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Research Article

EXPRESSION PATTERN OF CDX2 IN COMMON EGYPTIAN COLO-RECTAL LESIONS; IMMUNOHISTOCHEMICAL STUDY

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ABSTRACT

Background: Colorectal cancer was found to be one of the three most commonly diagnosed cancers in developed countries and one of the major mortality-causing cancers in industrialized countries. In Egypt, the incidence rates of CRC represent 6.5% of all diagnosed cancer cases. However, development of CRC could be effectively reduced if colonic adenomas were diagnosed early using an efficient screening method. The Caudal-related homeobox intestine-specific transcription factor was found to display tumor-suppressing activity in colorectal cancer.
Methodology: the current study, the pattern of CDX2 expression in colo-rectal mucosa was studied in relation to adenocarcinoma, pre-malignant colonic lesions of patients suffering from IBD, colitis, adenoma and for the first time -up to the most of our knowledge-to intestinal bilharziasis using immunohistochemical analysis.
Results: A significant difference between levels of CDX2 expression was displayed amongst the groups involved in this study
Conclusion: The immunohistochemical analysis has shown that measuring CDX2 expression patterns is a reliable method to distinguish between adenomas and adenocarcinomas, high grade and low grade tumors, and also between dysplastic and non-dysplastic inflammatory bowl diseases. However, CDX2 expression pattern failed to show any clear role of bilharziasis as premalignant colonic lesion

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide following lung and breast cancer respectively Ferlay *et al* (2012) (1). According to the American Cancer Society (ACS), approximately 134,490 new CRC cases were diagnosed in 2016 and CRC-related deaths represent 8% of all annual cancer deaths (Siegel *et al*., 2016) (2).Additionally, it was found that two-thirds of all CRC patients have been diagnosed in the more developed areas of the world. Gado *et al* (2014) (3). In Egypt, the incidence rates of CRC are prominently increasing, as it represents 6.5% of all diagnosed cancer cases with an unprecedented trend towards younger age at presentation (Soliman *et al*., 1997) (4). Nonetheless, the cure rate and management of this malignancy could be prominently enhanced if we were able to diagnose it early. Colorectal cancer (CRC) is amongst the most dreaded long-term complications of several diseases that when detected prior to their transformation into malignant tumors will significantly increase cure-rates and enhance cancer prevention. Ullman *et al* (2009) (5). These diseases include Colitis which is the inflammation of the inner lining of the colon, inflammatory Bowel Disease (IBD) which is classified into ulcerative colitis (UC) and Crohn's disease (CD), colon polyps which are common growths on the inner lining of the colon, and many others. Haggar *et al* (2009) (6) In IBD, the disease may or may not be associated with dysplasia, which is the stage that a cell experiences before becoming malignant. Overall, in the previously mentioned diseases the risk of development into colorectal cancer is dependent on the presence of primary sclerosing cholangitis, degree of colonic invasion, longer time interval of disease, and a family history of colorectal cancer. Rubin *et al* (2006) (7). Numerous studies have proven that there is a correlation between the level of expression of certain biomarkers and the stage and occurrence of colorectal cancer. Moskaluk *et al* (2003) (23) These biomarkers include the homeobox protein CDX2, which is a caudal-related homeobox transcription factor that is usually restricted to the intestinal epithelium, and plays a critical role in intestinal development

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and differentiation. Yan *et al* (2014) (8). CDX2 has been found to administrate the expression of a number of genes that regulate numerous processes which include proliferation, adhesion, cell migration, and tumorigenesis. Olsen *et al* (2014) (9) Due to the important role of CDX2 in intestinal differentiation and cell proliferation, the gene regulation of the transcription factor CDX2 has been the focus point of a number of studies, which lead to the outcome that the loss or reduction of the systematized regulation of CDX2 expression has many pathological consequences. It was found to mostly be reduced in colorectal cancer, which shows that CDX2 has tumor-suppressing potential in the colon. Coskun *et al* (2012) (10) In the current study, the pattern of CDX2 expression in colo-rectal mucosa was studied in relation to adenocarcinoma, pre-malignant colonic lesions of patients suffering from IBD, colitis, adenoma and for the first time-up to the most of our knowledge-to intestinal bilharziasis which is an endemic parasitic infestation affecting the colon in Egypt as well as in other parts of Asia and Africa.

MATERIALS AND METHODS

Case selection and tissue samples

Fifty six colorectal, biopsy specimens were retrieved from the archival files of the Department of Pathology, Theodor Bilharz Research Institute, Cairo, Egypt. Pathological examination was done and the final diagnosis was reported for each case from hematoxylin and eosin stained sections. The groups selected for our study include: 1) Control biopsies (6 cases) were considered in biopsies taken from colonoscopically free patients and proved histopathologically to be negative of any remarkable pathological findings, 2) Chronic non-specific colitis (4cases), 3) Chronic bilharzial colitis (6 cases), 4)Ulcerative colitis (12 cases), 5) Colo-rectal adenoma (10 cases) and 6) Colo-rectal adenocarcinoma (18 cases). Diagnostic features of malignant cases were determined according to criteria of the World Health Organization (WHO) Classification of Tumors. Well and moderately differentiated tumors were grouped together as low-grade tumors and were compared with high-grade tumors, which included poorly differentiated and undifferentiated tumors, and signet ring cell carcinomas (WHO, 2000). One paraffin block with the maximum amount of tumor and proper fixation was selected from each case for immunohistochemical studies.

Immunohistochemical Analysis

Four µm-thick sections were cut from blocks of paraffin embedded tissue, deparaffinized, and rehydrated as usual. To reduce non-specific background staining due to endogenous peroxidase, slides were incubated in Hydrogen Peroxide Block for 15 min. Before immunostaining, slides were microwaved in 10 mM of citric acid at pH6.0 for 20 min. The slides were incubated overnight with primary antibodies to CDX2 (clone AMT 28, Novo- Castra; 1:50) at room temperature. The Standard avidinbiotin- peroxidase complex (ABC) technique was performed using the LabVision Secondary Detection Kit (UltraVision Detection System Anti-polyvalent, HRP). AEC was used as chromogen. All slides were counter stained with Mayer's hematoxylin.

Microscopic Evaluation

For CDX2, only nuclear staining was considered positive. Cytoplasmic positivity was infrequently encountered, and was considered an artifact. The percentage of positive cells was scored in a semi quantitative method according to the following scheme: 0 (less than 5% of tumor cells); 1+ (positive signal of any intensity in 5- 25% of tumor cells); 2+ (26-50% of tumor cells); 3+ (51- 75% of tumor cells); and 4+ (greater than 75% of tumor cells). Furthermore, staining in less than 50% of the tumor cells was considered focal, and staining in more than 50% of the tumor cells was considered diffuse positivity. In general, cases showing 3+ and 4+ staining also had strong intense staining, so intensity was not used in determination of the final reactivity score. Normal colonic mucosal tissue was used as a CDX2-positive control. For negative control samples, the primary antibody was omitted for each run. Bayrak *et al* (2012).

Statistical analysis

Pearson's Chi square test was used to compare the differences in percentages of positive results between groups. ANOVA and student t-tests were used to compare groups' means. SPSS 20.0 for Windows was used for all statistical analyses. The sensitivity, specificity, and positive and negative predictive values of CDX2 expression were counted.

RESULTS

Our study was conducted on archival biopsy material from 56 cases undergone colonoscopic examination for colon-related

Table 1 Age and Gender distribution in studied cases

			Gender		Total	Age	
			females	males		Mean	S.D.
diagnosis	control	Count	2_a	4_a	6	45.33	15.397
		% within diagnosis	33.3%	66.7%	100.0%		
	colitis	Count	2_a	2_a	4	40.00	15.011
		% within diagnosis	50.0%	50.0%	100.0%		
	bilharzial	Count	0_a	6_b	6	47.33	14.038
		% within diagnosis	0.0%	100.0%	100.0%		
	IBD	Count	2_a	10_a	12	43.67	13.193
		% within diagnosis	16.7%	83.3%	100.0%		
	adenoma	Count	8_a	2_b	10	57.60	3.688
		% within diagnosis	80.0%	20.0%	100.0%		
	adenocarcinoma	Count	8_a	10_a	18	60.78	4.493
		% within diagnosis	44.4%	55.6%	100.0%		
Total		Count	22	34	56	51.96	12.602
		% within diagnosis	39.3%	60.7%	100.0%	**p < 0.001**	

Each subscript letter denotes a subset of gender categories whose column proportions do not differ significantly from each other at the .05 level.

symptoms refractory to conventional treatment. The mean age of these patients was 51.96±12.60 years. Most of the examined biopsy specimens were taken from male patients (34 males and 22 females).

The distribution of studied cases according to their age and gender are listed in table (1). Six cases with no abnormality detected either enoscopically or histopathologically were considered as controls.

The control group showed high levels of CDX2 expression parameters, however, the adenoma cases (8 tubular and 2 tubulo-vellous) showed the highest levels of CDX2 expression parameters compared to all other lesions and the control group. Both the chronic non-specific colitis and the bilharzial colitis cases showed lower levels of CDX2 expression compared to the controls, followed by cases of IBD. Cases of adenocarcinoma showed the lowest CDX2 expression. The differences between groups were statistically significant by all studied parameters (p<0.01) (Table 2).

Control cases as well as cases of bilharzial colitis and adenoma were all considered positive and showed more or less diffuse nuclear staining (homogenous pattern of CDX2 expression), while cases of IBD and adenocarcinoma showed focal variability in CDX2 expression (heterogenous pattern of CDX2 expression). Cases of chronic colitis showed equal percent of both expression patterns. These differences were statistically significant (p <0.001). (Table 3).

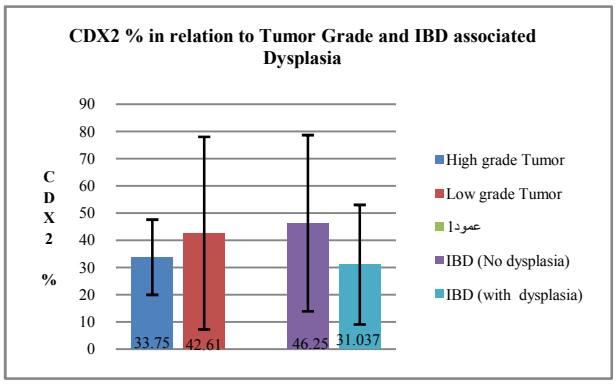
Both low and high grades adenocarcinoma cases showed high percentage of focal CDX2 positivity, however, the heterogenous pattern of CDX2 expression was more obvious in cases of high grade tumors (p <0.01).

Also, cases of IBD associated with dysplasia showed higher percentage of focal CDX2 expression distribution pattern compared to IBD cases without dysplasia, however, the difference was statistically non significant (p >0.05). (Table 4).

Table 2 Difference in means of CDX2 expression parameters between studied groups

diagnosis		CDX2percent	CDX2intensity	CDX2score
control	Mean	70.0000	3.0000	3.3333
	N	6	6	6
	Std. Deviation	8.94427	.00000	.51640
colitis	Mean	62.5000	2.2500	3.0000
	N	4	4	4
	Std. Deviation	14.43376	.28868	1.15470
bilharzial	Mean	60.0000	2.3333	3.0000
	N	6	6	6
	Std. Deviation	17.88854	.51640	.89443
IBD	Mean	41.1667	2.0000	2.0000
	N	12	12	12
	Std. Deviation	29.23520	1.04447	1.34840
adenoma	Mean	92.0000	3.0000	4.0000
	N	10	10	10
	Std. Deviation	7.14920	.00000	.00000
adenocarcinoma	Mean	38.3333	2.1111	1.8889
	N	18	18	18
	Std. Deviation	27.54675	.58298	1.02262
Total	Mean	55.9643	2.3750	2.6429
	N	56	56	56
	Std. Deviation	29.55609	.72143	1.24212
P value (ANOVA)		< 0.001	< 0.01	< 0.001

Low grade adenocarcinoma showed higher CDX2 expression than high grade tumors, also cases of IBD not associated with dysplasia expressed higher CDX2 values compared to dysplasia associated IBD lesions, however, these differences were statistically non-significant (p >0.1). (Graph 1).



Graph 1 CDX2 percent in relation to tumor grade and IBD associated dysplasia

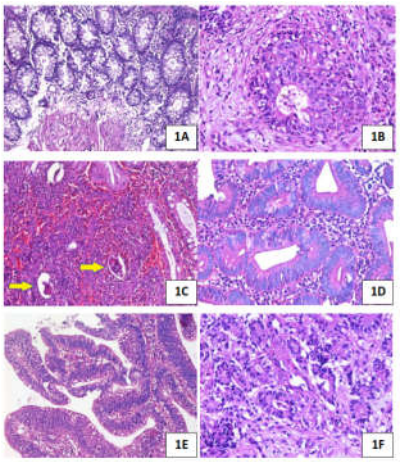


Fig (1A): Section in control case, showing regular crypt pattern and average mucous secreting cells population. (H&E stain, X200). Fig. (1B): Section in case of active ulcerative colitis, showing a crypt abscess associated with dysplasia. (H&E stain, X400). Fig. (1C): Section in case of active bilharsial colitis, showing two parasitic ova (arrows) surrounded by inflammatory reaction. (H&E stain, X200). Fig. (1D): Section in case of tubular adenoma with low grade dysplasia, showing loss of mucous secreting cells population and mild nuclear atypia. (H & E stain, X400). Fig. (1E): Section in case of tubulo-vellous adenoma, showing irregular villi and decreased mucous secreting cells population. (H&E stain, X100). Fig. (1F): Section in case of colonic adenocarcinoma, showing irregular acini infiltrating the stroma and lined by malignant cells. (H&E stain, X400).

The sensitivity of CDX2 negativity in diagnosis of colo-rectal malignancy is found to be 62.07% while its specificity was 90.48%.

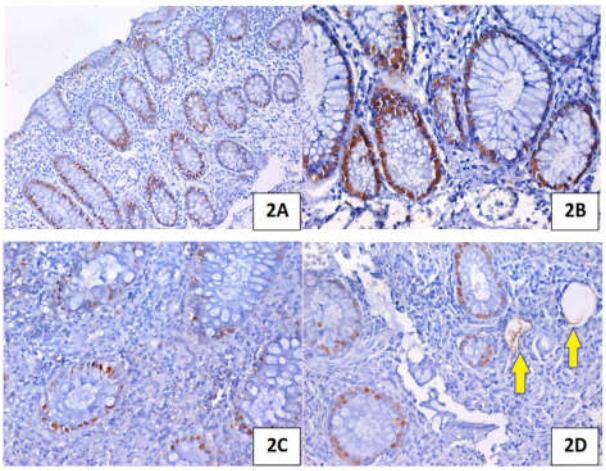


Fig. (2A): Section in control case, showing high nuclear expression of CDX2 within the mucosal crypts (IHC stain for CDX2, X200). Fig. (2B): Higher magnification of control case, showing high nuclear expression of CDX2 within the mucosal crypts (IHC stain for CDX2, X400). Fig. (2C): Section in a case of chronic colitis, showing less nuclear expression of CDX2 within the mucosal crypts compared to the previous photo (IHC stain for CDX2, X400). Fig. (2D): Section case of bilharzial colitis, showing remnants of bilharzia ova shells (arrows) and moderate nuclear expression of CDX2 within the mucosal crypts (IHC stain for CDX2, X400).

of cases suffering from colon disease-related symptoms Zakaria *et al* (2006) (14). Colorectal cancer incidence rates could be effectively reduced if colonic adenomas were diagnosed early using an efficient screening method, which was performed on premalignant colonic lesions Levin *et al* (2008) (15). Previous studies have found that the CDX genes are expressed in the colorectal epithelium, and they were proven to induce the transcription of numerous genes that play an important role in the differentiation of the intestinal epithelium, thus filling an essential role in in tissue-specific transcriptional regulation. Freud *et al* (1998) (16). Additionally a number of studies have found that there is a correlation between the down regulation of Cdx genes and the tumorigenesis of colorectal cancer, where the expression of CDX2 was found to be reduced in presence of tumors in both human cancer, and in mouse and rate models of the disease. Qualtrough *et al* (2002) (17). There have been numerous studies on the CDX2 expression in colorectal cancer and premalignant disorders such as IBD. However, there are no reports regarding the CDX2 expression in patients suffering from bilharzial infection, and this study aimed to verify the hypothesis that immunohistochemical detection of CDX2 protein expression could also be used to identify premalignant colonic lesions as well as malignant lesions.

Table 3 Difference in CDX2 expression distribution patterns in studied groups

			Expression		Distribution		Total
			negative	positive	diffuse	focal	
diagnosis	control	Count	0_a	6_a	6_a	0_b	6
		% within diagnosis	0.0%	100.0%	100.0%	0.0%	100.0%
	colitis	Count	0_a	4_a	2_a	2_a	4
		% within diagnosis	0.0%	100.0%	50.0%	50.0%	100.0%
	bilharzial	Count	0_a	6_a	4_a	2_a	6
		% within diagnosis	0.0%	100.0%	66.7%	33.3%	100.0%
	IBD	Count	4_a	8_a	4_a	8_a	12
		% within diagnosis	33.3%	66.7%	33.3%	66.7%	100.0%
	adenoma	Count	0_a	10_a	10_a	0_b	10
		% within diagnosis	0.0%	100.0%	100.0%	0.0%	100.0%
	adenocarcinoma	Count	7_a	11_b	4_a	14_b	18
		% within diagnosis	38.9%	61.1%	22.2%	77.8%	100.0%
Total		Count	11	45	30	26	56
		% within diagnosis	19.6%	80.4%	53.6%	46.4%	100.0%

Each subscript letter denotes a subset of Distribution categories whose column proportions do not differ significantly from each other at the .05 level. (Pearson Chi-Square $p < 0.001$)

Table 4 Difference in CDX2 expression distribution pattern in relation to tumor grade and IBD associated dysplasia

			CDX2 Distribution pattern		Total
			diffuse	focal	
Adenocarcinoma	High grade	Count	0_a	8_b	8
		%	0.0%	100.0%	100.0%
	Low grade	Count	4_a	6_a	10
		%	40.0%	60.0%	100.0%
		(Pearson Chi-Square $p < 0.01$)			
IBD associated dysplasia	No dysplasia	Count	4_a	4_a	8
		%	50.0%	50.0%	100.0%
	With dysplasia	Count	0_a	4_b	4
		%	0.0%	100.0%	100.0%
		(Pearson Chi-Square $p > 0.05$)			

Each subscript letter denotes a subset of Distribution categories whose column proportions do not differ significantly from each other at the .05 level.

DISCUSSION

Colorectal cancer was found to be one of the three most commonly found cancers in developed countries and one of the major mortality-causing cancers in industrialized countries. Jemal *et al* (2006) (13). In Egypt, it was proven that colorectal cancer is not uncommon, and it was found to represent 10.6%

As previously mentioned, this study was completed using archival biopsy material from 56 cases that have undergone colonoscopic examination for colon-related symptoms refractory to conventional treatment. The cases under study were divided into groups according to their diagnostic status. These groups included control cases (6 cases) and cases that suffered from colitis (4 cases), bilharzial infection (6 cases),

IBD (12 cases), adenoma (10 cases), and adenocarcinoma (18 cases).

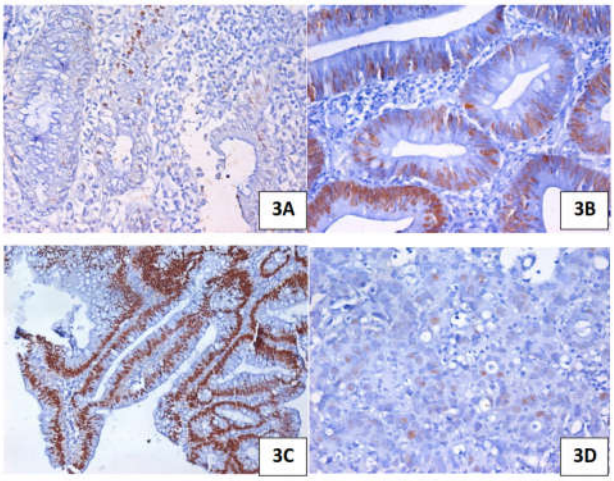


Fig. (3A): Section in case of active ulcerative colitis, showing mild focal nuclear expression of CDX2 within the mucosal crypts (IHC stain for CDX2, X400). Fig. (3B): Section in case tubular adenoma with low grade dysplasia, showing high nuclear expression of CDX2 within the mucosal glands (IHC stain for CDX2, X400). Fig. (3C): Section in case of tubulovillous adenoma, showing high nuclear expression of CDX2 within The mucosal glands and villi (IHC stain for CDX2, X100). Fig. (3D): Section incase of invasive high grade adenocarcinoma (another focus From the same previous case), showing moderate nuclear expression of CDX2 within the malignant acini (IHC stain for CDX2, X400).

A significant difference between levels of CDX2 expression was displayed amongst the groups involved in this study, where the control cases demonstrated high levels of CDX2 expression, whereas adenoma cases displayed the highest. Alternatively, the other cases including non-specific colitis and bilharzial colitis showed lower levels of CDX2 expression, and adenocarcinoma cases displayed the lowest, which proves that the CDX2 protein expression is higher in non-malignant lesions, and is relatively reduced in malignant lesions. These results were in agreement with the results of a study done by Qualtrough *et al* (2002) (17) where they also found that the level of CDX2 expression was significantly higher in adenomas than in adenocarcinoma cell lines. However, these results were contradictory to studies done by Werling *et al* (2003) (18), and Witek *et al* (2005) (19) where the majority of adenocarcinoma cases displayed high expression rates of CDX2.

In this study, we also examined the difference in levels of CDX2 expression in relation to tumor grade, and we found that the low grade adenocarcinoma displayed higher expression than high grade adenocarcinoma. These results were in agreement with several studies, including the studies done by Dalerba *et al* (2016) (20), Kaimaktchiev *et al* (2004) (21), and Choi *et al* (2006) (22) as they all came to the conclusion that CDX2 expression is inversely proportional to degree of invasiveness and aggression of the tumor and can be used to identify patients with stage 2 and 3 of colon cancer. Additionally, we also studied the difference in CDX2 expression between cases of IBD with dysplasia, and IBD without dysplasia. We found that cases of IBD not associated with dysplasia displayed higher CDX2 values compared to IBD associated with dysplasia. Even though these results were statistically non-significant, they were in alignment with the conclusion reached by Olsen *et al* (2014) (9) which states that there is an inverse correlation between grade of dysplasia and CDX2 protein expression.

In colon cancer, CDX2 expression is not solely restricted to the nucleus. It often extends into the cytoplasm, and can be heterogenous within the tumor. Olsen *et al* (2014) (9) Therefore, in this study we observed the difference in distribution pattern of the CDX2 expression within the tissue samples of the cases under study, and we found diffuse nuclear staining (homogenous patterns of CDX2 expression) in the control, bilharzial colitis, and adenoma cases, whereas the IBD and adenocarcinoma cases were found to exhibit focal variability (heterogenous patterns of CDX2 expression). Those results were in agreement with a study performed by Werling *et al* (2003) (18) where the observed heterogenous patterns of CDX2 expression have been shown to be associated with the presence of a malignancy.

Nonetheless, we also examined the correlation between CDX2 expression distribution pattern and pathological grade of tumor, and IBD-associated dysplasia. It was found that the heterogenous pattern of CDX2 expression was also more apparent in high grade tumor than in low grade tumor, thus confirming the inverse correlation between tumor grade and CDX2 expression distribution pattern. Additionally, it was also shown that focal CDX2 expression distribution patterns were higher in cases with IBD-associated dysplasia than in cases without dysplasia.

In conclusion, this study confirms the clinical utility of using CDX2 markers in the identification and classification of colorectal adenocarcinomas and adenomas. Conversely, a clear role of CDX2 expression in premalignant lesions, specifically bilharzial infection is not detected. This confirms the passive attribution of bilharziasis in colonic malignancy. Therefore, this study has confirmed that CDX2 has the ability to hold a diagnostic value in respect to early diagnosis, and detection of colorectal carcinoma and its various grades.

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