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CASE REPORT

Small bowel adenocarcinoma in Crohn's disease: A case report and review of literature

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Abstract

Small bowel adenocarcinomas are remarkable for their rarity, difficult diagnosis and poor prognosis. Here we report an unusual case of a 33-year-old patient in whom infiltrative adenocarcinoma of the small bowel was diagnosed after a 10-year history of Crohn's disease. In most previously reported cases, detection of Crohn's disease was subsequent to that of carcinoma of the small bowel or the patients involved had an even longer history of the disease. Our literature review suggests that the risk of small bowel adenocarcinoma is higher in patients with Crohn's disease than in the overall population. We present details on epidemiology as well as clinical and diagnostic aspects of this rare disease entity.

Key words: Crohn's disease; Small bowel adenocarcinoma; Case report

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INTRODUCTION

The incidence of inflammatory bowel disease (IBD) is increasing since World War II with levels around 6/100 000 for Crohn's disease (CD) and 15 to 20/100 000 for ulcerative colitis, a marked rise in the age group between twenty to forty years for both entities[1].

The ulcerations occur primarily in the small and large intestines, but may appear anywhere in the digestive tract from the mouth to the anus. Common symptoms of CD are abdominal pain, often in the lower right area, and diarrhoea, but rectal bleeding, weight loss and fever may also appear. Children with CD may suffer stunted growth and delayed development. The severity of the symptoms fluctuates erratically over time. Patients experience flare-ups between intervals of remission or reduced symptoms. The causes of this disease have not been identified yet; but both genetic factors that induce continued abnormal activation of the immune system[2,3] and environmental triggers, like Mycobacterium avium subspecies paratuberculosis[4], are likely to be involved.

Oral or topical preparations of 5-aminosalicylates represent first line therapy, and steroids and azathioprine are used in severe cases; metronidazole and TNF-alpha antibodies are used in fistulating disease. Fifty to seventy percent of Crohn's patients undergo surgery for progression of disease indicated by the presence of fistulas, tumor in the abdomen and development of ileus.

IBD is linked to large and small bowel carcinoma, especially to adenocarcinomas[5-7]. In the last twenty years, colorectal cancer has become the fourth most common cancer worldwide, and in Europe colorectal cancer represents the second most frequent cause of death from any cancer in men[8]. Even though only about 1% of all colorectal cancers is associated with ulcerative colitis or Crohn's colitis, the risk of colorectal cancer for any ulcerative colitis patient is found to be 2% at 10, 8% at 20 and 18% at 30 years, duration of disease, regardless of disease extent[9,10].

Small bowel carcinomas are uncommon representing only 1% to 5% of all gastrointestinal tract malignancies. The first observations suggested that particularly surgically bypassed bowel segments were exposed to high risk of small bowel adenocarcinoma[11,12]. However, the risk of small bowel carcinoma in patients with CD is much higher, being up to 60-fold of that in the general population[13, 14].

Neither clear risk factors nor methods for early diagnosis have been established by the few studies on this distinctly uncommon complication within this rare disease. Here we report on a patient in whom infiltrative adenocarcinoma of the ileum was diagnosed after a 10-year history of CD and also discuss possible risk factors, symptoms, feasible diagnostic approaches and treatment options on the basis of published reports.

CASE REPORT

A 33-year-old man presented in 1992 with recurrent pyrexia and abdominal pain but no diarrhoea. Enteroclysis

was performed and a diagnosis of ileal CD was made. His family history was negative for this disease. For persistent abdominal pain under therapy with 5-aminosalicylates, he was put on corticosteroids (prednisone, 12.5 mg daily). In the following four years the patient experienced repeated episodes of abdominal pain without diarrhoea.

Two years later, an abdominal ultrasound performed for reassessment of the disease, showed a thick intestinal loop from the left to the right upper abdomen. Unfortunately no further diagnostic or therapeutic steps were undertaken at that time.

In 2002, the patient, complaining of increasing abdominal pain, underwent ileocolonoscopy, which yielded no suspicious macroscopic or histopathological findings. Blood tests showed mild anaemia, signs of malabsorption (low proteins, phosphorous and iron deficiency) but none for inflammation. The recommended enteroclysis of the small bowel was not performed. In order to reduce corticosteroids, therapy with azathioprine was initiated (2 mg/kg weight/ per day).

In June 2003 he presented again with abdominal pain, vomiting and distended abdomen. Enteroclysis showed a dilated intestinal loop of the ileum, a pseudotumor in the right abdomen and two stenotic areas, one of which was high-grade and located in the right upper abdomen (Figure 1). Prednisone was increased to 50 mg/day, in addition to metronidazole and ciprofloxacine. Three weeks later, with a deterioration of obstructive symptoms, the patient underwent surgery.

The surgical specimens consisted of a 45 cm and a 7 cm long resected segments. Macroscopic examination showed high-grade inflammatory alteration of the ileum along a 20 cm segment and two upstream high-grade stenoses. The external surface of the diseased segment appeared brownish discoloured with adhering connective tissue. The internal surface of the ileum showed discontinuous mucous membrane, streaks of ulcers and whitened swelling of the bowel wall. Some foci had a 'cobblestone' appearance. The 7 cm long segment had a stenotic 'sandglass' formation.

Extensive histopathological examination in the first stricture revealed a poorly differentiated adenocarcinoma infiltrating the serosa, incipient infiltration of the mesenteric fat and lymphangiosis carcinomatosa as well as a metastatic peritoneal range. Tumor had seeded seven out of eleven lymph nodes examined. The resected specimen also showed adenoma's dysplasia adjacent to the carcinoma. Extended antral metaplastic lesions within agglutinated villi up to one margin were found.

The second specimen revealed proper margins of resection. In the centre of the macroscopic stricture was another focus of the adenocarcinoma. In addition, moderately florid inflammatory infiltrates with acute erosions were detected, compatible with Crohn's disease.

Immunohistochemistry was negative for NSE and chromogranin, only a few tumor cells were slightly positive for synaptophysin. CEA level determined only after surgery was 54.2 ng/ml (normal <50 ng/ml).

The patient recovered well from surgery and then underwent chemotherapy according to Folfox IV–scheme with oxaliplatin, 5-fluorouracil and leucovorin in six cycles.

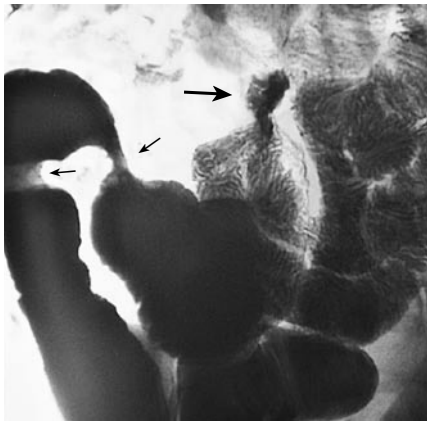

Figure 1 Enteroclysis: dilated intestinal loop of the ileum; altered Crohn's area (big arrow), one high grade and one low grade tumor stenosis in the right upper abdomen (two small arrows).

The patient tolerated the therapy quite well.

The computed tomography (CAT-scan) in October 2004 revealed up to two centimetres enlarged mesenteric and up to one centimetre enlarged retroperitoneal lymph nodes, without any further evidence for metastases. In November 2004 the patient presented with headache, vertigo and ambiopia and was diagnosed with meningeosis carcinomatosa. Intrathecal chemotherapy with methotrexate was started. He is now undergoing intrathecal chemotherapy with sustained-released cytarabine.

DISCUSSION

According to Parkin *et al* the age-standardized incidence of small intestine cancer (ICD-10 C17) ranges from 0.2 to 2.4 for males and from 0.2 to 1.8 for females worldwide[15]. The 'Statistik Austria' National Registry has 1384 documented cases of small intestine cancer between 1983-2000[16].

The association of CD with small bowel carcinoma is uncommon and to date only about 130 cases of small bowel carcinomas in patients with CD have been reported in the literature since the first description of this disease entity in 1956[17]. Cases and studies published in the last few decades, however, bear out from a 12-fold to an over 60-fold increased risk of small bowel cancer in CD[13, 14, 18]. This is in contrast to publications that still emphasize the popular position that CD is primarily associated with carcinoma of the colon. Adenocarcinoma is the most common forms of all small bowel malignancy and there appears to be an increased risk for developing ileal carcinoma in CD patients[19-23].

Most of ileal carcinoma in CD are located in strictures[11,24,25] and are often incidentally diagnosed postoperatively as in our case report. The occult carcinomas in strictures pose a challenge to diagnostic investigations using conventional modalities such as small bowel series and upper and lower gastrointestinal endoscopy. CT is now considered the imaging modality of choice[26-28], and a fat density target sign in CT[29] is also getting greater attention as reliable marker for diagnosing CD or even small bowel carcinoma. Abdominal MRI[30], double-contrast enteroclysis[31] and endoscopy[32], especially video wireless capsule endoscopy[33,34], are promising new diagnostic tools.

Other interesting characteristics are adjacent metapla-

sia, adenoma and epithelial dysplasia[35-38], which underline the importance of further research with respect to sequence-dysplasia in ileal adenocarcinomas in relation to Crohn's disease.

Risk factors for small intestine carcinoma in CD are chronic active course with stricture, fistulas and onset of disease before the age of 30 years[25,39,40]. Further reported risk factors are: early onset, age between 30 and 50 years, male sex and smoking[13,14,41-45]. Therapy of CD with corticosteroids, azathioprine and TNF-alpha antibodies are also considered as potential risk factors. It has been suggested in previous studies that azathioprine, administered mostly combined with steroids to patients with a long history of Crohn's disease, frequent recurrence or those allergic to 5-aminosalicylates has a carcinogenic potential[14,46-49]. In the light of these reports, it is interesting to raise the question whether azathioprine therapy initiated in our patient after normal ileocolonoscopy 18 mo before diagnosis of carcinoma might have contributed to the acceleration of the malignant disease. In contrast to azathioprine, 5-aminosalicylates are considered preventive against the development of large and small bowel adenocarcinoma in inflammatory bowel disease[13,23,50-53]. Mesalazine is now used for treating light to moderate Crohn's colitis and ileitis postoperatively to maintain remissions, but its potential to prevent malignancy needs to be evaluated. TNF-alpha antibodies, also mostly combined with immunosuppression, are used in patients with refractory, steroid-dependent and fistulating CD. There is a theoretical risk of increased rate of malignancies due to antagonism of TNF-alpha, but to date there is no clear proof of such an effect[54-56].

Prognosis of small bowel adenocarcinoma is poor, and the mortality at 1 and 2 years ranges from 30-60% dependent on the stage of the cancer[13,21,57-59].

Further prognostic factors are based on histologic findings such as positive surgical margins, poor differentiation, depth of tumor invasion, positive lymph nodes and extramural venous spread in small bowel adenocarcinoma[60].

CONCLUSION

Small bowel adenocarcinoma in Crohn's disease is rare and preoperative diagnosis continues to present challenges. Long-term prognosis is poor - all the more it is important to be vigilant. Patients with increased risk are those with longstanding complicated CD presenting with a 'de novo' clinical picture of obstruction. Male patients, in particular smokers, are considered to be at increased risk. Since the diagnosis is difficult to make, attending physicians must exercise a high level of clinical suspicion for operative cure. The preventive potential of 5-ASA in adenocarcinoma of the colon suggests that this drug should be preferred to azathioprine in patients to maintain remission.

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