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Immunohistochemical Expression of Epithelial and Stromal Annexin A2 (ANXA2) in Colorectal Adenocarcinoma

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ABSTRACT

Background: Colorectal cancer (CRC), the third leading cause of cancer death worldwide, shows rising incidence in developing countries. A combination of environmental and genetic/epigenetic factors contribute to CRC development. Adenocarcinoma not otherwise specified (NOS) is the most common histopathologic subtype. Annexin A2 (ANXA2) is a calcium-regulated phospholipid-binding protein. **Objective:** Evaluation of the ANXA2 immunohistochemical (IHC) expression in colorectal adenocarcinoma compared to normal mucosa and adenoma and investigating its association with clinicopathological parameters in CRC and adenoma cases.

Materials and Methods: This retrospective study included 108 formalin-fixed, paraffin-embedded tissue blocks divided into three groups: adenocarcinoma, normal mucosa**,** and adenoma. Immunohistochemical staining by ANXA2 antibody was done, followed by semiquantitative evaluation of staining and correlation with clinicopathological data.

Results: High ANXA2 expression was significantly increased in CRC compared to normal mucosa and adenoma. Correlation of epithelial and stromal ANXA2 expression with clinicopathological parameters showed a significant association with aggressive cancer phenotypes including higher grade (P =0.003 and<0.001), large size (P = 0.006 and<0.001), deeper depth of invasion (P = 0.003 but 0.084 in stroma), advanced stage (P <0.001 for both), lymph node metastasis (P= 0.001 and <0.001), low lymphocytic infiltration (P <0.001 for both) and high tumor budding grade (P = 0.005 and <0.001). **Conclusion:** The association of Annexin A2 with aggressive tumor characteristics points to its potential involvement in tumor development, invasion, and metastasis.

Keywords: Annexin A2, Colorectal cancer, Immunohistochemistry.

INTRODUCTION

The incidence of colorectal cancer (CRC), the third major cause of mortality from cancer worldwide, is rising in developing countries [(1)]**.** It results from a confluence of environmental, genetic/epigenetic, and molecular pathways [(2)]**.** Chromosomal instability, microsatellite instability, and CpG island methylator phenotype (CIMP) are the three main mechanisms implicated in the development of cancer [(3)]**.** The most prevalent histopathologic subtype is adenocarcinoma not otherwise defined (NOS) [(4)]**.** The incidence of early-onset colorectal cancer (before the age of 50 years) is increasing worldwide. This may be attributed to various risk factors such as a Western-style diet, obesity, physical inactivity, and antibiotic use. These not only induce genetic and epigenetic changes in the colorectal epithelium but also affect the host immunity and gut microbiota [(5)]**.**

The calcium-dependent phospholipid and membrane-binding protein annexin A2 (ANXA2) is a member of the annexin family and is called from the Greek word "annex," which means to bind [(6)]**.** For binding calcium-regulated membrane phospholipids, annexins share similar core domains. An exclusive N-terminal domain allows for interactions with other proteins in each annexin protein [(7)]**.** ANXA2 overexpression is seen in several cancers, including pancreatic duct adenocarcinoma, renal cell carcinoma, colorectal cancer, gastric cancer, hepatocellular carcinoma, and others [(8)]**.**

ANXA2 can be found in the nucleus, cytoplasm, or cell membrane [(9)]**.** The ANXA2 monomer is found in the cytoplasm, nucleus, and early endosomes of the cell, while the heterotetramer ANXA2 complex resulting from binding with S100A10 is found on cell membranes [(10)]**.** In this work, we evaluated the immunohistochemical expression of epithelial and stromal ANXA2 in colorectal adenocarcinoma compared to normal mucosa and adenoma and investigated its association with clinicopathological parameters in CRC and adenoma cases.

MATERIALS AND METHODS

108 formalin-fixed paraffin-embedded tissue blocks were used in this retrospective study. They were taken from the archives of the Pathology Department, Faculty of Medicine, Zagazig University. Adenocarcinoma, normal mucosa, and adenoma were separated into three groups, each with 36 individuals. The patient's medical records were used to gather clinicopathological information. CRC typing and grading were determined based on World Health Organization categorization, (5^{th} edition) [(11)]**.**

On an H&E-stained slide, a tumor bud is a single cell or a cluster of up to five cells [(12)]**.** A high tumor budding rate was considered to be 10 buds or more per 10 HPF on average [(13)]**.** The percentage score for lymphocytic infiltration was divided into three categories: low (0% to 10%), intermediate (15% to 50%), and high (55% to 100%) [(14)]**.** The staging was done according to the AJCC's eighth edition [(15)], and Dukes' systems [(16)]**.** The presence or absence of lymphovascular invasion, perineural invasion, lymph node, and distant metastases were determined. Tubular, villous, and tubulovillous adenomas were among the histologic subtypes of adenomas, while dysplasia grades were classified

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Immunohistochemistry:

Paraffin tissue sections (3-5µ) were prepared then deparaffinized and rehydrated by descending grades of alcohol. Antigen retrieval was performed using Dako target retrieval solution TRET EDTA (PH 6.0) and then boiled in a microwave at 97°c. Endogenous peroxidase activity blocking was done with 3% Hydrogen peroxide for 5 minutes. Tissue sections were incubated with primary rabbit polyclonal anti –ANXA2 (catalog no YPA2401) at 1:25-200 dilution. Secondary antibodies were added for 30 min then sections were incubated with streptavidin-biotin for 15 minutes followed by diaminobenzidine incubation for 5-10 minutes, counterstained with hematoxylin, and were cleared in xylene for 3 changes and finely mounted with a cover slip using DPX. Gastric carcinoma slides were used as positive controls while prostate carcinoma was used as a negative control.

Evaluation of ANXA2 expression:

The staining intensity was scored as 0 (no staining), 1 (weak), 2 (moderate), and 3 (marked). The percentage was scored as 1: 1-25%, 2: 26-50%, 3: 51-75%; and 4: 76-100%. The scores were multiplied to give a score of 0-12. A cutoff value ≥ 5 defines high expression, while ≤ 4 defines low expression **[17].**

The stromal staining, based on staining intensity, was classified into four groups (0-3). Group 0-1 represents low expression and group 2-3 represents high expression **[18].**

Ethical approval:

This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Zagazig University (IRB: #7023/30-6-2021), Written informed consent was taken from all participants. The study was conducted according to the Declaration of Helsinki.

Statistical analysis:

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) (Qualitative data were described using numbers and percentages. The Shapiro test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median, and interquartile range (IQR). Results were judged at the 5% level for Significance. To compare categorical variables, we used the chi-square test, fisher's exact test, or Monte Carlo correction: when more than 20% of the cells have an expected count that is less than 5, mc-near and the marginal homogeneity test is a tool for evaluating the relevance of the various stages. Student t-test: used to compare two groups of variables with normally distributed numerical data. To compare more than two categories and normally distributed quantitative variables, use the f-test (ANOVA). Whitney test: used to compare two groups under study when quantitative variables are abnormally distributed.

RESULTS

Clinicopathological data:

In adenoma cases, the mean age was 66.72 ± 8.79, with 63.9% of patients ≥ 65 years and 61.1% of them being males. Smokers represented 61.1%. Regarding site 44.4%, 38.9%, and 16.7% of cases were located in the right colon, left colon, and rectum respectively. Regarding the histologic type, 47.2%, 38.9%, and 13.9% of cases were tubular, tubulovillous, and villous respectively. Two-thirds (66.7%) of cases showed a low grade of dysplasia **(Table 1).**

Table (1): Clinicopathological parameters of 36 cases of colorectal adenoma.

Clinicopathological parameters of adenoma	No.	%
Sex		
Male	**22**	**61.1**
Female	**14**	**38.9**
Smoking		
Absent	**14**	**38.9**
Present	**22**	**61.1**
Initial site		
Right colon	**16**	**44.4**
Left colon	**14**	**38.9**
Rectum	**6**	**16.7**
Type		
Tubular	**17**	**47.2**
Tubulovilous	**14**	**38.9**
Villous	**5**	**13.9**
Dysplasia grading		
Low	**24**	**66.7**
High	**12**	**33.3**

In cancer cases, the mean age was 63.78 ± 14.65, 52.8% of them were < 65 years and 58.3% were males. Smokers represented 66.7%. Regarding site, 38.9 %, 30.6%, and 30.6% of cases were in the left and right colon as well as the rectum respectively. More than half 52.8% of cases were ≥ 5 cm. 38.9%, 33.3%, and 27.8% of cases were moderate, well, and poorly differentiated. 41.7% of cases showed low and moderate tumor lymphocytic infiltrates, while high tumor lymphocytic infiltrates represented 16.7%. 58.3% of cases showed low tumor budding while 41.7% of them showed high tumor budding. Regarding the pT stage, 2.8%, 8.3%, 69.4%, and 19.4% of cases were T1, T2, T3, and T4 respectively. No lymph node metastasis (N0) was found in 52.8% of cases, while 27.8% and 19.4% had N1 and N2 respectively. Only 8.3% of patients had distant metastasis. According to AJCC and Dukes' staging systems, 41.7% of cases were at stage II/ Dukes' B, 38.9% were stage III/ Dukes' C followed by 11.1% were at stage I/ Dukes' A and 8.3% were stage IV/ Dukes' D. Only 8.3% of cases had perineural and lymphovascular invasion **(Table 2).**

Table (2): Clinicopathological parameters of 36 cases of colorectal adenocarcinoma.

Adenocarcinoma clinicopathological parameters	Number (n =36)		Adenocarcinoma clinicopathological parameters	Number (n =36)	
	No.	%		No.	%
Age (years)			**T stage**		
<65	19	52.8	T1	1	2.8
≥65	17	47.2			
Min. – Max.	27.0 – 90.0		T2	3	8.3
Mean ± SD.	63.78 ± 14.65		T3	25	69.4
Median (IQR)	63.5 (59.5 – 72.0)		T4	7	19.4
Sex			**N stage**		
Male	21	58.3	N0	19	52.8
Female	15	41.7	N1	10	27.8
Smoking			N2	7	19.4
Absent	12	33.3	**Distant metastasis (M stage)**		
Present	24	66.7	Absent	33	91.7
Initial site			Present	3	8.3
Right colon	11	30.6	**Dukes' stage**		
Left colon	14	38.9	A	4	11.1
Rectum	11	30.6	B	15	41.7
Size			C	14	38.9
<5 cm	17	47.2	D	3	8.3
≥ 5 cm	19	52.8	**AJCC Stage**		
Grade			I	4	11.1
Well	12	33.3	II	15	41.7
Moderate	14	38.9	III	14	38.9
Poor	10	27.8	IV	3	8.3
Lymphocytic infiltrate			**Perineural invasion**		
Low	15	41.7	Absent	33	91.7
Moderate	15	41.7	Present	3	8.3
High	6	16.7	**Lymphovascular invasion**		
Tumor budding			Absent	33	91.7
Low	21	58.3	Present	3	8.3
High	15	41.7			
LN metastasis					
Absent	19	52.8			
Present	17	47.2			

Expression of ANXA2 in different studied groups: A significant association was detected between epithelial and stromal ANXA2 expression and colorectal adenocarcinoma compared to normal mucosa (P< 0.001 for both) **(Figure 1 & Table 3).**

Table (3): Comparison between epithelial and stromal ANXA2 expression in adenocarcinoma and normal mucosa.

Epithelial ANXA2	Adenocarcinoma (n =36)		Normal mucosa (n =36)		χ^2	P
	No.	%	No.	%		
Low	**9**	**25.0**	**30**	**83.3**	**24.671***	**<0.001***
High	**27**	**75.0**	**6**	**16.7**		
Stromal ANXA2						
Low	**16**	**44.4**	**33**	**91.7**	**18.463***	**<0.001***
High	**20**	**55.6**	**3**	**8.3**		

χ^2: **Chi-square test,** MC: **Monte Carlo,** FE**: Fisher Exact**
p: p-value for comparing between the studied categories. *: Statistically significant at $p \leq 0.05$

Correlation of ANXA2 expression and clinicopathological data:

In adenoma cases, there was a statistically significant association between epithelial but not with stromal ANXA2 expression as regards smoking (p=0.027 and > 0.05 respectively). A highly significant association was observed between epithelial and stromal ANXA2 expression regarding type and dysplasia grading (P< 0.001 for both). There was no significant association between neither epithelial nor stromal ANXA2 expression regarding age, sex, and initial site (P> 0.05) **(Table 4).**

Table (4): Relation between epithelial and stromal ANXA2 expression and the clinicopathological features in 36 cases of colorectal adenoma.

Clinicopathological parameters of adenoma	Epithelial ANXA2 expression						Stromal ANXA2 expression					
	Low (n =20)		High (n =16)		χ^2	P	Low (n =26)		High (n =10)		χ^2	P
	No.	%	No.	%			No.	%	No.	%		
Age (years)												
<65	8	40.0	5	31.3	χ^2= 0.295	0.587	11	42.3	2	20.0	1.558	FEp= 0.270
≥65	12	60.0	11	68.8			15	57.7	8	80.0		
Sex												
Male	11	55.0	11	68.8	χ^2= 0.707	0.400	15	57.7	7	70.0	0.460	FEp= 0.706
Female	9	45.0	5	31.3			11	42.3	3	30.0		
Smoking												
Absent	11	55.0	3	18.8	χ^2= 4.915*	0.027*	12	46.2	2	20.0	2.079	FEp= 0.255
Present	9	45.0	13	81.3			14	53.8	8	80.0		
Initial site												
Right colon	9	45.0	7	43.8	0.230*	1.000	11	42.3	5	50.0	0.459	MCp= 0.894
Left colon	8	40.0	6	37.5			10	38.5	4	40.0		
Rectum	3	15.0	3	18.8			5	19.2	1	10.0		
Type												
Tubular	15	75.0	2	12.5	χ^2= 16.019*	MCp <0.001*	16	61.5	1	10.0	15.262*	MCp <0.001*
Tubulovilous	5	25.0	9	56.3			10	38.5	4	40.0		
Villous	0	0.0	5	31.3			0	0.0	5	50.0		
Dysplasia grading												
Low	19	95.0	5	31.3	χ^2= 16.256*	<0.001*	22	84.6	2	20.0	13.569*	FEp= 0.001*
High	1	5.0	11	68.8			4	15.4	8	80.0		

χ^2: **Chi-square test,** MC: **Monte Carlo**, FE**: Fisher Exact**

p: p-value for comparing the studied categories

*: Statistically significant at $p \leq 0.05$

In cancer cases, epithelial and stromal ANXA2 expression showed significant association with higher grade (P =0.003 and<0.001), large size (P = 0.006 and<0.001), deeper depth of invasion (P = 0.003 but insignificant 0.084 in stroma), advanced stage (P <0.001 for both), lymph node metastasis (P= 0.001and <0.001), low tumor lymphocytic infiltration (P <0.001 for both) and high tumor budding grade (P = 0.005 and <0.001). There was no significant association between either epithelial or stromal ANXA2 expression regarding age, sex, smoking, and initial site (P> 0.05) **(Table 5).**

Table (5): Relation between epithelial and stromal ANXA2 expression and clinicopathological characteristics in 36 cases of colorectal adenocarcinoma.

Clinicopathological parameters of adenocarcinoma	Epithelial ANXA2 expression				χ^2	P	Stromal ANXA2 expression				χ^2	P
	Low (n = 9)		High (n = 27)				Low (n =16)		High (n =20)			
	No.	%	No.	%			No.	%	No.	%		
Age (years)												
<65	5	55.6	14	51.9	$\chi2$= 0.037	^{FE}p= 1.000	10	62.5	9	45.0	1.092	0.296
≥65	4	44.4	13	48.1			6	37.5	11	55.0		
Sex												
Male	5	55.6	16	59.3	χ^2= 0.038	FEp= 1.000	7	43.8	14	70.0	2.520	0.112
Female	4	44.4	11	40.7			9	56.3	6	30.0		
Smoking												
Absent	4	44.4	8	29.6	χ^2= 0.667	FEp= 0.443	8	50.0	4	20.0	3.60	0.058
Present	5	55.6	19	70.4			8	50.0	16	80.0		
Initial site												
Right colon	0	0.0	11	40.7	5.740	0.071	2	12.5	9	45.0	4.800	^{MC}p= 0.119
Left colon	5	55.6	9	33.3			7	43.8	7	35.0		
Rectum	4	44.4	7	25.9			7	43.8	4	20.0		
Size												
Less than 5 cm	8	88.9	9	33.3	8.359*	0.006*	13	81.3	4	20.0	13.380*	<0.001*
More than 5 cm	1	11.1	18	66.7			3	18.8	16	80.0		
Grade												
G1	7	77.8	5	18.5	10.179*	0.003*	11	68.8	1	5.0	19.270	<0.001*
G2	2	22.2	12	44.4			5	31.3	9	45.0		
G3	0	0.0	10	37.0			0	0.0	10	50.0		
Lymphocytic infiltrate												
Low	0	0.0	15	55.6	14.747*	MCp <0.001*	1	6.3	14	70.0	18.469*	^{FE}p <0.001*
Moderate	4	44.4	11	40.7			9	56.3	6	30.0		
High	5	55.6	1	3.7			6	37.5	0	0.0		
Tumor budding												
Low	9	100.0	12	44.4	8.571*	FEp= 0.005*	16	100.0	5	25.0	20.571*	<0.001*
High	0	0.0	15	55.6			0	0.0	15	75.0		
T stage												
T1	1	11.1	0	0.0	11.788*	0.003*	1	6.3	0	0.0	5.338	^{MC}p= 0.084
T2	3	33.3	0	0.0			3	18.8	0	0.0		
T3	5	55.6	20	74.1			10	62.5	15	75.0		
T4	0	0.0	7	25.9			2	12.5	5	25.0		
N stage												
N0	9	100.0	10	37.0	9.916*	0.005*	16	100.0	3	15.0	27.184*	^{MC}p= <0.001*
N1	0	0.0	10	37.0			0	0.0	10	50.0		
N2	0	0.0	7	25.9			0	0.0	7	35.0		
Distant metastasis (M stage)												
Absent	9	100.0	24	88.9	1.091	0.558	16	100.0	19	95.0	0.823	^{FE}p= 1.000
Present	0	0.0	3	11.1			0	0.0	1	5.0		
Dukes' stage												
A	4	44.4	0	0.0	15.966*	<0.001*	4	25.0	0	.0	27.618*	^{MC}p= <0.001*
B	5	55.6	10	37.0			12	75.0	3	15.0		
C	0	0.0	14	51.9			0	0.0	14	70.0		
D	0	0.0	3	11.1			0	0.0	3	15.0		
AJCC Stage												
I	4	44.4	0	0.0	15.966*	<0.001*	4	25.0	0	0.0	27.618*	^{MC}p= <0.001*
II	5	55.6	10	37.0			12	75.0	3	15.0		
III	0	0.0	14	51.9			0	0.0	14	70.0		
IV	0	0.0	3	11.1			0	0.0	3	15.0		
Perineural invasion												
Absent	9	100.0	24	88.9	1.091	0.558	16	100.0	17	85.0	2.618	^{FE}p= 0.238
Present	0	0.0	3	11.1			0	0.0	3	15.0		
Lymphovascular invasion												
Absent	9	100.0	24	88.9	1.091	0.558	16	100.0	17	85.0	2.618	^{FE}p= 0.238
Present	0	0.0	3	11.1			0	0.0	3	15.0		
LN metastasis												
Absent	9	100.0	10	37.0	10.737*	0.001*	16	100.0	3	15.0	25.768*	<0.001*
Present	0	0.0	17	63.0			0	0.0	17	85.0		

χ^2: **Chi-square test,** MC: **Monte Carlo,** FE**: Fisher Exact** , p: p-value for comparing the studied categories, *: Statistically significant at $p \leq 0.05$

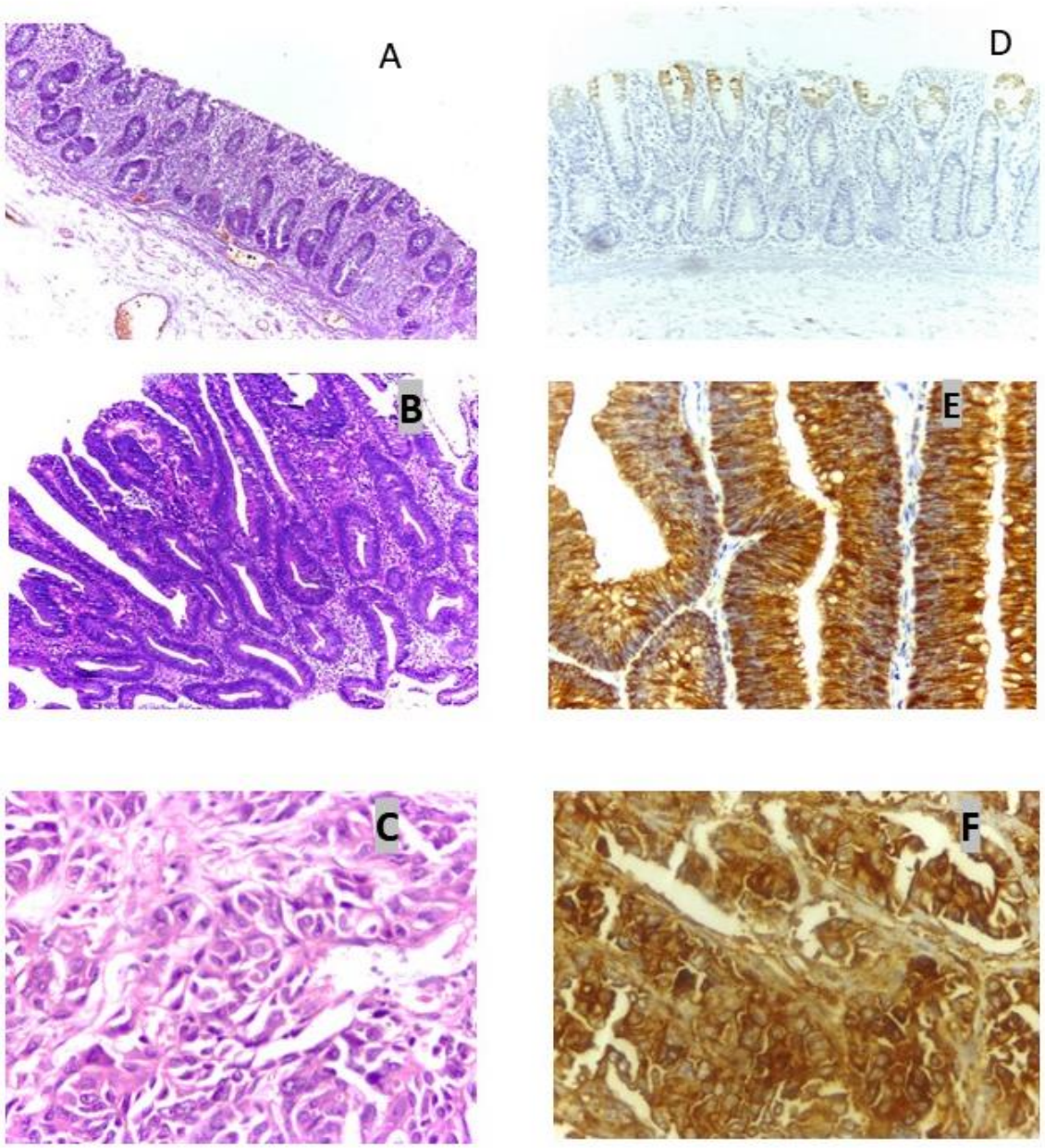

Fig. (1): (A&D) Normal colonic mucosa glands lined by columnar epithelium with goblet cells (H&E x100) (A), ANXA2 IHC staining show low epithelial and stromal expression (IHCx200) (D), **(B&E)** villous adenoma with a thin fibrovascular core lined by dysplastic epithelium (H&EX200) (B), ANXA2 IHC staining showing high epithelial and low stromal expression (IHC x400) (E). **(C&F)** A case of CRC showing groups of malignant cells with pleomorphic hyperchromatic nuclei (H&E X400) (c), ANXA2 IHC staining showing high epithelial and stromal expression (IHC x400)(F).

DISCUSSION

In the last two decades, low and middle-income countries showed rising CRC incidence. This may be due to increased red processed meat consumption, alcohol intake, obesity, and inflammatory bowel disease [(19)]. The calcium-dependent binding of ANXA2 is needed for biological functions including vesicular transport, exocytosis, endocytosis, cell survival, and proliferation [(9)]. In the present study, immunohistochemical expression of epithelial and stromal ANXA2 was detected in adenocarcinoma, normal mucosa, and adenoma each with 36 cases, and correlated with available clinicopathological data.

When compared to the normal mucosa in the current investigation, cancer samples had significantly higher epithelial ANXA2 expression (75 vs. 16.7%). Similar results have been found in earlier investigations detected by **Rocha *et al.* [(20)] and Xiao *et al.* [(21)].** Because it induces intestinal epithelial cells to quickly move to the site of injury to mend wounds, low expression of ANXA2 in nonmalignant adjacent mucosa may be explained by this function. These cells have an increased level of ANXA2, which aids in the healing of wounds [(22)]. ANXA2 increased expression in cancer indicates a role in carcinogenesis since it is induced/Tyr-phosphorylated by growth factors like

insulin, platelet-derived growth factor, and epidermal growth factor [23]. Oncogenes, including the human H-ras oncogene (v-H-ras), the viral mos oncogene (v-mos), and the Rous sarcoma virus gene (v-src), cause the production of ANXA2 [24].

In the current investigation, we observed a higher stromal ANXA2 expression in cancer than in normal mucosa. Similar outcomes in serous ovarian cancer were reported by **Lokman *et al.*** [25]. This may be explained by the findings of **Rocha *et al.*** [20] who found that ANXA2 overexpression is associated with TGF-ß-induced epithelial-mesenchymal transition (EMT) in CRC through Src/ANXA2/STAT3, as transforming growth factor (TGF- ß) signaling suppresses epithelial growth in normal tissues while promoting tumor cell progression. A high stromal TGF- ß level and activation in CRC with mesenchymal features (CMS4) point to its potential involvement in the tumor-stromal interaction that leads to malignancy and a poor prognosis [26].

High ANXA2 expression was found to significantly correlate with high-grade dysplasia and the adenoma types tubulovillous then villous followed by tubular in the current investigation. This makes sense given that villous adenomas were big, displayed greater grades of dysplasia, and frequently harbored the KRAS mutation [27]. An earlier study revealed that pancreatic duct cancer (NF-KB) is activated with both KRAS and ANXA2 [28]. As far as we are aware, no previous studies investigated the ANXA2 expression in colonic adenoma.

According to the current study, ANXA2 expression was significantly observed with higher grades of CRC. Similar results were found in earlier investigations [29]. There was a direct correlation between increased tumor size and high ANXA2 expression. This is because ANXA2 controls DNA synthesis, replication, and cell cycles, which plays a role in regulating cell proliferation. In vivo, ANXA2 promotes the NF-B and -catenin signaling pathways, increasing the growth of cells [9]. Similar results were obtained in laryngeal carcinoma by **Luo *et al.*** [30].

The current investigation found a statistically significant correlation between high ANXA2 expression with advanced stages, which is consistent with the findings of **Tristante *et al.*** [29]. This is because ANXA2 coordinates the assembly of tissue plasminogen activators, converting plasminogen into plasmin and activating pro-metalloproteases that lead to the breakdown of extracellular matrix, which facilitates invasion and metastasis [31].

ANXA2 expression also controls the adhesion, migration, and invasion of cancer cells. **Rocha *et al.*** [20] outline its significance in EMT using the Src/ANXA2/STAT3 axis and signal transducer and activator of transcription 3 (STAT3). Vimentin and matrix metalloproteinase 2 and 9 expressions are increased, and ANXA2 stimulates STAT3 phosphorylation and translocation to the nucleus, inhibiting E-cadherin gene transcription, and encouraging invasion and metastasis.

High ANXA2 expression was observed to significantly correlate with high tumor budding in the current study, which is consistent with earlier research [29]. This link is explained by how ANXA2 contributes to the development of cancer by altering the structural organization of the cytoskeleton, which promotes tubulin polymerization and facilitates motility and metastasis [7].

There was a strong correlation between high ANXA2 expression and low tumor-infiltrating lymphocytes, related to ANXA2's influence on the number of Treg cells d the production of checkpoint molecules, which aided in tumor immune escape [32].

CONCLUSION

Considering its function in the development of cancer, annexin A2 (ANXA2) has increased expression in CRC. Poor clinicopathologic characteristics in CRC are associated with high ANXA2 expression.

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