



BCL-2 EXPRESSION IN MALIGNANT LESIONS OF UTERINE CERVIX

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ABSTRACT

Background: Cervical cancer is the fourth most common cancer recorded in women worldwide. Human papilloma virus (HPV) infection appears to be the major cause of cervical carcinoma. Co-testing using the combination of pap cytology plus HPV DNA testing is the preferred cervical screening method. As HPV DNA test is costlier, expression of certain markers of cell proliferation and apoptosis have been studied. The present study was conducted to evaluate the expression of bcl-2 in malignant lesions of uterine cervix.

Methods: Specimens of cervical biopsy retrieved from incident cases for routine histopathological evaluation from the Department of Obstetrics and Gynaecology, Gauhati Medical College and Hospital, Guwahati, India formed the source of data.

Results: A total of 60 cases were studied in the present study comprising of 53 cases of squamous cell carcinoma, 5 cases of adenocarcinoma and 2 cases of adenosquamous carcinoma. It was observed that a higher percentage of adenocarcinomas (100%) showed Bcl-2 expression than squamous cell carcinomas (94.3%) and Bcl-2 positivity was higher in well-differentiated carcinomas (100%) than moderately differentiated (93.5%) and poorly differentiated carcinomas (90%).

Conclusions: Bcl-2 being an intracellular membrane protein prevents apoptotic cell death. Bcl-2 may play an important role in cervical tumorigenesis. Expression of bcl-2 can be used as an independent diagnostic marker for cervical carcinoma associated with HPV infection.

KEYWORDS : Cervical carcinoma, Malignant, Bcl-2.**INTRODUCTION:**

Cancer of uterine cervix is the fourth most common cancer recorded in women worldwide. It is also the fourth leading cause of cancer deaths among women worldwide. In Indian scenario, carcinoma of cervix is the second most common cancer in women.⁽¹⁾ India has a burden of cervical carcinoma accounting nearly 1/3rd of global carcinoma of cervix.⁽²⁾ The age distribution of cervical cancer is bimodal, with peaks at 35 to 39 years and 60 to 64 years of age.⁽³⁾

Ironically, carcinoma cervix is 100% preventable and potentially curable if diagnosed early. Cervical cancer is most commonly caused by human papilloma virus (HPV), about 80%, mainly HPV serotype 16 and 18.⁽⁴⁾ The major test for detection of carcinogenic HPV DNA is hybridization with signal amplification using PCR. HPV DNA testing being costlier, needs sophisticated equipment. Therefore, the biomarkers of cell proliferation and apoptosis like p53, Bcl-2, cytokeratin, cyclin E, p16 etc. indicate the initiation of carcinogenic process of HPV infection, thus can be used to identify those woman who will need more surveillance.⁽⁵⁾

Bcl-2 (B-cell lymphoma 2) is an intracellular membrane protein which prevents programmed cell death. Overexpression of Bcl-2 can block p53 mediated G1 arrest in cell cycle, as well as co-overexpression of Bcl-2 and c-myc can inhibit p53 induced apoptosis.⁽⁶⁾ Studies have revealed that overexpression of Bcl-2 is present in premalignant and malignant lesions of cervix.

It has been suggested that Bcl-2 overexpression may play an important role in early cervical tumorigenesis in association with Bax expression and HPV infection.⁽⁷⁾

The present study was done to evaluate the expression of bcl-2 in premalignant lesions of uterine cervix by immunohistochemistry. The bcl-2 expression will be correlated with the histological grade of the lesions.

MATERIALS AND METHODS:

Study sample: Specimens of cervical biopsy retrieved from incident cases for routine histopathological evaluation from the Department of Obstetrics and Gynaecology, Gauhati Medical College and Hospital, Guwahati, India from July 2019 to June 2020 formed the source of data for the study.

Study design: Cross sectional study.

Sample size: 60.

Study period: Archival cervical biopsy specimens over 1 year were studied.

STUDY METHOD:

The study comprised of 60 cases of malignant lesions of uterine cervix. The detailed clinical history including age, clinical signs and symptoms, and results of relevant investigations done were collected from the patients' case files.

Paraffin blocks of these patients were retrieved and 3-5 μ m thick sections were taken on poly-L-lysine coated slides. These slides were stained with Hematoxylin and Eosin and Immunohistochemical stain for bcl-2 protein were done.

The technique for IHC included antigen retrieval in citrate buffer in a microwave oven, blocking endogenous peroxidase with 3% hydrogen peroxide, incubating with primary mouse monoclonal antibody against bcl-2 protein. Positive and negative controls were run with each batch of slides. The H and E stained slides were studied for the histopathological changes and the categorization of the cervical lesion. The immunostained slides were examined for cytoplasmic staining of bcl-2. Bcl-2 immunostaining gave brown cytoplasmic reactivity. A case was taken as positive if more than 10% cells showed cytoplasmic reactivity.

Statistical Analysis:

Descriptive statistics of bcl-2 analysed and explained in percentage.

RESULTS:

In this study total 60 cases were studied comprising of 53 cases of squamous cell carcinoma(SCC), 5 cases of adenocarcinoma and 2 cases of adenosquamous carcinoma. Of 53 SCC cases, 12 were well differentiated, 31 were moderately differentiated and 10 were poorly differentiated. All 5 adenocarcinoma cases were well differentiated. Age range of the patients were 28 years to 73 years with mean age being 49.55 ± 11.32 years.

The immunostaining of bcl-2 was cytoplasmic. Total 60 out of 57 cervical carcinoma cases (95%) showed positive bcl-2 expression. Bcl-2 positivity was shown by 94.3% (50/53) cases of SCC, 100% (5/5) cases of adenocarcinoma and 100% (2/2) cases of adenosquamous carcinoma. 100% (17/17) cases of well differentiated, 93.5% (29/31) cases of moderately differentiated and 90% (9/10) cases of poorly differentiated cervical carcinoma showed bcl-2 positivity [Table-1] {Figure 1 to 3}.

Table 1: Bcl-2 positivity in malignant lesion of cervix.

Cervical carcinoma	Total	No. of bcl-2 positive cases	Percentage of bcl-2 positive cases
Invasive carcinoma	60	57	95
Histological type			
SCC	53	50	94.3
Adenocarcinoma	5	5	100
Adenosquamous carcinoma	2	2	100
Histological grade			
Well differentiated	17	17	100
Moderately differentiated	31	29	93.5
Poorly differentiated	10	9	90

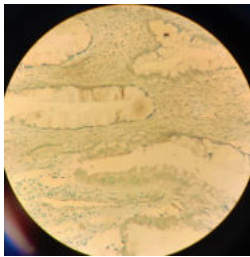


Figure 1: Bcl-2 positivity in well differentiated adenocarcinoma (IHC, 40x view).

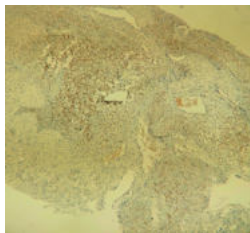


Figure 2: Bcl-2 positivity in well differentiated SCC (IHC, 10x view).

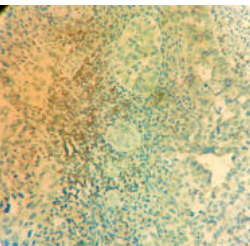


Figure 3: Bcl-2 positivity in moderately differentiated SCC (IHC, 40x view).

DISCUSSION:

Cancer of uterine cervix is the fourth most common cause of

cancer and fourth leading cause of cancer deaths among women worldwide.⁽¹⁾ Bcl-2 overexpression is present in both malignant and premalignant lesions of cervix. Limited numbers of studies are available on bcl-2 expression. This study was taken up to evaluate the bcl-2 expression on malignant lesions of uterine cervix by using immunohistochemistry.

In the present study, a higher percentage of adenocarcinomas (100%) was positive for bcl-2 compared to squamous cell carcinomas (94.3%) which was similar to the findings of Tjalma et al^(8,9), Shukla et al⁽¹⁰⁾ and Zhou et al⁽¹¹⁾ but contrary to findings of Dimitrakakis et al⁽⁷⁾. It was also observed that a higher percentage of well differentiated (100%) cervical carcinoma cases showed bcl-2 positivity than moderately differentiated (93.5%) and poorly differentiated (90%) carcinoma which was similar to the findings of Tjalma et al^(8,9), Giarnieri et al⁽¹²⁾ and Shukla et al⁽¹⁰⁾ but dissimilar to the findings of Zhou et al⁽¹¹⁾ and Touhetimulati et al⁽¹³⁾.

CONCLUSION:

Bcl-2 is an intracellular membrane protein which prevents apoptotic cell death. Bcl-2 may play an important role in cervical tumorigenesis. Hence, expression of bcl-2 can be used as an independent diagnostic marker for cervical carcinoma associated with HPV infection.

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