Original Article

CDX-2 expression in colorectal cancer: A single centre study from Pakistan

Muhammad Tahir[1], Bilqees Fatima[2], Arfa Nawazish[3], Iram Kehkashan Khurshid[4], Sana Gul[5]

[1] Associate Professor, Department of Pathology, RIHS, Islamabad.

[2] Lecturer, Department of Pathology, Fazaia Medical College Islamabad.

[3] Ex Post-graduate Trainee, Department Pathology, Federal Government Poly Clinic, Islamabad.

[4] Consultant Histopathologist, CITI Lab, Rawalpindi.

[5] House Officer, Federal Government Poly Clinic, Islamabad.

Author's Contribution

[1,3] Conception of study
[1] Experimentation/Study conduction
[1,2] Analysis/Interpretation/Discussion
[2] Manuscript Writing
[1] Critical Review
[4,5] Facilitation and Material analysis

Corresponding Author

Dr. Bilqees Fatima,
Lecturer,
Department of Pathology,
Fazaia Medical College,
Islamabad
Email: dr.fatiema@gmail.com

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Abstract

Introduction: Tumours of the gastrointestinal (GI) tract, share a major burden for mortality and morbidity all over the world. The most common site of carcinoma of GIT is colon and rectum (70%). The etiological factors may be environmental (diet) and genetic. CDX-2 has been proposed as being present in most of the cases with colorectal carcinoma.

Objective: To determine the frequency of positive expression of CDX2 in diagnosed cases of colorectal adenocarcinoma diagnosed on haematoxylin and eosin stain.

Material and Methods:

This was a cross-sectional study and was conducted at Histopathology department, Federal Government Polyclinic, PGMI, Islamabad over period of 2 years. We included all paraffin embedded tissue sections of colorectal carcinoma of both genders with an age range of 25-75 years. Specimens were stained with Heamatoxylin and Eosin (H & E) and examined microscopically for presence or absence of invasive cancer. Another specimen was taken and stained with CDX2. The data were analyzed using SPSS version 24.

Results: A total of 125 cases with colorectal carcinoma diagnosed on H & E stain were included in the study. The mean age of the patients was found to be 52.66 ± 14.62 years. In this study, 67 patients (53.6%) were male and 58 patients (46.4%) were having final diagnosis of Adenocarcinoma. Regarding the site, most common lesion involved rectum, followed by sigmoid colon and ascending colon. Among 125 specimens reviewed, 112 patients (89.6%) were CDX-2 positive while 13 patients (10.4%) were CDX-2 negative. Also we stratified the CDX-2 expression according to site and type of colorectal carcinoma and was found significant for both of these ($P<0.05$).

Conclusion: We concluded that CDX-2 was present in almost 90% of colorectal carcinoma specimens so it can be used as an important diagnostic tool for colorectal carcinoma during histopathological diagnosis.

Keywords: Colorectal carcinoma; CDX-2; Hematoxylin; Eosin.

Introduction

Colorectal carcinoma is one of the most frequent carcinomas and holds 3rd position in terms of the frequency following breast and lung. It was also reported as the second most common cause of cancer death (10%) after lung cancer in the UK in 2006.[1,2] Immunohistochemistry has been used for many decades for a definitive diagnosis of colorectal cancer. Different immune his to chemical markers have been used so far. The most popular among them is CK20. It is low molecular weight keratin, which is most commonly expressed in the gastrointestinal epithelium, urothelium, and Merkel cells. The CK7–/CK20 + expression pattern is known to be highly characteristic of colorectal Adenocarcinoma.[3] However, not all the colorectal Adenocarcinomas show this pattern. Therefore, there is a continuous need for more sensitive markers for intestinal epithelium and CDX2 appears to be a better marker than those existing before.[4]

CDX2 is a nuclear homeobox transcription factor that belongs to the caudal–related family of CDX homeobox genes. It is involved in the process of intestinal epithelial proliferation, differentiation, adhesion, and apoptosis. It is normally expressed within the nuclei of epithelial cells of GIT starting from the duodenum to the rectum. Recent histopathological studies have shown CDX2 to be a sensitive and specific marker for adenocarcinoma of the GIT, particularly those found in the colon and rectum.[5] Its expression is reported to be as high as 97% of specimens[3], while some studies have shown a loss of its expression in 14-37% of specimens, probably due to high tumour grade, microsatellite instability, or advanced tumour stage.[5, 6]

Immunohistochemistry using CDX2 is a reliable and quick method of detecting colorectal carcinoma [7, 8]. The objective of the study was to determine the frequency of positive expression of CDX2 in diagnosed cases of colorectal adenocarcinoma diagnosed on haematoxylin and eosin stain.

Patients and Methods

This study was conducted at the Histopathology Department, Federal Government Polyclinic, PGMI, Islamabad. It was a cross-sectional study and the duration was 2 years, from January 2017 to December 2018. We included all paraffin-embedded tissue sections of colorectal carcinoma of both genders with an age range of 25-75 years. Our exclusion criteria included endoscopic biopsies, autolyzed biopsies, tissues without proper formalin fixation, and resections after pre-surgical neoadjuvant therapy, and tissue blocks containing extensive necrosis and hemorrhage. SAMPLE SIZE of 125 cases was calculated according to WHO sample size calculator taking confidence Level of 95%, anticipated population proportion as 97%, and absolute precision as 03%. The sampling technique used was non-probability consecutive sampling. The criteria set for positivity of CDX2 were staining of at least 50% of tumour cells by CDX2. Freshly cut 3-5 microns thick sections stained with Heamatoxylin and Eosin (H&E) were examined microscopically by a consultant histopathologist. The presence/absence of invasive cancer was reported. Another 3-5 microns thick section of the original tumour, stained with CDX2 was looked at again for the uptake of stain by cancer cells by the same histopathologist and reported. The data was analyzed using SPSS version 24. The frequency was calculated for qualitative variables like the positive expression of CDX2, gender, and types of colorectal adenocarcinoma. Mean was calculated for quantitative variables like the age of the patients. Effect modifiers like age and gender were controlled by stratification. Post-stratification chi-square test was applied, and p-value ≤0.05 was considered as significant.

Results

A total of 125 cases with colorectal carcinoma diagnosed on H & E stain were included in the study. The mean age of the patients was found to be 52.66 ± 14.62 years. In this study, 67 patients (53.6%) were male and 58 patients (46.4%) were having a final diagnosis of Adenocarcinoma. Regarding the site, the most common lesion involved the rectum, followed by a sigmoid colon, ascending colon, transverse colon, and descending colon (Table 1).

Table 1: Distribution of the patients according to the site involved

Age (mean ± SD)	52.66 ± 14.62 years
Gender (n(%)	
Male	67 (53.6%)
Female	58 (46.4%)
Site (n(%)	
Ascending Colon	21 (16.8%)
Transverse Colon	11 (8.8%)
Descending Colon	8 (6.4%)
Sigmoid Colon	31 (24.8%)

Rectum	54 (43.2%)
Type of colorectal carcinoma (n(%)	
Adenocarcinoma	102 (81.6%)
Mucinous Carcinoma	16 (12.8%)
Signet ring Carcinoma	7 (5.6%)

Table 2: Stratification of CDX-2 expression for site and type of carcinoma

	CDX-2 Positive	Negative	Total
Site of Colon			
Ascending Colon	19	2	21
Transverse Colon	8	3	11
Descending Colon	5	3	8
Sigmoid Colon	29	2	31
Rectum	51	3	54
Total	112	13	125
P = 0.001			
Type of Colorectal Carcinoma			
Adenocarcinoma	95	7	102
Mucinous Carcinoma	12	4	16
Signet ring cell carcinoma	5	2	7
Total	112	13	125
P Value= 0.023			

Figure 1: High power view (x400X) of colorectal adenocarcinoma with atypical glands lined by pleomorphic cells having hyperchromatic nuclei, prominent nucleoli, high N/C ratio, infiltrating muscularis propria.

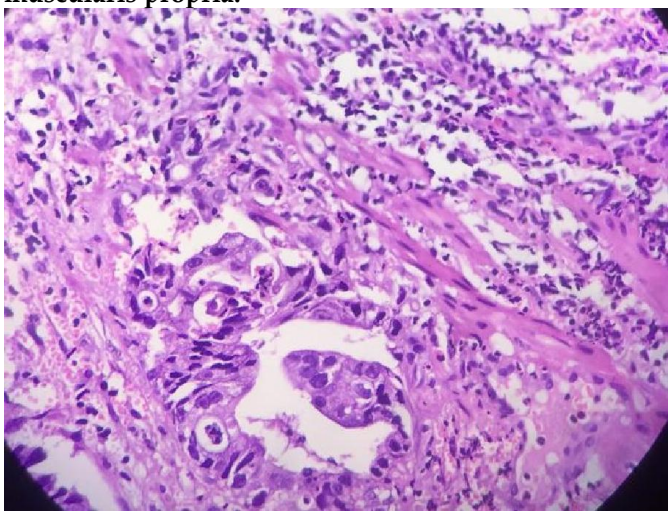
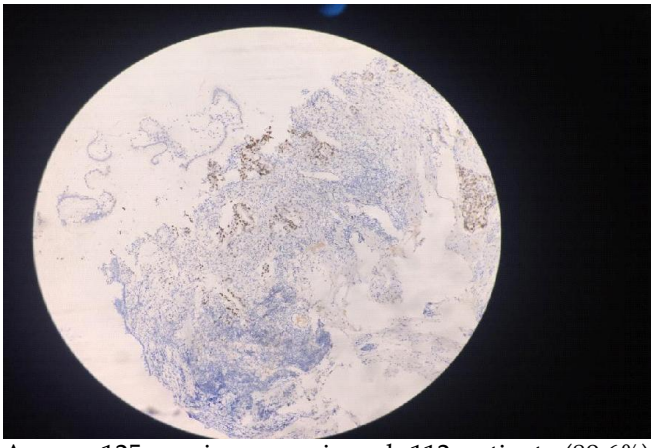


Figure 2: Low power view (x100X) of colorectal adenocarcinoma exhibiting nuclear positivity for CDX2 immuno-histochemical marker



Among 125 specimens reviewed, 112 patients (89.6%) were CDX-2 positive while 13 patients (10.4%) were CDX-2 negative. Also, we stratified the CDX-2 expression according to the site and type of colorectal carcinoma, and was found significant for both of these ($P<0.05$) (Table 2).

Discussion

Colon and rectum are the most common-place for carcinoma of GIT and it is related to higher morbidity and mortality. Its incidence is higher in older age and more than 90% of cases are found in individuals with age being higher than 55 years.[9] In this study, the mean age of the patients was found to be 52.66 ± 14.62 years which is comparable to previous literature.[10,11] In this study, 67 patients (53.6%) were male while 58 patients (46.4%) were females. In contrary to some foreign studies who have reported more preponderance of colorectal carcinomas in males (male vs. female 2:1), we found almost an equal distribution among both genders.[12] However, as there is no central registry program for carcinomas in our country, therefore exact incidence and gender variation are not known in our population. In another large study from Pakistan, gender distribution was equal in both genders for colonic carcinomas (1:1), higher in males for rectal carcinomas (2:1), and higher for males in cases of total colorectal carcinomas (1.7:1).[13]

The distribution of colorectal carcinoma according to the site was also assessed in this study. We found that the most common site of carcinoma was rectum and left colon. Classically, the most commonly left-sided colon is considered a frequent site for carcinoma. However, some recent studies have reported a higher incidence of the right colon in many parts of the world [(14)]. In this study, only a small number (16.8%) of the patients had right-sided or proximal colon cancer.

Amanda IP and colleagues surveyed a large number of patients with colorectal carcinoma and they found almost similar results. In their study, the most common location of colorectal carcinoma was found to be the rectum, similar to our study.[15]

Human CDX2 protein is a member of the homeobox genes that are found in the nuclei of the epithelium of GIT both in fetal life and after birth. Also, CDX2 mRNA expression is found only in gastrointestinal tract epithelium cells. The accuracy of CDX-2 expression among patients with colorectal carcinoma is reported to be greater than 90%.[5] Werling et al conducted a study and included 476 specimens and found it to be an excellent marker of adenocarcinomas of GIT, particularly for those arising from duodenum and colon. They found higher levels (>75% positive cells) of CDX2 expression in colorectal adenocarcinomas, while intermediate levels (26%-75% positive cells) of expression in adenocarcinomas arising elsewhere in the intestine. They also found that similar levels of expression of CDX2 staining are shown by primary and metastatic colorectal carcinomas. All primary and metastatic colonic adenocarcinomas (except one specimen in the metastatic group) showed higher levels of CDX2 expression (2+ or 3+).[16] Similar to it, in another study, the authors reported CDX2 expression in all colorectal metastatic specimens.[17]

In this study, CDX-2 expression was found positive in 112 of 125 (89.6%) cases, which is consistent with the previous studies reported. To the best of my knowledge, it is the only study conducted that has revealed the frequency of CDX-2 expression in patients with colorectal carcinoma in our population and no study has been done previously on this topic. I hope that this study will help us make the diagnosis of colorectal cancer easier and will help us making patient management better. However, more work and research is needed to explore other aspects of the disease and CDX-2 association.

Conclusion

We concluded that CDX-2 was present in almost 90% of colorectal carcinoma specimens so it can be used as an important diagnostic tool for colorectal carcinoma during histopathological diagnosis.

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