Isolated ileal blind loop inflammation after intestinal resection with ileocolonic anastomosis in Crohn's disease: an often neglected endoscopic finding with an unfavorable outcome

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Objective Postoperative endoscopic recurrence in patients with Crohn's disease (CD) is commonly classified using the Rutgeerts score. Ulcerations in the ileal blind loop are not taken into account in the Rutgeerts score, and the clinical relevance of these lesions is unknown. This study aimed to assess the outcome of isolated ileal blind loop inflammation (IBLI) in postoperative CD patients.

Methods Adult CD patients who underwent intestinal surgery with ileocolonic anastomosis between 1997 and 2017 were included and postoperative endoscopy reports were retrospectively reviewed. IBLI was defined as isolated inflammation of the ileal blind loop with or without ulcera confined to the anastomosis. Outcome was assessed using endoscopic recurrence (Rutgeerts >i2) and surgical recurrence (re-resection).

Results A total of 341 CD patients were included. In 125 out of 341 (37%) patients, the ileal blind loop was described in the endoscopy reports. IBLI was reported in 43 of 341 (13%) patients. Start or step-up drug therapy was initiated in 10 of 32 (31%) IBLI patients with abdominal symptoms within a median of 0.9 months [interquartile range (IQR) 0.7–1.4] after ileocolonoscopy. Endoscopic recurrence occurred in 4 out of 38 (11%) IBLI patients without re-resection, within a median of 12.4 months (IQR 6.8–13.3). Intestinal re-resection was performed in 5 out of 43 (16%) IBLI patients within a median of 3.7 months (IQR 3.5–10.8).

Conclusion IBLI is associated with symptoms and an unfavorable outcome, with a high risk of endoscopic recurrence in the neoterminal ileum and intestinal re-resection during short-term follow-up. Therefore, the blind ileal loop needs to be assessed during endoscopy in postoperative CD patients. Eur J Gastroenterol Hepatol 31: 1370–1375

Introduction

Intestinal surgery is a valuable treatment option in patients with Crohn's disease (CD). Intestinal resection rates in CD patients are estimated at 50–70% within 10 years after diagnosis [1,2]. Patients with ileal or ileocolonic CD localization have a higher likelihood of undergoing intestinal resection, with hazard ratios (HRs) of 3.4 and 3.3 respectively, when compared with isolated colonic disease localization [2,3]. Consequently, most frequently performed surgeries in CD patients are ileocecal resections or right hemicolectomies with ileocolonic anastomosis [2,4].

The benefits of surgery are substantial, and a recent randomized controlled trial demonstrated ileocolonic resection to be an alternative to step-up therapy with TNFα-blockers with regard to patient reported quality of life [5]. However, postoperative recurrence is highly prevalent, with endoscopic lesions recurring in up to 80% of patients within 1 year [6,7]. Current postoperative treatment strategies aim at prevention, early detection and early medical treatment of endoscopic lesions [8,9]. In particular, publication of the Rutgeerts score as a tool to classify endoscopic lesions has influenced postoperative treatment and follow-up strategies. In the landmark study from Rutgeerts *et al.*, the clinical recurrence rates 5 years after endoscopy were assessed in 89 postoperative CD patients, and estimated at 10% for Rutgeerts score of i0 or i1, 25% for Rutgeerts score i2, 60% for Rutgeerts score i3 and 100% for Rutgeerts i4 [6].

Following the observation of mucosal lesions preceding clinical symptoms, the Rutgeerts score at ileocolonoscopy has gained a central role in guiding decisions on drug therapy in postoperative CD patients. Pre-emptive ileocolonoscopy early after intestinal resection is recommended in international guidelines [9,10]. A randomised trial confirmed the importance of early ileocolonoscopy after

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6 months and subsequent step-up drug therapy for endoscopic recurrence, as endoscopic recurrence rates after 18 months were significantly lower compared to patients with conventional drug therapy without colonoscopy [8].

Although the Rutgeerts score is a convenient tool during postoperative endoscopy and widely used to estimate the risk of recurrence, it has some limitations. Currently, a side-to-side ileocolonic anastomosis is most often used during CD surgery. As end-to-end anastomosis was common at the time of publication of the original Rutgeerts score, assessment of the Rutgeerts score is limited to the anastomosis and neoterminal ileum, while the blind ileal loop is not taken into account. The prevalence and outcome of isolated inflammation of the ileal blind loop are unknown. In this study, we aimed to assess the occurrence of isolated ileal blind loop inflammation, associated risk factors and outcomes in postoperative CD patients.

Materials and methods

Study population

This multicenter, retrospective study was performed in the Erasmus MC, Rotterdam (academic center) and in the Amphia hospital, Breda (large teaching hospital). All adult CD patients (aged ≥18 years) who underwent an intestinal resection with ileocolonic anastomosis between January 1997 and June 2017 were included. The study population was identified using Endobase (Olympus corp. Tokyo, Japan), a hospital endoscopy registry system in which the type of endoscopy, the indication and the endoscopy report are stored [11]. In this endoscopy registry, a search was performed using the terms ('Crohn' and 'resection') or 'anastomosis' or 'Rutgeerts' or 'ileocecal'. Subsequently, all hospital records of the obtained patient population were hand searched for the date of surgery.

Data collection

Endoscopy reports of the selected patients were reviewed and endoscopic findings at the ileocolonic anastomosis were registered. Ileal blind loop inflammation (IBLI) was defined as isolated inflammation (erosions and/or ulcerations) of the ileal blind loop with or without aphtous ulcers confined to the anastomosis. CD patients after ileocolonic resection without IBLI were selected as background population. Patient and disease characteristics including demographics, disease phenotype and duration, smoking status and surgical history were collected from hospital records. Clinical charts were reviewed for the indication of colonoscopy and the presence of symptoms (increased stool frequency and/or abdominal pain) at the time of IBLI diagnosis. The start or step-up of CD medication within 3 months after IBLI diagnosis was recorded. Follow-up data including performed endoscopies and subsequent surgeries were collected up to June 2017.

Outcome measures

Endoscopic recurrence was defined as extension of IBLI to the neoterminal ileum with Rutgeerts score i3 or i4, and surgical recurrence was defined as an intestinal re-resection.

Data analysis

IBM SPS Statistics version 24.0 (IBM Corp. Released 2013, IBM Corp, Armon, New York) was used for statistical analysis. Continuous variables were described as medians and compared using Mann–Whitney U test. Categorical variables were described using proportions and percentages and compared using χ^2 test. Survival statistics using Kaplan–Meier analysis was used to describe occurrence and time to IBLI diagnosis. The index date for survival analysis for the IBLI population was the date of the last surgery after which IBLI was observed. For the background population, the most recent surgery was selected as index date. Associated factors for IBLI were identified using Cox proportional hazard analysis. A *P*-value of <0.05 was accepted as statistically significant.

This study was conducted in accordance with the protocol and the principles of the Declaration of Helsinki. The study protocol was approved by the Medical Ethical Review Committee of the Erasmus University Medical Center on the 16th of August 2017.

Results

In total, 341 [132 male (39%)] postoperative CD patients were included. The ileal blind loop was described in the endoscopy report in 125 (37%) patients. IBLI was reported in 43 of 341 (13%) patients, of whom 19 (6%) patients had ulcerations limited to the blind loop, and 24 (7%) patients had IBLI combined with aphthous ulcers confined to the anastomosis (Fig. 1). The main indication for the endoscopy revealing IBLI was symptoms in 26 (60%) IBLI patients, followed by standard work-up after intestinal resection in 9 (21%) IBLI patients and effect monitoring of medical therapy in eight (19%) IBLI patients.

The baseline characteristics in the IBLI population (n = 43) showed no significant differences to the background population (n = 298), with regard to sex, Montreal

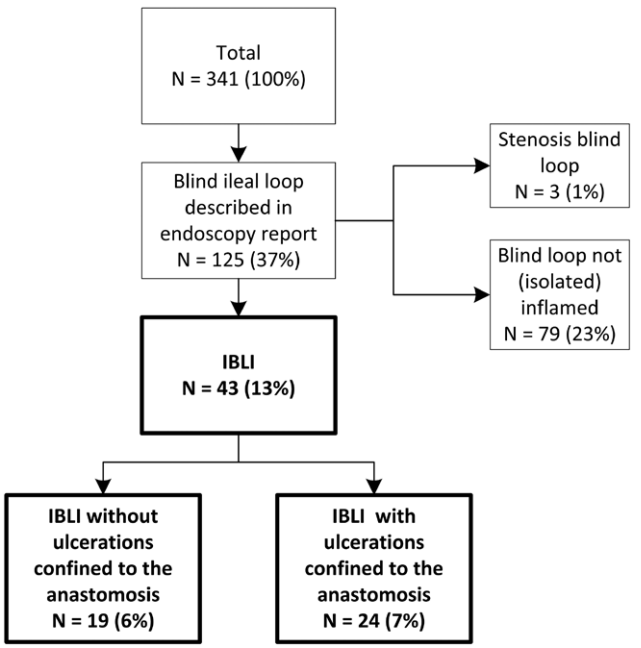

Fig. 1. Flow chart of IBLI occurrence. IBLI, ileal blind loop inflammation.

classification and smoking status. Family history of IBD was positive in 15 out of 43 (35%) IBLI patients, which was significantly more frequent compared to 57 of 298 (19%) patients in the background cohort (P = 0.002). Furthermore, a significantly higher proportion of IBLI patients, 16/43 (37%) vs. 67/298 (23%) in the background population, had undergone multiple previous ileocolonic resections, P = 0.035 (Table 1).

Risk of ileal blind loop inflammation

The median time between the last resection and description of IBLI in the endoscopy report was 2.9 years [interquartile range (IQR) 0.7–5.9] and the majority of IBLI cases (69.8%) occurred in the first 5 years after resection. Kaplan–Meier survival analysis showed that 5 years after the most recent intestinal resection, IBLI was described in the endoscopy report of 5.8% of the population. After 10 years, IBLI was described in 14.2% of the patients at risk. IBLI without anastomotic ulcers was described in 4.5% and 6.7% of patients, after 5 and 10 years, respectively (Fig. 2).

Consistent with the observed baseline characteristics, in univariable analysis, a positive family history of IBD [HR 3.7, 95% confidence interval (CI) 1.8–7.8] and multiple previous ileocolonic resections (HR 2.3, 95% CI 1.2–4.3) were identified as factors associated with the occurrence of IBLI. In multivariable analysis, a positive family history of IBD remained a significant risk factor, HR 3.5, 95% CI 1.5–7.4 (P < 0.001) (Table 2).

Clinical manifestation

A total of 32 out of 43 (74%) IBLI patients [14/19 (74%) IBLI without anastomotic ulcers and 18/24 (75%) IBLI with anastomotic ulcers] complained of abdominal pain and/or increased bowel movements at the time of endoscopy revealing IBLI. Subsequent start or step-up drug therapy was initiated in 10 out of 32 (31%) symptomatic patients [5/14 (36%) true IBLI and 5/18 (27%) IBLI with anastomotic ulcers], within a median of 0.9 months (IQR 0.7–1.4) after colonoscopy. The following therapies were initiated: mesalazine (one patient), budesonide (five patients), azathioprine (one patient) and anti-TNFα therapy (three patients). In one patient who underwent standard colonoscopy for recurrent inflammation, without clinical symptoms, budesonide was initiated after the diagnosis of IBLI.

Outcome

Extension of inflammation to the neoterminal ileum (Rutgeerts score i3 or i4) occurred in 4 out of 38 (11%) patients without a subsequent resection during follow-up, within a median of 12.4 months (IQR 6.8–13.3) after IBLI diagnosis. Endoscopic recurrence in the background population was comparable, 45 out of 298 (15%) (P = 0.452), although the time to recurrence, within a median of 42.8 months (IQR 16.7–90.2), was significantly longer compared to IBLI patients (P = 0.013). Median total follow-up time was also significantly shorter in the IBLI cohort,

Table 1. Baseline characteristics

		IBLI (n = 43)	Background (n = 298)	P value
Male sex, n (%)		19 (44)	113 (38)	0.430
Family history of IBD, n (%)		15 (35)	57 (19)	0.002
Montreal A,	<17 year	4 (10)	43 (14)	0.618
n (%)	17-40 year	32 (74)	203 (68)	
	>40 year	7 (16)	52 (18)	
Montreal L,	Ileum	20 (47)	131 (44)	0.889
n (%)	Colon	0 (0)	11 (4)	
	Ileocolonic	23 (53)	156 (52)	
Montreal B,	Luminal	15 (35)	135 (45)	0.294
n (%)	Stricturing	23 (53)	122 (41)	
	Penetrating	5 (12)	41 (14)	
Perianal disease, n (%)		6 (14)	67 (22.5)	0.196
Smoking, n (%)		23 (54)	138 (46)	0.270
Ileocolonic resections, n (%)	1	27 (63)	231 (77)	0.035
	>1	16 (37)	67 (23)	
Time from resection to endoscopic evaluation in years, median (IQR)		2.9 (0.7–5.9)	1.5 (0.6–4.8)	0.092

IBD, inflammatory bowel disease; IBLI, ileal blind loop inflammation; IQR, interquartile range.

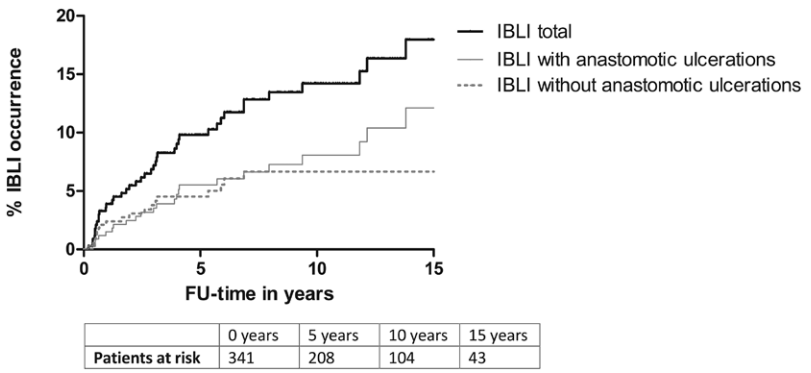

Fig. 2. Kaplan–Meier survival curve representing the percentage of IBLI occurrence during follow-up time after the most recent intestinal resection. IBLI, ileal blind loop inflammation; FU-time, follow-up time.

Table 2. Hazard ratios of factors possibly associated with ileal blind loop inflammation in univariable and multivariable regression analysis

		Univariable analysis			Multivariable analysis		
		HR	95% CI	*P* value	HR	95% CI	*P* value
Male sex		1.2	0.7–2.4	0.408			
Montreal A	<17 year	1	Ref	Ref			
	17–40 year	1.9	0.7–5.3	0.232			
	>40 year	1.6	0.5–5.4	0.463			
Montreal L	Ileum	1	Ref	Ref			
	Ileocolonic	0.8	0.5–1.6	0.666			
Montreal B	Luminal	1	Ref	Ref			
	Stricturing	1.6	0.8–3.0	0.168			
	Penetrating	1.2	0.4–3.3	0.741			
Perianal disease		0.5	0.2–1.3	0.164			
Active or previous smoking		1.4	0.7–2.8	0.312			
IBD family history		3.7	1.8–7.8	**<0.001**	3.5	1.6–7.4	**<0.001**
Time from diagnosis to first resection		1.0	0.9–1.1	0.256			
Age at first resection		1.0	0.9–1.0	0.676			
Multiple ileocolonic resections		2.3	1.2–4.3	**0.009**	1.4	0.6–3.2	0.376

CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; IBLI, ileal blind loop inflammation.

median 1.9 years (IQR 0.9–4.4), compared to 7.0 years (IQR 3.9–12.1) in the background cohort ($P < 0.001$).

In five patients (16%), clinical symptoms led to a subsequent resection during follow-up after IBLI diagnosis, within a median of 3.7 months (IQR 3.5–10.8). Three of these re-resections were revisions of the ileocolonic anastomosis, after which all three patients experienced an immediate relieve of symptoms.

Discussion

The blind ileal loop at the ileocolonic anastomosis after intestinal resection in CD is erroneously disregarded. In this study, we have shown that a description of the ileal blind loop is lacking in nearly two-thirds of endoscopy reports in postoperative CD patients with a side-to-side ileocolonic anastomosis. This finding is in sharp contrast to our results that demonstrate an unfavorable disease course after IBLI diagnosis, with regard to a considerable risk of endoscopic recurrence and surgical re-resection, both at short-term follow-up. Furthermore, despite its association with symptoms, drug therapy is infrequently initiated or changed after IBLI diagnosis.

To the best of our knowledge, this study is the first to assess the occurrence rate and prognosis of IBLI. The side-to-side anastomosis is the preferred technique in ileocolonic CD surgery after evidence of an advantage for the wider side-to-side when compared to end-to-end or end-to-side anastomosis in terms of anastomotic leakage, CD recurrence and re-resection risk [12–15]. Therefore, endoscopists are familiar with the anatomy of the side-to-side ileocolonic anastomosis. Nevertheless, we observed that a description of the ileal blind loop is missing in the majority of endoscopy reports. As a consequence, this retrospective cohort provides insufficient data to give an accurate estimation of IBLI prevalence. Considering that a description of the blind loop is often lacking in endoscopy reports, IBLI occurrence might yet be underestimated. Hence, the detection rate of IBLI needs to be confirmed in a larger prospective study.

The etiology of IBLI is unknown, and may be different from the etiology of recurrent CD lesions in the neoterminal (afferent) ileum. Hypotheses that warrant consideration include ischemia, disturbance of the microbiome by fecal stasis and diversion ileitis. The first potential mechanism underlying IBLI might be ischemia in the top of the blind loop, similar to the suggested pathophysiology of recurring ulcers confined to the anastomosis (Rutgeerts score i2a) [16]. Second, stasis of bowel content may cause bacterial overgrowth, similar to diarrhea caused by blind loop syndrome after bariatric surgery [17,18]. Although small intestinal bacterial overgrowth has previously been observed in CD patients [19], it has never been linked to the development of endoscopic ulcers. Third, diversion ileitis may be the most plausible etiology of IBLI. Diversion of the fecal stream could induce inflammation, similar to diversion colitis. The pathophysiology of diversion colitis is not fully elucidated, and may be a combination of ischemia caused by a shortage of short chain fatty acids causing increased arteriolar resistance and dysbiosis [20]. Current insights in the pathogenesis of CD advocate an important role for the decreased diversity of the gut flora in the perpetuating activation of inflammation [21]. Also in the setting of postoperative CD, early studies have suggested an important influence of the microbiota by demonstrating a benefit of metronidazole in the prevention of postoperative CD recurrence [22]. More recent studies showed microbiome diversity was decreased after CD surgery [23], and alterations in gut microbiota distribution around the anastomosis were associated with postoperative endoscopic recurrence [24]. The microbiome in the blind ileal loop needs to be further studied. In this respect, the length of the created ileal blind loop could be of interest, as a long segment may be associated with dysbiosis. Unfortunately, details on the length of the ileal blind loop in our series are lacking. Our results showed that three patients became asymptomatic after surgical revision of the side-to-side anastomosis, which supports that the anatomical composition of the side-to-side anastomosis could be relevant in the development of IBLI.

Known risk factors associated with postoperative endoscopic recurrence in the neoterminal ileum, for example, smoking and penetrating disease [9,25] were not associated with IBLI in our study. Significantly more IBLI patients had undergone multiple resections before baseline. Although this factor was not significantly associated with IBLI in multivariable analysis, it might suggest a more aggressive disease course and could have contributed to a higher postoperative recurrence rate in IBLI patients. Further assessment in a larger cohort is necessary to

provide a balanced analysis of this potential confounding factor. In our study, a positive family history for IBD was the only factor significantly associated with IBLI in multivariable analysis. Hypothetically, the association between a positive IBD family history and IBLI in postoperative CD patients might be explained by gene variations that play a role in microbiome dysbiosis. For instance, *NOD2* gene mutations are common in CD familial heredity and are associated with a deficient antimicrobial response and immune regulatory dysfunction [26–28].

IBLI patients seem to have an unfavorable prognosis considering high re-resection rates within a short time period after IBLI diagnosis. Endoscopic progression of the inflammation to the neoterminal ileum (i.e. Rutgeerts score i3/i4) was observed in 11% within 5 years. In the background population, we observed progression to Rutgeerts score i3/i4 within 5 years in 5% for Rutgeerts score i2a at first postoperative endoscopy, and 60% for Rutgeerts score i2b. It could be speculated that IBLI should be placed between i2a and i2b in a revised Rutgeerts score. However, the timing of the endoscopies in both groups in this study differs considerably and a firm conclusion cannot be drawn. Future prospective research with standardized timing of colonoscopies is needed before adding IBLI to a revised Rutgeerts score.

This retrospective study, assessing detailed information collected from endoscopy reports and hospital charts of an academic center and a large teaching hospital, serves as a plea for further prospective evaluation of IBLI, with regard to pathophysiology, prevalence and prognosis. Evidently, a few limitations of this study, inherent to its retrospective design, need to be considered. First, patients were not followed or treated according to a standardized follow-up protocol. This might have led to an underestimation of IBLI occurrence, since the majority of endoscopies were performed on indication of symptoms. Furthermore, the index date differed between both cohorts. For IBLI patients, the index date was the last surgery before the endoscopy revealing IBLI, while in the background population the last surgery overall was chosen. Although the index dates were deliberately determined to allow for the most reliable and accurate comparison between both cohorts, follow-up and outcome results need to be interpreted with care. Nonetheless, our retrospective data enable interpretation of the results in a real-world setting, which provides insight in the occurrence and consequences of IBLI in everyday clinical practice. Second, endoscopy reports were not uniform and endoscopists might have assessed the ileal blind loop during postoperative endoscopy, but might not have included a description in the endoscopy report. Especially during earlier follow-up years, when endoscopy reports were less standardized and guidelines on postoperative endoscopies were not yet published, blind loop assessments might have been underreported in our study. A sensitivity analysis regarding the outcome endoscopic recurrence was performed in a selection of patients with a description of the blind loop in the endoscopy report (n = 125), which showed an overall increase from 15 to 19% endoscopic recurrence in the background population compared to 11% in IBLI patients, P = 0.181. Third, because IBLI was described more often in endoscopy reports from more recent calendar years, total follow-up time was shorter in the IBLI cohort as compared to the background cohort, hampering interpretation of the comparison of endoscopic recurrence between both cohorts. Shorter follow-up might have led to lower endoscopic recurrence rates. Finally, the study population was too small to allow for in-depth analysis of risk factors for IBLI.

In conclusion, the blind ileal loop is often disregarded during postoperative ileocolonoscopy. Nevertheless, it is associated with symptoms and this study suggests an unfavorable prognosis of IBLI, as a high risk of surgical recurrence during follow-up was observed. Therefore, the blind ileal loop needs to be assessed during endoscopy in postoperative CD patients with ileocolonic anastomosis, both in clinical practice and in prospective research.

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Conflicts of interest

There are no conflicts of interest.

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