Spectrum, Clinicopathologic Profile, and p16 Expression Pattern of Nonmalignant Cervical Tissues in Enugu, South-East Nigeria

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Abstract

Background p16 is a marker for p16-induced transformation of high-risk human papilloma virus (hrHPV)-infected cervical epithelium. HPV is a known etiologic agent of cervical cancer. Persistent hrHPV infection of cervical epithelium causes transformation of the infected epithelial cells resulting in increased proliferative potential of the cells and subsequent progression to frank malignancy. Early detection of transformation in cervical cells is crucial in reducing morbidity and mortality associated with cervical cancer.

Materials and Methods We aimed to study the clinicopathologic profile of nonmalignant cervical lesions and their p16 staining pattern. Histopathology requisition forms, blocks, and slides of cases containing cervical tissue with nonmalignant diagnosis received into the morbid anatomy department of University of Nigeria Teaching Hospital, Enugu, from 2009 to 2018 were studied. Fresh sections from the blocks were immunohistochemically stained with p16 and examined.

Results One-hundred and ninety-one cases were studied. Majority of the cases are normal cervical epithelium. Chronic nonspecific cervicitis was the major non-neoplastic lesion present and accounted for 33.3% of the biopsy and the mean age was 50.5 years. Other lesions were nabothian cyst (8.4%), cervical polyp (10.5%), low-grade and high-grade squamous intraepithelial lesion (LSIL and HSIL; 6.3 and 2.6%, respectively). The mean age for LSIL was 40.3 years, while that of HSIL was 45.2years. Four LSIL, two HSIL, one polyp, one chronic nonspecific cervicitis, and one lobular endocervical hyperplasia stained positively with p16.

Conclusion The most common benign lesion of the cervix is cervicitis. Chronic cervicitis is negative to p16 immunoreactivity. There are more low-grade cervical intraepithelial neoplasia (CIN) than high-grade CIN. The low-grade CIN overexpress p16 in one-third of cases. There are more cases of p16-negative high-grade CIN in this study.

Keywords
- cervical lesions
- immunohistochemistry
- p16

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Introduction

Cervical cancer is the commonest cancer of the female genital tract and a major contributor to cancer mortality in Nigeria.[1,2] Human papillomavirus (HPV) DNA has been shown to be present in more than 99% of cancers of cervical epithelium.[3] Cervical cancer develops from the persistence of high-risk HPV (hrHPV) infection passing through sequential precancerous stages. The E6 and E7 viral oncoproteins have been shown to promote cell cycle by causing the inactivation of key regulators of cell cycle, p53 and Rb, respectively.[3] Persistent hrHPV infections with consequent deregulated production of these viral oncoproteins result in immortalization of infected cervical epithelial cells and their consequent transformation following incurrence of other relevant genetic mutations.[3]

Several markers have been studied for their potential utility in clinical setting to detect HPV transforming infections, high-grade cervical intraepithelial neoplasia (CIN) and cancers. $p16^{INK4A}$ (p16) seems to be a valuable marker either alone or in combination with other markers in detecting hrHPV-mediated transformation of cervical epithelial cells and neoplasia.[4,5] p16 is an inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6)mediated phosphorylation of pRb in G1-S transition and has a reciprocal relationship with pRb.[6] It is overexpressed in cervical cancers and vast majority of cervical epithelial precancers but its level of expression is very low (undetectable to focal weak expression) in normal cervical epithelial cells and non-neoplastic lesions of the cervix.[7] HPV E7 is believed to trigger p16 expression by involving histone demethylase KDM6B and epigenetic reprogramming.[8] p16 in turn maintains high levels of E7 oncoprotein. The use of p16 in identifying HPV-related diseases is based on its expression being directly linked to the HPV oncogenic action, and its independence on the HPV type.[6] It has also been found useful in predicting the progress of low-grade intraepithelial lesions. p16-positive CIN1 has been shown to be at higher risk of progressing to CIN 2/3 and invasive cancer than p16-negative CIN 1.[9] When added to morphologic interpretation, p16 improves agreement between pathologists in the diagnosis of CIN2+ diseases.[10] p16 has also been effectively used in cervical biopsies to discriminate between cervical precancer and its benign mimics such as immature squamous metaplasia, severe atrophy, reparative epithelial changes, and tangential sectioning.[11] Accurate histopathological interpretation of cervical biopsy specimens, following abnormal cytology results, is an important guide in the management of cervical abnormalities. It is, therefore, necessary to properly classify and grade abnormalities of the cervix. Significant variation exists in the histopathological interpretation of cervical abnormalities among pathologists,[12] leading to aggressive management of otherwise benign lesions and in some cases missed and/or delayed treatment of high-grade lesions. We aimed to study the clinicopathologic profile and p16 staining characteristics of nonmalignant cervical tissues seen in University of Nigeria Teaching Hospital (UNTH) over a 10-year period.

Materials and Methods

Scope of Study

The scope of this study was limited to the clinical clinicopathological profile and p16 staining pattern of all nonmalignant cervical tissue in UNTH, Enugu between January 2009 and December 2018.

The Study Design

This study was a 10-year retrospective study carried out in the morbid anatomy department of UNTH, Enugu. The study involved analysis of requisition forms, slides, and tissue blocks of all cervical tissue received in morbid anatomy department of UNTH including hysterectomy specimens. Immunohistochemical studies with p16 antibody (clone: 16P04 JC2, prediluted, source: Bio SB, California, United States) were used on fresh sections from the tissue blocks.

Inclusion Criteria

Only cases histologically diagnosed as normal cervix, cervicitis, reactive changes, and CIN between January 2009 and December 2018 were selected.

Exclusion Criteria

Cases for histology that were found to be inadequate or not representative were excluded from the study. Histologically confirmed cases of invasive cervical cancers were not part of this study.

The Procedure

Four-hundred and twenty-six (426) cervical specimens were received in the department within the period of this study. Two-hundred and one (201) of the cervical specimens (47.2%) were histologically confirmed to be malignant, while two hundred and twenty-five (225), constituting 52.8% of the specimens, were histologically nonmalignant. A total of 191 cases met the inclusion criteria and their slides were reviewed and reclassified morphologically. However, only 164 of these had sufficient tissue in their tissue blocks for immunohistochemistry; hence, only these were stained with p16 immunostain.

The age range of the patients in the study was from 16 to 78 years with mean age of 48.6 years. Majority of the patients were between 40 and 59 years and constituted 63.3% of the patients in the study (►**Table 1**).

The archival slides were reviewed and their diagnosis confirmed. For cases in which archival slides were not found or damaged, fresh sections were made from the tissue blocks and stained with hematoxylin & eosin (H&E) stains, and examined. The lesions were reclassified.

Then fresh sections of 2 to 3 microns were made from each tissue block and placed on negatively charged microscopic slides. The tissue sections on the slides were then stained with 200 µL of Mouse Anti-Human p16INK4a (clone: 16P04 JC2, prediluted, source: Bio SB, California, United States). Biopsies from a known p16-positive squamous cell carcinoma from the cervix was used as positive control, while tissue from normal cervix was used as negative control.

Table 1 Frequency of cervical lesions in different age groups

	<30	30–39	40–49	50–59	60–69	≥70	Total
Normal cervix	0	10	28	17	13	1	69
Chronic cervicitis	3	5	17	28	7	3	63
Nabothian cyst	0	3	1	4	2	0	10
Cervical polyp	3	5	12	2	3	1	26
Low-grade CIN	0	5	5	2	0	0	12
High-grade CIN (CIN2/3)	0	2	1	2	0	0	5
Atrophic cervicitis	0	0	0	1	2	0	3
Lobular endocervical glandular hyperplasia	1	0	0	0	0	0	1
Acute cervicitis	0	1	1	0	0	0	2
Total	7	31	65	56	27	5	191

Abbreviation: CIN, cervical intraepithelial neoplasia.

The steps are as follows:

The tissue sections on the slides were placed in an oven for 20 minutes at 60°C to remove water and melt the paraffin. The sections on the slides were deparaffinized by putting them in a xylene solution for 5 minutes with a repeat of the process to ensure complete removal of the embedding medium. The deparaffinized tissue sections were hydrated by passing them through decreasing concentrations of alcohol at 95 and 70%, allowing the slides to stay for 3 minutes in each solution and after which they were rinsed in running tap water for 30 seconds or more.

The epitope retrieval step was done by placing the slides in a diluted epitope retrieval solution (provided with the kit) that was heated to 90 to 95°C in a hot water bath and then incubated at this temperature for 10 minutes. Then the slides with the solution were removed from the water bath and allowed to cool at room temperature for 20 minutes or more. After this the slides were washed in a wash buffer by soaking the slides in the buffer for 5 minutes. Then peroxide blocking reagent (3% hydrogen peroxide, containing 15 mmol/L sodium azide (NaN3) was applied to cover the specimens and incubated for 5 minutes. The excess peroxide blocking reagent was tapped off and the specimens rinsed in a wash buffer for 5 minutes.

The excess wash buffer was removed, and the specimens covered with 200 µL of primary antibody (Mouse Anti-Human p16INK4a or Negative Reagent Control) and incubated for 30 minutes. After the incubation, the specimens were washed in a wash buffer bath for 5 minutes. The excess wash buffer was removed and the specimen covered with 200 µL of Horse Radish polymer (visualization reagent) and incubated for 30 minutes. After removing the excess solution, the specimens were rinsed in wash buffer bath for 5 minutes and repeated with a fresh wash buffer.

The specimens were covered with 200 µL of substrate-chromogen solution (3, 3′ diaminobenzidine chromogen solution prepared according to manufacturer's direction) and incubated for 10 minutes after which the excess was tapped off and the specimen rinsed in deionized water. The slides were then counterstained by immersing in a hematoxylin bath for 3 to 5 minutes. The hematoxylin was washed off by placing the slides in a tap water bath and the specimen gently rinsed in a running tap water. The cover slips were placed on the sections using permount and the slides allowed to dry.

The stained slides were assessed based on the following criteria:

a. Localization of staining cells in relation to layers of squamous epithelium: basal, intermediate, or superficial;
b. Distribution of staining cells: negative, sporadic, focal, or diffuse.
c. Staining intensity: weak, moderate, or strong.

Positive staining defined as strong nuclear or nuclear plus cytoplasmic staining in a continuous segment of at least 10 cells, and involving the basal and parabasal layers in squamous epithelium was applied.[13] Cytoplasmic only staining, diffuse bluish/weak intensity staining, focal or patchy staining patterns, single scattered cells blob-like staining were considered negative.[13]

The p16 staining pattern in the low-grade CIN was focal and limited to the lower one third (►**Fig. 1**). This was similar to the staining on the cervical polyp, chronic cervicitis, and lobular endocervical glandular hyperplasia. The staining was limited to the stratified squamous epithelial lining which on H&E showed mild koilocytic change. The intensity of the staining was strong on the nuclei of the cells but weak on the cytoplasm of some cases. In high-grade CIN, the staining was diffuse/continuous, of strong intensity, and extended to and beyond the upper two-thirds of the epithelium (►**Fig. 1**). There were both the nuclei and cytoplasmic staining.

Data Analysis

The data was analyzed and tabulated using the SPSS 24 statistical package. The chi-squared test was used for comparison of discontinuous variables, and *p*-value of less than 0.05 is considered significant.

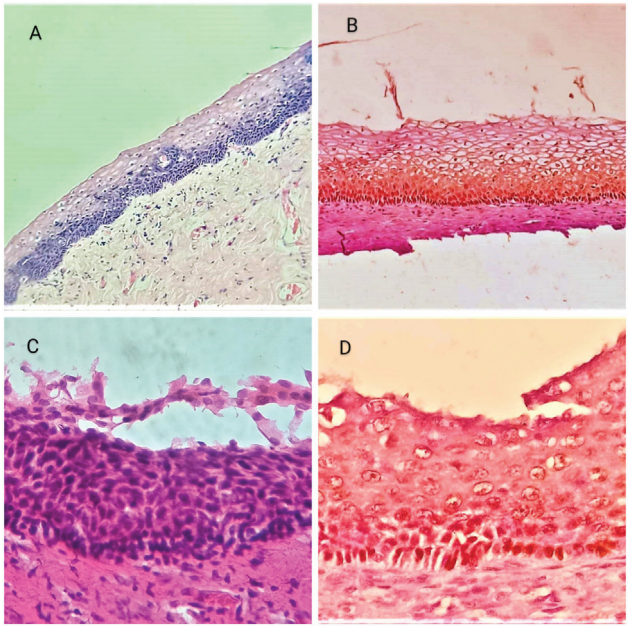

Fig. 1 (**A**) Low-grade cervical intraepithelial neoplasia (hematoxylin and eosin [H&E], X100). (**B**) p16-positive low-grade cervical intraepithelial lesion with strong nuclear and cytoplasmic staining (p16, X100). (**C**) High-grade cervical intraepithelial neoplasia (H&E, X100). (**D**) High-grade cervical intraepithelial neoplasia showing strong nuclear and weak cytoplasmic staining (p16, X100).

Results

Abnormal vaginal bleeding was the commonest presenting symptom and indication for cervical biopsy or hysterectomy (►**Table 2**). Seventy-seven (77) patients (40.3%), presented with abnormal bleeding, of which postmenstrual bleeding (37.3%) followed by postcoital bleeding (26.5%) was the major form of abnormal bleeding patterns seen in these patients. Vaginal discharge was seen in 17 patients (8.9%), while uterovaginal prolapse was seen in 10 patients (5.2%). The rest of the patients presented no symptoms but had cervical biopsy for either abnormal Pap smear results 12 (6.3%), or abnormal colposcopy findings 58(30.4%).

The histopathological diagnoses were normal cervix (in which there were insignificant minimal histopathological alteration of the cervical tissue), cervicitis (which comprises chronic non-specific cervicitis, acute cervicitis, and atrophic cervicitis), endocervical polyps, nabothian cyst, lobular endocervical glandular hyperplasia, and premalignant lesions. Normal cervix 69(36.1%) was the most common diagnosis in this study (►**Table 1**).

Sixty-three cases of chronic cervicitis constituted 33.0% of all the histopathological diagnoses and 92.6% of cervicitis. The mean age of patients with chronic cervicitis was 50.5 years and the patients were aged between 26 and 72 years. The peak age incidence was 50 to 59 years, having 28 cases (44.4%). There were two (2) cases of acute cervicitis which represented 1% of the total cases and 2.9% of cervicitis. Three cases of (3) atrophic cervicitis constituted 1.6% of all cases and 4.4% of cervicitis. Nabothian cysts accounted for 8.4% of the diagnoses. It was seen in patents aged between 31 and 61 years and had a mean age of 49.1 years. Cervical polyps accounted for 25(10.5%) cases of the cases. It had a mean age of 44.8 years and was seen in women aged between 16 and 78 years. The maximum number 12 (46.2%) was in the 40 to 49 years group. None of the cases showed significant dysplasia. There was only one case of endocervical glandular hyperplasia (0.4%) and was seen in a 24 years old woman. Squamous metaplasia was present in 21 (11%) of all the cases. It was commonly seen in association with chronic cervicitis. It was most common in patients aged between 40 and 49 years 7(33.3%). None was seen in patients below 30 years of age.

The premalignant lesions present were CIN1 that is classified as low-grade squamous intraepithelial lesion (LSIL),

Table 2 Crosstab of the major complaints with histological diagnosis

	Complaints						Total
	Abnormal/ excessive bleeding	Abnormal colposcopy	Abdominal swelling/fibroid	Uterovaginal prolapse	Abnormal pap smear	Vaginal discharge	
Normal cervix	35	15	13	2	2	2	69
Chronic cervicitis	22	22	2	8	3	6	63
Nabothian cyst	4	5	1	0	0	0	10
Cervical polyp	9	12	0	0	1	4	26
Low-grade CIN	4	2	1	0	2	3	12
High-grade CIN	0	1	0	0	4	0	5
Atrophic cervicitis	2	1	0	0	0	0	3
Lobular endocervical glandular hyperplasia	1	0	0	0	0	0	1
Acute cervicitis	0	0	0	0	0	2	2
Total	77	58	17	10	12	17	191

Abbreviation: CIN, cervical intraepithelial neoplasia.

Table 3 Patterns of p16 immunostaining in cervical lesions

	p16_Status		Total
	Negative	Positive	
Normal cervix	54 (100 %)	0 (0.0%)	54 (100%)
Chronic cervicitis	56 (98.2%)	1 (1.8%)	57 (100%)
Nabothian cyst	9 (100)	0 (0.0%)	9 (100%)
Cervical polyp	22 (9.5%)	1 (4.3%)	23 (100%)
Low-grade CIN	7 (63.4)	4 (36.35)	11 (100%)
High-grade CIN	3 (60.0%)	2 (40.0%)	5 (100%)
Atrophic cervix	3 (100%)	0 (0.0%)	3 (100%)
Lobular endocervical glandular hyperplasia	0 (0.0%)	1 (100%)	1 (100%)
Acute cervicitis	1 (100%)	0 (0.0%)	1 (100%)
Total	155	9	164

Abbreviation: CIN, cervical intraepithelial neoplasia.

CIN2, and CIN3 both of which were grouped as high-grade squamous intraepithelial lesion (HSIL). LSIL and HSIL were 17 and accounted for 8.9% of all the cases. There were 5(2.6%) cases of HSIL and mean age of HSIL was 45.2 years. The patients were aged between 38 and 55 years. LSIL accounted for 6.3% of all the cases and 70.6% of the premalignant lesions. It was seen in patients between 30 and 55 years of age and had a mean age of 40.3 years. The peak age incidence was seen in 30 to 39 years and 40 to 49 years, with both age groups having 5 cases (41.7%) each.

A total of 164 cases were subjected to p16 immunohistochemical staining and 9 cases stained positively (►**Table 3**). The distribution of the positive cases was as follows: chronic nonspecific cervicitis (1; 1.8%), cervical polyp (1; 4.3%), LSIL (4; 36.3%), HSIL (2; 40%), and lobular endocervical glandular hyperplasia (1; 100%). The results based on p16 were statistically significant (p-value $=0.023$) compared with previous diagnoses on the positive cases.

Discussion

Abnormal vaginal bleeding was the commonest complaint in this study, a finding that is consistent with that observed by Supriya et al in their study.[14] Poste et al recorded high abnormal vaginal bleeding as the commonest complaint with postmenopausal bleeding as the most common bleeding pattern.[15] Both studies included cancer cases and that may be the reason for high-level abnormal vaginal bleeding in these studies. Gupta et al in their study found abnormal menstrual bleeding as the most common bleeding pattern[16] and like the two last studies included malignant cervical lesions in their study. Postmenopausal bleeding was the commonest bleeding pattern seen in this study. Other studies documented whitish vaginal discharge as commonest complaint in their patients.[17] Jain et al observed that few patients presented with abnormal vaginal bleeding in his study which excluded malignant cases.[18] Other complaints observed in this study were vaginal discharge, uterovaginal prolapse, and abnormal colposcopy finding which include cervical masses, gross alteration in cervical appearance, and cervical erosion. Few patients had no symptom but had cytology report of high-grade intraepithelial lesion that led them to having cervical biopsy.

Cervicitis, the inflammatory lesion of the cervix, remains the commonest non-neoplastic lesion of the cervix and is classified into chronic and acute cervicitis.[19] In this study, cervicitis was the major non-neoplastic lesion of the cervix, finding similar to that of the studies done in Iran by Ameri et al in which cervicitis accounted for 35%.[20] Other related studies in Warri in South-south Nigeria showed that cervicitis constituted 59.8% of non-neoplastic lesions of the cervix.[21] The reason for this higher figures may be as a result of inclusion of HPV-related cervicitis, and also prevalent risk factors and lifestyle.

Chronic cervicitis accounted for majority of the inflammatory lesions in this study. It is characterized histologically by moderate-to-dense chronic inflammatory cell infiltration of cervical tissue.[19] In this study, chronic cervicitis was seen in women aged between 26 and 71 years, and the peak age incidence was seen in the 50 to 59 years age group. Lower peak age incidence was observed in other studies and these studies included HPV-associated cervicitis that has peak age incidence between third and fourth decades.[21,22] HPV-associated cervicitis is characterized by koilocytic change in the squamous epithelial cells.[19] Squamous metaplasia and nabothian cyst are changes usually associated with chronic cervicitis. In this study, about one-sixth of chronic cervicitis was associated with squamous metaplasia. This is higher than what Jyothi et al and Reddy et al reported in their studies.[23,24] Pallipady et al in their study found squamous metaplasia in 73.2% of cervical lesion that is very much higher than what was obtained in this study.[17] Chronic inflammation was also observed in all cases of nabothian cyst in this study and constituted less than a tenth of the diagnosis. This is similar to that in Reddy et al study in which chronic cervicitis with nabothian cyst constituted 7.4% of the benign lesions of the cervix and was common in women aged between 30 and 49 years.[24] This is lower than those observed

in studies by Bansal et al in which chronic cervicitis with nabothian cyst accounted for 19.6% of benign cervical lesions.[25]

Chlamydia trachomatis is the most common infective etiologic agent implicated in chronic cervicitis and causes follicular cervicitis characterized histologically by predominantly plasma cell infiltrate, intraepithelial neutrophil, fibrosis, and lymphoid follicles with or without well-formed germinal center.[19] None of the cases seen in this study had such characteristic feature. Tuberculous cervicitis is a rare cause of chronic cervicitis and constitutes 0.1 to 0.6% of chronic cervicitis.[26] No case of tuberculous cervicitis was seen in this study.

Acute cervicitis characterized histologically by marked neutrophilic infiltration of the cervical tissue was seen in a tiny fraction of the inflammatory lesions of the cervix, similar to findings in the studies by Bansal et al.[25] In this study, it was seen in women aged between 30 and 49 years, showing that it is common in sexually active women. Most cases of acute cervicitis are usually not biopsied but treated medically, explaining low figures.

Endocervical glandular hyperplasia is a rare disorder of the cervix and can be confused with low-grade malignant glandular lesion of the cervix.[27] In this study, it accounted for less than 1% of non-neoplastic lesions of the cervix. The finding is comparable to that observed by Hatwal D et al in their study.[28] Endocervical glandular hyperplasia appears to be relatively common in some parts of India where it accounted for 12.5% of non-neoplastic lesions of the cervix in a study done by Bansal et al.[25] Kour and Kaur found endocervical glandular hyperplasia to be common in women in their fifth decade.[29] The only case in this study was seen in a 24 years old woman.

Cervical polyp, a benign lesion of the cervix, may be ectocervical or endocervical. In this study, it accounted for about a tenth of benign lesions of the cervix with mean age of 43.9 years and peak age incidence of 40 to 49 years age group. Similar finding was documented by Nwachokor and Forae in his study in which he found that endocervical polyp constituted 16.3% of non-neoplastic lesions of the cervix.[21] A study by Reddy et al noted that cervical polyps were common in women aged between 30 and 59 years.[24] Ali et al in their study in Sudan observed that endocervical polyps were the dominant benign cervical lesion.[30] Similarly, Vaidya found high level of endocervical polyp in his study and also observed that majority of them present with whitish discharge (leucorrhea).[23] Histologically, endocervical polyps consist of dilated endocervical glands and hyperplastic glands in an edematous stroma that may sometimes be fibrous.[19] Squamous intraepithelial neoplasia (SIN) and glandular intraepithelial neoplasia (GIN) may occur in endocervical polyps.[29] No case in this study had SIN or GIN.

CIN accounts for 8.9% of the non-malignant lesions of the cervix. Studies in other southern parts of Nigeria have similar result with 13.9% in Ibadan.[31] Some northern parts have higher figures of 30.5%.[32] Study in Zaria on Hysterectomy specimens found that CIN constituted 12.5% of cervical lesions, of which 1.3% were incidental finding.[33] The higher prevalence in the northern part may be due to prevalent risk factors of HPV infection which is known cause of intraepithelial neoplasia among others. The risk factors include high parity, early marriage, and polygamous relationship. Lack of awareness and poor attitude to cervical cancer screening may also contribute to low figures observed in this study. The prevalence of CIN in Cameroon is 3.9%.[34] Similar to the findings in this, Vaidya et al in his study observed that low-grade CIN were more than the high-grade CIN.[22] Sanad et al in their study observed that high-grade CIN were more common than low-grade CIN.[35]

p16 in cervical epithelial lesions is an important indicator of HPV-induced neoplastic transformation and the level of expression increases with degree of transformation/dysplasia.[36] Our findings in this study are similar to what was obtained by Al-Asadi in Iraq with 9.62% in low-grade CIN and 46.15% in high-grade CIN.[37] Other studies showed high levels of p16 overexpression.[38] The low case in this study may not be unconnected to poor specimen handling and fixation technique, high level of p16 unreactive high-grade lesion, or methodology. It may also be that many of those cases were mimickers of cervical carcinoma like immature squamous metaplasia, and atrophic cervix cut tangentially. Some p16 CIN2-negative cases have been documented to regress and are not to be categorized as high-grade lesion.[39] Low-grade CIN (CIN1) has some morphologically altered glandular cells positively stained with p16. Cases of cervical GIN being immunohistochemically stained with p16 are known and are due to high-risk HPV-induced transformation.[38] In this study, the case that was classified morphologically as chronic nonspecific cervicitis, but showed focal p16 immunoreactivity, had focal koilocytic change. In the case of the polyp, the reactivity was seen on the epithelial lining and was focal and limited to the lower one-third of stratified squamous epithelium. Cases of low p16 expression in cervicitis have been documented.[39] This may be due to high-risk HPV-induced transformation of the cervical epithelial cells with minimal morphological alteration of the cervical epithelium. The inflammatory process in the underlying stroma may be a reaction of some other ongoing infection. In this study, lobular endocervical glandular hyperplasia stained positively but the staining is focal and limited to the lower one-third of the overlying stratified squamous epithelium adjoining the lesion but not on the glandular lesions. There have been reports of p16 immunoreactivity in lobular endocervical glandular hyperplasia and are more common in cases with atypia.[39] When diagnosis is compared with diagnosis based on p16 positive cases, the result is statistically significant.

A major limitation of this study is that it may not reflect the exact distribution of benign lesions of the cervix in the community. This is because it is a hospital-based study and not all the patients in the community will have their biopsies sent to UNTH as it is a tertiary health institution located at the outskirt of a city that has three other tertiary health institutions at the city center. Majority of the patients that use the facility are referred from numerous private hospitals in the city where majority of the patients first present.

However, it can suffice in the absence of a community-based study.

Conclusion

The most common benign lesion of the cervix is cervicitis and is most common in women in their fifth and sixth decades. Chronic cervicitis is negative to p16 immunoreactivity. Few of the cases of chronic cervicitis are associated with squamous metaplastic change and nabothian cyst. The squamous metaplastic cells did not demonstrate immunoreactivity to p16 antibody. All the cases of acute cervicitis and atrophic cervicitis showed no immunoreactivity to p16 antibody.

There are more low-grade CIN than high-grade CIN. The low-grade CIN are common in fourth and fifth decades of life and overexpress p16 in one third of cases. There are more cases of p16-negative high-grade CIN in this study.

Cervical polyps are the most common benign neoplastic lesion of the cervix and common in women in their fifth decade of life. None of the cervical polyp showed squamous intraepithelial neoplasia or GIN. All the cervical polyps showed negative immunoreactivity to p16 antibody.

Authors' Contributions

All authors contributed to data collection and writing/reviewing the article to fulfill the ICMJE authorship criteria.

Compliance with Ethical Principles

The study was approved by Research and Ethical committee of University of Nigeria Teaching Hospital. No personal identifiers were used in the study.

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None.

Conflict of Interest

None declared.

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