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Original Article

Role of p16 and Ki-67 immunostains in the diagnosis of cervical intraepithelial lesions or malignancy

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ABSTRACT

Background: Cervical cancer ranks as the fourth most common cancer in women worldwide. Accurate histologic interpretation of cervical intraepithelial neoplasia is often challenging due to significant interobserver variability. Immunomarkers such as p16/INK4a and Ki-67 have emerged as valuable tools in detecting high-risk HPV-associated dysplasia, and minimizing diagnostics inconsistencies.

Materials and Methods: A prospective cross-sectional study was carried out between June 16, 2019, to June 14, 2020, at Department of Pathology, Tribhuvan University Teaching Hospital, Nepal. Of 117 cervical biopsies received, 111 of these were included in the study. p16 and Ki-67 immunostaining were done on 71 cases with suspected intraepithelial lesion or malignancy.

Results: Among 111 cases, chronic cervicitis was most common [58 (52.70%)], followed by premalignant lesions [33 (30.63%)] and invasive carcinoma [20 (17.11%)]. None of the cases of chronic cervicitis expressed p16, while 24 (73%) premalignant lesions and 17 (94.73%) invasive carcinomas were positive. Ki-67 score was 0 in 15 (83.30%) cases of chronic cervicitis but premalignant lesions and invasive carcinomas showed increasing positivity (scores 1-3). A significant correlation was observed between Ki-67 score and cervical neoplasia grade (p-value < 0.001). Concordance between H&E diagnosis and final diagnosis after IHC was 88% ($\kappa = 0.853$, $P < 0.05$).

Conclusions: p16 and Ki-67 can be used as complementary, surrogate markers for HPV related cervical neoplasia and help in confirming the histologic diagnosis. These immunostains aid in accurate diagnosis of cervical intraepithelial lesions by reducing interobserver variability and aid in the distinction between reactive and neoplastic changes.

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INTRODUCTION

Globally, cervical cancer is one of the most common cancers among women, and its prevalence is estimated to be 604,127, with 341,831 deaths. The corresponding age-standardized incidence is 13.3 cases per 100,000 women-years (95% CI 13.3–13.3), and the mortality rate is 7.2 deaths per 100,000 women-years.[1] In Nepal, Cervical cancer is the second most common cancer among women with an incidence of 7.7%, and fourth leading cause of cancer related death in women.[2] However, cervical cancer is a preventable disease with a long period of precancerous stage, in which detection and timely treatment can prevent cancer. Early detection and treatment

of invasive carcinoma are the key to reducing cancer related morbidity and mortality.

The most common cause of dysplasia and subsequent cervical carcinoma is the Human Papilloma Virus (HPV), which is categorized as low risk (HPV type 6, 11, 42, 43, 44, and 53) and high-risk types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82) based on their association with cervical carcinoma.[3,4] Persistent infection of high-risk HPV is associated with the development of cervical cancer.[5,6]

In HPV-associated tumors, the inactivation of the RB gene by E7 leads to markedly increased levels of p16INK4a. This p16INK4a is a cyclin-dependent kinase inhibitor that regulates the activity of cyclin-dependent kinases 4 and 6 and is often inactivated in many cancers by genetic deletion or hypermethylation. The presence of strong and diffuse block-positive p16 staining has been shown by many studies to correlate with the presence of high-risk HPV that has integrated into the host genome and supports a diagnosis of Squamous intraepithelial lesion.[7,8]

Similarly, Ki-67 is a nuclear protein expressed only in an active phase of the cell cycle (G1, S, G2, and M phases), and not in resting phases (G0). Since HPV infection leads to increased epithelial cell proliferation in infected tissue, increased Ki-67 staining can also be an indicator of HPV.[9]

Thus, p16 and Ki-67 can be used as additional tools to improve the accuracy of histopathologic diagnosis in the cervix by offering a more objective, reproducible, and precise method for diagnosing and grading cervical neoplasia. Additionally, they help in the early detection of high-grade lesions, reducing overtreatment of low-grade cases and enhancing risk stratification for cervical cancer prevention. The use of immunostains p16 and Ki-67 is a relatively simple technique that is still not widely available in all centers in our region.

Through this study, we aim to increase familiarity with the method and improve proficiency in its interpretation. Our main goal is to assess the role of p16 and Ki-67 immunostaining in the diagnosis of cervical intraepithelial neoplasia.

MATERIALS AND METHODS

The study was a prospective cross-sectional study conducted in the Department of Pathology at the Institute of Medicine, Tribhuvan University Teaching Hospital, Maharajgunj, Kathmandu, Nepal, from June 16, 2019, to June 14, 2020 (12 months). During this period, 117 cervical biopsies were received in the Department of Pathology, and 111 biopsies were included in the study. The sampling method was non-probability, convenience sampling. Samples with insufficient tissue or the absence of epithelium were excluded from the study. Cases of chronic cervicitis, intraepithelial lesions, and malignancy were included.

All the received samples were submitted to the histopathology laboratory for processing and preparation of Hematoxylin and Eosin-stained sections. After careful examination of H and E slides, p16 and Ki-67 immunostaining was performed in 71 cases of cervical biopsies that included 18 cases of chronic cervicitis, where there was suspicion of premalignant lesion, and all cases were diagnosed on routine H and E as intraepithelial lesion or malignancy. The cases in which there was no suspicion of intraepithelial lesion or malignancy did not undergo immunohistochemistry. Sections were examined by two pathologists, and scoring of IHC was done according to the following criteria:

Interpretation of staining results

The results for p16 and Ki-67 were scored by a semi-quantitative scoring system as described below.[10,11]

Table 1: Scoring system used for assessment of p16INK4a

Scoring of p16INK4a	Interpretation
Score 0	No p16INK4a positivity or patchy staining
Score 1	Low intensity, diffuse positivity restricted to the lower one-third part of the epithelium.
Score 2	Continuous positivity in the lower two-thirds of the epithelium
Score 3	Diffuse full-thickness staining

Score 0 was considered negative for p16 immunostain; scores 1, 2, and 3 were considered positive for p16 immunostain.

Table 2: Scoring system used for assessment of Ki-67

Scoring of Ki-67*	Interpretation
Score 0	< 10% staining
Score 1	10-30% staining
Score 2	30-50%staining
Score 3	>50% staining

*Assessment was done at the suprabasal layers.

The association of p16 and Ki-67 expressions with cervical intraepithelial lesion (CIN) grade was evaluated with the Chi-square test using the software SPSS version 24.0. The results with a p-value smaller than 0.05 were regarded as statistically significant.

RESULTS

During a period of one year, a total of 117 cervical biopsies were received in the Department of Pathology, TUTH. One hundred and eleven cases of cervical biopsies were included in this study. Out of six excluded cases, four cases showed suboptimal tissue, and two cases were known cases of cervical dysplasia. Hence, these six cases were excluded. The age range was 21-86 years. The median age was 42 years. On initial histopathological examination with H&E stain, the majority of cases were chronic cervicitis [58 (52.2%)] followed by the premalignant lesion [34 (30.63%)] and invasive carcinoma [19 (17.11%)], as shown in Table 3.

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Table 3: Histologic diagnosis of cervical biopsies

S.N.	Histopathological diagnosis	Number of cases n (%)
1	Chronic cervicitis	58 (52.2)
2	CIN* 1	21 (18.9)
3	CIN 2	02 (1.8)
4	CIN 3	10 (9.0)
5	Squamous cell carcinoma	16 (14.41)
6	Adenocarcinoma in situ	01 (0.9)
7	Adenocarcinoma	03 (2.7)
	Total	**111 (100)**

*Cervical Intraepithelial Neoplasia

All the cases of chronic cervicitis and 26% (9 of 34 cases) of premalignant lesions did not show p16 expression. However, 73% of premalignant lesions and 94.73% of invasive carcinomas were positive for p16 immunoexpression, as shown in Table 4. One case of Adenocarcinoma was negative for p16 immunostain.

Table 4: Expression of p16 in cervical biopsies

Histological Diagnosis on H&E stain	Positive (%)	Negative (%)	Total (%)
Chronic cervicitis	00	18 (100)	18 (25.35)
CIN* 1	13 (61.90)	08 (38.09)	21 (29.57)
CIN 2	01 (50)	01 (50)	02 (2.81)
CIN 3	10 (100)	00	10 (14.08)
Adenocarcinoma in-situ	01 (100)	00	01 (1.4)
Squamous cell carcinoma	16 (100)	00	16 (22.53)
Adenocarcinoma	02 (66.67)	01 (33.33)	03 (4.22)
Total (%)	**43 (60)**	**28 (40)**	**71 (100)**

*Cervical Intraepithelial Neoplasia

All the cases of Squamous cell carcinoma (SCC) and 90% of CIN 3 showed score 3 expression with p16 immunostain. Among 21 cases of CIN 1, 13 cases showed positive p16 immunostain, of which 43% showed score 1 and 19% showed score 2 staining. Among the two cases of CIN 2, one showed score 2 staining and the other was negative, as shown in Table 5. The score of p16 expression correlated well with the grade of cervical neoplasia (P< 0.001).

Table 5: Score of p16 expression in Squamous intraepithelial lesions and Squamous cell carcinoma

Histological diagnosis on H&E stain 0		Expression of p16 0	1	2	3	Total
CIN* 1	Number of cases (%)	08 (38.09)	09 (42.85)	04 (19.04)	00	21
CIN 2		01 (50)	00	01 (50)	00	02
CIN 3		00	01 (10)	00	09 (90)	10
SCC**		00	00	00	16 (100)	16
Total (%)		**09 (18.36)**	**10 (20.40)**	**05 (10.20)**	**25 (51)**	**49 (100)**

*CIN: Cervical Intraepithelial Neoplasia; **SCC: Squamous Cell Carcinoma

Out of 34 cases of premalignant lesions, 30 cases showed scores 1 to 3, and four cases showed score 0. Of the 19 cases of invasive carcinomas, 18 cases showed scores 1 to 3. Score 0 was seen in 15 of 18 cases (83.3%) of chronic cervicitis, as shown in Table 6. The score of Ki-67 expression correlated well with the grade of cervical neoplasia (P< 0.001).

Table 6: Ki-67 expression in various premalignant and malignant lesions

Histological diagnosis in H&E stain 0		Expression of Ki-67 n (%) 0	1	2	3	Total
Chronic cervicitis	Number of cases (%)	15 (83.3)	03 (16.7)	00	00	18
CIN* 1		03 (14.3)	16 (76.2)	02 (9.5)	00	21
CIN 2		01 (50)	00	01 (50)	00	02
CIN 3		00	01 (10)	00	09 (90)	10
Adenocarcinoma In-situ		00	00	00	01 (100)	01
Squamous cell carcinoma		00	04 (25)	03 (18)	09 (56.2)	16
Adenocarcinoma		01 (33.3)	01 (33.3)	00	01 (33.3)	03
Total (%)		**20 (28.2)**	**25 (35.2)**	**6 (8.45)**	**20 (28.2)**	**71 (100)**

*CIN: Cervical Intraepithelial Neoplasia

Of 33 cases with histologic diagnoses of the squamous intraepithelial lesion on H&E stain, three cases were downgraded to reactive atypia, and one case was downgraded to CIN 1, after evaluation of immunostains. Four cases diagnosed on H&E as CIN 1 were upgraded to CIN 2 following p16 and Ki-67 immunostain. Following immunostain, CIN 1, CIN 2, and CIN 3 were 16, 05, and 09 cases, respectively, as shown in Table 7. The overall agreement between H&E diagnosis and final diagnosis after IHC was 88% ($\kappa = 0.853$, $P < 0.05$).

Table 7: Comparison of Histological diagnosis on H&E stain with Final Diagnosis with p16 and Ki-67 immunostain in squamous intraepithelial lesions

S.n.	Histologic diagnosis on H&E stain	Number of cases (n)	Final diagnosis after IHC (Number of cases) Chronic cervicitis with reactive atypia	CIN 1	CIN 2	CIN 3
1	CIN* 1	21	02	15	04	0
2	CIN 2	02	01	0	01	0
3	CIN 3	10	00	01	0	09
4	**Total**	**33**	**03**	**16**	**05**	**09**

*CIN: Cervical Intraepithelial Neoplasia

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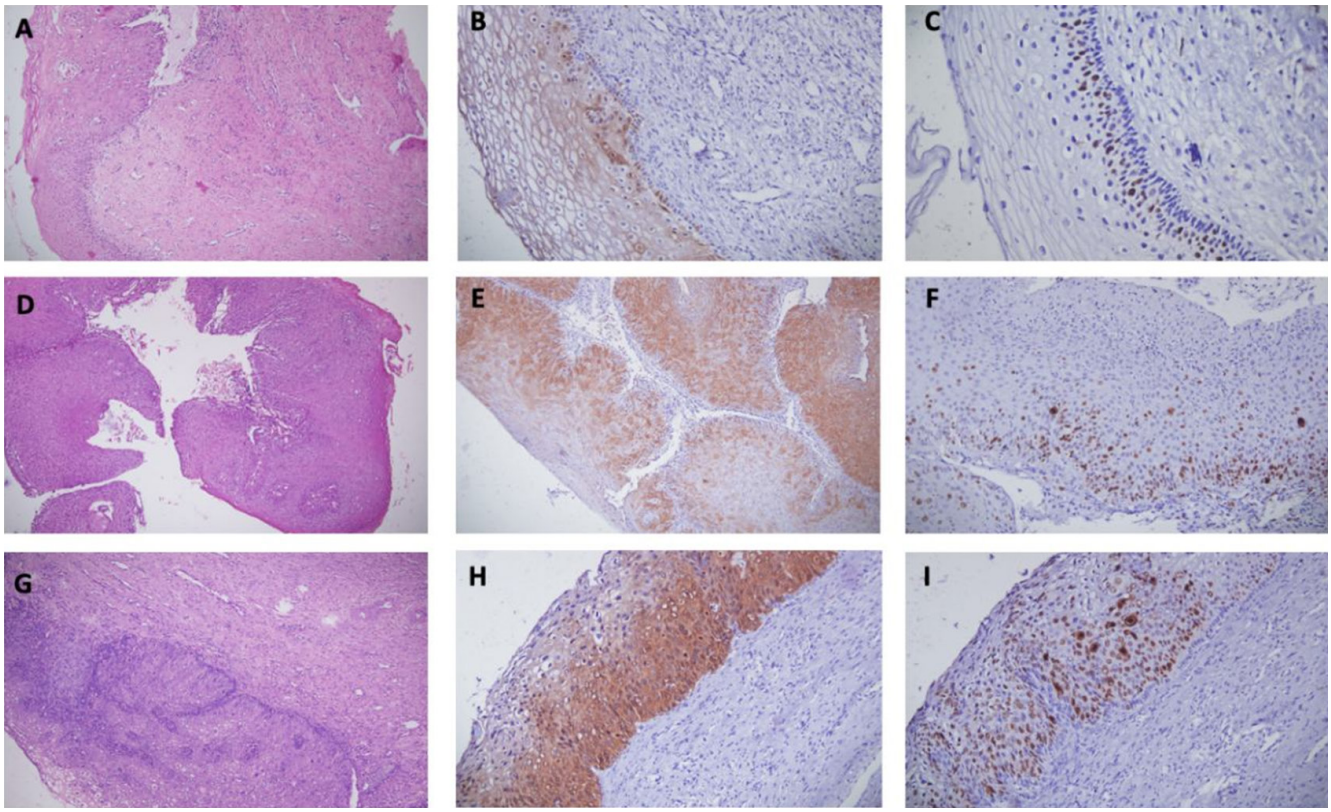

Figure 1: *A-C. CIN-1, H&E (A), p16 (B), Ki67 (C); D-F. CIN-2, H&E (D), p16 (E), Ki67 (F); CIN-3, H&E (G), p16 (H), Ki67 (I). [100x]*

DISCUSSION

Several studies have shown that conjunctive interpretation of p16 and Ki-67 stained slides could significantly improve the routine interpretation of cervical histopathology.[8,12-16] In our study, expressions of p16 and Ki-67 were scored from Scores 0 to 3. In a study by Shrivastav, in 63 cervical biopsies 100% of HSIL and LSIL showed p16 positivity, whereas in our study 83% of HSIL and only 62% of LSIL showed p16 expression.[17] 38% of LSIL did not show any p16 expression.[17] Our findings were similar to the findings of Ruediger et al., in which 60% of CIN 1 had p16 expression, while 40% did not show expression with p16 immunostain. p16 positivity is related to disease progression and high-risk HPV type.[7,18-21] A three-year follow-up study by Stefania et al. in Italy showed that the 216 patients (29%) with p16-positive CIN1 had a higher progression rate (12.3%) than the 523 patients with p16-negative CIN1 (2.2%) in the first year of follow-up. In the second and third years, differences were smaller and not significant. Moreover, the patients with p16-positive CIN1 also had a lower rate of regression to normal in the first year of follow-up and non-significant changes in the second and third years.[19] Likewise, another study done by Alberto et al. observed similar findings.[22] A follow-up in our cases will be needed to affirm the above findings.

There were only two cases of CIN 2 in this study on the initial H&E stain. One case was negative for p16 and showed a score of 0 Ki-67 expression, so it was downgraded to reactive atypia, and the diagnosis of another case was supported by positive p16 and Ki-67 stain (Tables 3, 4, 5, 6, and 7). CIN 2 is an equivocal diagnosis that can mimic both CIN 1 and CIN 3 as well as benign lesions. The CAP-ASCCP LAST Project recommends the use of p16 when considering the diagnosis of CIN 2.[23.] A large population-based National Cancer Institute study of women from Costa Rica found the diagnosis of CIN 2 to be significantly less reproducible than CIN 3. Two review pathologists agreed with 13% and 31% of CIN 2 diagnosis compared to 84% and 81% diagnosis of CIN 3.[24]

In a study done by Ruediger et al., 96% (58 out of 60 cases) of Invasive carcinoma of the cervix showed p16 expression. It included 98% of squamous cell carcinoma and 86% of Adenocarcinoma.[7] In our study, 100% of squamous cell carcinoma showed p16 expression, but only two out of three cases of Adenocarcinoma showed expression of p16 immunostain (Table 4). A study by Sano et al. showed an even lower frequency of p16 expression in the cases of Adenocarcinoma, with only 1 out of 5 cases of adenocarcinoma being positive for p16. When they correlated the findings of p16 expression with HPV status, they found these tumors to be HPV negative.[21]

Lars-Christian et al. proposed that p16 improves interobserver agreement in the diagnosis of cervical intraepithelial neoplasia. In their study, they observed significant discrepancies in the diagnostic interpretation of H&E-stained slides, particularly low-grade lesions, and there was a significantly better agreement in the interpretation of

p16 expression.[25] Similarly, Mark et al. and Rudiger et al. demonstrated an excellent interobserver agreement in the diagnosis of CIN with p16 IHC slides.[26,27] In our study also, four cases were upgraded to CIN 2 from CIN 1 following p16 immunostain showing score 2 expression. (Tables 4, 5, and 7)

A study by Nicholas et al. on 569 cervical biopsies showed that the degree of p16 and Ki-67 expression correlated with the degree of cervical neoplasia ($p<0.0001$). They found that there was no relation between p16 overexpression and inflammation. However, Ki-67 expression correlated with inflammation ($p=0.003$), similar to our study in which score 1 Ki-67 expression was observed in 16% of non-neoplastic cervical lesions (Table 6). Though Ki-67 expression is a sensitive marker of cervical neoplasia, overexpression is linked to both inflammation and reactive changes.[16]

Samawardana et al. have shown that p16 and Ki-67 co-expression was present in almost all high-grade squamous and glandular lesions and rarely in benign conditions, and that the markers in combination were more sensitive and specific than either of them used in isolation.[28] In our study, among 21 cases of CIN 1 on initial H&E stain, six cases showed negative p16 staining. However, the diagnosis of CIN 1 was favored by a score of 1 for Ki-67 expression.

In a study by Rananjit et al., they found that a combination of p16 negativity and absence of Ki67 staining beyond the lower third of the epithelium almost rules out high-grade lesions, and p16 positivity combined with increased expression of Ki-67 staining beyond the lower third of the epithelium was highly suggestive of high-grade lesions.[29] Similarly, in this study, three cases were downgraded to reactive atypia and four cases were upgraded to CIN-2 following p16 and Ki-67 staining (Table 7).

The overall agreement between H&E-only diagnosis and final diagnosis after IHC was 88% ($\kappa = 0.853$, $P < 0.05$) in this study. Though H&E and final diagnosis show strong agreement, there were discrepancies in the interpretation of cervical intraepithelial neoplasia in H&E stain alone. Various studies showed an improved interobserver agreement of the diagnosis of CIN with the conjunctive use of H&E morphology with p16 and Ki-67 immunostain than H&E morphology alone.[15,28]

The limitations of the study were that it was limited to a single institution. Therefore, the study could only be applied to those patients attending our hospital and only in the short period during which it was available. This may limit the generalizability of the findings to other populations or clinical settings. Also, this study focused solely on diagnostic correlation without any clinical follow-up to assess treatment outcomes or progression, which would have added prognostic value.

The use of immunohistochemistry in improving the diagnosis has been described above, and in the future, it would be most useful to have this as part of a diagnostic process.

CONCLUSIONS

Cervical cancer is a preventable disease with a long period of premalignant state, and most of them are associated with high-risk HPV. Despite the high accuracy of H&E stain in the interpretation of cervical biopsy, there is a risk of underdiagnosis as well as overdiagnosis in the grading of CIN on H&E alone. Reactive atypia is also a pitfall in the diagnosis of these premalignant diseases. Conjunctive interpretation of p16 and Ki-67 stained slides in cases suspicious of cervical intraepithelial lesions and malignancies helps improve the routine interpretation of cervical histology and thus contributes to improving the quality of current cervical screening programs. This is one of the few studies from Nepal highlighting how simple, cost-effective IHC markers like p16 and Ki-67 can meaningfully reduce diagnostic uncertainty and optimize patient management, especially in settings with limited access to advanced molecular diagnostics.

Conflict of interest: None

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