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Adenoma-Carcinoma Sequence in the Surgically Transposed Colon, not Exposed to the Fecal Stream. Correspondence with Adenoma-Carcinoma Sequence in Sporadic Colon Cancer in the General Population

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Colorectal cancer etiology; Inflammation and cancer; Adenoma-carcinoma colon sequence

1. Abstract

1.1. Objective: The aim of our study was to analyze the prevalence of secondary adenomas and adenocarcinomas arising de novo in the surgically transposed colon, not exposed to the fecal stream and its correlation with inflammation.

1.2. Methods: A literature search was carried out (PubMed, EMBASE, MEDLINE and Cochrane Database) including patients who developed de novo secondary adenomas and adenocarcinomas in the surgically transposed colon Main outcome was the correlation between occurrence of adenomas and adenocarcinomas and specific clinical factors including diet, obesity, age, clinical and histological signs of inflammation.

1.3. Results: Overall 112 patients with secondary adenocarcinoma or adenoma were identified. The most important factor related to the occurrence of the tumor was the age of the patient, more than the time of implantation in the new site. Severe clinical signs of local inflammation were associated with a diagnosis at a younger age, advanced stage, and worse clinical outcomes.

1.3. Conclusion: The only shared similarities between the generally proposed risk factors for sporadic colon adenomas and adenocarcinomas in the general population and the potential risk factors for tumor occurrence in the transposed colon, not in contact with the fecal stream, were aging and the presence of chronic inflammation.

Colorectal Cancer (CCR) is the third most commonly diagnosed malignancy and the fourth leading cause of cancer death in the world. Mutations in specific genes have been analyzed to explain the onset and progression of colorectal cancer. Inherited cancers account for 5%, and familial cancer for 25% of all colorectal cancers [1,2].

Point mutations affect individual cells, and they may lead to sporadic cancers, which account for 70% of all colorectal cancers. The molecular pathogenesis of sporadic cancer is heterogeneous as mutations may involve different genes [3,4,5].

Approximately 70% of CRC cases follows a specific succession of mutations starting with the formation of an adenoma and ending in the carcinoma: 15% of those adenomas are expected to degenerate in carcinoma within a period of ten years [4,5].

CRC incidence and mortality rates correlate with a western lifestyle, including alcohol consumption, poor diet (low consumption of fruits and vegetables, and high consumption of red/processed meats), obesity, physical inactivity, and smoking [6,7]. The relationship between these established risk factors, so heterogeneous in nature and characteristics, and the occurrence and expressions of the mutated genes, so various in their action, implies a probable common final effect and represents an important research field. Experimental and clinical research has been focused on several hypotheses: reduced colorectal transit time and motility and consequent longer exposure of the mucosa to proposed toxic agents; degradation products of substances at the basis of the daily diet; relative and absolute presence of specific bacteria in the colorectal flora [6,7,8]. The colon, as an autologous transplant, not in contact with the fecal stream, has been used in

reconstructive surgery. In these operations, the colon is implanted in a different physical, chemical and biological environment, ad it is not exposed to many of the proposed risk factors [9,10].

The aim of our study was to analyze the prevalence of secondary, denovo adenomas and adenocarcinomas arising in the colon-rectum, not exposed to the fecal stream. We analyzed the prevalence of adenomas, their progression to adenocarcinoma, and the potential risk factors.

2. Material and Methods

The methods used for the study and inclusion criteria were based on Preferred Reports Items for Systematic Reviews and Meta analyses (PRISMA) recommendations. A literature search was performed in January 2019, by two investigators who conducted a review of papers reported in PubMed, EMBASE, MEDLINE and Cochrane Database. The strings "COLON URINARY CONDUIT", "ADENOCARCINOMA IN URINARY DIVERSIONS" "URINARY DIVERSIONS" "COLON CONDUIT AFTER ESOPHAGECTOMY" "ADENOMA AND COLON CONDUITS" "ESOPHAGECTOMY" "COLON RECONSTRUCTION AFTER VAGINECTOMY" were used in combination with the Boolean operators "and" "or". Editorials, letters to the Editor, Chapter in Books, Abstracts in Symposia, were included in the search. There was no language or time restriction. The registration number at International prospective register of systematic review (PROSPERO) was CRD 42018089691. The study was approved by the Department Council.

2.1. Data Extraction

Data extraction was performed by two reviewers independently; a third reviewer was involved to solve any question in interpreting data. The primary outcome was to determine possible risk factors for adenomas and their progression to adenocarcinoma in the colon used as autologous transplant without contact with the fecal stream. Secondary outcomes were prevalence of the complication, stage at the time of diagnosis, therapy and clinical outcome.

2.2. Quality Assessment

Two independent reviewers determined the quality and risks of bias of analyzed studies by using the Newcastle-Ottawa scale [11]. This scale defines the quality of a paper with a score ranging from 0 to 9. Papers with a score greater than 6 were considered of good quality.

2.3. Statistical Analysis

All primary outcomes were analyzed by the fixed-effects models. Student's t test and X square test were used where appropriate.

3. Results

3.1. Literature Search

5620 papers published from June 1938 to April 2019 were identified. Five hundred five papers were fully evaluated, but only 100 papers clearly reported patients with a segment of transposed colon, not in contact with the fecal stream, in whom a de-novo, secondary adenoma or adenocarcinoma was diagnosed. We excluded the reports of patients in whom the adenoma or the adenocarcinoma were already present at the time of surgery, and reports of patients who developed other types of cancer (carcinoid 1, lymphoma 1, squamous cell carcinoma 2). Overall, 112 patients were identified in whom a diagnosis of secondary de novo adenocarcinoma (96 patients) [12-103] or adenoma (16 patients) [104-to-117] in the transposed colon, not in contact with the fecal stream, were identified (Suppl 1). We did not consider in the analysis 5 patients who had a secondary adenocarcinoma after pediatric kidney transplant, with consequent immune therapy, and 9 patients, in whom information was incomplete: therefore, 98 patients were included in the study. The quality of the papers was good (average 7,5) with a detailed description of the clinical characteristics of the patients in all but 8 patients. Follow up after the diagnosis of de novo adenocarcinoma ranged from 3 to 96 months (average 10 months) (Table1-3).

Table 1: Secondary Adenocarcinomas and Polyps - Colon as Neovagina (8 Patients)

	Mean Age –Years (Range)	M/F	Indication to Initial Surgery Benign/ Malignant	Mean Time from I nitial Surgery to Diagnosis (Years)	Endoscopic Resection	Surgical Resection	Supportive Therapy	Available Follow-Up
ADENOCARCINOMA (8 Patients)								
Localized Disease 0/8								
Locally Advanced Disease 7/8 (87.5%)	57.1(43-73)	0/7	4/3	29.7 (3-53)	0	7	0	Alive Without Disease 6/7(Mean Follow-Up 12 Months); 1 Patient Died at 16 Months with Diffuse Liver Metastases
Metastatic Disease 1/8 (12.5%)	33	0/1	1/0	20	0	0	1	No Available Follow-Up
Polyps (0 Patients)								

Table 2: Secondary Adenocarcinoma and Polyps -Colon Interpositon after Esophagectomy And/Or Gastrectomy (43 patients with complete information out of 49 patients)

ADENOCARCINOMA (37 Patients)	Mean Age – Years (Range)	M/F	Indication to Initial Surgery. Benign/ Malignant	Time From Initial Surgery and Diagnosis Years (Range)	Endoscopic Resection	Surgical Resection	Supportive Therapy	Available Follow-Up
Localized Disease 20/37(54%)	64.5 (40-80)	12/8	8/12	20 (1-55)	5	15	0	Alive without Disease 20/20 (Mean Follow-Up 17 Months-Range 1-108 Months)
Locally Advanced Disease 4/37(11%)	65,2 (53-83)	3/1	2-Feb	22(12-42)	0	4	0	Alive with Disease 1pt at 24 Months. Death from Disease 3 Pts (Mean Follow-Up 17 Months- Range 9-24 Months).
Metastatic Disease 13/37 (35%)	66.8 (41-83)	7/6	6/6(1 Unspecified)	20(28-47)	0	1	12	All Died from Disease within 12 Months (Mean 4 Months).
POLYPS (7 Patients)*	61.7 (1-15)	4/3	4/3	6.9(1-15)	6	0	0	Alive Without Disease 6/7 (Mean Follow-Up 4 Months). 1 Patient Diagnosis Adenocarcinoma in the Same Area 48 Months Later. Surgical Resection Alive without Disease At 48 Months.

*One patient with juvenile polyps is excluded from analysis

Table 3: Secondary Adenocarcinomas and Polyps - Urinary Colon Conduit Not Exposed to Fecal Stream (46 patients with complete information out 52 patients)

STAGE DISEASE	Mean Age – Years (Range)	M/F	Indication to Initial Surgery Benign/ Malignant	Mean Time from Initial Surgery to Diagnosis (Years)	Endoscopic Resection	Surgical Resection	Supportive Therapy	Available Follow-Up
Localized Disease 13/38(34%)	67.4(42-82)	8/5	3/10	13.0(2-29)	3	10	0	Alive without disease 12/13(mean follow-up 20 months); 1 patient died 3 months after resection from small bowel fistula
Locally Advanced Disease 13/38 (34%)	53.7(29-80)	7/6	8/5	19.5(8-40)	0	13	0	Alive without disease 12/13 (mean follow-up 7months); 1 patient died at 48 months from diffuse metastases
Metastatic Disease 12/38(32%)	61.2(47-80)	7/5	2/10	10.3(3-21)	0	6	6	Six patients who had only supportive therapy died within 6 months. Of the 6 patients who had resection, 3 died within 3 months, and 1 died at 17 months. Two patients are alive respectively at 1 and 18 months from surgery
Polyps 8*	58.7(23-82)	5/3	6/2	15.2(5-25)	3	5		Alive without disease 8/8 (mean follow-up 14 months)

*1patient who had diagnosis of large adenoma, surgical resected, and presented with diffuse metastatic disease at 48 months is included among patients with adenocarcinoma

3.2. Diagnosis

In all but 3 patients, the diagnosis was made for the presence of severe local symptoms: dysphagia for patients who had colon transplant after esophagectomy; bleeding in patients who had neo-vaginal reconstruction; bleeding, infection and difficulty in catheterization in patients who had colon transplant as urinary conduit not exposed to the fecal stream. Three patients were asymptomatic.

3.3. Polyps

There were 15 patients in whom a diagnosis of polyp was made. All, but one patient, were symptomatic;10 patients had areas of moderate-severe dysplasia in the context of a tubulo-villous adenoma. All polyps were removed but only a short follow up was available. One patient developed, 4 years later, an adenocarcinoma in the same area in which the adenoma was removed. Three patients had multiple secondary adenomas in the transposed colon. In 2 patients, a diagnosis of synchronous adenoma in the native colon was made (2/15= 13%).

3.4. Degenerated Polyps

In 33 patients the secondary adenocarcinoma was diagnosed at an early stage (T1-T2). Eighteen patients had areas of adenocarcinoma in the context of a polyp. One patient was diagnosed as having a large adenoma (4 cm in diameter). He presented 48 months later with diffuse metastatic disease. Three patients had a synchronous colon adenocarcinoma and 1 a synchronous polyp (4/33=12%).

3.5. Adenocarcinoma-Locally Advanced Disease

Twenty-four patients presented with locally advanced disease which required major surgery: 18 patients had a moderately differentiated adenocarcinoma and 6 a poorly differentiated adenocarcinoma. In two patients a synchronous (1 patient) or metachronous (1 patient) adenocarcinoma in the native, not transposed colon, was diagnosed. Two patients presented with a synchronous secondary de novo polyp in the transposed colon, and 1 patient had two adenocarcinomas in the transposed colon.

3.6. Metastatic Disease

26 patients had a diagnosis of metastatic disease. Almost all patients had poorly differentiated adenocarcinoma.

3.7. Follow-up

Table 1-3 shows the stage of the disease at the time of the diagnosis and follow-up (mean follow-up 10 months). Survival rates were closely correlated to the stage at the time of the diagnosis.

3.8. Risk Factors

Time interval between the initial surgery and the diagnosis of symptomatic polyps was shorter than in case of symptomatic adenocarcinomas ($p<0.001$). There was no close correlation between time from surgery and diagnosis of adenocarcinomas. The stage of the diagnosed adenocarcinoma was not correlated to time from implantation. The diagnosis of adenocarcinoma was more correlated to age of the patient than to time of implantation. (Table 4,5) ($p<0.001$. Patients who had surgery for benign disease had a longer time implantation before the diagnosis ($p=0.04$) (Table 6). However, they were younger than patients with an initial diagnosis of malignant disease ($p<0.001$). Patients with local signs of infection had the diagnosis at an advanced stage, after a shorter time implantation and at a younger age ($p<0.001$).

Table 4: Time-Interval Between Initial Surgery of Colon Transposition and the Diagnosis of Secondary Adenocarcinoma and Polyps

Time Interval (Years)	Neovagina (8)		Post-Esophagectomy And/Or Gastrectomy (44)		Colon Urinary Conduit Not Exposed to Fecal Stream (42)	
	Adenocar (8)	Polyps (0)	Adenocar (37)	Polyps (7)	Adenocar (34)	Polyps (8)
1 to 10	1		11	3	13	3
11/20	2		12	4	13	2
21-30	2		4	0	6	3
More than 30	3		10	0	2	0
Mean Interval	29.3		20.7	6.9	14.5	15.3

Table 5: Age of Patients at the Time of Diagnosis of Secondary Adenocarcinoma and Polyps.

AGE (YEARS)	Total (96)		Neovagina		Post-Esophagectomy And/Or Gastrectomy (44)		Colon Urinary Conduit Not Exposed to Fecal Stream (42)	
	Adenoc (81)	Polyps (15)	Adenocar (8)	Polyps (0)	Adenocar (37)	Polyps (7)	Adenocar (34)	Polyps (8)
<35	2	1	1		10	0	1	1
36-45	8	2	1		2	0	3	2
46-55	10	1	2		4	1	4	0
56-65	19	6	2		10	6	7	0
66-75	27	3	2		15	0	10	3
>75	15	2	0		6	0	9	2
Mean Age (Range)	62.2	56.7	54.1(33-73)		65.4(40-83)	54.3(54-65)	60.8(29-82)	58.8(23-82)

Table 6: Time Interval from Initial Surgery and Diagnosis of De Novo Adenocracinoma.

Time Interval Between Initial Surgery and Diagnosis of De Novo Adenocracinoma	Neovagina (8)		Post-Esophagectomy And/Or Gastrectomy (40)		Colon Urinary Conduit Not Exposed to Fecal Stream (38)	
1 to 10 years	1		12		15	
11-20 years	2		13		14	
21-30 years	2		4		7	
More than 30 years	3		11		2	
Mean Interval (years)	28.6		20.7		15.1	
Time Interval and Indication to Initial Surgery	Malignant	Benign	Malignant	Benign	Malignant	Benign
1 to 10 years	1		9	3	14	1
11-20 years	1	1	4	9	8	6
21-30 years	1	1	2	2	1	6
More than 30 years		3		11		2
Mean Interval (years)	14.3	37.2	9.2	27.2	9.8	23.2

4. Discussion

The analysis of the genetics of sporadic colorectal cancer has revealed a diffuse heterogeneity. Different gene mutations are related to colorectal carcinogenesis, but the role of these genes in the initiation and progression of the disease is uncertain. APC, K - ras, and p53 are the most common altered genes associated to sporadic colorectal cancer [2,3,4]. In more than 80% of the patients, sporadic colorectal cancer develops through a series of events that lead to the transformation of normal mucosa to adenoma and then to carcinoma. Genomic instability is an integral part in this transformation process [118]. Sequencing data have shown that in adenomas and carcinoma in situ there is a higher proportion of sub-clonal driver mutations than in the advanced tumors [118,119]. These studies have shown multiple subclones, generated by driver mutation acquisition, in adenomas and initial forms of adenocarcinoma, with subsequent selective sweep in advanced colorectal cancers. These findings support the hypothesis that early tumor growth, associated to multiple subclones, is hampered by environmental and immunological factors, and that few selected clones, which overcome the obstacles, form the advanced colorectal cancer [119-121].

The possibility to identify a common causal factor, which may represent the stimulus for so many and different acquired mutations, leading to adenomas and to its progression to early cancer, implies to define a basic mechanism, uniform and steady in time, with a multiple-faced action. Conceptually, this hypothetical mechanism should have a generalized action, to involve so many different mutations in the early stage of the development of the adenocarcinoma, and to be continuous in time to drive the growth of the few selected clones towards advanced adenocarcinoma. In our study, we found that adenocarcinoma, and presumably adenoma, arose in the autologous transplanted colon, not in contact with the fecal stream, with the same clinical and histological characteristics of sporadic cancer arising in the native colon in the general population, adjusted for age and sex. The prevalence of adenomas is much higher in the general population than in our analysis; our population included symptomatic adenomas in all but one patient. If we consider the prevalence of symptomatic adenomas in the general population, adjusted for age and sex, it is not much different from that found in the population analyzed in our study. Analyzing the results of our review, we may hypothesize that also in the transposed colon, not in contact with the fecal stream, the adenocarcinoma arises from an adenoma. In 33 patients (33/83=39.8 %), the adenoma presented areas degenerated in adenocarcinoma. In 10 patients (10/15= 66.7%) the adenoma presented area of moderate-severe dysplasia. Four patients had the simultaneous presence of an adenocarcinoma and polyps.

The chemical and biological stimuli to which the transposed colon is subjected in the new environment, away from the fecal stream, are quite different from those present in its native position. Despite the environment differences, the adenomas and adenocarcinomas had the same characteristics, independently from the anatomic position.

Inflammation, associated or not to infection, is a probable common factor which could explain the occurrence of adenomas and adenocarcinoma in so different anatomic positions. The many genes identified and related to the formation of colonic adenomas and adenocarcinomas, have in common a generic correlation with inflammation [3,4,121]. Inflammation is a natural response to offending stimuli. Inflammation might become a chronic state if the offending stimuli persist. The same tumor cells subclones, initially induced by inflammation, can favor persistence of chronic inflammation either directly or through activation of T and B lymphocytes, and the release of inflammatory cytokines like IL1, IL2, IL6, IL18 and Tumor Necrosis Factor alfa [122-124]. The active proliferation of tumor cells implies significant oxygen consumption: the relative acidification and hypoxia induce further production of cytokines and angiogenic growth factors, which give rise to neo-angiogenesis and lymph-angiogenesis, supporting the persistence of chronic inflammation [125,126]. Release of inflammatory cytokines is also promoted by accelerated necrosis of tumor cells, related to the high cellular proliferation rate and to impaired clearance [127,128]. Previous studies have overstated the importance of the time of implantation of the colon in the new position as a major risk factor for adenoma/adenocarcinoma occurrence [13,15] (Figure 1).

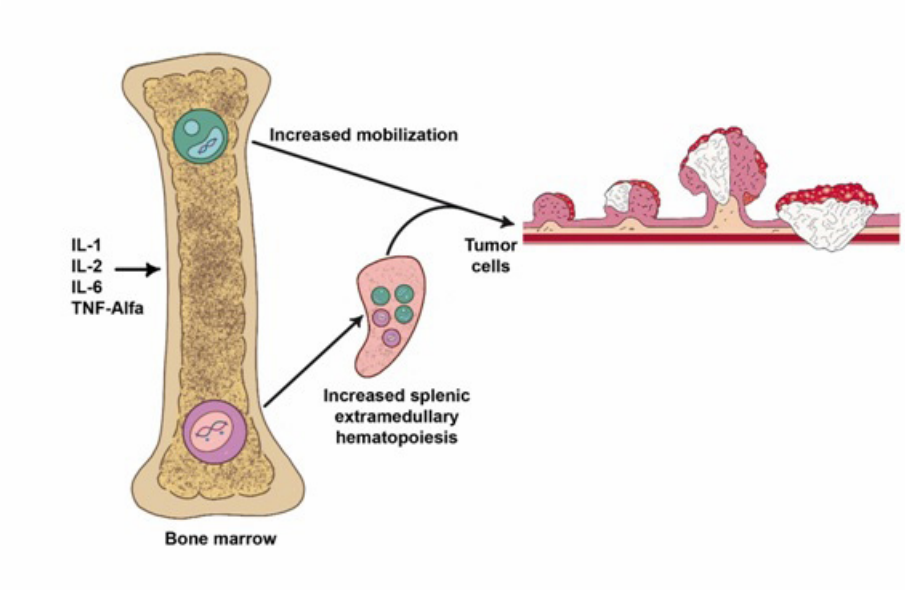

Figure 1: Chronic inflammation may lead to proliferation of abnormal clones of cells of the adaptive immunity (T and B lymphocytes). Hypothetically, inflammatory cytokines, like IL1 IL2 IL 6 and TNF alfa may contribute to deregulation of the immune system in the elderly. Chronic inflammation may determine this deregulation in the elderly either because of the long duration of the its action or because the immunologic system in the elderly is less effective.

It seems that the occurrence of colon adenoma and adenocarcinoma, independently from its position, natural or new, and independently by the many identified risk factors, is strictly age-related. Chronic nflammation could trigger an age-related activation of predisposed genes. The produced inflammatory cytokines might stimulate haematopoiesis in the bone marrow, with the possibility of abnormal proliferation of clones of genetically modified cells [123,124]. A low degree of chronic inflammation in genetically predisposed patients may promote somatic changes in hematopoietic cell lines which lead to the occurrence and progression from adenoma to adenocarcinoma.

The systemic action may explain the occurrence of synchronous/metachronous cancer in the colon, in two different anatomic positions. Studies have shown an increased prevalence of CRC in patients with esophageal cancer [129]. This finding can be interpreted merely as a genetic not specific predisposition. Alternatively, we may hypothesize that the simultaneous presence of an adenocarcinoma in two different physiologic environments, might depend on a systemic effect, related to inflammation.

The role of inflammation is also indirectly supported by what can be grossly defined as a "dose-dependent effect". In patients with clinical signs of active high-grade inflammation, associated to several stimuli, like radiotherapy or recurrent infections, the adenocarcinoma in the transplanted colon occurred at an earlier age, at an advanced stage, with poorly differentiated or mucinous histology, and worse clinical outcome. In patients without evident signs of inflammation, the clinical course was milder, with a more localized disease, and a more differentiated adenocarcinoma, not rarely found in the context of a degenerated polyp. Our study presents limits due to the retrospective nature of the analysis, as well as the absence of a numerator which could allow the determination of the prevalence of the phenomena. The possibility of biases exists because all patients were reported as case reports and almost all patients presented with significant symptoms. However, it is interesting to note that adenomas and adenocarcinomas can arise in the colon, not in contact for many years with the fecal stream. This fact may open new horizons as concern the etiology of sporadic colorectal cancer and its prevention.

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