Digestive and Liver Disease 48 (2016) 753–758

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Alimentary Tract

# Myenteric plexitis is a risk factor for endoscopic and clinical postoperative recurrence after ileocolonic resection in Crohn's disease

Stéphanie Decousus[a], Anne-Laure Boucher[b], Juliette Joubert[a], Bruno Pereira[c], Anne Dubois[d], Felix Goutorbe[b], Pierre J. Déchelotte[a], Gilles Bommelaer[b,e], Anthony Buisson[b,e,*]

[a] Pathology Department, University Hospital Estaing, Clermont-Ferrand, France
[b] Gastroenterology Department, University Hospital Estaing, Clermont-Ferrand, France
[c] DRCI, Biostatistics Unit, GM Clermont-Ferrand University and Medical Center, Clermont-Ferrand, France
[d] Digestive Surgery Department, University Hospital Estaing, Clermont-Ferrand, France
[e] Microbes, Intestine, Inflammation and Susceptibility of the Host, UMR 1071 Inserm/Université d'Auvergne, USC-INRA 2018, Clermont-Ferrand, France

ARTICLE INFO

*Article history:*
Received 5 January 2016
Accepted 28 February 2016
Available online 3 March 2016

*Keywords:*
Crohn's disease
Plexitis
Postoperative recurrence
Risk factors

ABSTRACT

*Background:* As surgical resection is not curative in Crohn's disease, postoperative recurrence remains a crucial issue. The selection of patients, according to available risk factors, remains disappointing in clinical practice highlighting the need for better criteria, such as histologic features.
*Aims:* To investigate whether submucosal and myenteric plexitis increase the risk of endoscopic, clinical and surgical postoperative recurrence in Crohn's disease.
*Methods:* From the pathology department database, we retrospectively retrieved the data of all the patients who have undergone ileocolonic resection for Crohn's disease. Two pathologists, blinded from clinical data, reviewed all specimens to evaluate the presence of plexitis at the proximal resection margin.
*Results:* Of the 75 included CD patients, 19 (25.3%) had histological involvement of resection margin. Inflammatory cells count for myenteric and submucosal plexus were performed in 56 patients. In multivariate analysis, the myenteric plexitis was a risk factor for endoscopic postoperative recurrence (HR 8.83 $CI_{95\%}$ [1.6–48.6], $p = 0.012$), and the presence of at least one myenteric lymphocyte (HR 4.02 $CI_{95\%}$ [1.4–11.2], $p = 0.008$) was predictive of clinical postoperative recurrence. We observed no histologic predictor for surgical postoperative recurrence.
*Conclusion:* Myenteric plexitis in proximal margins of ileocolonic resection specimens is independently associated with endoscopic and clinical postoperative recurrence in Crohn's disease.


## 1. Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) involving the digestive tract that could lead to bowel damage [1,2]. In the era of biologics, surgery is still required in half of the patients ten years after diagnosis [3]. Surgical resection is unfortunately not curative in CD, and postoperative recurrence (POR) remains a key point in these patients. Approximately one-third of the patients experience postoperative recurrence, warranting surgery for CD, 10 years after the baseline surgery [4–7]. Clinical POR occurs in approximately 25%, 40% and 50%, respectively 1, 5 and 10 years after surgery [8]. From 54% to 75% of the patients present with endoscopic recurrence in the neoterminal ileum within 1 year following surgery [8].

Many years ago, Rutgeerts et al. showed a wide panel of CD postoperative courses, highlighting the need of predictors to differentiate high-risk patients, requiring top-down strategy immediately after surgery, from low-risk patients, remains a crucial issue in postoperative management [9]. Several factors have been suggested to define high-risk patients such as smoking, perianal lesions, previous intestinal resection, fistulizing phenotype and resection length >50 cm [8,10]. However, the impact of these former factors remains debated and limited, which highlights the need to identify more efficient criteria for selecting the CD patients according to their risk of postoperative recurrence.

Inflammatory infiltrates associated with both the submucosal and myenteric plexus have been observed in CD patients [11]. It remains unclear whether these enteric nervous system changes are

* Corresponding author at: University Hospital Estaing, Gastroenterology Department, 1, place Lucie et Raymond Aubrac, 63003 Clermont-Ferrand, France. Tel.: +33 4 73 750 523; fax: +33 4 73 750 524.
*E-mail address:* a_buisson@hotmail.fr (A. Buisson).

http://dx.doi.org/10.1016/j.dld.2016.02.023
1590-8658/

the cause or the consequence of inflammation. However, it has been suggested that these histologic modifications may precede mucosal inflammation [12].

In the last decade, the presence of submucosal or myenteric plexitis in the proximal resection margin of ileocolonic CD resection specimen has been proposed as risk factor of endoscopic, clinical and surgical endoscopic POR in CD [13–16]. However, the definition of plexitis was not consensual and widely varies across the different studies published so far [12,17].

In the present study we aimed to assess the value of submucosal and myenteric plexitis in predicting endoscopic, clinical and surgical POR in CD.

## 2. Patient and methods

### 2.1. Ethical considerations

The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice and applicable regulatory requirements. The study was approved by local Ethics Committee (IRB #00008526–2014/CE86).

### 2.2. Patients

We performed a retrospective study of a single-centre cohort, in which standardized evaluation was performed by experienced clinicians, in all patients. From the electronic database of the Pathology Department of the University Hospital Estaing of Clermont-Ferrand, France, we identified 205 patients who underwent an intestinal resection for CD between 1986 and 2015 in our institution. The diagnosis of CD was based on clinical, radiological/endoscopic examination, and histological findings. Inclusion criteria were patients with confirmed diagnosis of CD with ileocolonic or ileocecal resection and ileocolonic anastomosis. Exclusion criteria were diagnosis of ulcerative colitis or unclassified colitis, definitive ileostomy, abdomino-perineal amputation, colocolonic anastomosis, ileo-ileal anastomosis, absence of labelled proximal margin, absence of macroscopic free resection margin and unavailable postoperative follow-up (Fig. 1). For each patient, the following data were extracted from medical charts: demographic information, CD clinical setting (age at diagnosis, age at the time of inclusion, disease duration, Montreal classification [18], prior intestinal resection and smoking status, etc.). Data regarding the surgery were also recorded: treatment before surgery and at the time of surgery, type of anastomosis, anastomosis location, anastomosis technique, perioperative complications and postoperative prophylactic or curative treatment.

### 2.3. Definition of recurrence

Surgical recurrence was defined as symptomatic recurrence warranting re-operation for CD. Clinical POR was defined, according to De Cruz et al. [19], as recurrence of CD symptoms leading to hospitalization or therapeutic modifications. Endoscopic POR was defined as Rutgeerts' score ≥i2 [9]. Regarding endoscopies performed before the widespread of Rutgeerts' score use or with no score specified on the colonoscopy report, the score was evaluated retrospectively based on the content of the colonoscopy report. The endoscopies were performed at the physician's discretion to assess potential subclinical disease.

### 2.4. Histological examination

The surgical specimens were conserved in either formol or AFA (alcohol–formol–acetic acid). For each patient, the histological specimens were prepared using haematoxylin–eosin–saffran

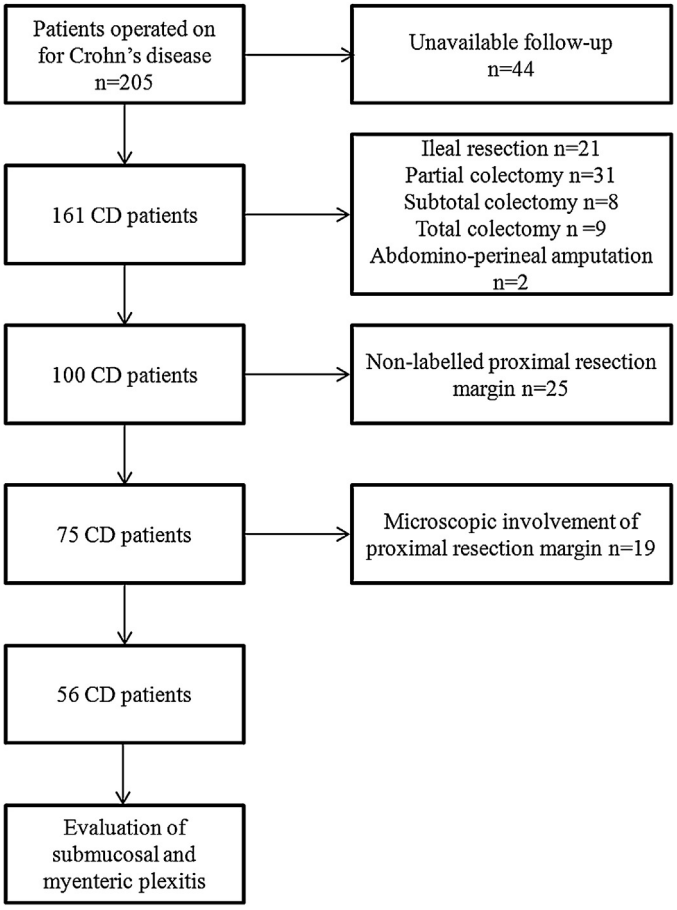


**Fig. 1.** Study flow chart explaining the CD patients' selection.

(HES) staining to analyse the proximal margin and to evaluate the presence of neutrophils, eosinophils and plasma cells. Additional immunostainings were performed for lymphocytes labelled in plexus by CD3 antibody, for mast cells labelled by MCT and for macrophages labelled by CD163 antibody. Two pathologists (SD, JJ) retrospectively reviewed all specimens to evaluate the presence or absence of plexitis at the proximal resection margin in selecting the most inflammatory plexus according to pathologist's judgement. Evaluation was made independently for each cellular type and blinded for clinical data. Plexitis was defined as presence of inflammatory cells (neutrophils, lymphocytes, plasma cells, macrophages, eosinophils, mast cells) within or in contact with ganglion cells or nerve bundles [13–17] (Fig. 2A and B). The grading of severity was undertaken in the most severe areas where Grade 1 was defined as <4 cells/high power field (HPF), Grade 2 as 4–9 cells/HPF and Grade 3 as >10 cells/HPF [13]. Presence of granuloma at the proximal margin was also investigated. Presence of granuloma within the surgical specimen was retrieved from Pathology Department reports. Microscopic proximal margin involvement was defined as histologic features of CD on the proximal margin (inflammatory cells, abscess, fissure, granuloma, etc.). Interobserver disagreement was solved by joint revision of the case with a multiheaded microscope.

### 2.5. Data management and statistical analysis

Study data were collected and managed using REDCap electronic data capture tools hosted at Clermont-Ferrand University Hospital [20]. REDCap (Research Electronic Data Capture) is a secure,