Original Article

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Evaluation of Immunoexpression of Vimentin in Squamous Cell Carcinoma of Uterine Cervix

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Abstract

Background: Uterine cervical carcinoma is one of the common malignancies in Bangladesh.In advance stages of thedisease manypatients die due to metastasis and recurrence.Vimentin immunoexpression is upregulated in various epithelial tumors during Epithelial Mesenchymal Transition (EMT) a crucial element of tumor progression and metastasis. This study aimed to assess the immunohistochemical expression of Vimentin in neoplastic cells of the tumor and its association with the histopathological grade of the tumor.

Materials and methods: This study was conducted in the Department of Pathology, Chittagong Medical College from September 2021 to August 2023. Fifty one cases of uterine cervical squamous cell carcinoma diagnosed by histopathological examination of colposcopic biopsy and hysterectomy specimens were included in the study. Additionally an immunohistochemical analysis was conducted to evaluate the vimentin immunoexpression.

Results: Forty seven (92.2%) cases showed positive Vimentin immunoexpression in neoplastic cells. Vimentin immunoexpression was positive in 100% cases of grade II and grade III tumors. Immunoexpression of vimentin was increased with increasing grade of the tumor and was statistically significant (p value <0.001).

Conclusion: This study supports that vimentin immunoexpression could be considered as a useful prognostic marker for uterine cervical squamous cell carcinoma.

Key words: Epithelial Mesenchymal Transition (EMT); Metastasis; Vimentin.

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Introduction

Uterine cervical cancer is one of the commonest malignant tumor in the female reproductive organs. Its incidence is next to breast cancer in countries like Bangladesh.[1] According to International Agency for Research on Cancer, about 58.9 million Bangladeshi women are at risk of developing cervical cancer and it is the second leading cause of female cancer in Bangladesh. About 8268 new cases and 4971 death soccur annually in Bangladesh due to cervical cancer and it's 5 year prevalence rateis 22.27%.[2] Squamous cell carcinoma is the most common histopathological type (Approximately 80%) of cervical carcinoma, whereas adenocarcinoma is less common histopathological type (Approximately 15%) of cervical carcinoma. Adeno squamous and neuroendocrine carcinomas are rare cervical tumorsoccurin the remaining 5% of cases).[3] Numerous risk factors for cervical cancerhave been identified by epidemiological studies, such as persistent infection with high risk Human Papilloma Virus (HPV) early age of sexual intercourse, multiple sexual partners, multiparity, use of oral contraceptive for long terms, smoking tobacco, low socioeconomic condition, Chlamydia trachomatis infection, deficiency of micronutrient, and low intake of vegetables and fruits, all of this contribute to the development of uterine cervical cancer.[4-5]

Human cancer cells have the capacity to invade surrounding tissues and to metastasize in distant organs. A biological process, known as Epithelial Mesenchymal Transition (EMT) is associated with cancer progression and metastasis, by which epithelial cells lose cellular adhesion and polarity, and achieve a mesenchymal phenotype.[6]Cancer cells can spread to distant organs of the body at a much quick erpace due to their loosing of epithelial phenotype and achieving of mesenchymal phenotype.[7-8] HPV16 E6 or E7 proteins have been shown to promote tumor invasion and metastasis by regulating EMT in

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uterine cervical epithelial cells.[9] Those patients who have metastatic uterine cervical carcinoma have poor outcomes.[10]

Vimentin is a cytoskeletal type III intermediate filament protein encoded by gene on chromosome 10p13.[11] It provides integrity and flexibility to cell that helps in movement and protection.[12] Vimentin intermediate filament proteins have been involved in various aspects of tumor initiation and development, such as tumorigenesis, Epithelial to Mesenchymal Transition (EMT) and metastasis.[13] EMT and accompanying vimentin expression are modulated upon TGF-β1 stimulation, snail overexpression, Slug phosphorylation and ZEB 2 over expression.[14-17] Higher vimentin immuno-expression has been seen in various epithelial cancers such as breast cancer, gastrointestinal tumors, prostate cancer, CNS tumors, lung cancer, malignant melanoma, and other types of cancer. It is also reported to be closely associated with tumor migration, progression and metastasis.[11]

The aim of our study is to evaluate the immunoexpression of vimentin in squamous cell carcinoma of uterine cervix and it's association with the histopathological grade of the tumor.

Material and methods

This analytical cross-sectional study was conducted at the Department of Pathology, Chittagong Medical College, Chattogram from September 2021 to August 2023. Before starting this study, ethical clearance was obtained from the Ethical Review Board of Chittagong Medical College (Memo No. 59.27.0000.013.19.PG.009. 2022/885, Date: 19/10/2022). Fifty-one conveniently selected patients who were diagnosed as uterine cervical squamous cell carcinoma by histopathological examination of colposcopic biopsy and hysterectomy specimens were included in this study. Patients with metastatic cases of uterine cervical squamous cell carcinoma and those who had received chemo or radiotherapy for uterine cervical squamous cell carcinoma were excluded.

Demographic, clinical and histopathological information were collected using a structured case record form containing all the variable of interest after obtaining proper written informed consent. Tumors were graded into well-differentiated, moderately differentiated, and poorly differentiated carcinoma.[18] Tissue processing was done in the laboratory of the Department of Pathology of Chittagong Medical College following standard protocol. The resected hysterectomy and colposcopic biopsy specimens were fixed in 10% formalin. The paraffin blocks were sectioned with a rotary manual microtome at 5-micrometer thickness. Two tissue sections were taken from each paraffin block. One section was stained with routine H & E stain in the laboratory of the Department of Pathology of Chittagong Medical College. Another section was processed to perform vimentin immunohistochemical staining in the laboratory of the Department of Pathology of BMU, Dhaka. Cytoplasmic vimentin expression of tumor cells was assessed. Positive control was taken from section of uterine leiomyoma.

Scoring system for assessment of Vimentin expression-

The total score of immunoreactivityof vimentin was evaluated semi-quantitivelyon the basis of staining intensity and the percentage of positive cells using immunoreactive score: intensity score x proportion score. Cytoplasm staining was considered as immunopositive.

Table I Scoring system for assessment of vimentin expression[10]

Intensity score	Stainingpattern
0	Negative
1	Weak
2	Moderate
3	Strong
Proportion score	Percentage of positive cells
0	Negative
1	10%orless
2	11%to 50%
3	51%to 80%
4	80% or more positive cells

The total score ranges from 0 to 12.

After collection, data were entered into Excel sheet to generate a master sheet. Further data processing and analyses were conducted using SPSS (Statistical Package for Social Sciences) version 23.0 for Windows. Qualitative variables were expressed as frequency (Percentage) and compared between groups by Chi-square test.

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Continuous variables (Age, age at first sexual exposure etc.) were expressed as frequency, percentage, mean (± SD) and range. p value <0.05 was considered statistically significant.

Results

Table IIshows that, the mean age (± SD) of the patients was 51.9(±9.5) years with the youngest and eldest patients in this study being 32 years and 70 years old respectively. Among the 51 cases of the present study, 26 patients (51%) were between 41 to 50 years of age, followed by 11 patients (21.6%) between 51 to 60 yearsofage. Majority of the patients were married (84.3%) 43 patients (84.3%) came from low socioeconomic conditions. Mean (± Standard deviation) of age of first exposure was 15.8 (±1.9) years and 72.5% had parity 3-5.

Table II Socio-demographic characteristics of the study population (n=51)

Variables	Frequency (n)	Percentage (%)
Age (Years)		
31-40 Years	06	11.8
41-50 Years	26	51.0
51-60 Years	11	21.6
61-70 Years	08	15.7
Mean (± Standard deviation)	51.9 (±9.5)	
Range	32.0-70.0	
Maritalstatus		
Married	43	84.3
Widowed	08	15.7
Socio-economicstatus		
Lower class	43	84.3
Middle class	08	15.7
Age at first sex, in years		
Mean (± Standard deviation)	15.8 (±1.9)	
<18 years	41	80.4
≥18 years	10	19.6
Parity		
≤ 2	08	15.7
3-5	37	72.5
>5	06	11.8
Mean (± Standard deviation)	3.9 (±1.4)	

Data are expressed as frequency (Percentage) if not mentioned otherwise

All of the samples were squamous cell carcinoma on histopathological examination. Based on histopathological grading, 5 out of 51 samples (9.8%) were well differentiated (GradeI) 43(84.3%) were moderately differentiated (Grade II) and rest 3(5.9%) were poorly differentiated (Grade III). No undifferentiated carcinoma cases were found.

Out of 51 cases, positive vimentin expression was detected in 47 (92.2%) cases, while negative vimentin expression was detected in 4 (7.8%) cases. Among 5 well-differentiated (Grade I) cases, 4 cases (80%) showed negative vimentin immunoexpression and only 1 case showed positive vimentin immunoexpression. All 43 (100%) moderately differentiated (Grade II) cases and 3 (100%) poorly differentiated (Grade III) cases showed positive vimentin immuno- expression (Table III).

The immunoexpression of vimentin was increased with increasing grade of the tumor. This association of vimentin immunoexpression with histological grade of the tumor was found to be statistically significant with a p-value of ≤ 0.05.

Table III Association between vimentin immunoexpression with histological grade of carcinoma cervix (n=51)

		Histopathological grade				
		GradeI	Grade II	Grade III	Total	p value
Vimentin expression	Negative	04 (80.0)	00 (00)	00 (00)	04 (07.8)	<0.001^{S}
	Positive	01 (20.0)	43 (100.0)	03 (100.0)	47 (92.2)	
	Total	05(100.0)	43 (100.0)	03(100.0)	51 (100.0)	

S: Significant statistically (p value was obtained by chi-square test (χ^2=39.93, df=2). Figure within parenthesis indicates in percentage

Vimentin expression was positive in 26 cases among 41-50 years age group, 11 cases in 51- 60 years age group, 6 cases in 61-70 years age group and 4 cases in 31-40 years age group. Negative expression was seen in 2 cases of 31-40 years and 61-50 years age groups respectively. A significant association between the expression of vimentin was found among different age groups (p<0.05) (Table IV). However, there was no significant association among vimentin expression of different age group of first exposure and parity.

Table IV Association between of vimentin expression with age, age at 1st exposure and parity of carcinoma cervix patients (n=51)

Characteristics		Vimentin expression		p value
		Negative (n=4)	Positive (n=47)	
Age	31-40 Years	02 (50.0)	04 (8.5)	0.008^{S}
	41-50 Years	00 (00)	26 (55.3)	
	51-60 Years	00 (00)	11 (23.4)	
	61-70 Years	02 (50.0)	06 (12.8)	
Ageat 1st exposure				
	<18 Years	04 (100.0)	37 (78.7)	0.340^{NS}
	≥18 years	00 (00)	10 (21.3)	
Parity	≤2	00 (00)	08 (17.0)	0.514^{NS}
	3-5	03 (75.0)	34 (72.3)	
	>5	01 (25.0)	05 (10.6)	

JCMCTA 2026 ; 37 (1) : 38-43
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S: Significant Statistically, NS: Not Significant statistically, p value was obtained by chi- square test.

Figure with in parenthesis indicates in percentage

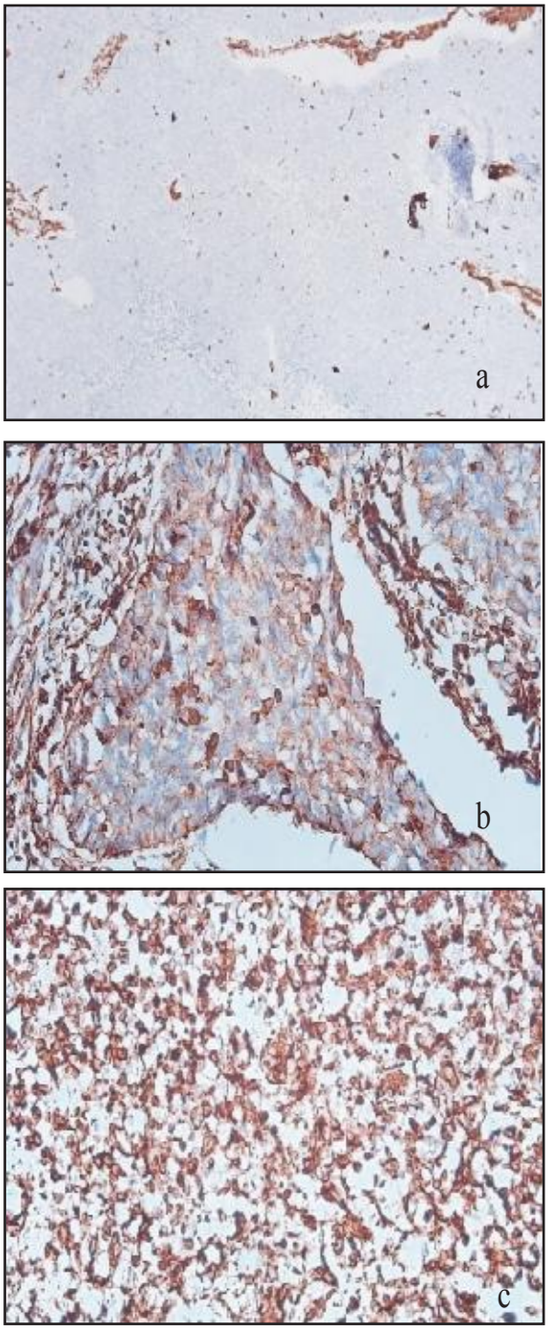

Figure 1 Photomicrograph showing uterine cervical squamous cell carcinoma a) Grade-I, (×10) Vimentin immunoexpression: Negative (-), b) Grade-II (×40) Vimentin immunoexpression: Positive (+), c) Grade-III, (x40) Vimentin immunoexpression: Positive (+)

Discussion

Cervical cancer is the fourth most common cancer in women globally and the second most common in developing countries.[20] In recent years, the screening of cervical cancer has been developed extensively. Therefore as a result the early diagnosis and treatment of cervical cancer and precancerous lesions have also been improved. But still postoperative recurrence and deaths ofpatients with cervical canceroccurs dueto infiltration, metastasis and poor differintation of the tumor.[21-22] Increased expression of vimentin is seen as an indicator of advanced disease having a poorer prognosis.[23] Keeping this in mind the aim of the study was to assess the expression of vimentin in uterine cervical squamous cell carcinoma. A total of 51 histopathologically diagnosed cases of uterine cervical squamous cell carcinoma were enrolled in this study.

In the present study, the mean age of the patient was found 51.9(±9.5) years with a rangefrom 32 to 70 years. This finding is nearly similar to the study of Santana et al. in which the age of cervical carcinoma patients ranged between 26 to 88 years with a mean age of51.2(±15.3) year.[24]

In this study, most cervical carcinoma patients have an early age of first exposure of sexual contact with a mean age of 15.8(±1.9) years. Khalaf et al. and El-Moselhyet al. also reported that marriage at or less than 18 years is strongly associated with cervical pre-cancer and cancer.[25,26] Mean parity of this study is 3.9(±1.4) nearly similar finding also observed by Nessa et al. that having parity more than 3 had a significant association with development of cervical pre cancer and cancer.[27]

Squamous cell carcinoma is the most common histologic subtype of uterine cervical carcinoma. In the present study, 51 cases of histologically diagnosed squamous cell carcinoma were included and graded according to WHO grading system. We observed that most of the cases were moderately differentiated (n=43, 84.3%) followed by 5 cases (9.8%)of well differentiated (Grade I) and 3 cases (5.9%) of poorly differentiated (Grade III) carcinoma. Similarly, another study by Nahar et al. found that majority of the cases (90%) were moderately differentiated (Grade II) carcinoma.[28]

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The primary aim of the study was to observe the immunohistochemical expression of vimentin in uterine cervical squamous cell carcinoma. In this study, Vimentin immunostaining was semi-quantitatively assessed based on intensity and the percentage of immune reactive cells. It was observed that only 4 cases (7.8%) showed negative vimentin immunoexpression and 47 cases (92.2%) showed positive vimentin immunoexpression.

All of the 43 cases of moderately differentiated carcinomas and 3 cases of poorly differentiated carcinomas showed positive vimentin expression and none showed negative expression. On the other hand, proportion of negative vimentin expression was significantly higher among patients with well differentiated carcinoma. This indicated that with the progression in tumor grade, the rate of vimentin expression significantly increased ($p<0.05$) which was similar to Husain et al. and Cheng et al.[29,30] Although, Santana et al. found no statistically significant difference between vimentin and tumor grade, they observed vimentin expressionin 100% of the tumor specimens. Several causes can be pointed out for this variation in results, such as differences in procedure of tissue processing (Specimen handling, fixation time, fixatives, paraffin block preparation, reagent quality etc) and immunohistochemistry technique (Antigen retrieval, antibody dilution, incubation period, washing etc).[24] Different cut off values for expression of vimentin is another important cause for difference of vimentin expression in different studies.

In the present study, an statistically significant ($p<0.05$) difference was observed between vimentin expression and different age groups. Husain et al. observed that with the age ≥55 years the expression of vimentin was higher (41%) as compared to the <50 years of age group (38%) although it was not statistically significant ($p> 0.05$).[29]

Limitations

Information regarding extra-uterine extension, lymph node and distant metastasis could not be included due to lack of logistic support, which could give more conclusive decision regarding prognostic significance of vimentin.Detection of HPV DNA could not be done due to financial constrains.

Conclusion

In this study, positive vimentin immunoexpression was seen in 92.2% cases and there was statistically significant association between vimentin immunoexpression and the grade of the tumor ($p<0.05$). This expression profile of vimentin may be useful for selecting high risk patients and predicting the subset of patients requring more comprehensive treatment and extensive follow up.

Recommendations

Further studies with larger sample size, more logistic support and proper follow up should be carried out.

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Contribution of authors

UKAA-Acquisition of data, data analysis, drafting & final approval.

MHM-Acquisition of data, data analysis, drafting, critical revision & final approval.

MFA-Acquisition of data, data analysis, interpretation of data, drafting, critical revision & final approval.

SR-Acquisition of data, drafting, critical revision & final approval.

MIH-Conception, design, interpretation of data, critical revision & final approval.

MSUA-Conception, design, critical revision & final approval.

Disclosure

All the authors declared that there is no conflict of interest.

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