

## Clinical significance of granuloma in Crohn's disease

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### Abstract

**AIM:** Granuloma is considered the hallmark of microscopic diagnosis in Crohn's disease (CD), but granulomas can be detected in only 21-60% of CD patients. The aim of this study was to evaluate the frequency of granulomas by multiple endoscopic biopsies in patients with CD and to examine whether group of patients with or without granuloma exhibit a different clinical course.

**METHODS:** Fifty-six patients with newly diagnosed CD were included in the study. Jejunoscopy, enterodysis and ileo-colonoscopy were performed in all patients. At least two biopsy specimens from each examined gastrointestinal segment were examined microscopically searching granuloma. The clinical course was followed in all patients, and extraintestinal manifestations as well as details of any immunosuppressive therapy and surgical intervention were noted.

**RESULTS:** Granuloma was found in 44.6% of the cases (25 patients). Patients with granuloma had higher activity parameters at the time of the biopsies. Extraintestinal manifestations were observed and surgical interventions were performed more often in the granuloma group. The need of immunosuppressive therapy was significantly more frequent in the patients with granuloma. Granuloma formation is more often seen in younger patients, and mainly in the severe, active penetrating disease.

**CONCLUSION:** The significantly higher frequency of surgical interventions and immunosuppressive therapy suggests that granuloma formation is associated with a more severe disease course during the first years of CD.

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### INTRODUCTION

Crohn's disease (CD) is a chronic transmural inflammatory bowel disease of unknown etiology. Granuloma is considered the hallmark of microscopic diagnosis in CD, but granulomas can be detected in only 40-60% of surgically resected bowel segments in CD patients<sup>[1]</sup>. The frequency of granuloma in bioptic samples varies in 15-36% according to different authors<sup>[2]</sup>. The severity of the disease shows a great variability as well. Several factors (e.g., localization of the disease, maximum extent of involvement, the behavior type: inflammatory, stricturing or penetrating) make influence on the clinical course of the disease. There are inconsistent data in the literature about the prognostic significance of the granuloma in CD. Our aim was to divide our newly diagnosed CD patients into two subgroups on the basis of the presence or absence of granuloma at the time of diagnosis. We have been accomplishing follow-up studies for at least 3 years in order to get information about these two different groups (patients with or without granuloma), whether they show any difference in the clinical course.

### MATERIALS AND METHODS

#### Patients

Fifty-six patients with newly diagnosed CD were included in this prospective study during the period from January 1997 to September 2000. Their CD was diagnosed on the basis of the standard clinical, radiological, endoscopic and histologic criteria. The female/male ratio was 31/25, the median age of the patients was 36.29 years (ranging: 18-65 years). Positive family history was observed only in one new case; this female patient with granuloma had a brother with diagnosed CD. The localization of CD was as follows: in 33 patients (59%) both small and large bowels were involved (among them in 6 patients upper gastrointestinal tract (UGT) involvement-esophageal/gastric/duodenal was also observed), in 18 patients (32%) the large bowel only, in 5 (9%) the terminal ileum alone was inflamed. The ethical committee of our department approved the study. Informed oral consent was obtained from the patients.

#### ***Diagnostic methods to determine the frequency of granuloma and the activity of CD at the beginning of the study***

**Clinical parameters** Blood samples were taken from all patients on each visit to determine the hemoglobin and

hematocrit, as well as the C reactive protein (CRP) values. The Crohn's disease activity index (CDAI) (Best)<sup>[3]</sup> was calculated to measure the clinical disease activity.

**Localization of CD, endoscopic activity index** To determine the severity of CD and the extent of the involved bowel segments, physical examination, abdominal ultrasound, jejunoscopy, small bowel enteroclysis, ileo-colonoscopy were performed in all patients at the time of the first admission, when the study started. Four large bowel segments (the caecum and ascending colon, the transverse colon, the descending colon, and the sigmoid colon and rectum) and the ileum were examined by colonoscopy and scored according to the findings. The proximal small bowel segment alterations (jejunum together with the duodenum) were detected by jejunoscopy. Each segment were scored by using the protocol of Mary and Modigliani with some modification (0 = normal mucosa, 1 = edema, erythema, granularity of the mucosa, and aphthous lesions, 2 = sporadic or superficial ulcerations, and 3 = extensive deep ulcerations, and stenosis). This way these diagnostic methods could produce quantifiable data about the severity of the inflammation in each part of the gastrointestinal tract<sup>[4]</sup>. At least two biopsy specimens from each examined gastrointestinal segment (esophagus, body and antral region of the stomach, bulb, distal part of duodenum, jejunum, ileum, ascending colon, transverse colon, descending colon, sigmoid colon and rectum) were examined microscopically searching granuloma by one pathologist using the standard methods.

**Follow up** Two gastroenterologists (T.M. and F.N.) followed all the patients. They were unaware of the presence of granuloma during the study.

### Disease behavior

According to the behavior of the inflammation (Vienna Classification)<sup>[5]</sup> patients were divided into three subgroups at the end of the study. Twenty-three patients were in the inflammatory (non-stricturing, non-penetrating) type, 15 patients in the stricturing and 18 patients in the penetrating-fistulizing type of CD.

### Severity of CD

Scheduling of follow-up visits depended on the actual severity of CD. The completely symptoms-free patients

were supervised by every 3 mo, and naturally, patients with active disease were observed more frequently. The following parameters were recorded during the follow-up period to determine the severity of CD: frequency of relapses (definition of relapse: CDAI above 150), frequency of extraintestinal manifestations (arthritis, sacroileitis, pyoderma gangrenosum, erythema nodosum, cutaneous vasculitis, episcleritis, uveitis, aphthous stomatitis), fistulas, need of immunosuppressive therapy, number of surgical intervention, as well as total number of hospitalization.

### Statistical analysis

Data are expressed as mean±SD. Correlation coefficients were calculated by using *t*- and  $\chi^2$ -tests.

## RESULTS

Granuloma was found in at least one tissue sample in 44.6% of the cases (25 patients). The average years of age of the patients in group I (patients with granuloma) and group II (patients without granuloma) was 29.6 and 36.4 years, respectively. The proportion of the female patients was moderately higher in the group with granuloma (60 *vs* 51.3%). Similar smoking status was observed in the two groups: 60 and 61.2% of the patients were smoker in group I and II, respectively. Involvement of the upper GI tract was about 2.5 times more frequent (16.0 *vs* 6.4%, *P*<0.05) in the granuloma group. Penetrating disease behavior was slightly more often associated with granuloma (44% *vs* 23%). The clinical characteristics of the two groups of patients are summarized in Table 1. Patients with granuloma had higher activity parameters at the time of the biopsies (CDAI: 218.9±108.2 *vs* 144.1±92.5, *P* = 0.01; CRP level: 62.7±84.9 *vs* 48.5±87.8). The overall endoscopic scores tended to be higher in group I than those in group II, but it did not reach the level of significance. The average follow-up times were similar in the two groups: 38.5±7.34 and 36.8±3.83 mo. The appearance of the extraintestinal manifestations was observed more often in the granuloma group, but there was no significant difference between the two groups. Arthritis occurred most frequently in both groups, sacroileitis and seronegative peripheral arthritis were the two most common disorders. Aphthous stomatitis was associated with

**Table 1** Clinical characteristics of patients (mean±SD)

	Patients with granuloma Group I	Patients without granuloma Group II	Significance
Number of patients	25	31	NS
Female/male ratio (No.)	15/10	16/15	NS
Median age (yr)	29.60±11.32	36.46±12.94	NS
Localization			
Small bowel only	1 (4%)	4 (12.9%)	NS
Large bowel only	10 (40%)	8 (25.8%)	NS
Small and large bowel	10 (40%)	17 (54.8%)	NS
UGT involvement	4 (16%)	2 (6.4%)	<i>P</i> <0.05
Disease behavior type			
Inflammatory	8 (32%)	15 (48.4%)	NS
Stricturing	6 (24%)	9 (29.0%)	NS
Penetrating	11 (44%)	7 (22.6%)	NS
Activity of CD			
CDAI	218.9±108.2	144.1±92.5	<i>P</i> = 0.01
Endoscopic scores	6.60±3.53	5.35±4.20	NS

UGT = upper gastrointestinal tract.

**Table 2** Frequency of different extraintestinal manifestations in patients with or without granuloma

	Patients with granuloma (%)	Patients without granuloma (%)	Significance
Number of extraintestinal manifestations	10/25 (40)	7/31 (22.6)	$P = \text{NS}$
Arthritis	6/25 (24)	4/31 (12.9)	$P = \text{NS}$
Eye manifestation	0/25	1/31 (3.2)	$P = \text{NS}$
Cutan manifestation	2/25 (8)	0/31	$P = \text{NS}$
Aphthous stomatitis	2/25 (8)	2/31 (6.4)	$P = \text{NS}$

NS = non-significant.

**Table 3** Frequency of relapses in the two groups

Number of relapse after the succesful treatment of fist attack	Patients with granuloma (25) (%)	Patients without granuloma (31) (%)
0	5 (20)	12 (38.7)
1	10 (40)	15 (48.4)
2	7 (28)	4 (12.9)
3	3 (12)	0 (0)

Trend - $P = 0.06$ ,  $\chi^2$  test.

CD in about 7% of all patients. Noticeably every aphthous stomatitis started simultaneously with the first symptoms of the CD. Iridocyclitis, cutaneous vasculitis and metastatic CD were the other extraintestinal manifestations (Table 2). There was a strong trend towards significantly increased frequency of relapses in the granuloma positive group ( $P = 0.06$ ,  $\chi^2$  test) (Table 3). The number of hospitalization was significantly higher in granuloma group (20 *vs* 12,  $P < 0.05$ ). Surgical interventions were performed more often in the granuloma group (48% *vs* 22.5%,  $P < 0.05$ ). Stenosis, abscess, fistula and perforation were the indications for surgery. The use of immunosuppressive drugs was significantly more frequent in the patients with granuloma (60% *vs* 32.2%,  $P < 0.05$ ). The most frequent indication of immunosuppressive therapy was the prevention of postoperative relapse in both groups (10/15 in group I, 7/10 in group II); steroid dependency was the other cause (5 *vs* 3 in group I *vs* II). As the follow-up periods after the start of the immunosuppression were mainly short and different between the cases and groups, the response rate to immunosuppressive therapy was incomparable between the groups.

## DISCUSSION

The granuloma formation is a host response reaction by the localized accumulation of epitheloid cells, macrophages and lymphocytes. Granulomas can be found in many infectious, allergic and neoplastic disorders<sup>[6]</sup>. Although the first description of granuloma in CD was in 1913 by Dalziel<sup>[7]</sup>, the exact role and significance of this "specific" histologic lesion remain a puzzle. It is a plausible idea that the granuloma is the site where the etiological agent resides, the antigen specification occurs and the T cells differentiation into Th1 cells starts<sup>[8]</sup>, but there is no evidence to confirm this theory. The pathological host response is one of the important basic concepts in the development of CD besides the genetic predisposition and the environmental factors. The different individual host response may explain the presence or absence of granuloma.

The first publication which tried to examine whether the presence of granuloma is associated with good or poor

prognosis was printed more than forty years ago<sup>[9]</sup>. A few studies have been published since then which examine the prognostic role of the granuloma, although, their results are controversial. The most studied topic was the postsurgical recurrence of CD. Anselme *et al* examined several factors that might predict recurrence after the operation in 130 patients over a 24-year period. A highly significant positive association was revealed between the presence of the granuloma and the likelihood of recurrence ( $P = 0.003$ ) on the basis of the multivariate regression analysis<sup>[10]</sup>. A similar tendency was published by Trnka *et al*<sup>[11]</sup>; they found that there was an increasing chance for the recurrence in a subgroup of patients with ileocolonic disease. On the other hand, some studies suggest just the opposite<sup>[12-14]</sup>. These publications suggest that patients with granuloma have less frequent postoperative recurrence and/or have a better prognosis. These studies were the pioneers in this topic, therefore the selection of patients, the diagnostic and the statistical methods might have been less accurate than the ones in the latest publication. There has been only some studies so far where the presence of granuloma was determined by endoscopic biopsies<sup>[15]</sup>. Markowitz *et al*, examined a pediatric population, and rectosigmoid biopsies were taken from 58 subjects. All biopsies had been obtained from newly diagnosed patients before any therapies were started and the children were followed for at least one year. The frequency of granuloma was 32.7%. More severe perianal complications, a higher frequency of surgery and more extensive inflammatory involvement were observed in patients with granuloma. The medical treatment and the need of hospitalization were similar in both groups. Ramzan *et al*<sup>[16]</sup>, published a paper recently in the Inflammatory Bowel Diseases, in which they performed a study with a similar goal like us. Although the granuloma was sought not only in bioptic samples but also in resected bowel, they found a surprisingly low prevalence (25.6% *vs* our 44.6%), but we do not know how many biopsies were taken from how many and which gastrointestinal segment. The other weak point of this study is the retrospective way of the analysis. Although the crucial point of the study is the frequency of relapse, the authors did not give a definition of the relapse, and it is not very

easy to calculate the number of relapses retrospectively. We have found a higher frequency of granuloma in the biopsies of our patients than Markowitz and Ramzan, however, we took biopsies from more (even intact) segments of the entire gastrointestinal tract. We have examined newly diagnosed patients, and we have also found a more severe clinical course like Markowitz in the first two years of the disease in patients having granuloma in any part of the gastrointestinal tract. As the smoking status of the groups was similar, this environmental factor did not influence our result. Considering that these were the first symptoms and the first examinations of the patients, we can conclude that the onset of CD was also more severe in the granuloma group. Our results, naturally, with small number of cases are not capable to solve the controversy about the prognostic significance of epithelioid granuloma in CD, but suggest that being aware of the fact whether the patient has or has not granuloma is a useful prognostic marker. We propose that all endoscopically available parts of the gastrointestinal tract should be examined histologically as well at the time of the first examination of the patient to search granuloma. The presence of granuloma may suggest a more aggressive form of inflammatory bowel disease and this fact has to influence the management of patients.

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