Endoscopic Features of Postoperative Anastomotic Lesions in Patients with Crohn’s Disease Compared with Right-side Colon Cancer: Are Anastomotic Linear Superficial Ulcers Recurrent in Crohn’s Disease?

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Abstract

Objectives: Many patients have endoscopic evidence of recurrent Crohn’s disease (CD) 1 year after intestinal resection, and endoscopic lesions predict future clinical recurrence. The aim of this study was to describe some anastomotic lesions including changes in endoscopic features in CD patients and to discuss recurrence. We also compared anastomotic lesions in CD patients and in right-side colon cancer (rt-CC) patients.

Methods: We enrolled patients with CD and rt-CC who underwent surgical resection between 2008 and 2014. Eleven CD patients underwent postoperative endoscopy at least twice, with the first time being from 6 months to 1 year after surgery and the second time being from 2 to 3 years after surgery. Eighty-six patients with rt-CC underwent postoperative endoscopy after approximately one year.

Results: A total of 90.9% of CD patients had postoperative lesions around the anastomosis at the first postoperative ileocolonoscopy, which was markedly higher than that in rt-CC patients (3.5%, p<0.001). Many of these lesions in CD required enhanced treatment. However, linear superficial ulcers at the anastomotic line at the first ileocolonoscopy did not worsen with the same treatment (18.1%).

Conclusions: Postoperative anastomotic lesions were detected at a higher rate in CD cases than that in rt-CC cases. Many anastomotic lesions were recognized as recurrent disease and required enhanced treatment, whereas linear superficial ulcers did not require treatment changes. Therefore, linear superficial ulcers might not be recurrent disease. As this issue is related to recurrence, it should be further explored with the accumulation of more cases in a multicenter analysis.

Keywords

Crohn’s disease, anastomotic lesion, linear superficial ulcer, colonoscopy, inflammatory bowel disease

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Introduction

Some epidemiological studies have reported that Crohn’s disease (CD) most commonly involves the terminal ileum and proximal colon, and approximately 70% of CD patients require intestinal resection for complications related to strictureing or penetrating disease at least once in their life, resulting most commonly in an ileocolonic anastomosis[1-3].
One year after intestinal resection, 70%-90% of patients have endoscopic evidence of recurrent CD[4-7]. Endoscopic recurrence correlates with the likelihood of future clinical recurrence and predicts the development of Crohn’s disease-related complications and the need for re-operation[4,5]. Therefore, an endoscopic follow-up evaluation 6-12 months after surgery has been preferred[8]. The randomized controlled trial of the POCER study indicated that early colonoscopy and enhanced treatment for recurrence is better than conventional drug therapy alone for prevention of postoperative CD recurrence[9].

In the endoscopic evaluation of CD patients, Crohn’s disease endoscopic index of severity score (CDEIS), simple endoscopic score for Crohn’s disease (SESCD) and Rutgeerts endoscopic score are often used. In particular, regarding the postoperative perianastomotic endoscopic evaluation, Rutgeerts endoscopic score has been used in several trials[4,6]. However, the presence of worse than i2 lesions is defined as recurrent disease and a risk of a further exacerbation or progression of the disease, wherein i2 lesions include various lesions, such as perianastomotic aphthous lesions or larger lesions with a normal mucosa and lesions confined to the ileocolonic anastomosis[4]. Lesions on the anastomotic line include linear ulcers, irregular ulcers, and longitudinal ulcers, and these lesions are sometimes suspected of being postsurgical sequelae and may thus be less predictive of progressive lesions than perianastomotic inflammatory lesions. In particular, linear superficial ulcers are sometimes encountered during the daily treatment of inflammatory bowel disease and may be considered mild lesions on the anastomosis. However, linear superficial ulcers have not been clearly described in the literature, and their details are unclear at present.

The aim of this study was to describe some anastomotic lesions, including changes in endoscopic findings in CD patients, and to discuss recurrence. We also compared the anastomotic lesions in CD patients with those in right-side colon cancer (rt-CC) patients.

Methods

Study design and data collection

We conducted a retrospective observational single-institution study in Nara Medical University. This study was approved by the institutional review board of Nara Medical University. Written consent to participate was obtained from the patients in this study. We enrolled the patients with CD and rt-CC who underwent surgical resection in Nara Medical University hospital between 2008 and 2014. Regarding CD, patients without anastomosis, such as stricture plasty, stoma creation, and perineal operation, were excluded. Endoscopic observations were performed in our institution, and we excluded patients who received follow-up at other institutions. We reviewed the data on age, gender, Montreal classification (date of onset of the symptoms, disease type and location), surgical procedure (indication and operation type), endoscopic findings around anastomosis, and treatment change. Preoperative and postoperative treatment included an elemental diet, 5-aminosalicylate, prednisolone, an immunomodulator and anti-tumor necrosis factor-α (anti-TNF-α) antibody. Regarding rt-CC, patients without postoperative endoscopy were excluded. We reviewed the patient characteristics including age, gender, anastomotic method (hand-sewn end-to-end anastomosis, or stapled side-to-side anastomosis), and endoscopic findings around anastomosis.

Definitions

Regarding CD, patients who undergo ileal or ileocolonic resection subsequently underwent postoperative endoscopy twice, with the first time being from 6 months to 1 year after surgery and the second time being 2-3 years after surgery. Regarding rt-CC, the patients with ileocolonic anastomosis underwent postoperative endoscopy after approximately one year.

Montreal classification of Crohn’s disease considered age at onset (A), disease location (L), and disease behavior (B) as the predominant phenotypic elements. Possible classifications were A1: below 17 years old, A2: between 17 and 40 years old, and A3: above 40 years old; L1: ileal, L2: colonic, and L3: ileocolonic; and B1: non-stricturing and non-penetrating, B2: stricturing, B3: penetrating, and P: perineal disease.

The endoscopic findings included the site at the anastomotic line and perianastomosis, shape (aphthous, irregular, and longitudinal), depth (superficial, middle, and deep), the number of ulcers, stenosis, and inflammatory mucosa. Endoscopic recurrence was defined in cases ≥i2 based on the Rutgeerts endoscopic score. A linear superficial ulcer on the anastomotic line was evaluated as an independent lesion separate from i2 according to the Rutgeerts score.

Treatment changes were considered based on endoscopic findings of a non-linear superficial ulcer on the anastomotic line and/or perianastomotic multiple ulcers or inflammatory mucosa. Prophylactic anti-TNF therapy was considered for the patients with high-risk factors for recurrence, such as perforating type and smoking. Ultimately, however, treatment changes and prophylactic anti-TNF therapy were performed at the surgeon’s choice.

Statistical analyses

All statistical analyses were performed using the StatMate IV statistical software program (Advanced Technology for Medicine and Science, Tokyo, Japan). Statistical differences were determined using Mann-Whitney U test and the chi-squared test. p-values < 0.05 were considered to be statisti-
Table 1. Characteristics of CD Patients.

| Case no. | Age at operation | Sex | Montreal classification‡ | Smoking | Preoperative Therapy | Operation |
|----------|------------------|-----|--------------------------|---------|----------------------|-----------|
|          |                  |     | Age | Location | Behavior | Method | Times | indication               |
| 1        | 27               | F    | A2  | L3      | B1       | ED, 5ASA, AZA, IFX | ICR      | 1               | active disease         |
| 2        | 41               | M    | A2  | L3      | B2       | ED, 5ASA, IFX    | ICR      | 1               | stenosis               |
| 3        | 20               | M    | A2  | L1      | B3       | 5ASA, PSL       | ICR      | 1               | fistula, abscess       |
| 4        | 35               | M    | A2  | L1      | B2       | 5ASA           | PI       | 1               | stenosis               |
| 5        | 28               | M    | A2  | L1      | B1       | -               | PI       | 1               | hemorrhage             |
| 6        | 38               | M    | A2  | L3      | B3       | ED, 5ASA, IFX   | ICR      | 2               | perforation, abscess   |
| 7        | 35               | F    | A2  | L3      | B3       | 5ASA, PSL      | ICR      | 1               | fistula, abscess       |
| 8        | 59               | F    | A3  | L3      | B2       | 5ASA, PSL      | ICR      | 1               | stenosis               |
| 9        | 24               | M    | A2  | L1      | B3       | +             | PI       | 1               | perforation            |
| 10       | 57               | M    | A2  | L3      | B2       | ED, 5ASA, AZA, IFX | PI    | 2               | stenosis               |
| 11       | 25               | F    | A2  | L3      | B1       | ED, 5ASA, IFX  | PI       | 1               | active disease         |

no., number; F, female; M, male; 5ASA, 5-Aminosalicylate; PSL, Prednisolone; AZA, Azathioprine; IFX, Infliximab; ICR, Ileocecal resection; PI, Partial resection of ileum.

‡Montreal classification of Crohn’s disease considered age of onset (A), disease location (L), and disease behaviour (B) as the predominant phenotypic elements. A2, between 17 and 40 years; A3, above 40 years; L1, ileal; L3, ileocolonic; B1, non-stricturing and non-penetrating; B2, stricturing; B3, penetrating.

cally significant.

Results

Data were collected from 19 patients with CD and 146 patients with rt-CC. Regarding CD, three who did not receive intestinal anastomosis and two who only received strictureplasty were excluded. Three patients did not undergo postoperative endoscopy because they had previously been followed up at other institutions. None of the patients underwent postoperative endoscopy only once at our institution. Regarding rt-CC, 60 patients who did not undergo postoperative endoscopy due to Stage IV disease or old age were excluded. Ultimately, 11 patients with CD and 86 patients with rt-CC were analyzed in this study (Figure 1).

Perianastomotic observations of CD (n = 11)

The CD patient characteristics, treatment, surgical procedures, and ileocolonoscopic findings are all summarized in Table 1 and Table 2. All patients underwent ileocecal resection or partial resection of the ileum reconstructed by hand-sewn end-to-end anastomosis. Two patients had a history of intestinal resection; five patients received anti-TNF therapy in the preoperative period and continued this therapy after the operation; and four patients started anti-TNF therapy to prevent recurrence after the operation.

The median duration from resection to the first endoscopic observation was 239.5 days (98-451 days). Six of the 11 patients (54.5%) had lesions on the anastomotic line with
Figure 2. Perianastomotic endoscopic images of CD patients with a linear superficial ulcer (case 3). (a) A linear superficial ulcer on the anastomotic line at the first ileocolonoscopy. (b, c) A linear superficial ulcer did not disappear or worsen without treatment change during the follow-up period (b: second ileocolonoscopy, c: 5 years after the operation).

Table 2. Perianastomotic Endoscopic Findings of CD Patients.

| Case no. | Postoperative Therapy | 1st Endoscopy | 2nd Endoscopy | additional intervention$ |
|----------|-----------------------|---------------|---------------|-------------------------|
|          | Anastomotic line      | Perianastomosis | Rutgeerts score | treatment change‡ | Anastomotic line | Perianastomosis | Rutgeerts score | treatment change‡ |
| 1        | ED, 5ASA, AZA, IFX    | -              | Multiple irregular middle ulcers | i3 IFX dose | -              | Multiple irregular middle ulcers | i4 IFX dose | re-SR          |
| 2        | ED, 5ASA, IFX         | Erosion       | -              | i2               | Irregular middle ulcer | Aphtha | i2 IFX dose | EBD          |
| 3        | ED, 5ASA, IFX         | Linear superficial ulcer | - | NA | Linear superficial ulcer | - | NA | -          |
| 4        | ED, 5ASA, ADA         | -              | -              | i0               | -              | - | i0 | -          |
| 5        | ED, 5ASA, AZA         | -              | Aphtha         | i1               | -              | - | i0 | -          |
| 6        | ED, 5ASA, IFX         | Irregular superficial ulcer | - | i2 | Irregular middle ulcer, stenosis | Aphtha | i2 IFX dose | EBD          |
| 7        | ED, 5ASA, AZA, IFX    | Linear superficial ulcer | - | NA | Linear superficial ulcer | - | NA | -          |
| 8        | ED, 5ASA, AZA         | Irregular middle ulcer, >5 Aphthae | - | i3 IFX add | - | >5 Aphthae, stenosis | i2 | EBD          |
| 9        | 5ASA, IFX             | Irregular superficial ulcer | 3 Aphthae | i2 | Irregular superficial ulcer | 3 Irregular superficial ulcers | i3 | IFX duration | -          |
| 10       | 5ASA, AZA, IFX        | Irregular superficial ulcer | - | i2 | Irregular superficial ulcer | stenosis | i3 | EBD          |
| 11       | ED, 5ASA, IFX         | -              | 4 Aphthae      | i1               | -              | 4 Aphthae      | i1 | -          |

no., number; ED, elemental diet; 5ASA, 5-Aminosalicylate; AZA, Azathioprine; IFX, Infliximab; ADA, Adalimumab.
NA, not applicable
‡treatment changes are as follows; IFX dose, the dose increase of IFX; IFX add, addition of IFX; IFX duration, shorter duration of IFX.
§additional intervention during the observation period; re-SR, re-surgical resection; EBD, endoscopic balloon dilatation.

erosions, linear superficial ulcers, and irregular superficial ulcers (Figure 2a). Five patients (45.5%) had various perianastomotic lesions from one small aphtha to multiple irregular ulcers. Overall, 10 of the patients (90.9%) had some
lesions around the anastomotic site at the first ileocolonoscopy. The Rutgeerts endoscopic score at the first ileocolonoscopy was 1 for i0, 2 for i1, 4 for i2, 2 for i3, and 2 for linear superficial ulcers. Regarding endoscopic recurrence, the recurrence rate was 72.7% if the linear superficial ulcer was deemed to be recurrent disease, and the recurrence rate decreased by 54.5% if the linear superficial ulcer was not considered to be recurrent disease.

The median duration from resection to the second endoscopic observation was 957 days (826-1268 days). One patient (case 4) continuously exhibited no endoscopic lesions, and the lesions in another patient (case 5) had disappeared by the second endoscopy. Three patients had the same lesions during the observation period (cases 3, 7, and 11). Notably, two patients had a linear superficial ulcer on the anastomotic line at the first ileocolonoscopy, and the lesions did not disappear or worsen without treatment change during the follow-up period (cases 3, Figure 2a-c). The lesions in five patients were worse at the second ileocolonoscopy than at the first ileocolonoscopy (cases 1, 2, 6, 9, and 10). In case 2, erosion with edema at the anastomotic line gradually became an irregular ulcer with stenosis, and endoscopic intervention was needed 6 years after surgery (Figure 3a-c). In a patient who received anti-TNF therapy after the first ileocolonoscopy, a perianastomotic irregular ulcer was found to have developed both stenosis and aphthae during the second endoscopy (case 8, Figure 4a, b). In five patients, the detected lesions grew and became deeper at the second ileocolonoscopy and required further anti-TNF therapy, including a dose increase or a change in the doing interval (cases 1, 2, 6, 9, and 10). Overall, 9 of the 11 patients (81.8%) had some lesions around the anastomotic site at the second ileocolonoscopy. The Rutgeerts endoscopic score on the second ileocolonoscopy was 2 for i0, 1 for i1, 3 for i2, 2 for i3, 1 for i4, and 2 for linear superficial ulcers. The recurrence rate was the same at the second ileocolonoscopy as it had been at the first. Ultimately, five patients presented with clinical symptoms during the subsequent observation period. One case with multiple irregular ulcers ultimately needed repeat surgical resection (case 1, Figure 5), and four cases with anastomotic stenosis needed endoscopic dilatation during the subsequent observation period (cases 2, 6, 8, and 10).
Perianastomotic observations of rt-CC (n = 86)

Eighty-six patients with rt-CC underwent resection reconstructed by ileocolonic anastomosis and postoperative endoscopy. The median age at resection of rt-CC was 60 years old, which was older than the age at CD surgery (35 years old; p < 0.001, Table 3). Seventy-two patients underwent hand-sewn end-to-end anastomosis, and 12 underwent reconstructed stapled side-to-side anastomosis. The median duration from resection to endoscopic observation was 378 days (130-2070 days). Only one patient with stapled side-to-side anastomosis (1.2%) had redness at the anastomotic line (Figure 6a), and two cases with hand-sewn end-to-end anastomosis (2.3%) had an ulcer at the perianastomotic site on the oral side (Figure 6b-d). No linear superficial ulcers at the anastomotic line were detected in rt-CC patients. There were no patients with inflammatory bowel disease (IBD), and none of the three patients with anastomotic lesions received treatment with non-steroidal anti-inflammatory drugs. No patients presented with anastomotic stenosis or needed any additional therapy for anastomotic lesions. When CD and rt-CC cases were compared, CD cases had significantly more lesions on the anastomotic line and the perianastomotic site than those in rt-CC cases (both p < 0.001, Table 3).

Discussion

Postoperative anastomotic ulcers on CD patients are considered to be the most common, recurrent form[3-5]. Among them, typical endoscopic findings around the anastomosis of experienced cases were submitted. In the present cases, 10 of 11 CD patients (90.9%) had postoperative lesions around anastomosis at first postoperative ileocolonoscopy. These anastomotic lesions were rarely observed in patients with rt-CC (3.5%) and even rarer than in CD cases (p < 0.001). Although the difference in the incidence of inflammatory lesions in the residual intestine between CD and colon cancer patients is well recognized, no reports have described the difference in the frequency of anastomotic lesions between patients with CD and those with other diseases. Many of these lesions with CD required enhanced treatment including addition of anti-TNF agents, endoscopic or surgical interventions, and gradually worsened. However, linear superficial

![Figure 5. Multiple irregular ulcers on the proximal ileum at the second ileocolonoscopy.](image-url)
Figure 6. Perianastomotic endoscopic images of rt-CC patients. (a) Mucosal redness of the ileocolonic anastomosis after stapled side-to-side anastomosis. (b) Deep isolated ulceration of the ileum up to the anastomosis after hand-sewn end-to-end anastomosis. (c, d) Deep isolated ulceration near the site of anastomosis after hand-sewn end-to-end anastomosis (c: a distant view of the anastomosis, d: a close view of ulcer).

CDEIS and SESCD include some factors concerning the presence of ulcers, an ulceration depth, an ulcerated surface, and the affected surface, but it is difficult to evaluate linear ulcers on the anastomotic line at the first ileocolonoscopy did not disappear and worsen without treatment change.

Weinstock et al. demonstrated a prevalence of 2.5% of 321 cases for ulcerations in endoscopic findings of anastomosis with colonic neoplasm, and Harris et al. did not find any anastomotic ulcers in 117 consecutive patients with colonic anastomoses[10,11]. In addition, two cases with a superficial aphthous ulcer along the anastomotic line were reported in adults with iron-deficiency anemia or gastrointestinal bleeding[12]. In this study, 3.5% of 86 cases with ileocolonic resection for colonic carcinoma had anastomotic lesions without symptoms. However, some studies have indicated that 40%-80% of Behçet’s disease patients have postoperative anastomotic recurrent lesions, such as volcano-type and deep intestinal ulcers[13-16]. Although postoperative anastomotic lesions are frequently detected in cases of IBD, no patients had linear superficial ulcers similar to those observed in CD in this study or in other studies.

Regarding enhanced treatment after ileocolonoscopy, in general, endoscopic recurrent lesions are considered to require some treatment changes. Endoscopic recurrence was found to be predictive of subsequent clinical recurrence. Early intervention for endoscopic lesions has been reported to reduce the risk of clinical recurrence. In the present study, many endoscopic lesions were detected at the first endoscopy, and enhanced treatment including further anti-TNF therapy was required for typical recurrent lesions such as irregular deep ulcers and multiple aggressive mucosal inflammations. These lesions were typically considered recurrent disease, and several lesions required ultimately surgical procedure or endoscopic dilatations for their management. However, not all lesions always required treatment, although various perianastomotic lesions are found to be associated with CD. In particular, the linear superficial ulcers detected at the first endoscopy maintained their shape without any treatment changes during the observation period, although prophylactic postoperative anti-TNF therapy was performed. Although these lesions may be associated with CD, whether or not they were actually recurrent disease it is difficult to judge because of the lack of any treatment change. To our knowledge, there have been no reports clearly describing the presence of linear superficial ulcers.

CDEIS and SESCD include some factors concerning the presence of ulcers, an ulceration depth, an ulcerated surface, and the affected surface, but it is difficult to evaluate linear
superficial ulcers and determine whether or not they represent recurrent disease. Rutgeerts endoscopic score is often used in endoscopic perianastomotic evaluation of postoperative CD patients, and i2 lesions or higher lesions are defined as recurrent disease. In addition, i2 lesions are subdivided into i2a: lesions confined to the ileocolonic anastomosis and i2b: lesions in the neoterminal ileum with normal intervening mucosa in a modified Rutgeerts score[17,18]. In the current study, i2a lesions included erosion with edema, linear superficial ulcer, and irregular ulcer. As in case 2, erosion with edema or irregular ulcer on the anastomotic line had become deep irregular ulcer with stenosis, which ultimately required endoscopic interventions. By contrast, linear superficial ulcers at the anastomotic line maintained their shape without any treatment change. Therefore, there were various patterns of lesions on the anastomotic line defined by i2a, and it was difficult to determine whether all lesions were recurrent. When evaluating the endoscopic findings were evaluated using the Rutgeerts endoscopic score in this study, when linear superficial ulcers were deemed to be recurrent diseases, the recurrence rate at the first ileocolonoscopy was 72.7%, and when linear superficial ulcers were not considered to be recurrent lesions, then the recurrence rate at the first ileocolonoscopy dropped to 54.5%. The recurrence rate was same at the second ileocolonoscopy as it was at the first procedure. At the very least, as the endoscopic recurrence rate greatly depends on whether linear superficial ulcers at the anastomotic line are recurrent disease. Since endoscopic recurrence and the operative procedure and postoperative treatment correlate with the likelihood of future clinical recurrence, the accumulation of further cases is required in order to resolve this issue[19-22].

Several limitations associated with the present study warrant mention. First, this was a retrospective study with a small number of patients in each group, so our results may not clarify the actual characteristics of such lesions. Second, as there was some case variation with regard to the treatment history and disease activity, the rate of anastomotic lesions may be different. Despite these limitations, however, we believe that the results of this study reflect the actual clinical features of perianastomotic lesions in postoperative CD patients.

Conclusions

Postoperative anastomotic lesions were detected at a higher rate in CD cases than that in rt-CC cases. Although anastomotic lesions are generally recognized as recurrent disease, some lesions did not require enhanced treatment, such as linear superficial ulcers in anastomotic lesions. Therefore, these lesions may not be recurrent disease. Furthermore, as there have been no reports clearly describing the presence of linear superficial ulcers, it is difficult to consider whether these lesions were recurrent disease. Therefore, as this issue is related to CD recurrence, it should be further explored through the accumulation of more cases in a multicenter analysis.

Conflicts of Interest

There are no conflicts of interest.

Author Contributions

T.U.: study concept and design; data collection, analysis and interpretation; and preparation of the manuscript

T.N., S.O., T.I., Y.S., and H.K.: data collection and decision to publish

F.K. and H.F.: study supervision and decision to publish

M.S.: Department chairman.

All authors approved the final manuscript.

Approval by Institutional Review Board (IRB)

This study was approved by the Institutional Review Board of Nara Medical University. (approval code: 1025)

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