Is the degree of i2a recurrence in Crohn’s disease secondary to ischemic phenomena?

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ABSTRACT

Introduction: the Rutgeerts score is used to assess post-surgical recurrence of Crohn’s disease (CD). The score initially consisted of four grades, with a subsequent sub-classification of grade 2, under which ulcers confined to the anastomosis (i2a) are considered to be of a probable ischemic origin. The aim of this study was to assess whether ulcers confined to the anastomosis appear at the same frequency in patients undergoing surgery for other causes and can therefore be attributed to post-surgical changes.

Material and methods: this was a retrospective cohort study with patients who had undergone colonoscopy as per clinical practice between 2017 and 2018. There were two cohorts, one cohort of patients to assess the post-surgical recurrence of CD and another cohort for follow-up after colorectal cancer (CRC) treated with ileocolonic anastomosis.

Results: a total of 185 patients were included; 33 % had undergone surgery for CD and 67 % had undergone surgery for CRC. Fifty-six percent of patients were male. Of the
patients in the group with ulcers confined to the anastomosis, 75 % had CD and 25 % had been operated on for CRC; the difference was statistically significant (p < 0.0001). In turn, of the patients operated on for CRC, 95 % had no anastomotic lesions compared to 18 % of patients with CD. These differences reached statistical significance (p < 0.0001).

**Conclusions:** In our experience, the occurrence of ulcers on the ileocolonic anastomosis is uncommon in patients that have undergone surgery for CRC, in comparison to patients operated on due to CD. It is possible that these alterations in CD cannot therefore be attributed to solely ischemic or post-surgical phenomena.

**Keywords:** Post-surgical recurrence. Rutgeerts score. Crohn’s disease. Ileocolonic anastomosis. Ischemia.

**INTRODUCTION**

Despite the broad therapeutic arsenal available for the medical treatment of Crohn’s disease (CD), surgery continues to be a mainstay in the management of the disease. Ten years after diagnosis, almost 50 % of patients need to resort to surgical resection as curative treatment, whether due to fistulating complications or to the presence of stenosis refractory to pharmacological treatment. Of these, half will undergo further interventions throughout their disease (1-3).

In 1984, Rutgeerts demonstrated the endoscopic appearance of a new disease in previously healthy intestines after surgery, which he called post-surgical recurrence. This appeared in up to 70 % one year after the procedure and included patients that did not receive any treatment after surgery, thus describing the natural history of the disease (4). In addition, they established a classification that related endoscopic findings in the first year post-surgery to the probability of clinical recurrence (5).

To date, no validated score has been developed to replace Rutgeerts for the assessment of post-surgical recurrence (6). Post-surgical recurrence of CD is a constant in virtually all patients over time, despite the early initiation of preventative treatment after surgery. Currently, patients at high risk of post-surgical recurrence (smoking, previous history of intestinal resection, habits involving anal penetration or perianal
contact), immunosuppressants or biologic therapy are introduced promptly after surgery in an attempt to prevent the appearance of CD in the anastomotic region (2,7-13). An early ileocolonoscopy (six months post-surgery) is performed and, depending on the endoscopic findings, treatment is optimized.

In the most widespread current management of post-surgical recurrence, grades i3 and i4 are considered as subsidiary to optimizing treatment, since they are more likely to have clinical recurrence, whereas grades i0 and i1 are considered to have no significant recurrence and therefore do not need treatment. Grade 2 is more controversial as these patients may be candidates for therapeutic escalation, depending on the clinical and/or individual assessment of each patient and each situation (2,3,14,15).

The POCER study (10) included two cohorts of patients with CD who were assessed after undergoing ileocolonic resection; patients were randomized for therapeutic management based on either endoscopic or clinical findings. This study demonstrated that the strategy of prophylaxis against recurrence with immunosuppressant drugs and therapeutic intensification based on endoscopic findings (using the Rutgeerts score) after the first ileocolonoscopy after surgery decreased the incidence of recurrence and severe forms. Therefore, there was a change in the management of the disease and the appearance of symptoms were anticipated, thus controlling the disease from early stages.

In 2008, Domènech et al. performed a study with the primary objective to evaluate the efficacy of azathioprine in the prevention of post-surgical recurrence. The secondary conclusion was that patients with lesions confined to the anastomosis do not evolve like other more serious degrees of endoscopic recurrence. Therefore, they do not seem to benefit from the same therapeutic strategy, as the cause of these lesions may be related to ischemic phenomena produced after an attack. This may be due to intestinal resection with subsequent anastomosis, involving a devascularisation of intestinal tissue in which the restitution of vascularisation depends on the submucosal plexus. In patients with CD, this is usually compromised by vasculitis secondary to chronic inflammation and therefore may explain poor anastomotic revascularisation in these patients and the appearance of ulcers confined to that area (14,16). This study
proposes a sub-classification of the Rutgeerts score, subdividing the i2 grade into i2a (ulcers confined to less than 1 cm from the anastomosis) and i2b (more than five sores on ileum with normal mucosa between them) with an intermediate risk of clinical recurrence.

In view of the idea that anastomotic ulcers can be considered as signs of post-surgical ischemia, the aim of this study was to evaluate whether the appearance of ulcers confined to the ileocolonic anastomosis in CD patients undergoing surgery occurs at the same frequency as in patients operated on for other causes, such as colorectal cancer (CRC).

**MATERIAL AND METHODS**

**Patient selection**

The study used a retrospective cohort design and included patients who had undergone clinical colonoscopy between January 2017 and June 2018. The indication in one cohort was to assess the post-surgical recurrence of CD and for follow-up after CRC in another cohort; patients had undergone surgery via ileocolonic anastomosis in both cases.

Patients from the first cohort were included consecutively after establishing the described time period and 61 patients were selected with CD who had undergone an endoscopic study during the study period. At least twice as many patients in the CRC cohort were randomly recruited (2:1 design, no sample size calculation was performed) to increase the statistical power. The variables deemed relevant to the study that were related to the patient’s baseline characteristics and their CD were collected.

**Data collection**

Endoscopic examinations were performed using an Olympus 2T160L, H185L/l and H190L/l colonoscopes and the EVIS EXERA III system. Examinations of patients with CD were performed by endoscopists that specialize in inflammatory bowel disease. Endoscopic recurrence was established as per the modified Rutgeerts classification (3,5). Patients with CD were excluded from examinations in which the neo-ileum could
not be assessed (and therefore the Rutgeerts score could not be calculated) due to technical difficulty or stenosis.

The images and written reports from colonoscopies indicated after CRC surgery were reviewed to confirm that there were no ulcers confined to the anastomosis that had not been described on the scan report. Patients were excluded from the study due to possible information bias when there were no scan images on the system (Endobase). The patients in this cohort were classified as either the presence (Fig. 1) or absence of ulcers in the ileocolonic anastomosis and placed in group i2a or i0, respectively, for ease of interpretation of the results.

**Statistical analysis**

Categorical variables were described and analyzed as absolute values and percentages. The hypothesis contrast test used to compare them was the $\chi^2$. A value of $p < 0.05$ was considered as statistically significant. The analysis was performed using Stata for Mac.

**RESULTS**

A total of 185 patients were included in the study, 33 % (61 patients) were operated on for CD and 67 % (124 patients) for CRC. Fifty-six % (104 patients) of the cohort were male. Of the cohort, 20 % (12 patients) were smokers and 28 % (17 patients) were ex-smokers (Table 1). Of the patients with ulcers confined to the anastomosis (24 patients), 75 % (18 patients) were i2a CD patients and 25 % ($n = 6$) were CRC patients. Among the patients in the CRC surgery cohort, most (118/124 patients, 95 %) had no lesions on the anastomosis or the neo-ileum, while only 18 % (17 patients) in the CD cohort had no lesions and were therefore classified as i0. These differences reached statistical significance ($p < 0.0001$). The results are shown in table 2.

Patients with CD were classified according to the modified Rutgeerts score as follows: i0 = 17 patients (28.8 %), i1 = 2 patients (3.4 %), i2a = 18 patients (30.5 %), i2b = 10 patients (16.9 %), i3 = 2 patients (3.2 %) and i4 = 12 patients (19.7 %) (Table 3).

A history of smoking in CD patients was also examined. In relation to the appearance of ulcers and smoking, most non-smoking patients (65 %; eleven patients) had no lesions on endoscopy (i0) compared to 67 % (eight patients) of smoking patients with a
significant endoscopic recurrence (i3 and/or i4). These differences were not statistically significant \( (p = 0.277) \).

**DISCUSSION**

The term *post-surgical recurrence* was described in 1984 and endoscopic findings were subsequently stratified into several grades according to the probability of clinical recurrence. Since then, it has been postulated that ulcers confined to the anastomosis could correspond to post-surgical ischemic phenomena (14,16).

In 1993, a study was reported using an animal model to attempt to explain this phenomenon, which concluded that ulcers appear more frequently on the anastomosis of an intestine that previously presented chronic inflammation. Furthermore, its circulation in the submucosal plexus was compromised prior to surgery due to inflammatory phenomena (13). However, the appearance of perianastomotic ulcers has not been described in the literature or the usual clinical practice as a common post-surgical phenomenon in cases that had undergone ileocolonic resection surgery for other reasons, such as CRC.

Our study compares the frequency of anastomatic ulcers in both populations and showed that most of the patients operated on for CRC at our center did not present ischemic phenomena, in the form of ulcers in the successive colonoscopies of their disease control. Furthermore, this percentage is much higher in CD patients, i.e. it is more common to find ulcers on the anastomosis in patients with CD (75 % of cases). This difference was statistically significant.

In 2008, Domènech suggested that cases where ulcers appear exclusively on the anastomosis do not evolve in the same way as those that also present sores on the terminal ileum. Thus, modifying the Rutgeerts score and splitting the i2 group into 2a and 2b respectively, reinforcing the theory of the ischemic nature of these lesions. This study compared (despite not being the prime objective of the study) the evolution of patients with i2a recurrence \( (n = 21) \) with i2b, i3 and i4 \( (n = 16) \). The hypothesis that the former present a better clinical and endoscopic evolution with a lower percentage of recurrences was established. Of them, only 29 % progressed to more advanced stages versus 100 % of those classified in the second group, where no patient had a
remission. Since then, the results of this study have been incorporated into the regular clinical practice, using the modified Rutgeerts score in many centers, resulting in different treatment strategies for i2a versus i2b. However, this hypothesis was later reconsidered in the study by Bayart in 2016. This study compared the probability of clinical and secondary global recurrence, including endoscopic recurrence, in patients classified after the first control ileocolonoscopy (55 patients) as i2a (n = 23) and i2b (n = 27). In both groups, the treatment was modified according to successive endoscopic findings as reflected in the current clinical practice guidelines. As a result, at one, three and five years, there were no significant differences in the appearance of clinical or global recurrence across the two groups. There was a clinical recurrence in 24 %, 52 % and 58 % of i2a patients and 19 %, 40 % and 52 % of i2b. Thus, suggesting similar therapeutic strategies for both, since they present the same risk of progression towards post-surgical recurrence (17).

Other subsequent studies continue to confirm the similar evolution of all i2s towards clinical recurrence (18). In 2018, Rivière studied two groups (i2a and i2b) for three years after surgery and found no differences between the two groups with regard to clinical recurrence or the need for further surgery (19).

However, another study from 2019 reported contradictory results, in which 149 patients with post-surgical recurrence classified as i0-i1, i2a and i2b in the first colonoscopy were monitored for one year after surgery. The progression towards more severe stages (> i3) was observed in 7 %, 20 % and 55 % of the groups, respectively. These differences were significant, supporting the theory that progression is more frequent in i2b patients, tending towards intensification (20).

With regard to limitations to our study, we did not take into account the timing of the colonoscopy, as not all of these were the first examination post-surgery and the frequency of occurrence of transient ischemic ulcers after surgery in both CD and CRC patients may vary. This was a retrospective and descriptive study under the common clinical practice, meaning that there are no ulcer biopsies which could provide additional information about their causes via a histological study. However, the histological alterations found in these biopsies are often of low quality (4). To support these results, it will be interesting to perform a prospective study with a larger number
of patients, including the first colonoscopy post-surgery. Furthermore, the evolution should be monitored in terms of endoscopic and clinical recurrence of patients using the modified Rutgeerts score.

Therefore, the results of our study reinforce the theory that the ulcers found in the ileocolonic anastomoses of patients with inflammatory bowel disease could correspond not only to ischemic signs but also to a recurrence of the disease, at least endoscopically. Since they are not found with the same frequency in other anastomoses. This could translate into true chronic inflammatory involvement and therefore require therapeutic intensification in order to achieve the recovery targets recommended under the current clinical guidelines. Despite the fact that most of the patients without ulcers were non-smokers and that tobacco is known to be an independent risk factor for post-surgical recurrence (3,10), no statistically significant differences were found in our study, although this was not the main objective.

REFERENCES


Table 1. Patient baseline data

<table>
<thead>
<tr>
<th></th>
<th>n = 185</th>
<th>%</th>
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<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>81</td>
<td>43.78</td>
</tr>
<tr>
<td>Male</td>
<td>104</td>
<td>56.22</td>
</tr>
<tr>
<td><strong>Tobacco use</strong></td>
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<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>12</td>
<td>19.67</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>32</td>
<td>52.46</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>17</td>
<td>27.87</td>
</tr>
<tr>
<td><strong>Reason for surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRC</td>
<td>124</td>
<td>67.03</td>
</tr>
<tr>
<td>CD</td>
<td>61</td>
<td>32.97</td>
</tr>
</tbody>
</table>

CRC: colorectal cancer; CD: Crohn’s disease.
Table 2. Classification of the sample according to the endoscopic findings on the anastomosis

<table>
<thead>
<tr>
<th>Ulcers in anastomosis</th>
<th>CRC surgery n (%)</th>
<th>CD surgery n (%)</th>
<th>Total n</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ulcers</td>
<td>118 (87 %)</td>
<td>17 (13 %)</td>
<td>135</td>
</tr>
<tr>
<td>Ulcers</td>
<td>6 (25 %)</td>
<td>18 (75 %)*</td>
<td>24</td>
</tr>
</tbody>
</table>

Chi^2 = 94.3830  
p = 0.0000

CRC: colorectal cancer; CD: Crohn’s disease. *Classified as per Rutgeerts score in the i2a group.
Table 3. Patients with CD classified according to Rutgeerts score

<table>
<thead>
<tr>
<th>Rutgeerts classification</th>
<th>n = 61</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>i0</td>
<td>17</td>
<td>28.8</td>
</tr>
<tr>
<td>i1</td>
<td>2</td>
<td>3.4</td>
</tr>
<tr>
<td>i2a</td>
<td>18</td>
<td>30.5</td>
</tr>
<tr>
<td>i2b</td>
<td>10</td>
<td>16.9</td>
</tr>
<tr>
<td>i3</td>
<td>2</td>
<td>3.2</td>
</tr>
<tr>
<td>i4</td>
<td>12</td>
<td>19.7</td>
</tr>
</tbody>
</table>
Fig. 1. Rutgeerts i2a post-surgical recurrence. Endoscopic image of the ileocolonic anastomosis of a patient operated on for Crohn’s disease. Medium depth ulcers are observed, with well-defined borders, covered with fibrin, occupying 100% of the circumference. They are confined to the anastomosis, with the rest of the colon mucosa visible and without pathological findings.