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BACKGROUND MUCOSAL CHANGES OF PRIMARY COLORECTAL CANCER IN EGYPTIAN PATIENTS

By
Ahmed M. Hussein and Suzan F. Helal*
Unit of Colon and Rectal Surgery, Department of Surgery and Department of Pathology*, Faculty of Medicine, University of Alexandria

Background: Egypt has an unusually high proportion of early-onset colorectal cancer under age 40 years. Adenomatous polyps are not common among Egyptians. Aberrant crypts foci (ACF) have been postulated to be the earliest identifiable precursor of colon cancer developing prior to adenoma-carcinomas sequence.

Objectives: The objective of the present study was to determine whether aberrant crypt foci (ACF) could be identified in the colon of Egyptian patients with colorectal cancer.

Material and Methods: colorectal surgical resections from 42 consecutive patients with primary colorectal cancer. Examinations were made on the macroscopically normal mucosa surrounding the cancer and on the resection margins (at least 2 cm from the tumor).

Results: In the mucosa surrounding the tumors, microadenomas were seen in 11 patients (26.13%), adenomatous changes in the basal cells in 11 patients (26.13%) and hyperplastic glands in 7 patients (16.67%). In the mucosa taken from the resection margins (at least 2 cm from the tumor), macroscopic adenomas were found in two patients (4.76%), while microadenomas were seen in another two patients (4.76%). Neither hyperplastic glands nor adenomatous changes in the basal cells could be demonstrated in the colorectal resection margins.

Conclusions: The present study is the first to demonstrate the presence of pre-neoplastic lesions in the grossly normal-appearing colonic mucosa of Egyptian patients with colorectal cancer that resemble those described previously in the colons of western patients. Accordingly, it is suggested that accelerated progression of ACF to carcinoma is the accepted model for development of colorectal cancer in Egypt and may explain the low incidence of adenoma and higher rate of colorectal cancer in young Egyptians.

Key words: cancer – colorectal – aberrant crypt foci – microadenoma – adenomatous changes – basal cells – glandular hyperplasia.
Abbreviations: ACF, aberrant crypt foci; MA, microadenoma; ACBC, adenomatous changes in the basal cells; GH, glandular hyperplasia.

INTRODUCTION

Egypt has an unusually high proportion of early-onset colorectal cancer [1,2]. This young age incidence might be due to hereditary and/or environmental factors. Adenomatous polyposis coli is not common among Egyptians. Studies conducted to investigate the familial aggregation of colorectal cancer and hereditary non-polyposis colorectal cancer (HNPCC) among Egyptians could not prove that hereditary factors play a role in the development of colorectal cancer [3]. Environmental factors namely pollution and endemic diseases are suggested to play a role in the development of malignant neoplasms [4-9].

It is generally believed that colorectal cancer, like many other types of cancer, evolves from precursor lesions. The adenoma-carcinoma sequence for the development of colorectal cancer has become a well-accepted model for the development of colorectal neoplasms [10]. Nevertheless, adenomas are rarely seen in Egypt. The incidence of synchronous adenomas with colorectal caner is 5.2% in

Egyptian patients [11] while in the western countries it is 25-30%[12]. Accordingly, it is suggested that the dysplasia-carcinoma is the prevalent sequence in Egyptian patients [11].

Aberrant crypts foci (ACF) are morphologically altered crypts that have been hypothesized to represent the precursor or pre-neoplastic lesions of colon cancer developing prior to adenoma-carcinomas sequence [13,14]. Histologically, ACF may show hyperplasia, adenomatous changes in the basal cells or microadenoma (MA) [15].

The purpose of this study was to determine if similar lesions could be identified in the background mucosa of primary colorectal cancer in Egyptian patients.

PATIENTS AND METHODS

The study included colorectal surgical resections from 42 consecutive patients with primary colorectal obtained from The Department of Pathology, Faculty of Medicine, University of Alexandria. None of these patients had familial polyposis coli, ulcerative colitis or schistosomiasis of the colon. All the surgical resection had grossly normal-appearing mucosa. Examinations were made chiefly on the macroscopically normal mucosa surrounding the cancer and on the resection margins (at least 2 cm from the tumor). Strips of mucosa were peeled from the submucosa, stretched for ten minutes, and then preserved in 10% formalin, processed and embedded in paraffin blocks. From each paraffin block, 5µ thick sections were cut and mounted on slides. The prepared sections were examined for histopathological changes after conventional haematoxylin and eosin staining. We investigated the background mucosa for presence of ACF concerning the demonstration of their histological features as: glandular hyperplasia, adenomatous changes in the basal cells and microadenomas (single gland adenoma). The study protocol was registered and approved by the Committee of Postgraduate Studies and Medical Research, Faculty of Medicine, University of Alexandria.

Data analysis and statistical methods:

The mucosa surrounding the cancer was compared with the mucosa taken from the resection margins (at least 2 cm from the tumor) using Mc Nemar test, while comparison between tissue source subgroups was made using Fisher's Exact test.

RESULTS

Clinical Data:

Age and Sex:

Ages ranged from 19 to 75 years, with a mean of 41.8±13 years. Age distribution depicted the peak incidence in the fourth and fifth decades of life. Twenty-one patients (50%) were under the age of 40 years and 31 patients (73.81%) were under the age of 50 years. There were 23 males with a mean age of 37.8 years and 19 females with a mean age of 42.8 years. The ratio of males to females was 1.21:1.

Sites of Cancer:

The sites of cancers were the rectum, 18 patients (42.86%); sigmoid colon, 8 patients (19.05%); descending colon (including the splenic flexure), 4 patients (9.52%); transverse colon, 3 patients (7.14%); ascending colon (including the hepatic flexure), 4 patients (9.52%); and the caecum, 5 patients (11.9%), with prevalence for the rectum and sigmoid colon.

Histopathologic Findings:

Pathologic staging of the tumors was assessed according to Duke's system. Two tumors were Duke's A stage (4.76%), 17 (40.48%) were Duke's B stage and 23 (54.76%) were Duke's C stage.

Adenocarcinoma was found in 33 patients (78.57%) that was classified into well-differentiated adenocarcinoma, 8 patients (19.05%); moderately differentiated adenocarcinoma, 22 patients (52.38%), or poorly differentiated adenocarcinoma, 3 patients (4.76%). Mucoid carcinoma was found in 9 patients (21.43%).

Background Mucosal Changes:

The mucosa surrounding the cancer was compared with the mucosa taken from the resection margins (at least 2 cm from the tumor) in 42 patients with primary colorectal cancer. (Table 1)

In the mucosa surrounding the tumors, microadenomas (Fig. 1.1) were seen in 11 patients (26.13%), adenomatous changes in the basal cells (Figs 1.2,1.3) in 11 patients (26.13%) and hyperplastic glands (Fig 1.2) in 7 patients (16.67%). Microadenomas were found in combination with hyperplastic glands in 5 patients (11.9%) and with adenomatous changes in the basal cells in 9 patients (21.42%), while in absence of microadenoma, hyperplastic glands were found in combination with adenomatous changes in the basal cells in 6 patients (14.29%). The combination of the three histologic features was seen in 5 patients (11.9%).

In the mucosa taken from the resection margins (at least 2 cm from the tumor), macroscopic adenomas were found in two patients (4.76%), while microadenomas (Figure 2.1, 2.2) were seen in another two patients (4.76%). Neither hyperplastic glands nor adenomatous changes in the basal cells could be demonstrated in the colorectal resection margins.

Although, the aberrant crypts were more frequent in the left colons and rectum than the in the right colons resected for colorectal carcinoma, yet the difference was not significant (Table 2). The frequency of adenomatous changes in the basal cells in the colons of cancer patients less than 40 years was greater than those at least 40 years old, p=0.0036 (Table 2). In association with adenocarcinomas, ACF were more frequent as compared to mucoid carcinomas, but the difference was of no statistical significance (Table 2).

Table (1): ***The frequency of ACF in the mucosa surrounding the cancer compared with the mucosa taken from the resection margins in patients with primary colorectal cancer.***

ACF Features	*Mucosa surrounding the cancer n=42*	*Mucosa taken from the resection margins n=42*	*p*
• Gross Adenoma	-	2 (4.76%)	<0.001
• Microadenoma	11 (26.13%)	2(4.76%)	0.022
• Adenomatous changes in the basal cells	11 (26.13%)	-	0.001
• Hyperplastic Glands	7 (16,67%)	-	0.016

Significant if p<0.05

Table (2): ***The distribution of aberrant crypts surrounding the tumor in relation to the source of tissue.***

Source of tissue	*n*	*H.G*	*A.C.B.C.*	*M.A.*	*Total ACF*	*Gross Adenoma*
Rectum	18	1	3	3	7	1
Sigmoid Colon	8	2	5	4	11	-
Lt. Colon	4	2	1	2	5	-
Transverse Colon	3	-	-	1	1	-
Rt. Colon	4	2	1	1	4	1
Caecum	5	-	1	-	1	-
X^2		0.210*	0.249*	0.249*		
P		1.00*	0.635*	0.635*		
<40 years	21	3	10	8	21	1
>40 years	21	4	1	3	8	1
X^2		0.00	7.883	1.971		
P		1.00	0.0036	0.1589		
Adenocarcinoma	33	6	9	10	25	2
Mucoid Carcinoma	9	1	2	1	4	-
X^2		0.00	0.015	0.537		
P		1.00	1.00	0.479		

* comparison between the Lt. Side (rectum, sigmoid, lt colon) and Rt. Side (Tr. Colon, Rt. Colon, Caecum), significant if p<0.05

Table (3): ***The frequency of ACF in the current study in the view of western reports***

ACF Features	*Mucosa surrounding the cancer*				*Mucosa taken from the resection margins*			
	Egypt	Japan	U.S.	Canada	Egypt	Japan	U.S.	Canada
M.A	26.13%	6.8%	-	-	2(4.76%)	12.5%	59.09% (ACF)	100% (ACF)
A.C.B.C	26.13%	62.6%	-	-	0	38.3%		
H.G	16..67%	49.6%	-	-	0	11.95%		

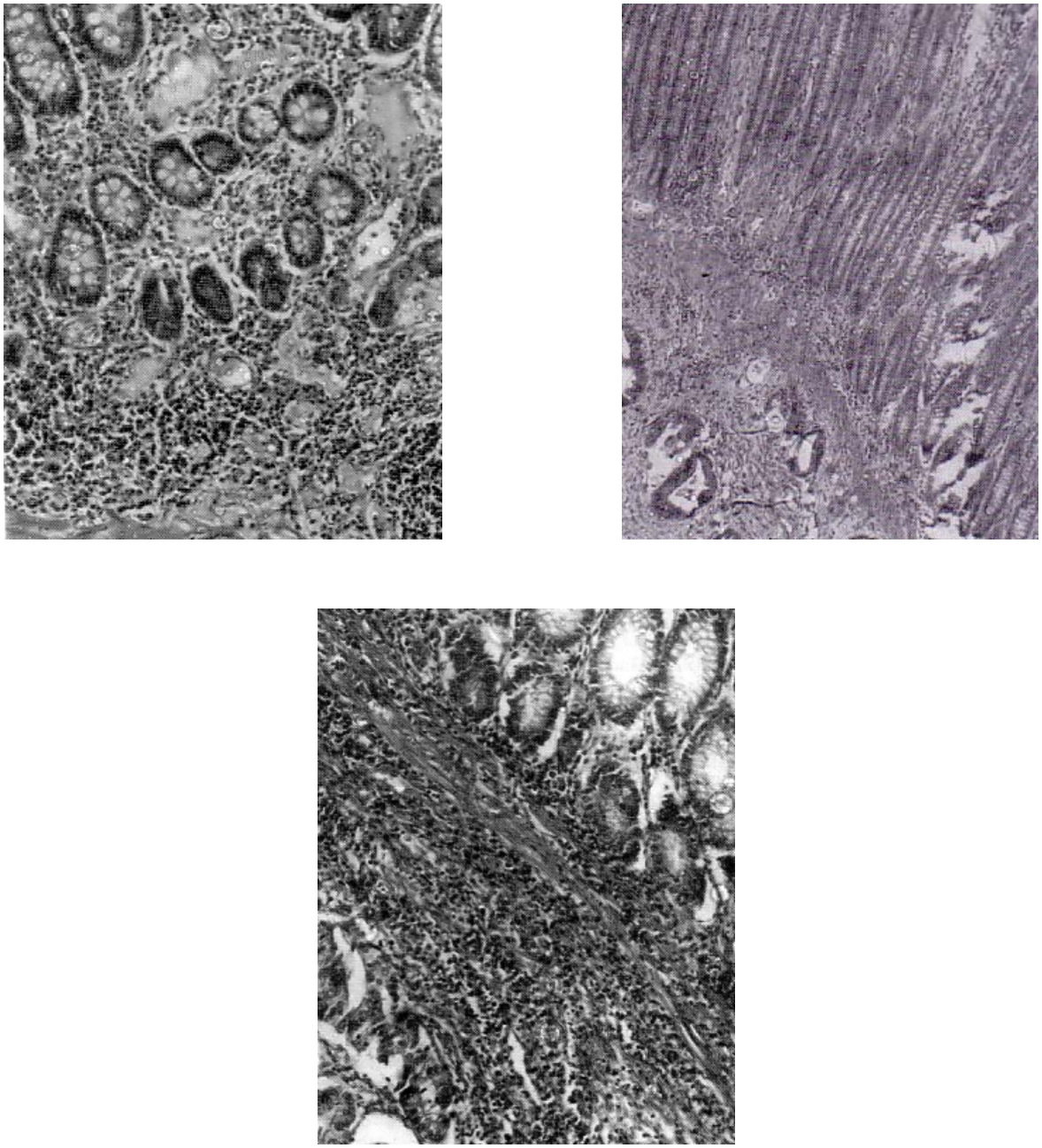

Fig.(1): *(.1) Mucosa surrounding the tumor showing three aberrant crypts surrounded by normal crypts (H&E X100).*

(.2) Mucosa surrounding the tumor showing glandular hyperplasia and adenomatous changes in the basal cell layer with loss of goblet cell population. Note submucosal infiltration from near by tumor (H&E X100).

(.3) Mucosa surrounding the tumor showing adenomatous changes in the basal cell layer. Note submucosal malignant glandular sturctures from near by tumor (H&E X200).

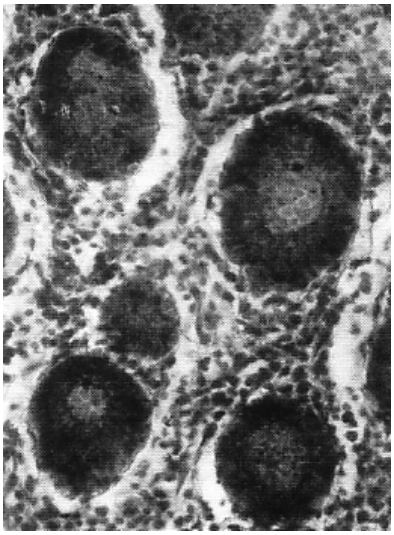

Fig (2): (.1) Mucosa from resection margin far from the tumor showing microadenoms with pseudostratification of the gland lining, loss of mucus goblet cells and complete luminal obliteration (H&E X400).

(.2) Mucosa from resection margin far from the tumor showing microadenoms with pseudostratification of the gland lining, loss of mucus goblet cells, slit like glandular lumina and complete luminal obliteration (H&E X400).

DISCUSSION

Although colorectal cancer is not common in Egypt, the age distribution shows higher proportion occurs under 40 years of age [1]. In the current study 50% of the patients were under the age of 40 years. This finding confirms the earlier observations about the occurrence of high colorectal cancer rate in young Egyptians [1,2].

In the present study, synchronous macroscopic adenomas were found in two patients (4.76%). Similar low incidence of synchronous adenoma was previously reported in Egyptian patients with colorectal cancer [11].

If compared to the western reports, the histologic features of ACF were less frequent in the resected colons of our patients (Table 3). In the mucosa surrounding the tumors, microadenomas were seen in 26.13%, adenomatous changes in the basal cells in 26.13% and hyperplastic glands in 16.67%. In the mucosa taken from the resection margins (at least 2 cm from the tumor), microadenomas were seen in 4.76% and macroscopic adenomas were seen in 4.76%. Neither hyperplastic glands nor adenomatous changes in the basal cells could be demonstrated in the colorectal resection margins. In Japanese patients with colorectal cancer, Oohara et al [15] reported an incidence of adenomas (including microscopic adenoma) in 6.8%, adenomatous changes in the basal cells in 62.6% and hyperplastic glands in 49.6% in the mucosa surrounding the large bowel cancers, while in the mucosa taken at least 10 mm from cancer, adenomas, adenomatous changes in the basal cells, and hyperplastic glands were reported in 12.5%, 38.3%, and 11.95 respectively. Pretlow et al [14], from the United States, could identify ACF in 59.09% of patients with sporadic colorectal cancer. In Canada, Roncucci et al [16] found at least one ACF in every colon resection from colorectal cancer patients.

In American and Japanese reports, the aberrant crypts were found more frequent in the left colons and rectum than the in the right colons resected for colorectal carcinoma [14,15]. These finding are consistent with our observation in the current study. However, we could not demonstrate a significant difference because of the small sample. The frequency of ACF, particularly the adenomatous changes in the basal cells, in the colons of cancer patients less than 40 years was greater than those at least 40 years old. Similarly, higher incidence of ACF in young patients had been reported by Pretlow et al [14]. Although the difference was not significant, ACF were observed more frequently in association with adenocarcinomas, as compared to mucoid carcinomas. To our knowledge, no previous reports were

concerned with the relation between ACF and the histologic type of the tumor.

The present study is the first to demonstrate the presence of pre-neoplastic lesions in the grossly normal-appearing colonic mucosa of Egyptian patients with colorectal cancer that resemble those described previously in the colons of western patients. The ability to identify multiple early potential precursors of colon cancer may facilitate the study of pathological and molecular changes that take place in these lesions as they progress to cancer.

The risk that a particular microadenoma will end its natural history as a carcinoma varies according to clinical context. The risk is very low in familial adenomatous polyposis (FAP), but relatively high in hereditary non-polyposis colorectal cancer (HNPCC). This variation is governed by the timing and ordering of the underlying mutational events. In FAP, inactivation of the wild-type APC gene occurs early, whereas K-ras mutations are late events. The converse appears to apply in the case of sporadic adenomas. In flat adenomas, which are known to be relatively aggressive, K-ras mutations may not occur at all. In HNPCC, mutational events are accelerated as a result of defective DNA mismatch repair. The evolution of colorectal adenoma occurs through a variety of quite distinct genetic pathways [17].

Soliman et al [18] could identify reduced expression of DNA mismatch repair genes with unique involvement of low hPMS2 expression in Egyptian patients with colorectal cancer. Accordingly, the defect in DNA mismatch repair may accelerate the progression of ACF to carcinoma and subsequently this may explain the low incidence of adenoma and higher rate of colorectal cancer in young Egyptians.

Activation of mutational events in pre-neoplastic lesions, as ACF, implies that other environmental factors such as diet are required for progression to colorectal cancer [19]. In experimental animals, cooked sugar and protein contain promoters of the growth of colonic microadenomas. 5-Hydroxymethylfuraldehyde was identified as a promoter in cooked sugar [20]. The demonstration of significant higher serum organochlorines levels in colorectal cancer patients than in controls may indicate a possible association between organochlorine pesticides and colorectal cancer in Egypt [4].

Finally, we should emphasize the fact that we need larger study of grossly normal mucosa from colonic resections from patients with colorectal cancer as well as from those without conditions that predispose to colorectal cancer. The next step in study of ACF is the use methylene blue in whole-mount segments of grossly normal mucosa as it provides a rapid method to screen large areas of colonic mucosa for the presence of these lesions [13].

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