ISSN: 0975-3583, 0976-2833 VOL 13, ISSUE 04, 2022

IMMUNOHISTOCHEMICAL EXPRESSION AND PREVALENCE OF HUMAN PAPILLOMA VIRUS (HPV) and HERPES SIMPLEX VIRUS (HSV) IN CERVICAL LESIONS

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Conflict of Interest – None

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ABSTRACT

Background:- Human papilloma virus (HPV) infection is the most important cause of cervical cancer.Since Herpes Simplex Virus (HSV) and HPV are transmitted sexually and infect the same cell type, both viruses have the potential to interact with each other, impacting neoplastic progression.

Aimand Objective: - This study was conducted to find out association between HPV and HSV in the causation of cervical cancer by immunohistochemistry.

Method:- A prospective study of 12 months duration was conducted in department of pathology government medical college of central India. This Immunohistochemical studies were carried out on 50 paraffin-embedded tissue samples by using antibodies against HPV L1 capsid protein and HSV.Later on, HPV and HSV expression was assessed in different type of cervical lesion

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starting from chronic cervicitis to cervical intraepithelial neoplasia grade III.The data was presented in form of table and graphs using statistical software epi-info version 7.

Result:- HPV positivity for all cases of chronic cervicitis was found to be 29.3% (10/34 cases), for mild dysplasia(CINI), it was 20% (1/5 cases).For CIN III, Squamous cell carcinoma andadenocarcinoma the rate of positivity was 0 %. HSV positivity for all cases of chronic cervicitis was found to be 32% (11/34 cases), for mild dysplasia(CINI), it was 40% (2/5 cases).The rate of positivity was 0% for CIN III, Squamous cell carcinoma and adenocarcinoma. Co-expression of both HPV and HSV was seen in 5/50(10%) cases of chronic cervicitis, 1/5(20%) cases of mild dysplasia(CINI) and in none of the cases of cervical cancer.

Conclusion:- The study suggested that with decreasing differentiation, there is loss of expression of HPV L1 capsid protein in the cervical epithelial cells. This study confirmed the association of HPV presence with benign, precancerous and cancerous lesions of uterine cervix, it also suggested the role of HSV as a cofactor in the causation of cervical cancer.

Keywords:-Cervical cancer, Human Papilloma Virus (HPV), Herpes Simplex Virus (HSV), L1 capsid protein, immunohistochemistry, epitheliotropic.

INTRODUCTION

Cervical cancer is the most common form of cancer in females of developing countries and is the second most common cancer, ranking after breast cancer in females of developed world. [1] Cervical cancer is the most common cancer of female genital tract in India with approximately 1,00,000 (one lakh) new cases occurring each year. This accounts for almost 20% of all new cases diagnosed in the world annually. [2]

Human papillomavirus (HPV) infection is the main etiologic factor for invasive and pre-invasive cervical neoplasia. [3] Recent studies suggest that HPV infection is necessary for the development of invasive cervical cancer.[4]Papilloma virus are epitheliotropic viruses that predominantly infect skin and mucous membrane and produce epithelial proliferation at the site of infection.[5]Herpes simplex virus type 2 (HSV-2) act as a co-factor for development of cervical cancer. [6, 7]Since HSV and HPV are transmitted sexually and infect the same cell type, both viruses have the potential to interact with each other, impacting neoplastic progression. Additionally, different epidemiological studies on the association of cervical carcinoma with HPV and HSV have been reported. [8-13]

There were various methods available for detection of HPV include immunohistochemistry, polymerase chain reaction(PCR), liquid phase hybridization (hybrid capture test), in situ hybridization etc.This study principally aimed to find out association between human papilloma virus (HPV)and herpes simplex virus (HSV) presence in benign, precancerous and cancerous lesions of uterine cervix by immunohistochemistry.

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MATERIAL AND METHODS

This prospective study was conducted at Department of Pathology of Government Medical College of Central India. All prospective cases of cervical lesions in females received for histopathological examination in Department was included in the study. The exclusion criteria were age less than 18 years, pregnancy, cases of secondary malignancy and cases exposed to radiotherapy or chemotherapy.Tissue blocks of 50 cases reported as chronic cervicitis, CIN I, II, III (Cervical intraepithelial neoplasia), Squamous cell carcinoma (SCC) received in Department were processed for histological examination. Immunohistochemistry was done on all cases for HPV and HSV markers.

Specimen Processing: The biopsy specimens were fixed in 10% buffered formalin and processed for routine paraffin section, using the conventional methods. The original histological diagnosis was obtained on the hematoxylin and eosin slides by an experienced pathologist. Immunohistochemistry was performed on 50 samples. Kits for performing IHC were purchased from Biogenex, USA. 4μm sections of formalin-fixed, paraffin-embedded tissues were cut and placed on clean microscopic slides. Sections were incubated at 60°C for 30 minutes. The sections were dewaxed in xylene, rehydrated in graded alcohol, and rinsed in water. For antigen retrieval, the sections were immersed in preheated citrate buffer, pH 6.0, in-pressure cooker for one whistle, then allowed for natural cooling for 20 min. A peroxidase block was added on the specimen according to the tissue size and was incubated for 10 minutes at room temperature. Sections were rinsed with PBS for 3 times 3 minutes each. Next, power block was added and incubated for 10 minutes at room temperature. An appropriate volume of mouse monoclonal antibody (HPV16 and HSV) was added for one hour on the specimen. Sections were rinsed with PBS for 3 times 3 minutes each. Then super enhancer reagent was added and incubated for 20 minutes, followed by rinsing with phosphate buffer, pH 7.4 to 7.6 for 10 minutes. Next secondary antibody (polymer HRP) was added and incubated for 30 min at room temperature in moist chamber. The slides were drained and blotted around the sections, to which an appropriate volume of substrate (3, 3'-diaminobenzdine) solution was added, and they were incubated for 10 minutes at room temperature followed by rinsing thrice in phosphate buffer. Finally, the sections were counterstained inhematoxylin bath for 3 minutes and then rinsed with tap water. The negative control consisted of the same section where the diluents without primary antibody were applied.

Reporting Criteria: - L1, or the major capsid protein, is 1 of 8 known HPV-specific proteins (E1, E2, E4, E5, E6, E7, L1, and L2). During the productive phase of the viral life cycle, the L1 capsid protein (together with L2, the minor capsid protein) is produced within the cytoplasm and translocated into the nucleus, immunochemically visible by a strong nuclear staining reaction in intermediate and superficial squamous epithelial cells. [14]

The L1 capsid protein represents approximately 90% of the total protein on the virus surface and is generally detectable during the reproductive phase of HPV infection. The L1 protein is

ISSN: 0975-3583, 0976-2833 VOL 13, ISSUE 04, 2022

abundant in productive infections;[15,16] Conversely, it is found only in rare cases of CIN III, and it is not produced in carcinomas. In general, CIN II/III lesions are unlikely to support productive HPV infection, because viral maturation depends on squamous maturation that, by definition, is arrested in CIN II/III. It was suggested that a loss of viral L1 capsid protein, a major target of the immune response in HPV-infected SIL, could function as a prognostic marker for the development of CIN lesions. [16, 17]

HPV-L1 is a capsid protein that is expressed in the early, productive phase of cervical carcinogenesis and is progressively lost in the later proliferative phase when p16 gets overexpressed. [18]Any nuclear staining was considered a positive result, regardless of the quantity of cells having expression.

This study was approved by institutional scientific and ethical committee of Medical College. Confidentiality was maintained at each and every step. All finding were entered in Microsoft office excel then analyzed using free software epi-info version 7. Data was presented in the form of frequency and percentage.

RESULTS

In this study, total 50 cases were studied, analyzed, and classified histologically through conventionalclassification method. Majority of the cases 34 (68%) under study were chronic cervicitis, which is the most common lesion found in the uterine cervix. 5 (10%) patients were reportedmild dysplasia (LSIL/ CINI) along with 2(4%) cases had CINIII and 8(16%) cases had squamous cell carcinoma. Apart from this, 01 cases of adenocarcinoma were also included in the study. (Table I, Image I - III)

Expression of HPV in cervical lesions: HPV positivity for all cases of chronic cervicitis was found to be 29.3% (10/34 cases), for mild dysplasia(CINI), it was 20% (1/5 cases). (Table II).

For CIN III, Squamous cell carcinoma and adenocarcinoma the rate of positivity was 0 %.Overall, HPV positivity for all 50 cases of cervical lesions was found out to be 22% (11/50 cases). (Image IV – V)

Expression of HSV in cervical lesions: HSV positivity for all cases of chronic cervicitis was found to be 32% (11/34 cases), for mild dysplasia(CINI), it was 40% (2/5 cases). (Table II) For CIN III, Squamous cell carcinoma and adenocarcinoma the rate of positivity was 0 %.Overall, HSV positivity for all 50 cases of cervical lesions was found out to be 26% (13/50 cases). (Image VI – IX)

Relationship between HPV and HSV expression: 5/50(10%) cases of chronic cervicitis were positive for both HPV and HSV, where as1/5(20%) cases of mild dysplasia(CINI) were showing co-expression of both HPV and HSV.

DISCUSSION

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Human papillomavirus has been considered as the most significant risk factor for cervical cancers. Infection with HPV is necessary but not sufficient for the development of cervical cancer.It is hypothesized that HPV leads to the transformation and the subsequent expression of the malignant phenotype that influences the deregulation of the proliferating cell. This is a multistep process and the long period of latency from the initial time of infection to the development of malignancy suggests that other determinants may be involved as possible cofactors in the pathogenesis of HPVrelated genital cancers.[19] Since HSV and HPV are transmitted sexually and infect the same cell type, both viruses have the potential to interact with each other and play a role in neoplastic progression.

Overall 29.3% and 32% of cases of chronic cervicitis were positive for HPV and HSV respectively on immunostaining. This can be compared with positivity rate of 41.3% for HPV as reported byXu X et al[20] for Semi-quantitative detection of HPV L1 capsid protein in exfoliative cytological examination facilitates the differential diagnosis of cervical lesions.

Haiying Wu et al. [21] reported the positive rate of 100, 65.8, 13.8, 0, 0 and 0%, respectively for HPV L1 expression in cervicitis, CIN I,CIN II, CIN III, cervical SCC and cervical adenocarcinoma for the study on Relationship of HPVL1 and p16 expression with different cervical lesions .HPVL1 expression was not observed in CIN III, cervical SCC and cervical adenocarcinoma patients.

The higher HPV prevalence in cases of cervicitis may be due to a difference in the number of samples, the type of case group (high-risk or low-risk group), cultural limitations, and environmental factors.Further studies are required in this regard to ascertain the cause of increase prevalence of HPV and HSV in pts of chronic cervicitis.20% cases of CINI(mild dysplasia) was positive for HPV and 40% were positive for HSV. Our data are consistent with previously published studies using histologic specimens that demonstrated L1 expression in 30–65% of LSIL/CIN 1. [22-25]

Immunohistochemical detection of viral protein expression has been described in prior studies in cervical specimens. Kurman et al. [26]reported immunohistochemical expression of HPV in 43% of mild dysplasia, 15% of moderate dysplasia and only in a rare case of severe dysplasia.[26]
No case of CINIII, SCC and adenocarcinoma were positive for either HPV or HSV. Results are comparable to 0% positivity for SCC, adenocarcinoma and 9.1% for high grade CINIII as reported by Izadi-Mood Net al. [27] for Immunohistochemical expression of p16 and HPV L1 capsid proteins as predictive markers in cervical lesions.[27]Likewise, Melsheimer et al. [16] found loss of the viral L1 capsid antigen in HSIL in their study.

The L1 capsid protein reportedly was positive in 30% of low-grade squamous intraepithelial lesion (LSIL), 12% of high-grade squamous intraepithelial lesion (HSIL) and 0% of SCCs in liquid-based cytology.[28]In the study of Xiao et al. [29] L1 capsid protein was positive in 69.79% of cervicitis, 83.53 % of CIN I, 41.81% of CIN II, 3.13% of CIN III and 0% of SCC.In

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addition, the positive rates of HPVL1 decreased gradually according to the severity of cervical neoplasia. [30]

Results showed that HPVL1 expression is reduced with the increase of the grade of cervical lesions, and was almost not found in CIN III, Squamous cell carcinoma and adenocarcinoma.Recent studies evaluating methylation of HPV genes, specifically L1, found high levels of methylation of this gene associated with high-grade cytology. [31-32]Consistent intense methylation of L1 gene was shown in HPV 18-related cervical carcinomas. [33]These findings may provide further insight into the mechanisms of loss of capsid protein expression in higher-grade SILs.

The absence of capsid proteins expression in LSIL-associated HSIL/CIN 3 may be related to molecular alterations that are associated with lesion progression but occur before the morphologic changes take place (eg, integration, gene methylation, etc). However, the exact mechanism responsible for the loss of L1 and L2 expression in these lesions is not known. [34]

This could also be attributed to viral load in the cervical lesions. High viral load is often considered to be indicative of persistent infection and progression, while low viral load has been interpreted to reflect HPV viral clearance. A fundamental pitfall of this concept, however, is that CIN1 lesions reflect productive infections and may have thousands of viral copies/cell in upper layers of the cervical mucosa, but CIN2/3 and SCC lesions may have as low as a single copy of viral DNA/cell (commonly integrated into the host genome but not supporting viral replication). [35]

In our study 5/50(10%) cases of chronic cervicitis were positive for both HPV and HSV, where as1/5(20%) cases of mild dysplasia(CINI) were showing co-expression of both HPV and HSV. This finding was reported by various studies conducted in different parts of world. [8-13]

Women infected with HSV-2 and HPV are at a greater risk for the development of cervical carcinoma compared to women infected with only one virus.[8]Early studies showed a prevalence of higher titers of HSV-2-specific antibody in women who developed cervical cancer. [36]
This study may have some limitation in the form of low case enrollment; this may be because of short span of study. There was unequal distribution of cases in different histological types which may affect the association between both the variables.

CONCLUSION

In conclusion, the results suggest that with decreasing differentiation, there is loss of expression of HPV in the cervical epithelial cells. This study confirmed that there is a correlation of HPV presence with benign, precancerous and cancerous lesions of uterine cervix.It also suggests the HSV also was plays a role of co-factor in the causation of cervical cancer. However further studies with greater no of cases are advised for more conclusive results in view of the small no of cases of the current study.

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Ethical permission – Study was approved by institutional ethical committee of GMC Bhopal
Institution where work has been carried out - Gandhi Medical College, Bhopal, Madhya Pradesh

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TABLES

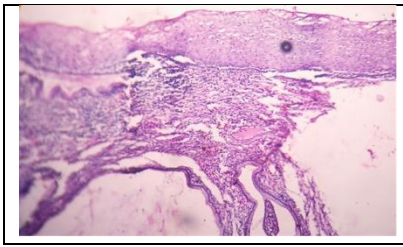
Table I: - Table showing the distribution of cervical lesion.

Cervical Lesions	Average age (years)	N=50	%
Chronic cervicitis	42	34	68
Chronic cervicitis with mild dysplasia	40	5	10
CIN III	38	2	4
Squamous cell carcinoma cervix	58	8	16
Adenocarcinoma cervix	65	1	2

Table II: - Table showing distribution of cervical lesion as per positivity of HSV and HPV

Cervical Lesions		**Positive for HPV**	**Positive for HSV**
Chronic cervicitis	Nuclear expression	2 (5.8%)	11 (32%)
	Cytoplasmic expression	8 (23.5%)	
Chronic cervicitis with mild dysplasia		1 (20%)	2 (40%)
CIN III		0	0
Squamous cell carcinoma cervix		0	0
Adenocarcinoma cervix		0	0

IMAGES

	Image I - Hand E Staining - Chronic Cervicitis

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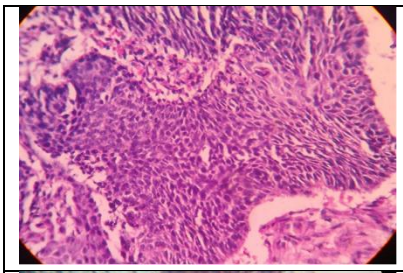
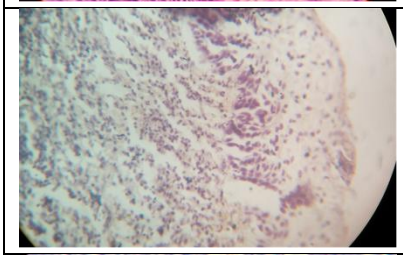
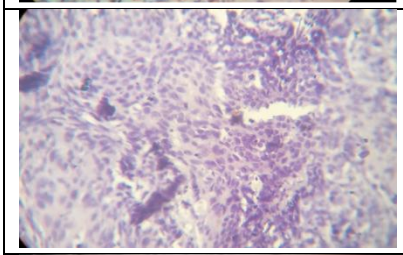
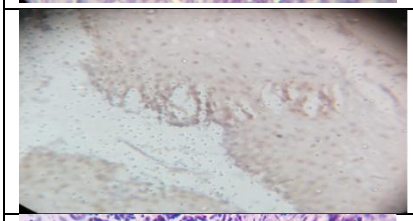
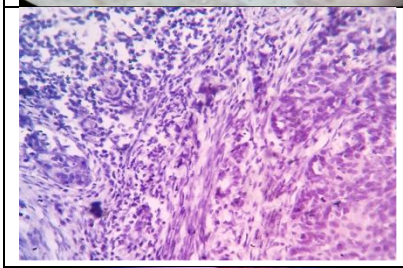
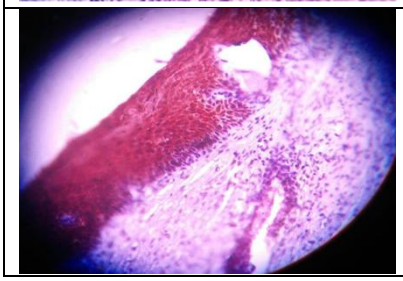
	Image II - HandEstaining Squamous cell carcinoma
	Image III - HandEstaining of cervical dysplasia
	Image IV – IHC Staining HPV negative
	Image V – IHC Staining HPV Positivity in cervical dysplasia
	Image VI – IHC Staining HSV Negative
	Image VII - IHC staining HSV Positivity in chronic cervicitis

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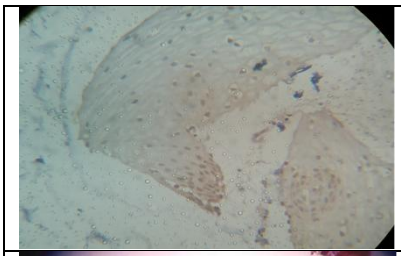
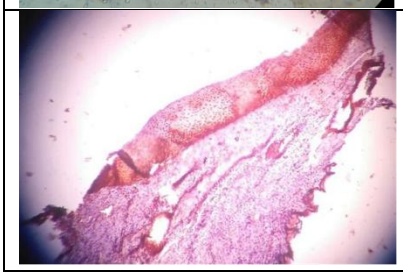
	Image VIII – IHC Staining HSV Positivity in Dysplasia
	Image IX – IHC staining HSV positivity in chronic cervicitis