

Large bowel familial cancer in patients without familial polyposis



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Four members of a family, thirteen subjects of which developed cancer for three consecutive generations were surgically treated in our Unit for colon cancer.

It is well known to day that adenocarcinoma of the colon, as well as of other organs, has been proved to occur in certain families by a dominant trait, in the absence of any precancerous lesions.

Due to this and because none of our patients has had any of the above mentioned lesions and because their tumors developed in the colon de novo, we have to accept that there is a hereditary predisposition in the development of familial cancer generally, which holds for our patients too.

Because of a very high incidence of cancer, close follow-up of these families is recommended, that must start early and completed by chromosome and immunobiologic studies for all first, second and third dergee relatives.

KEY WORDS: Cancer, Colon, Colon polyposis, Familial cancer, Large bowel cancer.

Introduction

Large bowel cancer is one of the most common malignancies in the human being (15% of all malignant lesions) ¹.

Epidemiologic studies have shown that there are two factors which contribute to the appearance of this disease. On the one hand there are dietary and environmental factors, and on the other there are various syndromes which are believed to be precancerous lesions.

Environment as well as human habits influence the appearance of the disease. This has been proved by the fact that colonic cancer is rising in the USA and the countries with a high social and economic level, representing 15% of all malignant neoplasms, while this incidence remains low in countries such as Japan, Finland, Puerto Rico and Africa ¹.

In addition to these exogenous factors, there are also familial syndromes which are accompanied by a large incidence of malignant degenerations.

These syndromes are transmitted by a dominant trait

and have been studied sufficiently (e.g. familial polyposis coli) ^{12,13}. On the other hand there are international reports in the literature on rare cases of families which, without any relation to the above precancerous lesions, have shown for a consecutive series of generations an increasing incidence of some neoplasms especially those of the breast and colon.

These neoplasms are met either exclusively in the above reported organs or in other organs i.e. colon, uterus and so on.

In these cases we have to accept that a hereditary tendency is transmitted to successive generations and for unknown reasons, many members of such a family are prone to cancer development.

Personal experience

We studied four members of a same family affected by colon cancer.

Observation and information acquired from other hospitals where these patients were treated, showed that 9 more members had developed cancer of which all died. Eight of them had developed cancer of the colon and one cancer of the esophagus. The disease was confirmed by histologic examination of the surgical specimens, as well as from death certificates that also confirmed the

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presence of cancer of the colon. In order to assure the credibility of our information we cross examined them with statements of the patients' relatives.

Three of the 4 cases which were treated by us were females and one was male. All of them belonged to the third generation. Out of these 3 female patients, 2 were sisters while the other 2, i.e one female and the male, were also siblings. All four were first cousins.

A) The first sister, aged 33, was treated twice in our Unit. During her first admission she underwent a wide resection of the transverse colon and an end to end entero-entero anastomosis due to an adenocarcinoma of the middle of the transverse colon.

Her second admission was 12 years later, in 1984, because of enterorrhagia and metrorrhagia, due to carcinoma of the descending colon and a primary carcinoma of the uterus. The patient underwent a total hysterectomy and a standard left hemicolectomy. This patient is the only one of our series who developed simultaneously a primary carcinoma of the uterus and another primary carcinoma of the descending colon. Today she is still alive in a perfect condition and is doing very well.

Postoperatively, the patient underwent a complete examination of her immunobiologic system which however did not show any suppression of immunological stimulation of lymphocytes. Therefore we considered that there was no reason for supplementary chemotherapy with cytotoxic drugs.

B) The second female patient, the sister of the first one, was operated elsewhere in 1976 when she was 40 years old and underwent an anterior resection with an end to end anastomosis of the bowel for an adenocarcinoma of the sigmoid colon. She was admitted to our Unit three times.

Her first admission was immediately after the above mentioned operation due to peritonitis after rupture of the entero-anastomosis.

The second was 7 years later due to incomplete intestinal obstruction. Radiological examination showed a tumor of the cecum spreading into the ascending colon, as well as a polyp in the descending colon near the left colon flexure.

In view of these findings the patient underwent a right hemicolectomy with an end to side ileotransverse anastomosis and simultaneous excision of a small pedunculated polyp from the descending colon as well as several swollen lymphnodes from the mesocolon. All other abdominal organs were normal.

The histologic examination showed: 1) A Duke's B adenocarcinoma of the cecum; 2) A Duke's A adenocarcinoma and an adenomatous polyp of the right colon as well as an adenomatous polyp of the left colon without any malignant degeneration; and 3) changes of reactionary lymphadenopathy.

A year later she was readmitted with obstructive jaundice. Laparotomy revealed metastases to the liver and

pancreas. She died six months later after the last operation.

C) The third case was a 29 year old female patient, a first cousin of the two previous cases who in 1974 was admitted to our Unit with large bowel obstruction, anemia and extreme debility. Laparotomy revealed 3 malignant lesions, one in the right colon, the second in the left colon, near the splenic flexure and the third one in the sigmoid colon respectively. We think that we have to take under consideration the synchronous appearance of these tumors.

The surrounding structures were infiltrated by all three tumors. To by-pass the intestinal obstruction we performed an ileosigmoidostomy as the case was inoperable. Biopsy of these malignant lesions confirmed the diagnosis of adenocarcinoma for all three of them. The patient died two months later after this palliative operation.

D) The fourth case was a male patient aged 34. This patient who was the brother of the latter female patient was admitted to our Unit in 1977 in a very poor risk condition, with a carcinoma of the transverse colon.

The patient was operated on and, except for the tumor, laparotomy also revealed infiltration of the greater omentum, greater curvature of the stomach and superior mesenteric vessels by the tumor. The operative procedure consisted of a right hemicolectomy with excision of the transverse colon, 10 cm distally to the tumor and an ileostomy with suturing of the distal stump of the colon, excision of the infiltrated omentum, and subtotal Billroth II gastrectomy.

Histology showed a tubular adenocarcinoma of the transverse colon with mucous production and metastases to the regional and distal lymphnodes. The patient died one month postoperatively. Out of the remaining cases, 7 were males and 2 females. Eight developed cancer of the colon and one cancer of the esophagus. The colonic cancer developed between the age of 20 and 50 years (mean age 37 years) except for one case in which the patient developed cancer at the age of 65.

Discussion

It is well known that there is a predisposition for the development of cancer of the colon in patients with familial polyposis coli.

Apart from familial polyposis coli, there are also syndromes or diseases which are considered as precancerous lesions e.g. ulcerative colitis, Gardner's, Peutz Jegher's of Turcot's syndromes, solitary polyps of the colon and rectum and Crohn's disease ¹.

All of these lesions favour the development of colonic cancer, not only in patients who suffer from these lesions but to their descendants as well, in whom they are transmitted by a dominant trait.

It is well known today that adenocarcinoma of the colon, as well as of other organs, particularly of the endometrium, has been proved to occur frequently in certain families by a dominant transmission in the absence of any of the previously mentioned syndromes or diseases ^{1,3}. In this case the incidence of cancer is 2-3 times more frequent than in the other population.

There is a predisposed gene responsible for some of the precancerous lesions, such as familial polyposis coli ¹². Every subject who bears this predisposed gene is bound to develop colonic cancer and his children have a 50% possibility to inherit this gene.

The international literature reports cases of such families with cancer of the large bowel ⁴.

The first systematic studies were those of Warthin (5, 6) and were related to a family of 378 members 45 of which, for five consecutive generations, had developed cancer of the colon.

Apart from cancer of the colon in 8 out of these 45 individuals carcinoma of other organs had also occurred. Savage ⁷ reported in 1956 a family with a tendency for familial concentration of adenocarcinomas, particularly of the colon and endometrium and an early age of onset. In 1964 Heinzelman ⁸ reported a family which he followed up for five generations and in which 13 out of the 85 members developed adenocarcinoma at young ages. Ten out of these 13 members of this family had adenocarcinoma of the colon.

In the same year ⁹ Bieler and Heim reported a family in which 13 out of 34 members developed adenocarcinoma of the gastrointestinal tract. Two sisters of this family had primary malignant neoplasms of the transverse colon and of the uterus. In 1967 Lynch and Krush (1) studied five more families. Ninety one out of a total number of 347 individuals developed cancer in various organs. Of these 91 patients 44 had an adenocarcinoma of the colon, while 21 others with multiple malignant neoplasms also developed cancer of the large bowel.

Eileen Lovett in 1976 ¹⁰ reported a family, members of whom through 4 consecutive generations developed gastrointestinal cancer at young ages. Ten out of 27 patients of this family died of colonic cancer.

Finally in our country Chelas et al ¹¹ reported in 1979 a family in which 4 out of 5 children belonging to the second generation developed cancer of the large bowel. To the above cases we add our case which supports the view of a hereditary predisposition in the development of familial cancer.

Of course special investigators working in the field of heredity and genetics are more likely to illustrate completely the role of various factors that contribute to the development of hereditary predisposition and further development of cancer in various organs, particularly of the large bowel.

It is not clear whether these factors are transmitted by themselves or simply activate other environmental or dietary factors. However the development of familial can-

cer of the large intestine at young ages shows that the main factor in the development of this malignant neoplasm is heredity. This view is corroborated by the observation of Lovett ¹⁰ who showed that the members of the family with colonic cancer she investigated, grew up under different circumstances. According to the same author the pattern of appearance of familial cancers is consistent with a dominant type of inheritance.

We consider important to emphasize that cancer of the large bowel appeared in individuals of our case for three consecutive generations, and rather early during their lifetime.

None of these individuals had any of the known syndromes, which predispose to the development of colonic cancer, except for one patient in whom two adenomatous polyps were found, one in the right and the other in left colon, near the splenic flexure but without any evidence of malignant degeneration.

Schrock ³ reports a 3% incidence of primary cancer which is a new primary cancer of the large intestine after operative excision of a previous one in such families.

It is worthwhile saying that development of a second primary malignant neoplasm may be more dangerous for a patient's life than the original one ¹.

In our case, the appearance of a second primary cancer occurred in two occasions, after 7 and 12 years respectively, with coexistence of a primary cancer of the uterus in one occasion.

In this last occasion, where the patient is still alive, an examination of her immunobiologic mechanism was performed without evidence of any disorder.

Chromosome studies were not done in our patients. This study as well as the study of the immunobiologic mechanism of the disease in the descendants of this family is in progress and their results will be the material of a future report by the authors.

It is obvious that follow-up of these families must be very close. The purpose is early diagnosis and management of the cancer.

Experience with this lesion has shown that the members of cancer families refuse or fear to cooperate with the doctor and that any delay in the diagnosis of cancer may have disastrous results. Follow-up must begin at an early age.

Siblings or children of affected individuals should have a sigmoidoscopy, barium enema, Mayer or hemocult tests and ophthalmoscopy (to evaluate the existence of an hypertrophy of retinal pigmented epithelium - a good clinical marker used by many Authors in the last years for the identification of the affected by familial polyposis coli subjects before the onset of the colonic polyps in them) ¹⁴. If any of these examinations is doubtful, colonoscopy should follow. If either of the barium enema study or sigmoidoscopy are normal, in the absence of any symptoms, we are of the opinion that sigmoidoscopy should be repeated annually and barium enema should also be done every 5 years. Symptoms indicative

of an abnormal lesion warrant immediate full investigation¹⁰.

To complete the above examinations we recommend chromosome and immunobiologic study for all first, second and third degree relatives of such families.

With all these studies we hope to discover and treat malignant lesions early with good results, giving the chance to these patients to live a normal life for the rest of their life. Finally we believe that further chromosome and immunobiologic studies with monoclonic antibodies will contribute to the elucidation of the pathogenesis of familial cancer.

Riassunto

Sono stati trattati chirurgicamente nella nostra Unità per cancro del colon quattro dei componenti di una famiglia, tredici membri della quale avevano in precedenza sviluppato un cancro in tre generazioni consecutive.

È ben noto oggi che l'adenocarcinoma del colon, come pure l'adenocarcinoma di altri organi extracolici ed anche altri tipi di tumore, possono riscontrarsi e ripresentarsi in alcune famiglie con un carattere dominante, anche in assenza di vere e proprie lesioni precancerose.

Per questa particolare situazione, e poiché nessuno dei quattro pazienti da noi esaminati presentava lesioni precancerose, ma in tutti lo sviluppo del tumore del colon era avvenuto ex novo, abbiamo dovuto accettare l'esistenza in generale di una predisposizione ereditaria allo sviluppo di un cancro a carattere familiare, il che non poteva che riguardare anche i nostri pazienti.

In considerazione della incidenza molto alta del cancro nelle famiglie con la suddetta predisposizione ereditaria, si raccomanda il loro stretto e continuo follow-up, che deve essere iniziato al più presto possibile e completato sempre con studi cromosomici ed immunobiologici, che a loro volta devono essere effettuati su tutti i collaterali di primo, secondo e terzo grado, di queste famiglie.

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