p53, Bcl-2 and C-Myc expressions in colorectal carcinoma associated with schistosomiasis in Egypt

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Abstract. *Background and aims:* Oncogenes and tumor suppressor genes expression are well described in bladder cancer associated with schistosomiasis especially in Egypt. Scarce studies were directed to colorectal cancer (CRC) associated with *Schistosoma mansoni* (*S. mansoni*). Apoptosis (programmed cell death) and the genes regulating this process (e.g., Bcl-2) have recently become a focus of interest in the study of cancer development and progression. In the present study, we aimed to investigate the expression pattern of p53, Bcl-2 and C-Myc in CRC tissues obtained from Egyptian colorectal cancer patients divided in two different groups, one associated with *Schistosoma mansoni* (CRC-Sm) and the other without *Schistosoma mansoni* (CRC-NSm). *Methods:* Seventy-five CRC tumors containing 36 draining lymph node metastatic tumors were immunohistochemically stained using specific monoclonal antibodies for p53, Bcl-2 and C-Myc, in addition the apoptotic activity of these tumors were analyzed. *Results and conclusions:* Regardless of the *S. mansoni* infection, the obtained results showed that the apoptotic activity was more evident in p53 diffuse positive tumors ($P = 0.021$). There was a significant correlation between p53 diffuse positive staining and Bcl-2 positive immunostaining ($P = 0.011$). Signet ring cell carcinoma and mucinous adenocarcinoma exhibited both intense C-Myc expression than non-mucinous carcinoma ($P = 0.001$). When adjusting for *S. mansoni* infection, 58.3% of CRC-Sm cases were Bcl-2 positive compared to only (33.3%) of CRC-NSm ($P = 0.046$). Apoptotic activity was more evident in the latter group than of CRC-Sm tumors ($P = 0.009$). p53 and C-Myc expressions were found insignificantly different in CRC-Sm compared with CRC-NSm ($P > 0.05$). These observations suggest that the genotoxic agents produced endogenously through the course of schistosomiasis *mansoni* may play a role in CRC-Sm pathogenesis through the dysregulation of apoptosis by alteration the expression pattern of Bcl-2 protein differently from CRC-NSm suggesting a different biological behavior.

Keywords: Colorectal carcinoma, *Schistosoma mansoni*, p53, Bcl-2, c-Myc

1. Introduction

In spite of many studies regarding oncogene expression in colorectal carcinoma (CRC), as a whole, no such specific studies were directed to CRC-Sm cases. Schistosomiasis is a chronic parasitic disease caused by a trematode blood fluke of genus schistosoma [7].

Schistosomiasis a widespread endemic disease currently found in 74 countries. It is estimated that more than 200 million people residing in rural and agricultural areas are infected and that between 500 million and 600 million people are at risk of infection [15,32]. Schistosomiasis is a major problem in many countries with suggested relation to colorectal carcinoma. Prevalence of schistosomiasis was found to be significantly correlated with increased colon cancer mortality in China [16]. Ming-Chai et al. [29] proposed a similarity between chronic schistosomiasis and ulcerative colitis (UC) regarding predisposition to carcinoma in that pseudopolyposis, ectopic regenerating glands, epithelial proliferation and ulceration are common in both of

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them. They suggested a strong relation between *Schistosoma japonicum* and CRC.

In Egypt, CRC represents 6.1% of cancers, comes fourth after bladder, breast carcinoma and lymphoma [10,43]. *Schistosoma mansoni* (Sm) is endemic in Egypt with prevalence of about 45% of the population in the delta of the Nile river including Dakhlia state, where the material under study were obtained [8]. Regarding SM intestinal lesions, polyp formation is the commonest and mostly rectal followed by sigmoid colon [2]. Interestingly up to 17–20% of proctoscopically examined Egyptian patients have bilharzial rectal polyps [1]. In late *Schistosoma mansoni* infection, distortion, irregularity and branching of rectal mucosal glands is seen in addition to granulomatous and fibrous reaction [11]. However, the relation between schistosomiasis and colonic dysplasia and carcinoma is still unclear. Many investigators deny any association between schistosomiasis and CRC [12,13,31].

p53, Bcl-2 and C-Myc are important regulating elements for apoptosis. The mutations affecting these genes have a role in cancer development and progression. Therefore, the present work was carried out to examine the expression of the protein products of these three genes in colorectal cancer associated with and without schistosomiasis in Egyptian patients.

2. Materials and methods

2.1. Patients

Eighty-three consecutive patients with CRC (44 males and 39 females), underwent radical colectomy from 2002–2004 in the regional Mansoura University Hospitals, Mansoura, Egypt. The youngest patient was 22 years old, the oldest 80 years with mean age 46.6 years. An informed consent was obtained from the patients included in this study or their guardians. Specimens were examined grossly and representative sections from the tumor and resection margins were fixed in 10% formalin for 24–48 hours and paraffin blocks were prepared. From each block, hematoxylin and eosin (H&E) stained sections were prepared and examined for histopathological tumor typing, degree of differentiation and depth of infiltration, according to the World Health Organization (WHO) typing of CRC and the AJCC/UICC staging system for CRC [20,21]. Sixty-five tumors were tubular adenocarcinomas, 11 mucinous adenocarcinomas and seven signet ring cell carcinomas. Eight cases were grade I; 65, grade II; and

10, grade III. Eleven cases were stage I; 32, stage II; 36, stage III; and four, stage IV. *Schistosoma mansoni* ova were detected in 24 cases within or away from the tumor tissue. In other 6 cases no ova were seen but mild to moderate degree of colitis with some eosinophilic cellular infiltrate. These cases were excluded from the non-schistosomal cases when compared with the schistosoma associated tumors.

2.2. Apoptosis detection

Apoptosis within the tumor tissue; apoptotic bodies were seen as single dark stained roundish or pyknotic nuclear remnants, two or more nuclear fragments with uneven sizes and cytoplasmic eosinophilia located within or between adjacent tumor cells. Scores were given for each case based on the apoptotic bodies/HPF as follows: negative, 0; mild, 1–2; moderate, 3–5; and severe >5. Areas with much necrosis were excluded [39,26].

2.3. Immunohistochemical detection of p53, Bcl-2 and C-Myc expressions

p53, Bcl-2 and C-Myc protein products were detected by specific monoclonal antibodies. From each tumor block and positive draining lymph nodes, 4 μm thick sections were cut on Neoprene coated slides. The immunostaining was performed using the avidin–biotin complex (ABC) method and an automatic autostainer (CODE-ON Immuno/DNA slide stainer) (Biotek solution, Santa Barbara, CA). Slides were deparaffinized and blocked for endogenous peroxidase with 1.75% hydrogen peroxide in methanol for 20 minutes, antigen retrieval for 15 minutes using Biogenex Antigen Retrieval Citra solution in a 90°C water bath for 30 minutes. The slides were allowed to cool for 20 minutes before continuing. Slides were then blocked by normal horse serum for 5 minutes at 37°C. The monoclonal antibody was applied over night in humid medium at room temperature followed by a biotinylated secondary antibody for 15 minutes at 37°C and the ABC complex for 15 minutes at 37°C (Vectastain Elite ABC Kit, Vector Laboratories, Burlingame, CA). Diaminobenzidine (DAB) was applied for 20 minutes at room temperature as chromogen, slides were counterstained with Mayer's hematoxylin, dehydrated and covered by cover slips. In negative control slides the same system was applied with replacement the monoclonal antibody by diluted nor-

mal bovine serum. All negative control slides were strictly negative.

p53 immunostaining was carried out on 75 tumor cases containing 36 metastatic lymph node tumors. It was performed by applying mouse IgG1 monoclonal antibody (clone 1801) (Biogenex, San Ramon, CA) at a dilution of $1:50$ that detects both the wild-type and mutant p53 proteins and works on formalin fixed tissues. Staining results were interpreted according to the scheme reported by many authors who considered diffuse and focal patterns of p53 immunoreactivity representing the mutated p53 protein and wild-type p53 respectively [5,17]. Where, it was categorized as diffusely positive; when more than 30% of tumor cell nuclei were positive, focally positive; when occasionally scattered tumor cell nuclei were positive and negative; showing no stain at all.

Bcl-2 immunostaining was carried out on 75 tumor cases containing 35 metastatic lymph node tumors. This was performed by applying mouse IgG1 monoclonal antibody (clone 124) (Dako, Glostrup, Denmark) at a dilution of $1:20$. Staining results were interpreted according to the percentage of stained tumor cells ($<25\%$, >25–50%, >50–75% and $>75\%$) and the specific localization of the stain within the cell (Nuclear "N" or Cytoplasmic "C").

C-Myc immunostaining was carried out on 73 tumor cases containing 34 metastatic lymph node tumors. Staining was performed using Mouse IgG2a monoclonal antibody (clone 9E11) (Novocastra laboratories LTD, Newcastle, UK) at a dilution of $1:400$. Staining patterns were interpreted as (diffusely positive, $>50\%$ of tumor cells, focally positive, 50% or less and negative). Intensity of the stain was graded into ($1+$, $2+$ and $3+$). Cellular localization of the stain was recorded as; cytoplasmic (C), perinuclear (PN) or both (PNC).

2.4. Statistical analysis

Data were analyzed for significance by Chi-square or Fischer-Exact test as appropriate using SPSS version 11 for Windows software (SPSS, Chicago, IL, USA). Statistical significance was considered at P-values $\leqslant 0.05$.

3. Results

3.1. Apoptosis

In CRC associated with schistosomiasis mansoni, there was a male predominance (66.7%) compared to only 47.5% of CRC-NSm cases. Rectum was the commonest site of CRC-Sm cases (45.8%), statistically significant in comparison to the caecum which was the least (8.3%), $P = 0.024$. In CRC-NSm cases, tumors were distributed all over the colorectum.

Apoptotic activity was significantly more evident in CRC-NSm than CRC-Sm tumors ($P = 0.009$). The majority of CRC-Sm cases showed a mild degree apoptosis (78.6%). On the other hand, 20% of CRC-NSm cases revealed severe apoptotic activity and 31.4%, mild activity. Hyperplastic lesions were identified in 22 cases (12 SA and 9 NSA, and one unclassified), as well as 14 microscopic adenomas (6 SA and 7 NSA, and one unclassified).

3.2. Immunohistochemical findings of p53 expressions in CRC-NSm and CRC-Sm

Out of 75 tumor sample, 29 (38.7%) were diffusely positive and 46 (61.3%) were either negative or focally positive (Fig. 1). Table 1 illustrates the relation of p53 staining patterns to pathological parameters and schistosomal condition. No significant correlation was found between staining patterns and tumor site, pathological type, tumor grade or stage. However, there was a trend of signet ring cell carcinoma to be negatively stained (71.4%). CRC-NSm tumors were more frequently positive (44.4%) than the CRC-Sm tumors (33.3%), $P = 0.073$. Of 36 stained lymph node tumors, 18 (50%) were diffusely positive; 4, focally positive; and 14 negative. Metastatic tumors were more frequently diffusely positive than the primary tumors; however, the difference was not statistically significant ($P = 0.258$).
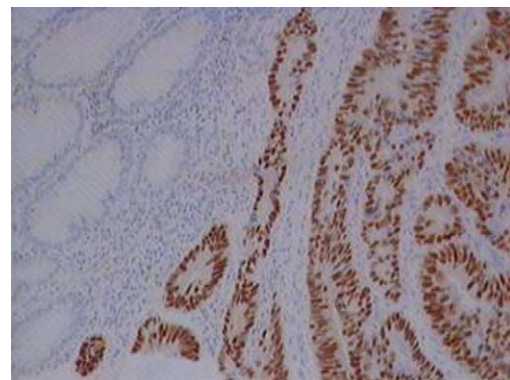

Fig. 1. Positive p53 immunostaining of CRC. There is strong nuclear reactivity of most of the neoplastic cells. Adjacent normal mucosa is completely negative. (Immunoperoxidase staining with MAb 1801, hematoxylin counterstain, $\times 200$.)

Table 1
p53 staining pattern, pathological parameters and schistosomal condition of colorectal carcinoma (CRC)

Parameter		P53					
		Total		Positive		Neg. + Focal	
		no.	%	no.	%	no.	%
Total		75	100	29	38.7	46	61.3
Site	Rectum	27	36	12	44.4	15	55.6
	Caecum	19	25.3	8	42.1	11	57.9
	Sigmoid	19	25.3	5	26.3	14	73.7
	Others	10	13.3	4	40	6	60
Pathology	Adc.	58	77.3	24	41.4	34	58.6
	Muc.	10	13.3	3	30	7	70
	Sig.	7	9.3	2	28.6	5	71.4
Grade	I	8	10.7	2	25	6	75
	II	57	76	23	40.4	34	59.6
	III	10	13.3	4	40	6	60
Stage	I	8	10.7	1	12.5	7	87.5
	II	27	36	11	40.7	16	59.3
	III	36	48	15	41.7	21	58.3
	IV	4	5.3	2	50	2	50
Schisto.		69					
	CRC-Sm	24	34.8	8	33.3	16	66.7
	CRC-NSm	45	65.2	20	44.4	25	55.6

Adc = adenocarcinoma; Muc = mucoid adenocarcinoma; Sig = signet ring cell carcinoma; Neg = negative; Schisto = schistosomal condition; CRC-Sm = schistosoma associated; CRC-NSm = non-schistosoma associated-colorectal carcinoma.
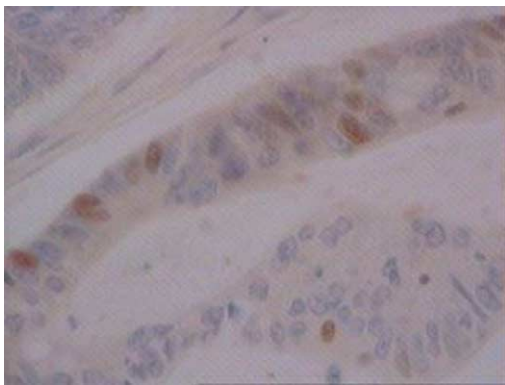

Fig. 2. Positive Bcl-2 immunostaining of CRC. (Immunoperoxidase staining with MAb clone 124, hematoxylin counterstain, $\times 200$.)

3.3. Immunohistochemical findings of Bcl-2 expressions in CRC-NSm and CRC-Sm

Out of 75 tumors, 31 (41.3%) were positive and 44 (58.7%) negative (Fig. 2). Table 2 illustrates the relation of Bcl-2 staining patterns to pathological parameters and schistosomal condition. All signet ring cell carcinomas were negative. Only two of 10 mucinous adenocarcinomas were positively stained. The difference in staining between mucin-producing tumors (both signet ring cell and non-signet-ring cell types) and the non-mucinous tumors was statistically significant ($P = 0.005$). Bcl-2 was positive in 58.3% of CRC-Sm tumors, and 33.3% of CRC-NSm tumors ($P = 0.046$). Of 35 stained lymph node metastatic tumors, 11 (31.4%) were positive and 24 (68.6%) were negative. This lower incidence of Bcl-2 positivity in the lymph nodes compared to that in the primary tumors is not statistically significant ($P = 0.32$).

3.4. Immunohistochemical findings of C-Myc expressions in CRC-NSm and CRC-Sm

The data showed that, out of 73 stained tumor cases, 68 (93.2%) were positive (Fig. 3) and only 5 (6.8%) cases were negative. The relation of the staining pattern to pathological parameters is illustrated in Table 3. In signet ring cell carcinomas and mucinous adenocarcinoma, the combined PNC staining site was significantly higher than in non-mucinous carcinoma ($P = 0.001$). Of the 34 stained lymph nodes 31, were positive and 3, negative.

The relation between apoptotic activity, presence of schistosoma and immunostaining patterns of p53, Bcl-

Table 2
Results of Bcl-2 staining pattern to pathological parameters and schistosomal condition of colorectal carcinoma (CRC)

| Parameter | Bcl-2 | | | | | | | |
| | Total | | | Site | | % of stained cells | | |
				N.	C.	<25%	>25 to 50%	>50%
Total								
no.	75	44	31	9	22	12	6	13
%	100	58.7	41.3	29	71	38.7	19.4	41.7
Grade								
I	8	4	4	3	1	2	1	1
II	57	33	24	4	20	7	5	12
III	10	7	3	2	1	3	0	0
Pathology								
Adc	58	29	29	9	20	12	5	12
Muc[#]	10	8	2	0	2	0	1	1
Sig[*]	7	7	0	0	0	0	0	0
Stage								
I	8	6	2	0	2	0	1	1
II	27	16	11	1	10	2	2	7
III	36	18	18	8	10	10	3	5
IV	4	4	0	0	0	0	0	0
Schisto.	69							
CRC-Sm[+]	24	10	14	4	10	4	3	7
CRC-NSm[+]	45	30	15	3	12	6	3	6

N = nuclear; C = cytoplasmic; Adc = adenocarcinoma; Muc = mucoid adenocarcinoma; Sig = signet ring cell carcinoma; Schisto = schistosomiasis; CRC-Sm = schistosoma associated; CRC-NSm = non-schistosoma associated colorectal carcinoma.
*Comparison of Sig with Adc ($P = 0.035$). #Comparison of Sig + Muc with Adc ($P = 0.005$). +CRC-Sm were significantly more positive for Bcl-2 ($P = 0.046$).
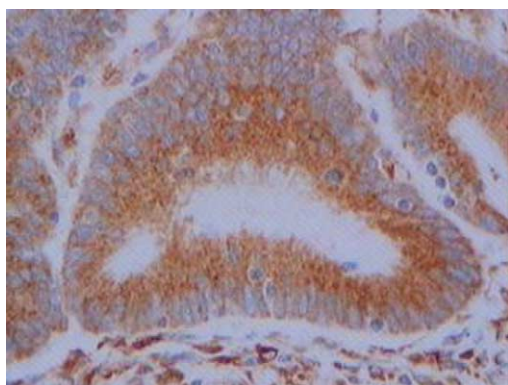

Fig. 3. C-Myc positive immunostaining of colonic adenocarcinoma. (Immunoperoxidase staining with MAb clone 9E11, hematoxylin counterstain, ×200.)

2 and C-Myc is illustrated in Table 4. Apoptotic activity was more evident in p53 diffusely positive tumors than in tumors that were either negative or focally positive ($P = 0.021$).

Non-neoplastic and hyperplastic mucosa were strictly negative for p53, while the lower third of the crypts were positively stained with Bcl-2 and C-Myc. Out of the 14 adenomas; 11, were p53 negative; one diffusely positive (CRC-Sm); one focally positive (CRC-NSm); and the last one revealed cytoplasmic reactivity (CRC-NSm). For Bcl-2; 10 adenomas were negative and 4 (2, CRC-Sm and 2, CRC-NSm) positively stained (cytoplasmic reactivity in 25–50% of cells). All adenomas were diffusely positive for C-Myc with predominant cytoplasmic pattern.

Regarding the relation of p53, Bcl-2 and C-Myc immunostaining to each other, there was a significant correlation between p53 diffuse positive staining and Bcl-2 positive immunostaining ($P = 0.011$).

4. Discussion

The relation between colorectal cancer and schistosomiasis has been debated for decades [36]. This re-

Table 3

Results of C-Myc staining pattern to pathological parameters and schistosomal condition of colorectal carcinoma (CRC)

Parameter	C-Myc										
	Total	Neg.	Positive								
			Total	Pattern		Intensity			Site		
				D.	F.	1+	2+	3+	PN	C	PNC
Total											
no.	73	5	68	50	18	15	32	21	28	15	25
%	100	6.8	93.2	73.5	26.5	22.1	47.1	30.8	41.2	22.1	36.7
Histology											
Adc	56	4	52	39	13	14	24	14	25	14	13
Muc	10	0	10	9	1	0	4	6	3	1	6
Sig	7	1	6	2	4	1	4	1	0	0	6*
Grade											
I	7	1	6	4	2	2	3	1	3	1	2
II	56	3	53	39	14	10	28	15	19	13	21
III	10	1	9	7	2	3	1	5	6	1	2
Stage											
I	7	0	7	4	3	1	4	2	5	1	1
II	27	4	23	15	8	7	8	8	8	5	10
III	35	1	34	27	7	7	18	9	13	9	12
IV	4	0	4	4	0	0	2	2	2	0	2
Schisto.	67										
CRC-Sm	23	1	22	16	6	5	9	8	11	7	4
CRC-NSm	44	1	43	31	12	10	22	11	16	7	20

D = diffuse; F = focal; PN = perinuclear; C = cytoplasmic; PNC = perinuclear and cytoplasmic Adc = adenocarcinoma; Muc = mucoid adenocarcinoma; Sig = signet ring cell carcinoma; Schisto. = schistosomiasis; CRC-Sm = schistosoma associated; CRC-NSm = non-schistosoma associated colorectal carcinoma.

*In Sig, the combined PNC staining site is significantly higher than in non-mucinous adenocarcinoma ($P = 0.001$).

lationship was confirmed by several studies based on histological examinations. Shindo [41] reviewed 276 cases of large intestine cancer with schistosomiasis and found significant differences between carcinoma with schistosomiasis and ordinary carcinoma in symptoms, age, sex and histological findings, suggesting that schistosomiasis could induces the carcinoma.

p53 gene is commonly mutated in a wide variety of cancers [19,27]. Normal tissues express very low levels that cannot be detected by immunohistochemical methods [4,6,25]. The wild-type p53 protein accumulation can be detected as occasionally stained nuclei in contrast to the diffuse staining pattern that present in case of mutation [5,17]. In colorectal carcinoma, p53 mutations was found in 50–60% of cases as a late event in adenoma–carcinoma sequence [18,40]. In the present study, p53 staining pattern was nuclear and diffuse in 38.7% of cases that is lower than previous studies (57–70%), however in most of these, any percent of p53 positive staining was considered positive [23]. No statistical significance was found between p53 staining pattern and pathological parameters that is consistent

with previous studies [34]. However, there was a trend of mucinous carcinoma and signet ring cell carcinoma to be p53 negative (71.4%) that is consistent with previous reports [9]. Regarding schistosomal association, CRC-NSm cases were slightly more positive (44.4%) compared to CRC-Sm (33.3%). The higher percent of p53 diffuse positive staining pattern in the lymph node metastatic tumors may indicate that these tumors with p53 overexpression have a higher tendency for metastasis.

Bcl-2 is involved in the regulation of cell death by inhibiting apoptosis [35]. Increased Bcl-2 expression has been reported in different malignancies with better prognosis [45]. Overexpression of Bcl-2 was described as an early event in epithelial malignancies [38]. There is evidence that Bcl-2 is regulated by p53. Levels of p53 in breast carcinoma were inversely related to the expression of Bcl-2 [22]. However, in bladder carcinoma p53 and Bcl-2 are coexpressed at high levels. Expression of both mutant p53 and Bcl-2 could confer a survival advantage to tumor cells [28]. A better clini-

Table 4
The apoptotic activity, schistosomal condition and immunostaining patterns in colorectal cancer patients

Marker		Apoptosis			
		0	1+	2+	3+
Schisto.	77				
CRC-Sm*	24	10	11	3	0
CRC-NSm*	53	18	11	17	7
p53	75				
Negative	33	12	15	4	2
Focal	13	5	4	3	1
Diffuse[#]*	29	8	5	13	3
Bcl-2	75				
Negative	44	20	10	10	4
<25%	12	1	4	6	1
>25–50%	7	2	4	1	0
>50–75%	6	2	3	1	0
>75%	6	1	2	2	1
C-Myc	73				
Negative	5	2	2	1	0
Focal	8	7	4	4	3
Diffuse	13	16	17	14	3

Schisto. = schistosomiasis; CRC-Sm = schistosoma associated; CRC-NSm = non-schistosoma associated colorectal carcinoma. *CRC-NSm show significantly more apoptotic activity than CRC-Sm ($P = 0.009$). [#]p53 diffuse positive tumors show significantly more apoptotic activity ($P = 0.021$).

cal course was described with Bcl-2 expression in CRC [3].

Kaklamanis et al. [24] found positive Bcl-2 reactivity in 82% of adenomas and in 33% of carcinoma. Baretton et al. [3] found positive cytoplasmic immunoreactivity for Bcl-2 in 67% of colorectal carcinoma and 86% of adenomas. On the other hand, Ofner et al. [33] found 55% of tumors completely negative for Bcl-2, 24% have only <5% of tumor cells positive for Bcl-2, 16% of tumors exhibit 5–50% positive tumor cells, and more than 50% of tumor cells positive in only 5% of cases. In the present study, we applied a semi-quantitative evaluation method in the analysis of our cases, 58.7% were completely negative and 41.3% positive. For Bcl-2 staining site, it was mainly cytoplasmic in 71% and nuclear in 29%. No correlation was found between Bcl-2 staining and tumor grade and stage. In contrary to Kaklamanis et al. [24] Bcl-2 positive staining was significantly correlated with p53 diffuse staining pattern. Lower incidence of Bcl-2 positivity (31.4%) in metastatic lymph node tumors may suggest less aggressive behavior of Bcl-2 negative tumors that is different from previous studies demon-

strating favorable clinical outcome of CRC associating Bcl-2 expression. In contrast with Baretton et al. [3] who demonstrated a higher incidence of Bcl-2 positivity in adenomas than in carcinomas, only 28.6% of adenomas in our study were positive. Regarding schistosomal association, CRC-Sm cases were significantly more positive for Bcl-2 (54.5%) in comparison to CRC-NSm cases (35.8%), that is consistent with decreased apoptotic activity demonstrated in our CRC-Sm cases. *Schistosoma mansoni* was found to reduce the apoptotic activity in patients with gastritis [14].

Elevated expression of C-Myc mRNA and increased C-Myc oncoprotein expression was reported in the majority of CRC [42]. It has been implicated as an initiating event in colorectal carcinogenesis. By immunohistochemistry, colonic tumors are stained positively for C-Myc with different localization patterns [37,46]. Stewart et al. [44] found the staining to be predominantly cytoplasmic, in normal and tumor tissue but more intense in dysplastic adenomatous tissue. In our cases, all adenomas and >92% of both schistosoma associated and non-associated carcinomas were positive for C-Myc. The stain was diffusely distributed in 73.5% of tumors. Regarding the intracellular localization of C-Myc, it was mainly perinuclear (PN), followed by combined perinuclear and cytoplasmic (PNC) pattern. This combined PNC staining pattern was significantly associated with signet ring cell carcinoma and mucinous carcinoma in comparison to non-mucinous tumors ($P = 0.001$). This may be related to the previously reported poor prognosis of signet ring cell carcinoma and mucinous carcinoma of the colorectum [30].

p53 diffuse staining pattern was associated with higher apoptotic activity. On the other hand, no correlation was found between apoptotic activity with Bcl-2 or C-Myc staining patterns. This is agreement with previous reports regarding Bcl-2 and C-Myc and in contrast to p53 [47].

In summary, no significant difference was seen between CRC-Sm and CRC-NSm cases in respect to p53 and C-Myc expressions. CRC-Sm is characterized by less apoptotic activity and Bcl-2 protein overexpression. In conclusion, these observations suggest that the genotoxic agents produced endogenously through the course of schistosomiasis *mansoni* may play a role in CRC-Sm pathogenesis through the dysregulation of apoptosis by alteration the expression pattern of Bcl-2 gene differently from CRC-NSm suggesting a different biological behavior.

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