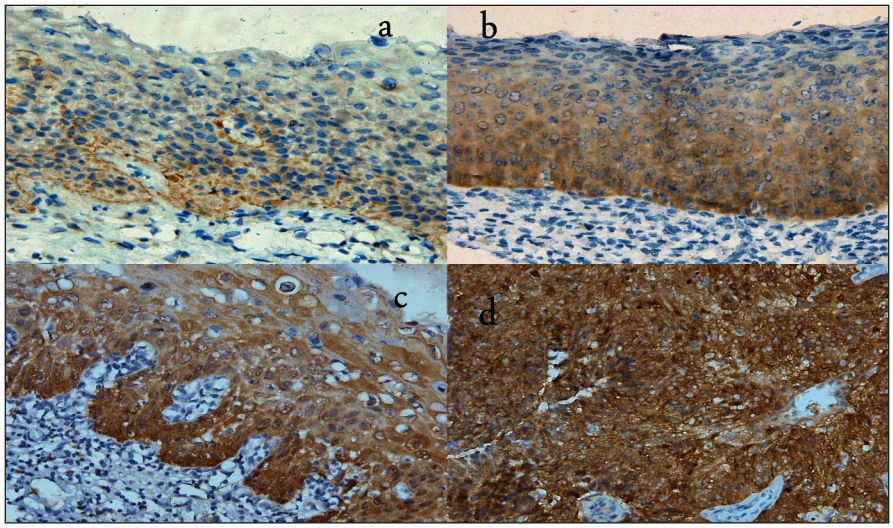

Figure 2. P16 immunostained photomicrographs showing- (a) CIN I – grade 2, cytoplasmic staining, (b) CIN II – grade 3, nuclear and cytoplasmic staining, (c) CIN III – grade 3, nuclear and cytoplasmic staining, (d) carcinoma of cervix – grade 3, nuclear and cytoplasmic staining (IHC staining, 200X).

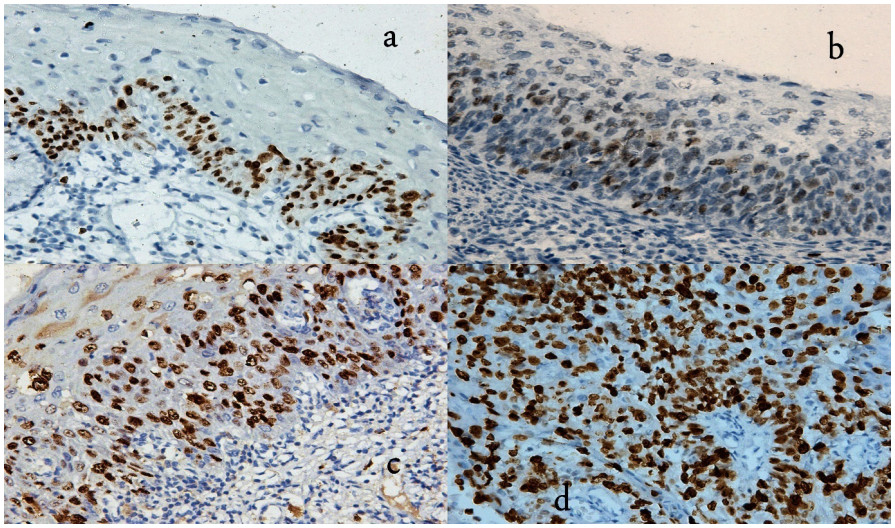

Figure 3. Ki-67 immunostained photomicrographs showing- (a) CIN I – labelling index I, nuclear staining, (b) CIN II – labelling index II, nuclear staining, (c) CIN III – labelling index III, nuclear staining, and (d) carcinoma of cervix – labelling index III, nuclear staining (IHC staining, 200X).

Discussion

The term dysplasia is employedwhen the mentioned atypical cytological features areaccompanied by a partial retention of normal maturation pattern and preservation of organization of the basal layer. Dysplasia is further subdivided into mild, moderate, and severe, depending on the severity of the changes. The terminology of cervical intraepithelial lesions is composed of squamous epithelium and is thought to represent the precursor of invasive carcinoma evolved over the years and continues changing today. The concept is of great practical and historical importance (14).

CIN I –mild dysplasia

CIN II –moderate dysplasia

CIN III/carcinoma in situ –severe dysplasia

Invasive squamous cell carcinoma is the most common malignant tumor of the female genital tract in most countries. Its incidence decreased in some countries in the last several decades; presumably as a result of widespread use of cervical cytological screening programmes (15). Carcinoma of the uterine cervix is the second most common and perhaps one of the foremost causes of cancer-related mortality in females. An estimated 4,93,000 new cases with 2,74,000 deaths occurred due to cervical cancer worldwide according to one recent analysis as reported in the year 2002 (16). In India, cervical cancer ranks the first most frequent cancer among females in the age range of15-44 years. The current estimates indicate that every year 132,082 femalesare diagnosed with cervical cancer and 74,118 die forthis disease in India alone (17).

Many different HPV types associated with CIN-are discovered including HPV 6, 11, 16, 18, 30, 31, 33, 34, 35, 39, 40, 42, and 51-58. However, they are divided into high- and low-risk categories based on their association with invasive cervical carcinoma, of which HPV 16, 18, and 31 are more commonly implicated in cervical carcinoma. Experimental data indicated that viral E6 and E7 genes of high-risk HPV E7 protein specifically bind to and inactivate pRb (retinoblastoma gene product) (15).

A wide array of potential bio-markers is evaluated for their diagnostic valuein cervical cancer and its precursors. Identification of these bio-markers in cervical neoplasia is necessary to distinguish CIN from other non-neoplastic cervical lesions to prevent under treatmentor overtreatment. Since HPV disrupts the normal cell cycle, leading to cell death, a number of genes/proteins are de-regulated;thereby, such genes/proteins can be used as surrogate diagnostic markers (18,19). Two markers with a potential in this direction are P16/INK4a and Ki-67.

P16/INK4a

P16/INK4a is a cyclin dependent kinase-4 inhibitor expressed in a limited range of normal tissues and tumors (20). HPV E7 protein binds and inactivates Rb; thereby, releases E2F which in turn can activate genes required for entry into S-phase of cell cycle, resulting in increased levels of P16 through negative feedback regulation. The pRb disruption leads to accumulation of the E2F transcription factor which in turn induces the overexpression of P16/INK4a (21).

Overall, previous studies by Aoyama C et al. ,Simionescu C et al., and Looi ML et al.showed a positive correlation between P16 expression and the grade of the CIN;ie, P16 expression increases as the grade of the lesion increases (22,23,24).The currentstudy wasin accordance with the results of the previous publications as shown in Table 3.

However, the current studyhad only one case of carcinoma negative for P16 protein, which is in concert with a study by Volgareva et al. (25). reporting that P16/INK4a negative carcinomas do exist. Another probable explanation, however, could be that in these P16 negative cases there is a suppression of its upregulation through epigenetic mechanisms, as mentioned previously, such as promoter methylation or through genetic mechanisms such as deletion or loss of heterozygosity. Tripathy et al. (26) from India, in a study on invasive cervical cancer showed P16 promoter hypermethylation and homozygous deletion in 6.5% and 8.7% of the samples, respectively. Thus, the current study concluded that cases withP16 negative squamous cell carcinoma do exist.

Morphological criteria by themselves are not useful to distinguish lesions that regress from the ones-

that have a tendency to progress (27).Several recent studies proved that P16 can serve as an excellent biomarker to identifycells infected with HPV and recognizethelesions with a propensity to progress to higher grades.

Ki-67

Ki-67, the marker of proliferation, was first identified by Gerdes J. in early 1980s. It is a nuclear non-histone protein and was named after the researcher's location. The *Ki-67* gene is located on the long arm of human chromosome 10 (10q25) (28). The *Ki-67* is universally expressed among proliferating cells and absent in quiescent cells. Although little is known about the exact function of the protein in cell division, *Ki-67* is expressed during GI, S, and GII phases of cell cycle with a peak during mitosis and an absence in G0 phase (29). The protein has a function of growth in human tumor and expression of this marker could suggest the degree of malignancy. The interaction of E6 and E7 HPV DNA withthe host cell disturbs the cell cycle, expressing themselves by the abnormal expression of proteins including Ki-67. Some studies show that Ki-67 immunohistochemistry positivity demonstrates the increasing proliferation in low and high grades of intraepithelial lesions (11).

In low-grade CIN lesions, Ki-67 positive cells were present in lower and middle one-third of stratified squamous epithelium, while in high-grade CIN lesions, Ki-67 positive cells were present in all layers of squamous epithelium. In the currentstudy, the results showed that the labeling index (LI) increasedas the histological grade of the cervical lesion increased, which wasin accordance with the findings of other studies by Srivastava(6),Simionescu et al.(23), and Looi et al. (24). as shown in Table 3.

The potential efficacyof determining the LI of tumors lies in the application of this knowledge to predict the behavior and prognosis of individual tumors and formulate treatment strategies based thereon. Useful information is gained in this respect for a number of tumors (30).

Conclusion

In a tropical country such asIndia, any premenopausal femalereferring to the gynecological outpatient department with any complaint is subjected to a single Pap smear test. However, single Pap test is subjected to suboptimal sensitivity, limited reproducibility, and many a times with high rate of false positive and false negative along with equivocal results. To compensate for the aforementioned deficiencies, a screening program with repeated testing, and follow-up of positive cases is warranted. Moreover, colposcopically directed biopsy is performedin any suspicious case. This subjects the patient to unnecessary surgical intervention. This overdiagnosis followed by overtreatment, affects the reproductive life of young females and also hasemotional consequences. Therefore, additional diagnostic and prognostic markers to detect cervical cancer precursors are required to save the patients from surgical intervention and high screening cost associated with repeated testing. Also, biomarkers that can help withscreening, detection, diagnosis, and prognosis of the disease as well as reducing equivocal diagnosis of suspect lesions can guidethe clinicians in correct management of the patients. P16 and Ki-67 are two such candidate markers that fit well in the above mentioned criteria.

Conflict of Interest

The authors declare that there was no conflict of interest.

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