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A STUDY OF EXPRESSION OF P53 IN PREMALIGNANT AND MALIGNANT LESIONS OF UTERINE CERVIX

Pathology

Dr. Kalpana B. Rathod* — Associate Professor, Department of Pathology, B. J. G. M. C, Pune. *Corresponding Author

Dr. Sudeshna S. Gajbhiye — Senior Resident, Department of Pathology, B. J. G. M. C, Pune.

Dr. Leena A. Nakate — Professor and HOD, Department of Pathology, B. J. G. M. C, Pune.

Mrs. Shweta Jadhav — Lecturer, Pharmacy College.

ABSTRACT

Carcinoma of the uterine cervix is one of the leading causes of mortality in women worldwide(1,2). There are primary and secondary biomarkers in cervical carcinoma. The primary marker being HPV DNA and secondary markers like p53, c-fos, p50, fra 1, p16, notch 1, rb and telomerase. The secondary marker p53 has been found to be helping in differentiating neoplastic from non-neoplastic and CIN lesions in various studies(3). Thus, it may be used as a marker of prognostication for the patients with cervical lesions(4). The current study was aimed to analyze p53 expression in malignant and premalignant epithelial lesions of the uterine cervix and to correlate p53 expression with histological types and grades of carcinoma cervix. Out of 60 cases included in this study, p53 positivity was observed in 85% of the cases, excluding CIN-II and CIN-III. CIS and invasive SCC exhibited positive p53 expression. Higher tumor stages showed increased p53 expression. Statistically significant associations were found between p53 positivity and microscopic type, clinical stage, and grade of cervical carcinoma. Further studies with larger sample sizes and patient follow-up are warranted to investigate the correlation of p53 expression with clinicopathological parameters. Such research could facilitate the development of p53-targeted therapy for cervical carcinoma.

KEYWORDS

Cervical carcinoma, p53, CIN(Cervical intraepithelial neoplasia), CIS (Carcinoma In Situ)

INTRODUCTION

Carcinoma of the uterine cervix is the second most common cancer in Indian females[5]. In India, the incidence of carcinoma of the cervix accounts for 86-90% of all genital cancers[6]. It is the major health problem, faced by the women in reproductive age group[7]. Among the various screening methods for early detection of cervical carcinoma Pap smear has been the most effective[8]. Among the various biomarkers of cervical carcinoma, the primary marker-HPV DNA, has been widely studied in India and not many studies have been done on secondary markers. The secondary marker p53 has been studied at various centers in the world and has been found to be deregulated in cervical cancers[9].

As carcinoma cervix is a slowly progressive tumor; the transformation of cervical epithelial cells from CIN to carcinoma takes 10-20 years[10], which provides a great opportunity to study the expression of biomarkers of tumor progression. In this regard, the p53 protein is useful in differentiating neoplastic from non-neoplastic and CIN lesions[3].

p53 is a regulator of apoptosis and it can inhibit cell proliferation. Thus, p53 tumor suppressor gene expression may be used as a marker to prognosticate the outcome of the patients[4]. Some studies have shown that the low expression of p53, in carcinoma cells before radiotherapy, is regarded as a predictive factor for good prognosis[11,12] and positive staining for p53 was associated with survival disadvantage.

MATERIALS AND METHODS

The present cross sectional observational analysis of histologically proven cases of premalignant and malignant epithelial lesions of cervix was conducted in the department of pathology at tertiary care center of Maharashtra over a period of 18 months (January 2020 to June 2021).

The study was performed with respect to the parameters such as patients age, chief complaints, clinical staging, and other clinical data including menopausal status and obstetric history obtained from the pathology records and from case sheet of the patients.

A total of 60 cases were included in the present study, having histologically proven cases of premalignant and malignant epithelial lesions of cervix from cervical biopsies and cervix resected from hysterectomy specimens of females above 20 years of age. Inadequate biopsies were excluded.

Cervical biopsies and hysterectomy specimens received were fixed in 10% formalin and processed routinely. All the 60 cases were subjected to hematoxylin and eosin (H & E) staining and IHC study for p53. The tumors were typed according to the WHO classification system. The modified Broder's grading was used to grade the tumors as Grade 1- Well differentiated, Grade 2- Moderately differentiated and Grade 3- Poorly differentiated.

Assessment of expression of p53: Nuclear staining either as coarse or fine granular dots was considered positive. The intensity of staining (Absent:0, Mild:1+, Moderate:2+, Severe:3+) and the number or percentage of positive cells (1-5%: Grade 1, 6-25%: Grade 2, 26-50%: Grade 3, 51-75%: Grade 4, >75%: Grade 5) were graded.

For statistical analysis, the value of $p<0.05$ was taken as significant and <0.01 as highly significant, whereas $p>0.05$ was taken as non-significant.

RESULTS

In the present study of 60 cases, the age of patients ranged from 28 to 83 years. The peak incidence of carcinoma of cervix was seen in the seventh decade; 15 cases(25.0%).

All the cases included were married and had childbirth, most women [20 cases(33.3%)] had parity of 2. Out of 60 cases, 25 women(41.67%) were pre-menopausal and 35 women(58.33%) were post-menopausal. Cases included in this study, presented with presence of cervical mass, pain in abdomen, complaint of post coital bleeding, per-vaginal bleeding, foul smelling vaginal discharge and per rectal bleeding with overlapping of these complaints. The most common clinical complaint being per-vaginal bleeding; 38 cases(63.3%). None of the cases had positive family history or a past history of carcinoma cervix.

Among the 60 cases of present study, clinically 6 cases (10%) were of Stage IB, 11 cases (18.3%) of Stage IIB, 5 cases (8.3%) of Stage IIIA, 15 cases (25.0%) of Stage IIIB and 4 cases (6.7%) were of Stage IVB.

Clinical stage was not available in 19 cases. Microscopically, among the 60 cases studied, 45 cases were squamous cell carcinoma(75%)

(Image 1), 6 cases were carcinoma in situ (CIS) (10%), 3 cases were adenocarcinoma(5%), 1 case was adenosquamous carcinoma(1.7%), 1 case was adenoid cystic/adenoid basal cell carcinoma(1.7%), 2 cases were CIN-II (3.2%), 1 case was CIN-III(1.7%) and 1 case was positive for malignancy without frank tumor(1.7%).

Among the 43 cases of squamous cell carcinoma, 27 (62.8%) were large cell non-keratinizing type and 16 (37.2%) were large cell keratinizing type.

p53 Expression:
p53 was expressed in 51 cases and negative in 9 cases. Among the positive 51 cases, 49 (96.1%) were found to be malignant (Image 1, Inset) and 2 (3.9%) were premalignant cases. Highly significant association was noted between p53 expression and malignant/ premalignant status of tumor (P value=<0.0001).

The distribution of expression of p53 (graded) in various histological types of cervical carcinoma and premalignant lesions is shown in table 1.

Table 1: Correlation Between p53 Grade And Histological Types Of Cervical Lesions

HPE DIAGNOSIS	p53 Grade						p Value
	1	2	3	4	5	Negative	
Adenocarcinoma(2)	1	0	1	0	0	1	0.022
Adenosquamous carcinoma(1)	0	0	0	0	1	0	
Adenoid basal/ adenoid cystic(1)	0	0	1	0	0	0	
CIN-II, CIN-III(3)	0	0	0	0	0	3	
CIS(6)	1	0	1	0	0	4	
Positive for malignancy without frank tumor (1)	0	0	1	0	0	0	
Squamous cell carcinoma (45)	5	14	9	7	9	1	

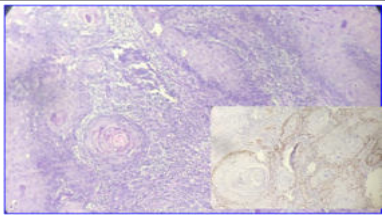

Image 1: Well differentiated squamous cell carcinoma; H & E 10X Inset: Severely intense p53 positivity, Grade 3

Highly significant association was noted between p53 expression and various histological types of lesions of uterine cervix (P value= <0.0001) as well as between p53 grade and histological types of cervical lesions (P value=0.022) (Table 1).

No statistically significant association was noted between p53 positivity and clinical parameters such as age, parity and menopausal status as well as p53 grade and clinical stage (p value=0.165).

In the present study, statistically significant association was noted between clinical stage and p53 positivity (P value=0.03).

Statistically highly significant relation was noted between histologic (Broder's) grade and p53 positivity(P value=<0.0001) as well as p53 grade (P value=<0.001).

While correlating the histologic subtypes of squamous cell carcinoma with over expression of p53, 26 out of 27 (96.3%) cases of large cell non-keratinizing (LCNK) type and 16 out of 16 (100%) cases of large cell keratinizing (LCK) type showed p53 positivity. No statistically significant association was noted between p53 grade and histologic subtypes of squamous cell carcinoma.

DISCUSSION AND CONCLUSIONS

In our study it was noted that the positivity was present in the dysplastic nuclei and with the increase in pleomorphism of the nuclei the intensity of p53 expression increased. Similar finding was observed by Geok Chin et al[13].

In the studies done by Krishnan Baskaran et al[14] and Abeer A.Bahnassy et al[15], a gradual increase in p53 positivity was observed as the lesion progressed from CIN to invasive SCC. The p53 was expressed in 85% of the cases of premalignant and malignant lesions of uterine cervix in our study. The p53 expression in various studies ranged from 42% to 85.2%. The varying range in different studies may be because of the fixation and AR methods.

In present study, majority of cases of carcinoma cervix showed moderate intensity of p53 expression (60%) similar to the study done by Sandhu JK et al[16] (50%).

Significant association was found between clinical stage and p53 overexpression in our study (P value=0.03). Similar finding has been observed by Ikuta et al[17] (P value=0.03) and Abeer A.Bahnassy et al[15] (P value=0.003).

Whereas no significant association was found between clinical stage and p53 grade in our study (P value=0.166). This is in contrast to study done by Ne Win et al[18].

A statistically strong significant relation was found between the microscopic type and p53 positivity (P value=<0.001) in our study. Similar to observed by Annika K. Lindstrom et al[19] (P=0.02) and Abeer A.Bahnassy et al[15] (P=0.01).

A highly statistically significant relation was found between the Broder's grade and p53 positivity (P value=<0.0001), similar to the studies done by Tjalma WA et al[20].

A strong statistical significant relation was observed between tumor grade and p53 grade (P value=<0.0001).

In our study no statistically significant relation was observed between histologic subtypes of SCC and p53 grade(P value=0.211).

In conclusion the expression of p53 was high in malignant cervical lesion compared to premalignant lesions due to high proliferative index and p53 marker can be used to differentiate these. The p53 expression was greater in invasive cervical carcinoma. High positivity in low grade lesions of carcinoma cervix could be due to lesser cases of low grade carcinoma of cervix included in the study. The higher p53 expression in higher stage of tumor suggests expression of p53 is a late phenomenon in the pathogenesis of cervical cancer. Our study indicates that p53 is a powerful prognostic marker.

In future it is necessary to carry out studies with large samples of carcinoma cervix and correlating p53 expression with the clinicopathological parameters with follow up of the patients. This will provide an opportunity for development of p53 targeted therapy for carcinoma cervix.

Few cases of carcinoma cervix were p53 negative suggesting that other factors may be involved in the carcinogenesis. Therefore, further HPV studies and other markers of carcinoma cervix should be studied.

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