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Alimentary Tract

Mucosal inflammation in the terminal ileum of ulcerative colitis patients: Endoscopic findings and cytokine profiles

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Abstract

Background. Currently, published reports of mucosal inflammation in the terminal ileum of ulcerative colitis (UC) before colectomy are scarce.

Aim. To investigate inflammation in the terminal ileum of UC patients by endoscopic examinations and measurement of mucosal cytokine profiles.

Methods. Fifty consecutive patients with active UC were studied. At ileocolonoscopy, mucosal biopsies were taken from the terminal ileum. As control, mucosal biopsies from 20 patients without inflammation were examined.

Results. Thirty-eight patients showed endoscopically normal terminal ileum, four showed backwash ileitis, and eight showed non-backwash ileitis (ileitis with normal caecum). Pancolitis was observed in all of four patients with backwash ileitis, in 4 of 8 (50%) with non-backwash ileitis, and in 4 of 38 (11%) without ileal inflammation ($P = 0.0002$). Extraintestinal manifestations were observed in none of 4 patients with backwash ileitis, in 6 of 8 (75%) with non-backwash ileitis, and in 3 of 38 (8%) without ileal inflammation ($P < 0.0001$). In patients with backwash ileitis and non-backwash ileitis, ileal interleukin [IL]-1β, IL-6, IL-8 and tumour necrosis factor-α levels were significantly elevated compared with the control group. Only extraintestinal manifestation was associated with higher ileal cytokine levels, whereas age, sex, and duration, extent and severity of UC did not show any apparent association.

Conclusions. In patients with backwash ileitis, elevated ileal cytokines might reflect a reaction to regurgitation of colonic content into the ileum, but in patients without backwash ileitis, alternative factors are expected to contribute to the aetiology of ileal inflammation. Patients with extraintestinal manifestations had elevated ileal cytokine levels.

Keywords: Backwash ileitis; Cytokine; Extraintestinal manifestations; Immunological reactions; Mucosal inflammation; Terminal ileum; Ulcerative colitis

1. Introduction

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD) primarily affecting the large bowel; the extent and severity of colonic involvement are variable. In its most limited form it may be restricted to the distal rectum, while in its most extended form the entire colon is involved [1,2]. Further, in 10–20% of patients with total colitis, the terminal ileum is also affected as a continuation of colonic involvement (backwash ileitis) [3–6]. Backwash ileitis may progress up to 15 cm along with the terminal ileum, and is indistinguishable from colonic lesions.

Restorative proctocolectomy with ileal pouch-anal anastomosis has become the surgical procedure of choice for patients with UC [7,8]. After restorative proctocolectomy, inflammation in the ileal pouch (pouchitis) is the most common complication, and clinical presentations and immunological profiles in patients with pouchitis have been investigated in many studies [9–12]. However, little is known about mucosal inflammation in the terminal ileum before proctocolectomy because in clinical practice, endoscopic and

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radiological assessment of the terminal ileum is not routinely performed in patients with UC.

Cytokines are low molecular weigh regulatory proteins produced by most cells in response to injury, infection or antigen challenge. Gut epithelial cells, together with intramucosal inflammatory cells are capable of secreting a large range of cytokines like interleukin (IL)-1β, IL-6 IL-8 and tumour necrosis factor (TNF)-α, which are known as major pro-inflammatory cytokines in the intestinal tissue of patients with IBD [13–15]. Accordingly, several recent research [16–21] found that cytokine measurement can detect an ongoing escalating subtle inflammation in the mucosa of patients with IBD. Such information should help to design effective medical interventions for patients with IBD.

A number of studies have examined immunological profiles in the ileal pouch after restorative proctocolectomy for UC [22–25]. However, there is no published report on cytokine profiles in the terminal ileum before colectomy in patients with UC. Investigating dysregulated immune activities in the terminal ileum preoperatively might contribute to better understanding of the immunopathogenesis of ileal pouch inflammation after surgery. This prospective study was designed to examine immunological reactions in the terminal ileum by measurement of mucosal cytokine profiles and to investigate inflammation in the terminal ileum of UC patients by endoscopic examinations and measurement of mucosal cytokine profiles. Factors affecting mucosal inflammation in the terminal ileum were also investigated.

2. Patients and methods

2.1. Patients

This prospective study was conducted in accordance with good clinical practice and the Declaration of Helsinki. Inclusion criteria were: (i) patients who were between 18 and 70 years of age; (ii) patients with endoscopic and histological diagnosis of UC; (iii) patients with colonic involvement; (iv) patients who had a disease activity index (DAI) score [26] $\geq$3; and (v) patients who agreed to have ileocolonoscopy. Exclusion criteria were: (i) patients who had an urgent need for surgery; and (ii) patients who were treated with (oral or rectal) corticosteroids or immunosuppressive drugs for current episodes. These drugs may affect cytokine production. Patients treated with (oral or rectal) sulfasalazine or mesalamine as a maintenance treatment were not excluded. Fifty consecutive patients were investigated after giving informed consent. Patients' demographic characteristics and disease history are shown in Table 1.

Table 1
Demographic characteristics and disease history

Age (mean ± S.E.) (years)	37 ± 3
Male:female	31:19
Duration of UC before entry (mean ± S.E.) (months)	32 ± 5
Medication for previous episodes (*n*)	
Corticosteroids	32
Sulfasalazine or mesalamine	43
Immunosuppressive drugs	3
Disease severity (*n*)	
Mild (3 ≤ DAI ≤ 6)	18
Moderate (7 ≤ DAI ≤ 10)	22
Severe (11 ≤ DAI)	10
Extraintestinal manifestations (*n*)	
Peripheral arthritis	5
Pyoderma gangrenosum	4

DAI: disease activity index [26].

2.2. Endoscopic assessments

Ileocolonoscopy was performed for all patients to determine the severity of mucosal inflammation and to take mucosal biopsy. The endoscopic severity of mucosal inflammation was graded (normal/mild/moderate/severe) according to the endoscopic criteria in the DAI [26]. Biopsies were taken from the terminal ileum (within 20 cm from the ileocaecal valve) and the site most severely affected in the large bowel in each patient. From each biopsy site, two specimens were taken for histological examinations, and three or four additional samples were taken from a contiguous area for cytokine measurements. The mucosal specimens for cytokine measurements were stored as previously reported [16–18]. As a control group, normal mucosal samples from the terminal ileum and large bowel were obtained from 20 patients (12 men and 8 women; mean age, 49 years) who underwent endoscopy for colonic polyps.

2.3. Measurement of cytokines

Mucosal concentrations of IL-1β, IL-6, IL-8 and TNF-α were measured by using enzyme-linked immunosorbent assay kits as previously reported [16–18]. The detection level was 2.0 pg/ml for IL-1β, IL-6 and TNF-α, and 10 pg/ml for IL-8. Results of cytokine levels in the mucosa were expressed according to the weight of the corresponding mucosal specimen (pg/mg of tissue). Laboratory investigators were blinded to the clinical data.

2.4. Statistical analysis

Comparisons of frequencies between the groups were analyzed using the Chi-square test with Yates' correction. Mean values between two groups were compared using the unpaired Student's *t*-test. For comparisons involving more than two groups, a one-way analysis of variance (ANOVA) was initially used. If a significant level was obtained ($P < 0.05$), multiple comparison post hoc tests (Bonferroni test) were done. Correlations were calculated using Spearman's *r* test. $P < 0.05$ was considered significant.