

## Development of adenocarcinoma in chronic fistula in Crohn's disease

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### Abstract

The authors report the case of a 55 yr-old woman suffering from Crohn's disease since 31 years with stricture and fistulas developed in the ileocolic junction and anorectal portion. Long-standing anorectal fistulas and stricture led to adenocarcinoma and finally fistulisation in the vagina. Diagnosis was made by perineal examination with biopsies under general anaesthesia. Treatment was first posterior pelvicotomy with resection of the anterior wall of vagina. Secondly, radiochemotherapy was administered. The authors discuss the incidence and risk factors of carcinoma in Crohn's disease with chronic fistulas. (*Acta gastroenterol. belg.*, 2005, 68, 98-100).

**Keywords** : fistula, Crohn's disease, surgery, cancer.

### Introduction

In contrast with ulcerative colitis where the risk of colorectal carcinoma is clearly established, this risk in Crohn's Disease (CD) remains controversial. Some studies reported increased comparative risk of colorectal carcinoma in individuals with CD (1-4), but to our knowledge few have been population based studies (5,6). This increased risk ranges from 2.1 to 20.0. The largest series were done by tertiary referral centres with selection bias. Some other studies, based on population, failed to demonstrate an increase in the incidence of any type of cancer, including colorectal cancer, in CD (7-9). Several investigators have noted the development of carcinoma at small bowel or large bowel fistula sites in CD (10-13) whereas carcinoma arising in anorectal fistula in the absence of CD occurs rarely (14).

The authors herein describe the case of a woman with CD suffering of cancerisation of a rectovaginal fistula, and discuss the incidence and the risk factors of adenocarcinoma in CD with chronic fistulae.

### Case report

The patient was a Caucasian woman born in 1949. She was diagnosed with CD in 1972 after development of abdominal pain and diarrhoea. Barium transit imagery showed CD located in ileum. She had no extra intestinal manifestation and no family history of inflammatory bowel disease. From 1972 to 1977 intermittent pain with diarrhoea persisted without complication. In 1977, she was operated on of an ileocolic resection for a sigmoido-ileal fistula. Major symptoms were pain in the right lower quadrant, low grade fever, diarrhoea and weight loss. Histological examination of the 40 cm resected ileum confirmed CD despite absence of typical granuloma. From 1972 to 1977 the patient was irregularly treated with sulfasalazine (Salazopyrine®, Pharmacia) or prednisolone (Deltacortril®, Pfizer). From 1977 to 1995, CD was stable with diarrhoea treated by colestyramine (Questran®, Bristol-Myers Squibb). In June 1995, the patient complained of bloody stools and anal pain exacerbated by defecation. Barium examination of the small bowel demonstrated CD recurrence on the last 30 cm of ileum and two short stenosis on this segment without any consequence on the transit. Proctologic examination was impossible because of the anal pain. Methylprednisolone (Medrol®, Pharmacia) was started at 16 mg/day and majored to 32mg/day with improvement of diarrhoea but exacerbation of anal pain. Proctologic examination was then performed under narcosis and showed two trans-sphincteric fistulae located under a rectal stenosis. Rectum was dilated and seemed to be normal above the stricture. The lowest fistula was opened and the second was drained with an elastic seton. In the post operative course, azathioprine (Imuran®, GSK) was started at 100 mg

per day and in 1997, methylprednisolone was progressively stopped and replaced by sulfasalazine. In 1997 the patient presented to the outpatient clinic with 3 diarrhetic stools per day and good clinical status. The rectal diameter was evaluated to 1.5 cm and the seton was removed. The patient did not show up before 2003. In July 2003, the patient came back with severe diarrhoea (15 per day), pelvic pain, anal pain, and bloody loss by anus and vagina. Pelvic magnetic resonance showed perirectal collections drained in vagina and rectum. Gynaecologic examination showed granulation tissue developed on a rectovaginal sinus. Histological sample suggested enteric adenocarcinoma. Proctologic examination was performed under narcosis with a new dilatation of the rectum and biopsies. No endoluminal tumour was found in the rectum. A total colonoscopy demonstrated only a fibrous zone ulcerated in its center at the place of the fistula above the stricture. No other lesion was described. Computed tomography of the abdomen and pelvis demonstrated a heterogeneous mass in the rectum wall with a collection drained in the vagina and in a blind ending fistula towards the sacrum. No metastatic disease was objected by abdominal tomodensitography or thorax roentgenogram. Tumour markers were positive (CA 19-9: 113.5U/ml (normal value: 0-56.0); CEA : 16.8U/ml (normal value : 0-5.0)). In September 2003, the patient underwent a posterior pelvicotomy with en bloc resection of uterus, annexa uteri and rectosigmoid colon. The total meso-rectal excision was performed and the anterior portion of the vaginal wall was resected. No metastatic disease was found intraperitoneally. Histological examination of the surgical specimen confirmed the presence of a colloidal pT4N0M0 enteric adenocarcinoma in the wall of the rectum infiltrating all the layers and the vaginal wall. The postoperative course was good and the patient was discharged on the 23<sup>rd</sup> day of hospitalisation because of long learning time for stomy management. A radio-chemotherapy was scheduled as adjuvant therapy.

## **Discussion**

Historically, the first case of carcinoma associated with CD was reported in 1948 by Warren and Sommers (15). Since then, many reports suggested the association between CD and the developpement of carcinoma. The increased incidence of carcinoma of small bowel or colon in CD is still controversial but most studies demonstrated an increased comparative risk ranging from 2.1 to 20.0 (1-6). Three population based studies previously failed to demonstrate an increased incidence of any type of cancer, including colorectal cancer, in CD (7-9). In the three studies, the lack of association could be ascribed either to the small number of patient studies, the short duration of follow-up or the large proportion of patients receiving colectomy (1).

Among these carcinomas, some developed on chronic fistula. Ky's personal serie demonstrated carcinoma related to fistula eight times in seven patients, seen during a 14-year period. It represents an incidence of approximatively 0.7 percent of CD patients (16). The overall incidence of anorectal fistulae associated with CD is between 20 and 25 percent when CD is limited to ileum, and increases to 60 percent when CD affects the rectum (16).

Traube in 1980 identified risk factors that have been associated with adenocarcinoma in CD and confirmed the frequent association with fistulae (17). Most of those risk factors are positive in our case report (table 1).

An increased risk of cancer in patient with CD had already been showed to be related to an early onset and a prolonged duration of the CD in 1973 (4). In our case, the age at which CD was diagnosed is 25 years, and the duration of CD before diagnosis of the carcinoma was 31 years.

A review of the literature done by Alex Ky in 1998, concentrated all the reported cases of anorectal carcinoma associated with CD that could be related to anal fistulas (16). The author reported 33 cases among which 15 fistulas were clearly located (45%). In this review average duration of CD before carcinoma was 19.9 years. In the Ky's own series of 6 cases the average age at which CD was diagnosed is 25.6 years and the average duration of the disease before diagnosis of carcinoma was 14 years. Those two risk factors seem to be the same for development of cancer in colonic CD as for development of carcinoma in anorectal fistula in CD.

Most colonic carcinomas in CD are poorly differentiated and mucinous compared with sporadic colon malignancies (18-20), and prognosis could be poorer (20). Relation between cancer and fistula is not known but some authors postulate that fistulas might lead to carcinoma because of the constant mucosal regeneration (16). Supporting this theory, some authors noted a strong association between high grade dysplasia and invasive adenocarcinoma in ileocolonic carcinoma in CD patient (18-21). Dysplasia adjacent to colorectal carcinoma has been reported in 83-100% of cases (18-20) while dysplasia distant from the cancer has been found in 23-70% (18,19,22). In contrast, only 2% of colectomy specimens of CD without carcinoma contained mild dysplasia (23). Because fistulas are frequently ulcerated, with chronic ulcerations or recurrent mucosal regeneration, this could lead to dysplastic changes that are precursors for malignant transformation. If this theory is supported by

further studies, the early recognition of fistula should lead to biopsies and brushing to reveal dysplasia in chronic fistula if their resection is not wished.

**Table 1.** Risk Factors for carcinoma in CD

Risk factors	Case reported
Onset of CD in 2 <sup>nd</sup> or 3 <sup>rd</sup> decade of life	+
Recrudescence of symptoms after an extended asymptomatic period	+
A 20- to 30-yr lag between diagnosis of CD and diagnosis of carcinoma	+
Fistula associated with near obstructing stricture	+
Bypassed segment of bowel	-

CD : Crohn's Disease.

Many patient with anorectal lesions have few symptoms despite grossly distorted perianal anatomy. A recent change in symptoms may herald the onset of malignancy. The authors suggest then that patient with distal disease and chronic anal lesions should be monitored regularly for dysplasia or adenocarcinoma. Computed tomography and magnetic resonance examinations should be performed to analyse the situation. Concerning rectal ultrasound examination, this technique should probably be the best to diagnose carcinoma arising in fistula if rectal pain or stricture does not preclude the examination. A high degree of suspicion for carcinoma must be considered in CD suffering of chronic fistula. In those cases, as in our case, in which clinical or ultrasonographic examination is limited by pain or stricture, rectal examination under anaesthesia with biopsy, curettage or brushing of the fistulous tract is recommended.

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