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Original Research Article

Histopathological Evaluation of Non-Neoplastic and Neoplastic Lesions of Cervix

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Abstract

Background: Cervix is one of the most common target organs for both non neoplastic and neoplastic diseases of the female genital tract. Cervical cancer is the second most common cancer worldwide having poor prognosis. Carcinoma cervix is the commonest malignancy in Indian women. (Human papilloma virus) HPV infection plays major role in cervical lesions; in which high risk types particularly HPV 16 causes dysplasia and Carcinoma of cervix.

Materials and Methods: This prospective study was undertaken in the Department of Pathology, Vydehi Institute of Medical Sciences and Research Centre for a period of 1.5 year from January 2015 to May 2016.

Results: 100 cases were included in the study. Out of 100 cases majority were inflammatory i.e. 54% followed by 21% of Cervical Intraepithelial Neoplasia (CIN), 17% invasive carcinoma, 6% benign and 2% of non-neoplastic cervical glandular lesions. Immunohistochemistry was done in (Chronic non-specific cervicitis) CNSC associated with squamous metaplasia and koilocytosis, all non-neoplastic cervical glandular lesions, precancerous lesions and invasive carcinomas.

Conclusion: However, there are many lesions that are mistakenly over diagnosed to be neoplastic. Therefore, it is recommended to further studies to evaluate these non-neoplastic lesions of the uterine cervix on a community basis. Overexpression of the protein p16INK4A encoded by tumor suppressor gene INK4A is a characteristic of dysplastic & neoplastic alterations of cervical epithelium. The proportion of p16INK4A positive samples increases in the following row: CIN I- CIN II- CIN III- Invasive carcinomas. However p16INK4A negative cervical neoplasms & carcinomas do exists.

Keywords: Neoplastic Lesions; Cervix; Carcinomas.

Introduction

The infections of female genital tract are the gateway predisposing the women not only to tubal infertility but also increase risk of ectopic pregnancy [1]. Cervical lesions are more frequent and commonly encountered day today problem of gynaecological lesions in women. Cervical lesions, both neoplastic & non-neoplastic, are prime reason for morbidity and mortality. Sexually active women are more prone for cervical disease [2, 3].

Incidence of cervical lesions varies according to age. Early recognition of infections & inflammatory lesions can prevent considerable damage to the cervix. It also helps to decrease morbidity and mortality. Cervical cancer is the second most common cancer worldwide. Carcinoma cervix is the commonest malignancy in India. Early sexual activity, sexually

transmitted diseases, viral infections, low socio economic status, injury related to multiple births are the various factors contributing for the carcinoma cervix [4]. According to World Health Organisation (WHO 2012) cervical cancer is said to be the world's second deadly cancer with an estimate of about 493,243 women diagnosed with it & 273,505 dying from it per year. Cervical cancer is most commonly seen in women of reproductive age group. Human Papillomavirus infection (HPV) is the central cause of cervical cancer along with several host and environmental factors. HPV 16 & 18 is known to cause majority of cervical cancers [5, 6]. Though HPV is a necessary cause of cervical cancer, other cofactors are also necessary for progression of HPV infection to cancer. Screening for precancerous lesions can help in early detection and treatment. PAP smear is the most commonly used screening test for cervical cancer. Other methods are visual inspection of the cervix with acetic acid (VIA), magnified visual inspection with acetic acid (VIAM), & visual inspection with lugols iodine [7].

Cervical screening with PAP smear has dramatically reduce the number of mortality from cervical cancer. With the introduction of HPV vaccination there is significance decrease in the number of cervical cancer cases. Prophylactic vaccines for cervical cancer target HPV 16 & 18. Two commonly available vaccines in India are Ceravarix & Gardasil.

The aim of the present histopathological study is to evaluate the neoplastic & non neoplastic lesions of the cervix along with various types of cervical lesions showing incidence and age wise distribution and to study the histopathological features of all the lesions of cervix.

Materials and Methods

The present study was undertaken in the Department of Pathology, Vydehi Institute of Medical Sciences and Research Centre, Bangalore, India. One and a half year prospective study was done for a period of 1 ½ years from January 2015 to May 2016, and consists of 100 patients. The specimens included in the study will be received in different forms such as, punch biopsy, hysterectomy, endocervical curettage and polypectomy specimens. The entire specimen were fixed in 10% neutral buffered formalin; tissues processed; paraffin embedded tissue blocks will be prepared which will be cut at 4-5 microns thickness. They will be subsequently stained with Haematoxylin and Eosin. Immunohistochemistry was done in all precancerous and non neoplastic cervical glandular lesions. The histopathological classification of tumors was done according to recommendation by WHO.

$P16^{INK4A}$ Immunohistochemistry staining

- Cut the tissue section on a microtome with a thickness of 3 microns.
- Bake sections for 1 hour at 60^{o} prior to test
- De- paraffinize& re hydrate the tissue slides and wash in running tap water for 5 minutes.
- Allow sections to soak in PBS (wash buffer) for 2 minutes in staining jar.
- Antigen retrieval by using EZ AR1 or EZ AR2 in microwave oven or EZ RETRIVER at -

  Cycle 1: 85^{0} for 5min or 500 watts for 5 min

  Cycle 2: 98^{0} for 15 min or 750 watts for 15 min
- Allow the slides to cool at room temperature for 15 mins
- Wash with PBS (WASH BUFFER) for 2 times with a time gap of 30 secs for each wash.
- Mark around the sections with HYDROPHOBIC (PAP) pen (if available).
- Apply Peroxidase block (3% H_2O_2) and incubate for 10 mins at room temperature (20^{0}-25^{0}C).
- Wash with PBS (WASH BUFFER) for 3 times with a time gap of 30 secs for each wash.
- Apply Power Block & incubate for 5 mins at room temperature (20^{0}-25^{0}C).
- Drain the excess power block. DO NOT WASH SLIDES with PBS (WASH BUFFER) after Power Block.
- Apply Primer antibody & incubate for 1 hour in a closed chamber at room temperature.
- Wash with PBS (WASH BUFFER) for 3 times with a gap of 30 sec for each wash.
- Apply Super Enhancer & incubate for 20 min in a closed chamber at room temperature (20^{0}-25^{0}).
- Wash with PBS (WASH BUFFER) for 4 mins with a time gap of 30secs for each wash.
- Apply Polymer HRP and incubate for 30 mins in a closed chamber at room temperature (20^{0}-25^{0}).
- Wash with PBS (WASH BUFFER) for 4 times with a time gap of 30 sec for each wash.
- Apply DAB Substrate and incubate for 7-10 mins.
- Wash with PBS (WASH BUFFER) for 4 times with a time gap of 30 sec for each wash.
- Wash with DI water for 4 times with a time gap of 30 secs for each wash.
- Counter stain with Hematoxylin.
- Dehydrate, Clear & Mount.

Interpretation of p16INK4a staining

The distribution of p16INK4a positivity was done, as follows

Negative (< 1% of the cells were positive),

Sporadic (isolated cells were positive, but < 5%),

Focal (small cell clusters, but < 25% of the cells were positive) and,

Diffuse (> 25% of the cells were stained).

Results

The present study was done to analyse the Non neoplastic & neoplastic lesions of cervix encountered in our institution. The study was done for a period of January 2015 to May 2016 (11/2years), and consists of 100 patients.

Punch biopsy was the most common type of specimen received for histopathological evaluation followed by hysterectomy, endocervical curettage & Polypectomy (Table 1).

The most common age group of the study was 41-50 years, with the mean age of 43.46 years (Table 2).

Among 54 inflammatory lesions, chronic nonspecific cervicitis was the commonest inflammatory lesion found in 94.5 % of the cases followed by 5.5% cases of polypoidal endocervicitis. Chronic non-specific cervicitis was associated with other histological changes like nabothian cyst, squamous metaplasia, epidermidisation & koilocytic change (Table 3).

Only 2 categories of benign cervical lesions were observed: endocervical polyp and leiomyoma (Table 4).

CIN III was the most common precursor lesion accounting for 57.14% of the cases (Table 5, 6).

Table 1: Distribution of types of specimen in the study

Type of specimen	No of cases (n)	%
Punch biopsy	47	47%
Hysterectomy	40	40%
Endocervical curettage	08	8%
Polypectomy	05	5%

Table 2: Age distribution of cervical lesions

Age group	Type of lesion					Total
	Inflammatory	Non neoplastic glandular lesions	Benign	CIN	Malignant	
21-30	13	-	1	-	1	15
31-40	15	-	2	8	4	29
41-50	20	2	3	5	4	34
51-60	5	-	-	2	7	14
61-70	1	-	-	6	1	8
Total	54	2	6	21	17	100

Table 3: Histopathological distribution of cervical lesions

Cervical lesions	n	%
Non- neoplastic		
Inflammatory	54	54 %
Non-neoplastic cervical glandular lesion	2	2%
Neoplastic		
Benign	6	6%
CIN	21	21%
Malignant	17	17%
Total	100	100%

Table 4: Distribution of benign cervical lesions

Type of lesion	No of cases	Percentage
Leiomyoma	2	33.33%
Endocervical polyp	4	66.66%
Total	6	100%

Squamous cell carcinoma was the most common invasive carcinoma, followed by neuroendocrine carcinoma and adenocarcinoma (Table 7).

Invasive carcinomas were common in the females with age more than 31 years. Only 1 case of malignancy was seen in the age group of 21-30 years [Table 8].

Squamous cell carcinoma was further graded as well differentiated SCC comprising of 50% cases, moderately differentiated SCC 35.71% cases and poorly differentiated SCC 14.28% cases [Table 9].

Immunohistochemistry (p16 expression)

Following histopathological reporting all the cases of CNSC associated with squamous metaplasia and koilocytosis, cases of non-neoplastic glandular lesions, all precancerous lesions & invasive carcinoma were taken up for p16 marker study/ staining. In this research study, all the cases of CNSC and non- neoplastic glandular lesions were negative for p16.

In the present study CIN accounted for 21 cases; p16 was positive in 15(71.42%) cases and negative in 6(28.57%) cases.

Table 5: Age distribution of benign cervical lesions

Age group(years)	Lesion		Ttal
	Leiomyoma	Endocervical polyp	
21-30	1	-	1
31-40	1	1	2
41-50	-	3	3
51-60	-	-	-
61-70	-	-	-
Total	2	4	6

Table 6: Age wise distribution of Cervical Intraepithelial Neoplasia

Age in years	CIN I	CIN II	CIN III	Total
21-30	0	0	0	0
31-40	3	1	4	8
41-50	2	0	3	5
51-60	0	0	2	2
61-70	1	2	3	6
Total	6	3	12	21
Percentage	28.57	14.28	57.14	100

Table 7: Histologic types of Invasive carcinoma

Cervical malignancy	Number	Percentage
Squamous cell carcinoma	14	82.35%
Adenocarcinoma	1	5.88%
Neuroendocrine carcinoma	2	11.76%
Total	17	100%

Table 8: Histologic types & age wise distribution of Invasive cancers

Cervical malignancies	21-30 years	31-40 years	41-50 years	51-60 years	61-70 years	Total
Squamous cell carcinoma	1	2	3	4	4	14
Adenocarcinoma	-	1	-	-	-	1
Neuroendocrine carcinoma	-	1	1	-	-	2
Total	1	4	4	4	4	17

Table 9: Distribution of Squamous cell carcinoma according to grades

Grades	No of cases	Percentage
Well differentiated	7	50%
Moderately differentiated	5	35.71%
Poorly differentiated	2	14.28%
Total	14	100%

Out of 12 cases ofCIN III,11 cases were positive & only one case was negative. Most cases of CIN III showed diffuse positivity. 17 cases of carcinoma cervix were observed which included 14 cases of SCC, 2 cases of Small cell carcinoma & 1 case of Adenocarcinoma.

All of the cases of carcinoma were positive for p16 i.e. 100%. Adenocarcinoma & Small cell carcinoma showed diffuse positivity, while 10 cases of Squamous cell carcinomashowed diffuse positivity (Table 10).

Discussion

Cervix is one of the most common target organs for both non-neoplastic and neoplastic diseases of female

Table 10: p16 expression in cervical lesions

Lesions	Staining				Total
	Negative	Sporadic	Focal	Diffuse	
CNSC with koilocytic change and squamous metaplasia	5	-	-	-	5
Non neoplastic glandular lesions	2	-	-	-	2
CIN I	4	-	1	1	6
CIN II	1	1	1	-	3
CIN III	1	1	3	7	12
SCC	-	1	3	10	14
Adenocarcinoma	-	-	-	1	1
Neuroendocrine carcinoma	-	-	-	2	2
Total	13	3	8	21	45

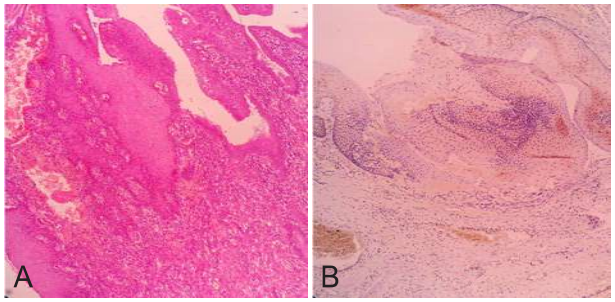

Fig. 1: Chronic non specific Cervicitis with squamous metaplasia
A: Hematoxylin& Eosin stain (40x). **B:** Negative for p16 stain (40x)

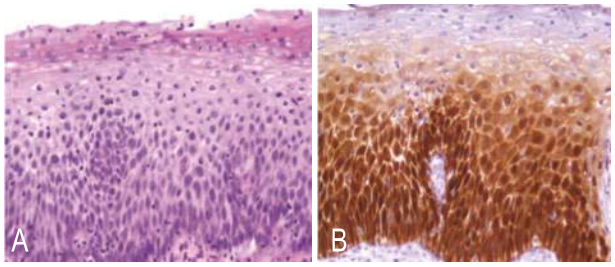

Fig . 2: Cervical Intraepithelial Neoplasia-I
A: Hematoxylin& Eosin stain (40x). **B:** p16 stain showing diffuse positivity (40x)

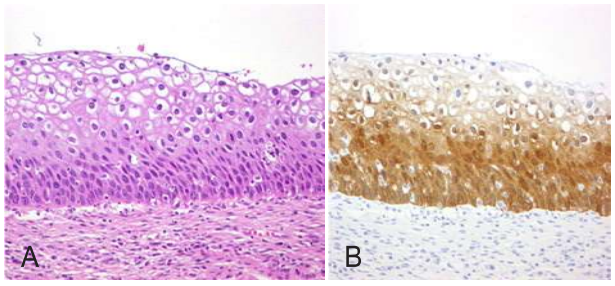

Fig. 3: Cervical Intraepithelial Neoplasia- II
A: Hematoxylin& Eosin stain (40x). **B:** p16 showing focal positivity (40x)

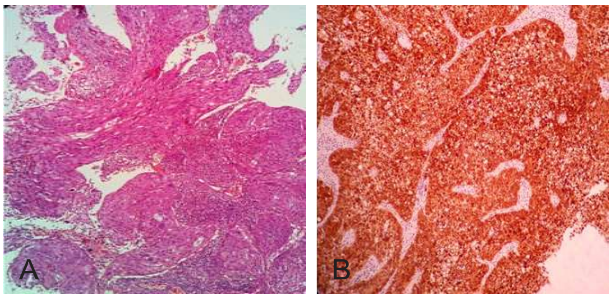

Fig. 4: Poorly Differentiated Squamous cell Carcinoma - Cervix
A: Hematoxylin& Eosin stain (40x). **B:** p16 showing diffuse positivity(40x).

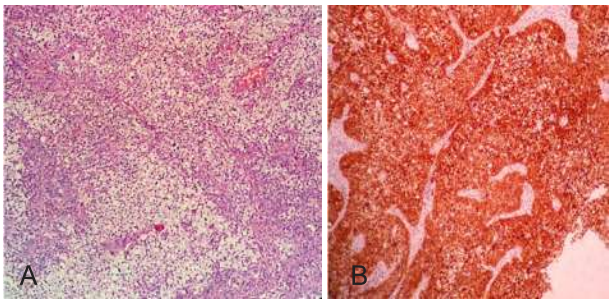

Fig. 5: Clear cell Adenocarcinoma- Cervix
A: Hematoxylin& Eosin stain (40x). **B:** p16 stain showing diffuse positivity (40x)

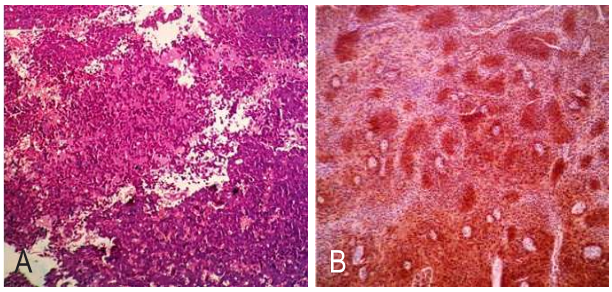

Fig. 6: Neuroendocrine tumor - Cervix
A: Hematoxylin& Eosin stain (40x). **B:** Diffuse positivity for p16 (40x).

genital tract. If untreated reproductive tract infections can lead to adverse health outcomes such as infertility, ectopic pregnancy. Sexually transmitted causes include viruses such as HPV and HSV.

HPV cervicitis is a causal risk factor for condylomataacuminatum, pre invasive CIN I, II, III and eventually cervical cancer. These lesions constitute a source of morbidity and mortality in women worldwide hence the need to analyze them to provide a baseline data of the pattern of these lesions in our local environment.

In the present study 100 cases of cervical specimens were sent to department of pathology, in our tertiary institute from January 2015 to May 2016. The specimens were processed routinely and sections were stained by H&E and pre-cancerous and cancerous lesions were stained with p16.

Distribution of types of specimens

In the present study majority were punch biopsy specimens (47%), followed by 40% specimens of hysterectomy. Grewal et al (2016) in their study on 311 cases found 70% specimens were hysterectomy specimens followed by 23.7% cervical punch biopsy specimens [8].

Mainali N et al (2014) in their study on 100 cases also found 71% hysterectomy specimens and 29% cervical biopsies [9].

Age distribution of cervical lesions

The age of presentation of various cervical lesions was between 21 to 70 years. The mean age of the study was 43.46 years. Nwachokor FN et al (2013) in their study found maximum no. of non-neoplastic lesions in the age group 40-49 years [10].

Histopathological distribution of cervical lesions

In the present study, non-neoplastic lesions were more common than neoplastic lesions. Non neoplastic lesions comprised 56% of cases, 6% lesions were benign, 21% CIN and 17% lesions were malignant. Non neoplastic lesions included non- specific cervicitis, granulomatous cervicitis and non-neoplastic cervical glandular lesions.

This study showed more cases of CNSC were associated with nabothian cyst as compared to study done by Grewal et al [8]. Number of cases of CIN was more as compared to the other studies by Jyothi et al and Grewal et al [1, 8]. (Table 11).

Non-neoplastic cervical glandular lesions

In the present study 2 non neoplastic cervical glandular lesions were encountered. 1 case of microglandular hyperplasia was observed in the present study.

Pallipady et al (2011)in their study encountered 2.6% cases of microglandular hyperplasia and 2.46% tunnel clusters [11].Hatwal et al (2016) in their study found 1.26% cases of microglandular hyperplasia [12].

Table 11: Comparative analysis of cervical lesions

Cervical lesions	Jyothi et al (2016)[1]	Grewal et al (2016)[8]	Present study
Non-specific cervicitis	45.11%	70.92%	53%
Granulomatous cervicitis	0.66%	-	1%
Non- neoplastic cervical glandular lesions	-	6%	2%
Benign lesions	5.5%	2.82%	6%
CIN	5.6%	11.58	21%
Malignant lesions	43.2%	8.68	17%

Benign cervical lesions

Table 12: Comparative analysis of benign cervical lesions

Lesions	Usha et al[13]	Jyothi et al (2015)[1]	Present study
Endocervical polyp	84.48%	73.5%	66.66%
Leiomyoma	6.03%	26.47%	33.33%

Results were concordant with the results of Usha et al and Jyothi et al [13,1]. (Table 12).

Cervical Intraepithelial lesions

Table 13: Comparative analysis of CIN

Lesions	Hall et al[14]	Zhao et al (2015)[15]	Present study
CIN I	47.8%	95.9%	28.57%
CIN II	41.1%	2%	14.28%
CIN III	11.1%	2.1%	57.14%

In the studies done by Hall et al and Zhao et al maximum no. of cases were CIN I which is not comparable with this study as in the present study we encountered maximum no of cases of CIN III [14, 15]. (Table 13).

Invasive Carcinomas

17 cases of invasive carcinomas were encountered. Maximum no. of the carcinomas was squamous cell carcinoma followed by neuroendocrine tumour and adenocarcinoma. Malignancy was more commonly observed above the age of 31 years.

Adenocarcinoma shows columnar cells with elongated, hyperchromatic nuclei that may show marked atypia with nuclear pleomorphism and coarse chromatin. Microscopic features of neuroendocrine tumours include cells arranged in sheets and cords with inconspicuous cytoplasm. The cells have hyperchromatic nuclei with ûnely stippled chromatin, inconspicuous nucleoli, and high nuclear to cytoplasmic ratio.

Table 14 showed maximum number of squamous cell carcinomas. The results are concordant with the studies done by Sapurkar et al, Menczer and Jyothi et al [16,17,and 1]. In the present study 11.76% of neuroendocrine tumours were seen which were not observed in the studies done by the above authors.

$p16^{INK4a}$ expression in cervical lesions

Immunochemical detection of $p16^{INK4a}$ shows that majority of the cases of CIN, invasive cervical carcinoma differ from normal cervical epithelium of healthy women. In the present study we found that all cases of CNSC which were associated with squamous metaplasia, koilocytic change & non neoplastic cervical glandular lesion were negative for p16. Volgareva et al in their study also observe that that no cases of non-specific cervicitis & cervical ectopia showed focal, diffuse, sporadic positivity, so the results of the present are in concordant with the study done by Volgareva et al [18,19].

These observations support that p16 is a specific marker for cells that express the viral E6-E7 oncogenes and retain the capacity to replicate thus displaying a high degree of genetic instability

In conclusion, the results of the present study indicate that p16 INK 4a expression in tissues can be used to identify progressive cervical neoplasia and hypothesized to be HPV-transformed cells. (Table 15).

Conclusion

Cervical lesions are more frequent and commonly encountered day today problem of gynaecological lesions in women. Cervical lesions, both neoplastic and non-neoplastic, are prime reason for morbidity and mortality in women. Inflammatory lesions are the most frequent non- neoplastic cervical lesions. These lesions therefore account for significant amount of gynecological problems in our environment. Adequate cervical screening with follow up histological biopsies is a relevant tool in diagnosing them to enhance early detection of premalignant and malignant cervical lesions.

Financial Disclosure Statement: No

Conflict of Interest: Nil

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Table 14: Comparative analysis of invasive carcinomas

Lesions	Solapurkar et al[16]	Menczer 2011[17]	Jyothi et al[1]	Present study
Squamous cell carcinoma	95.70	80.6	98.89	82.35
Adenocarcinoma	1.28	11.8	0.70	5.88
Adenosquamous carcinoma	0.64	3.9	0.36	--
Neuroendocrine carcinoma	-	-	-	11.76

Table 15: Comparative analysis of $p16^{INK4a}$ in dysplasia and neoplastic lesions

Lesions	Volgareva at el[18]		Klaes et al[19]		Present Study	
	Positive	Negative	Positive	Negative	Positive	Negative
CIN I	14%	63%	63.82%	36.17%	33.33%	66.66%
CIN II	32%	68%	56.25%	43.75%	66.66%	33.33%
CIN III	54%	46%	85%	15%	91.6%	8.33%
Invasive carcinomas	96.2%	3.8%	91.67%	8.33%	100%	-

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