

The risk of small bowel adenocarcinoma in patients with Crohn's disease

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Abstract

Introduction: Small bowel adenocarcinoma (SBA) is an unusual complication of Crohn's disease (CD).

Aim: To describe the incidence rate, clinical features, and outcomes of SBA in a group of subsequent patients with CD.

Material and methods: We retrospectively analysed outpatient and hospital records and identified a group of patients with diagnosed CD. Then we reviewed all medical records of patients who reported for follow-up visits in a 14-year period. We identified a group of 103 patients, whose medical records were evaluated for the presence of SBA.

Results: Long-term follow-up carried out in the group of consecutively treated patients with CD revealed an 0.97% incidence rate of SBA. Cancer was located in the ileum and the clinical presentation was subileus and anaemia. The patient underwent ileocaecal resection, and the postoperative period was uneventful.

Conclusions: SBA is a rare complication of CD. Although the authors are aware that the number of patients enrolled in the study is insufficient to draw far-reaching conclusions, the results obtained are significant for determination of the incidence rate of SBA in the Caucasian population of patients with CD. The key issue of effective treatment of patients with SBA was early detection of the lesion and R0 resection with proper lymphadenectomy. However, it is worth noting that in more advanced stages of SBA the future belongs to, and outcome improvement depends on, new regimes of adjuvant personalised chemotherapies. Further studies on the mechanisms of carcinogenesis in patients with CD are essential.

Introduction

It is difficult to identify all factors increasing the risk of small bowel adenocarcinoma (SBA) due to the low prevalence of this cancer. The first case report with a demonstrated relationship between SBA and Crohn's disease (CD) was published by Ginzburg in 1956 [1]. It is a common belief that CD increases the risk of small bowel neoplasms, the most prevalent of which is SBA, accounting for 57% of cases [2]. According to the literature, SBA develops in 0.08% to 5% of patients with CD [3–8]. A meta-analysis, published in 2010, of 20 papers from 1965 to 2008 based on 40,547 cases revealed that the incidence rate of SBA in patients with CD is 0.3 per 1000 patient-years (95% CI: 0.1–0.5/1000) [9]. The authors demonstrated a 18.75-times higher risk of

SBA in patients with CD compared with a standard population from the same age group. Four meta-analyses published in the past [10–13] confirm a high relative risk for developing SBA, ranging from 17.4 to 28.37. Alternatively, its cumulative risk is 0.2% after 10 years and 2.2% after 25 years of the disease [14].

Aim

The aim of this paper was to describe the incidence rate, clinical features, and outcomes of small bowel adenocarcinoma in a group of subsequent patients with CD.

Material and methods

We retrospectively analysed the outpatient and hospital records and identified a group of patients with

diagnosed CD treated in our department before 2003. The diagnosis of CD was established on either clinical, endoscopic, radiological, or histopathological evaluation. Then we retrospectively reviewed all the medical records of patients who reported for follow-up visits in our institution in a 14-year period of time (2003–2016). We identified a group of patients with diagnosed CD, whose medical records were evaluated for the presence of SBA. Patients with CD but whose medical records were incomplete were excluded. All patients included in the study met the criteria issued by the ECCO consensus recommendation for diagnosis and treatment [15]. The patients provided written informed consent. No approval was needed from the Local Ethics Committee because this was a retrospective study.

Results

The study group consisted of 103 Caucasian patients (56 female and 47 male) with mean age 49.3 ± 12.8 years (Table I). The mean CD duration in the study group was 19.0 ± 4.6 years. Patients' mean age at diagnosis was 29.0 ± 9.1 years. According to Montreal classification the assessed group consisted of 59 patients with disease location in terminal ileum (L1), 13 patients with Crohn's colitis (L2), 15 patients with multifocal CD affecting both ileum and large bowel (L3), and 16 patients with upper GI location of disease (L4). Our investigation revealed that CD behaviour evolved over the time and found 21.4% patients with penetrating type of disease (B3), 40.8% with stricturing disease (B2), and 37.8% with non-stricturing non-penetrating disease (B1). Pharmacological treatment in the investigated group of patients depended on disease activity and behaviour. 5-aminosalicylic acid agents (mesalazine and/or less commonly sulphasalazine) were administered in 96.1% of patients. Steroid-dependent disease was considered in 18.4% of patients, among whom 89.4%

were on oral prednisone or prednisolone and 10.6% were on budesonide. Azathioprine was used in 12.6% of patients. 9.7% of patients with objective evidence of active disease refractory to corticosteroids were treated with anti-TNF agents. Systematically acting antibiotics (metronidazole, ciprofloxacin) and anti-mycobacterial medications were administered occasionally as well. Despite intensive pharmacological treatment, the majority (77.6%) of patients were treated surgically, and 28.7% among them were operated several times. Long-term follow-up (14 years) revealed 1 case of small bowel adenocarcinoma (0.97%) out of 103 investigated patients with CD. SBA developed in a male patient (48 years old) with negative family history to either inflammatory bowel diseases or cancer. Crohn's disease duration at the time of SBA diagnosis was 6 years. Disease location was terminal ileum (L1) and it had stricturing behaviour (B2). The patient was previously treated chronically with amino salicylates during remission periods and periodically with oral glucocorticosteroids while the disease symptoms flared. He had not been operated before diagnosis. SBA was located in the ileum, and the clinical presentation comprised symptoms of subileus and anaemia: abdominal pain with bloating that exacerbated after meals, nausea, periodic vomiting, and significant fatigue. The patient underwent ileocaecal resection with primary anastomosis. Histopathology of a surgical specimen showed adenocarcinoma of the ileum G2 pT3N0M0R0. The postoperative period was uneventful.

Discussion

Compared to *de novo* lesions, SBA secondary to CD develops in relatively young patients, and the median age at diagnosis ranges from 43.0 to 55.4 years [2, 3, 6, 7, 16–24]. In most patients, median duration of disease until cancer diagnosis is 12–24 years, but in 14–17% of patients SBA develops significantly earlier, within 5 years of diagnosis of CD [2, 6, 16–23]. In the whole group of patients with CD, cancer is more likely to affect men (62.5–80%) [20–23] and develops mostly in the ileum (73–89%) and less frequently in the jejunum (11–25%) [3, 6, 16, 18, 20–23]. In the examined group of patients with CD, the patient with SBA was typical in terms of the following: sex, age at diagnosis, location of tumour, and shortened duration of disease until cancer diagnosis. His medical history was negative regarding any factors predisposing to SBA: young age at diagnosis of CD, long-term remission, fistulas, bowel bypass, strictures or strictureplasty, and contact with chemical compounds.

The patients with CD, who were later diagnosed with SBA, presented with the following: abdominal

Table I. Characteristics of the enrolled patients

Parameter	Value
Number of patients	103 (56 female, 47 male)
Mean age at diagnosis [years]	29.0 ± 9.1
Mean duration of disease [years]	19.0 ± 4.6
Disease location	Terminal ileum (L1) – 59, large bowel (L2) – 13, multifocal (L3) – 15, upper GI (L4) – 16
Disease behaviour	Non-stricturing non-penetrating (B1) – 37.8%, stricturing (B2) – 40.8%, penetrating (B3) – 21.4%

pain (85.3–100%), signs of GI obstruction (30–89%), weight loss (14.3–78%), anaemia (28.5–50%), diarrhoea (20.5%), palpable tumour in the abdominal cavity (4.6–14.3%), fever (14.3%), GI bleeding (3.9–5.9%), and bowel perforation (5.4%) [6, 17, 18, 20, 21, 24]. Two highly pathognomonic clinical manifestations include recurrence of symptoms after a long-term remission and small bowel ileus resistant to treatment [6, 20]. The patient described in our paper had recently complained of abdominal pain with bloating that exacerbated after meals, nausea, periodic vomiting, and significant fatigue. The previous long-term clinical history included periodic abdominal pain with diarrhoea and periodic nausea, iron-deficiency anaemia, skin lesions, arthralgia, and cholelithiasis.

Because it is difficult to distinguish these symptoms from Crohn's exacerbation, early diagnosis of cancer poses a significant challenge. These patients, often with a long-term history of inflammatory bowel disease, usually undergo endoscopy of the upper GI tract and colon as a part of screening. When new symptoms develop or old ones exacerbate, initial imaging tests of the abdominal cavity are performed, i.e. an abdominal ultrasound and/or computer tomography (CT). A difficulty of imaging diagnostics of the small intestine in CD lies in differentiating small neoplastic lesions from severe CD. Contemporary diagnostic methods include advanced endoscopy and radiological techniques. Generally, if SBA is suspected in a patient with CD, detailed diagnostics begins with non-invasive radiological examinations. CT or magnetic resonance enterography is a good, frequently used, and safe diagnostic method that is well-tolerated by patients and achieves a sensitivity of above 70% [21]. Both tests may also be performed using enteroclysis; however, a nasoduodenal tube is not tolerated well by the majority of patients. Comparing the effectiveness of small bowel dilatation in both methods, greater intestinal distension was observed in enteroclysis, although it does not have a significant impact on the quality of intestinal assessment and accuracy of test results [25]. A pathological mass in imaging tests strongly suggests SBA in patients with CD; however, cancer may be completely indistinguishable from benign fibrosis or stricture secondary to acute inflammation [6, 17, 18, 21, 26]. In 1 case of SBA in the investigated group, a radiological CT examination revealed a concentric ileal stricture 60 mm in length. If diagnosis cannot be made after radiological examinations, enteroscopy or video capsule endoscopy (VCE) may prove useful. VCE is the least invasive method of endoscopy, with a high sensitivity (5–67%), allowing physicians to detect minor mucosal lesions that are not visualised in radiological examinations [27]. This meth-

od often precedes enteroscopy, in particular in patients whose first symptom of SBA is GI bleeding. It should be used with great caution in patients with suspected mass in the small bowel and it is important to exclude subileus before VCE. Other diagnostic methods used in oncology, such as positron-emission tomography, have also become more available recently [28]. It was demonstrated that blood biochemistry and CEA levels are not useful indicators of both SBA development and its detection [6, 20]. Due to diagnostic difficulties, SBA is detected incidentally (3.1–14%) preoperatively and mostly postoperatively based on histopathology report. Lymph nodes are already involved in 33–55% of cases, and in 38–56% of cases metastases are observed [6, 8, 17, 18, 20, 24]. Currently there is no standard management of SBA in patients with CD. The R0 resection is the only approved radical treatment, and its area depends on disease severity and location of primary lesion. Surgery should result in a negative surgical margin and proper lymphadenectomy. Cancer of the jejunum and ileum should be resected with a margin of 5–10 cm of the macroscopically healthy intestine and corresponding mesentery up to superior mesenteric vessels in order to remove the appropriate amount of lymphatic tissue [26, 29–34]. Ileocaecal resection or right hemicolectomy should be performed if a tumour is located in the last ileal loop or has infiltrated the ileocaecal valve [5, 30–32, 35]. In the examined group of patients with CD, the patient diagnosed with SBA was treated with ileocaecal resection. Planned radical resection is successful in 49–68% of surgeries, while palliative surgery is performed with a success rate of 12–35%. Patients are mainly found ineligible for radical resection if their tumour has spread deeply to intestinal mesentery and distant organs [36]. The presence of distant metastases is a factor significantly increasing the incidence of postoperative complications and mortality. The overall survival (average 10 months) is comparable to non-operated patients. Despite this fact, as much as 30% of patients with stage IV SBA are found to be eligible for palliative surgery, mainly due to heavy bleeding from the tumour site, or obstruction or perforation of the intestine [37]. Bowel bypasses and palliative resections are the most frequently performed palliative procedures [30, 32]. Postoperative complications significantly decrease the quality of life and are observed in 14.5–60% of patients [33, 36, 38, 39]. It was demonstrated that radical surgery has no significant impact on the number of postoperative complications. Total perioperative mortality ranges from 1% to 12% [36, 39].

Currently available data on adjuvant chemotherapy in patients with SBA are very limited and provide discrepant information. In the investigated group, the

patient diagnosed with SBA has not received adjuvant chemotherapy due to stage II cancer. It should be emphasised that only French guidelines (<http://www.tncc.org>) on adjuvant chemotherapy are available at present (updated in 2017). The authors recommend stage III cancer be treated with FOLFOX4 regimen (5-fluorouracil, oxaliplatin, folinic acid) for 6 months or, if tolerated poorly, with LV5FU2 regimen (5-fluorouracil, folinic acid) or capecitabine. Chemotherapy is not recommended in stage II cancer, except for T4 tumours when chemotherapy should be considered.

Optimistic information about a cytoreductive treatment in combination with hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with colon cancer raises the hope that a similar outcome could be achieved in patients with SBA. The mean survival in one of the larger groups of 16 patients who underwent a cytoreductive treatment (CC-0 in 93.8% of them) and HIPEC was 30.8 months (3.4–94.4 months), and the time to recurrence amounted to 9.5 months (4.6–14.4 months) [40]. Intraperitoneal metastases were noted in 7 of 8 patients with recurrent disease. Indications for HIPEC should be considered each time in patients with intraperitoneal metastases due to prolonged survival observed in the discussed patients with SBA, along with acceptable toxicity of this treatment.

Data on the prognosis in patients with SBA secondary to CD vary depending on the source, but it is commonly believed that it is poorer than in the case of *de novo* lesions. The 5-year survival rates are 3.7–35% and 14–45%, respectively [4, 6, 18–22]. Mean survival is 13–40 months [5, 21, 26, 29, 32, 33, 35–39].

Conclusions

The long-term follow-up carried out in the group of consecutively treated patients with CD revealed a 0.97% incidence rate of small bowel adenocarcinoma. Although the authors are aware that the number of patients enrolled in the study is insufficient to draw far-reaching conclusions, the results obtained are significant for the determination of the incidence rate of SBA in the Caucasian population of patient with CD. The key issue of effective treatment of patient with SBA was in fact early detection of the lesion with typical symptoms and R0 resection with proper lymphadenectomy. However, it is worth noting that in more advanced stages of SBA the future belongs to, and outcome improvement depends on, new regimes of adjuvant personalised chemotherapies. That is why further studies on the mechanisms of carcinogenesis in patients with CD are essential.

Conflict of interest

The authors declare no conflict of interest.

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