Frequency of epithelioid granulomas in colonoscopic biopsy specimens from paediatric and adult patients with Crohn's colitis

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Aims: To test the assumption that epithelioid granulomas found in colonoscopic biopsy specimens in patients with Crohn's colitis are markers of a different clinical behaviour.

Methods: Sections from colonoscopic biopsy specimens from 352 consecutive patients (119 children and 233 adults) were investigated.

Results: A total of 1117 colonoscopies were performed: 293 in children (mean 2.46 per patient) and 824 in adults (mean 3.53 per patient) ($p < 0.05$). Granulomas at initial colonoscopy were recorded in 67.2% (43/64) of children and 65.9% (27/41) of adults ($p > 0.6$), and at subsequent colonoscopies in 53.8% (64/119) of children and 17.6% (41/233) of adults ($p < 0.05$). Surgical intervention was required in 6.3% (4/64) of the children having previous granuloma, but also in 14.5% (8/55) of those without previous granuloma, the rate for operated adults being 26.8% (11/41) and 24.5% (47/192), respectively ($p > 0.6$).

Conclusions: Granulomas in entry and/or in subsequent colonoscopic biopsy specimens in patients with Crohn's colitis did not predict the need for subsequent surgical intervention. The fact that the frequency of granulomas was significantly higher in children than in adults with Crohn's colitis (despite a higher mean number of colonoscopic biopsies in adults), and that granulomas were present in colonoscopic biopsy specimens but not in the subsequent surgical specimens from 50% of the paediatric and 36% of the adult patients strengthen the conviction that granulomas in Crohn's colitis might evolve or regress at different time intervals during the course of the disease. This behaviour would reflect a particular immunological reaction, an epiphenomenon from immature tissues—as in children—when challenged by the so far elusive aetiological agent responsible for Crohn's disease.

In 1923 Wilensky and Moschowitz¹ (the latter a pathologist) from Mount Sinai Hospital in New York, described four cases of a new pathological entity characterised by chronic inflammation and non-specific granulomas of the intestine. That condition was called "non-specific granulomas of the intestine".¹ Years later, other investigators from the same hospital^{2–4} presented additional cases and called the condition "granulomatous disease of the bowel"² and "regional ileitis".⁴ That novel illness, known today as Crohn's disease (CD), was until 1932 believed to affect exclusively the small intestine.^{5–6} In a letter, Kirsner⁷ indicates that the first clear reference to what is known as "Crohn's colitis" was given by Ginzburg and Oppenheimer in a paper entitled 'Non-specific granulomata of the intestine' published in the *Annals of Surgery*, December 1933.⁸ In Europe, Morson,⁹ from St Mark's Hospital in London, studied the histopathological differential diagnosis between Crohn's colitis and ulcerative colitis in detail.

Because granulomas are found in only some patients with CD, the possibility that these structures could be markers of a different clinical behaviour was investigated. Based on that assumption it was speculated that if granulomas heralded the biological behaviour in Crohn's colitis, it would be important to determine this at initial biopsies in order to plan future therapeutic strategies in individual patients. Unfortunately, there are few reports in the literature regarding the frequency of granulomas in Crohn's colitis at baseline (initial) colonoscopies. Molnar *et al*¹⁰ found granulomas in 10/18 adults (55.6%), and Schmitz-Moormann *et al*¹¹ postulated that "repetitions of the endoscopy raised the frequency of finding a granuloma from 23% for one endoscopy to 48% for 4 endoscopies". As the series of Schmitz-Moormann *et al* also included rectoscopic

biopsies, it is unclear how many "endoscopies" were colonoscopies and how many only rectoscopies.

The purpose of the present work was to explore the frequency of epithelioid cell granulomas at initial and/or at subsequent colonoscopic biopsies from a cohort of paediatric and adult patients with CD, attending this hospital for medical treatment. Surgery was undertaken in patients with an unsuccessful response to medical treatment, or in those with a more aggressive disease having complications requiring surgical intervention. The possibility that epithelioid cell granulomas at initial and/or at subsequent colonoscopic biopsies could

Table 1 Paediatric patients with Crohn's disease (n = 119) with and without granulomas at colonoscopy

No. colonoscopies	No. patients with granulomas	No. patients with granulomas at 1st colonoscopy	No. of patients without granulomas
1	7	7	17
2	28	17	19
3	19	14	11
4	5	3	4
5	4	2	4
6	—	—	—
7	—	—	—
8	—	—	—
9	1	—	—
Total	64	43	55

Abbreviations: CD, Crohn's disease

predict which cases would require surgical treatment at follow-up was explored.

MATERIALS AND METHODS

A total of 352 consecutive patients with CD having colonic or colorectal localisation (Crohn's colitis) were studied; 119 were children (≤ 16 years of age) and 233 were adults. All endoscopic biopsy specimens obtained from the colon at nine different levels (caecum, right colon, right flexure, transverse colon, left flexure, proximal left colon, distal left colon, proximal sigmoid colon, distal sigmoid colon) and from the rectum were investigated. From each biopsy specimen, six H&E sections were done.

Since 1989, all pathological reports at the Department of Pathology have been transferred to a database. The reports concerning baseline (initial) and subsequent colonoscopic biopsies in patients with Crohn's colitis were retrieved and reviewed. It was apparent that only specialised gastrointestinal pathologists had signed all reports. In all microscopic descriptions, the presence or absence of a granuloma (in the mucosa or in the superficial submucosa) was stated. Nevertheless, one set of colonoscopic biopsy specimens from 60 consecutive paediatric and 40 consecutive adult patients was retrieved from the files of the Department of Pathology and reviewed by one of us (CAR), blinded to the original pathological report. In reviewing the sections, particular attention was paid to the presence of epithelioid granulomas in addition to acute and/or chronic inflammation, and distribution of that inflammation (focal or diffuse).

An epithelioid cell granuloma has been defined as a focal area of granulomatous inflammation,¹² consisting of a microscopic aggregation of macrophages that are transformed into epithelial-like cells. In H&E stained preparations the epithelioid cells have a pale, pink granular cytoplasm with indistinct cell boundaries, often appearing to merge into one another. The relatively pale nucleolus is vesicular, oval or elongated, and may show folding of the nuclear membrane. Occasionally, the epithelioid cells fuse to form multinucleated giant cells. Epithelioid cell granulomas can be surrounded by a collar of lymphocytes occasionally admixed with plasma cells.

The presence of granulomas was investigated: (a) in baseline (entry) colonoscopic biopsies; (b) in subsequent colonoscopic examinations; and (c) in sections from surgical specimens.

The study was approved by the ethics committee at Karolinska Institutet, Karolinska Hospital, D-nr 01-444.

For statistical analysis, the Fischer exact test was used to assess differences between groups. A value of $p < 0.05$ was considered to be significant.

RESULTS

The results show that granulomas were found in 53.8% (64/119) of the colonoscopic biopsies performed in paediatric patients and in 17.6% (41/233) of those done in adult patients with Crohn's colitis. The difference was significant ($p < 0.05$).

Gender

Of the 64 paediatric patients with granulomas, 43 (67.2%) were boys and 21 were girls. Boys accounted for 69.1% (38/55) of the paediatric patients without granulomas; the remaining 17 were girls.

Of the 41 adult patients with granulomas, 22 (53.7%) were male and 19 were female. Men accounted for 56.8% (109/192) of the adults without granulomas; the remaining 84 were female.

Although there were more paediatric male patients than adult male patients, the difference was non-significant ($p > 0.6$). No significant differences in gender were found

between paediatric and adult patients having granulomas at colonoscopies.

Age

The age at first appearance of granulomas was investigated. Of the 64 paediatric patients with granulomas, 17 (26.6%) were between 2 and 9 years of age and the remaining 47 (73.4%) between 10 and 16 years of age. Thus, a lower number of younger (2–9 years) paediatric patients had granulomas at colonoscopies than older (10–16 years) paediatric patients ($p < 0.05$).

Of the 41 adult patients with granulomas at colonoscopy, 21 patients (51.0%) were ≤ 39 years of age and 20 (49.0%) were ≥ 40 years of age. Of the 192 adult patients without granulomas at colonoscopy, 113 (58.9%) were ≤ 39 years of age and 79 (41.1%) were ≥ 40 years of age. The difference between the two groups was not significant ($p > 0.6$).

Colonoscopic biopsies in patients with Crohn's colitis

The blind review of unselected colonoscopic biopsy specimens from 60 consecutive paediatric and 40 consecutive adult patients showed no discrepancies with the original report as regards presence or absence of granulomas. Consequently, the data appearing in the original pathology report were considered to be reliable.

A total of 1117 colonoscopies were performed in the 352 patients with CD in this study: 293 in the 119 paediatric patients (2.46 colonoscopies/paediatric patient), and 824 in the 233 adult patients (3.53 colonoscopies/adult patient). The difference between the mean number of colonoscopies performed in adults and children with CD was significant ($p < 0.05$).

- *Paediatric patients with granulomas at colonoscopy.* Of the 119 paediatric patients with CD (table 1), 64 (53.8%) had granulomas. These structures were present at the initial (baseline) colonoscopic biopsy in 67.2% ($n = 43$) of the 64 paediatric patients with granulomas. The total number of colonoscopies performed in the 64 paediatric patients in this subgroup was 158 (mean 2.47 colonoscopies/paediatric patient).
- *Paediatric patients without granulomas at colonoscopy.* Of the 119 paediatric patients with CD (table 1), 55 (46.2%) had no granulomas in colonoscopic biopsy specimens. The total number of colonoscopies performed in the 55 paediatric patients in this subgroup was 135 (mean 2.45 colonoscopies/paediatric patient).
- *Adults patients with granulomas at colonoscopy.* Of the 233 adult patients with CD (table 2), 41 (17.6%) had granulomas. These structures were present at initial (baseline) colonoscopic biopsy in 65.8% ($n = 27$) of the 41 adult patients with granulomas. The total number of colonoscopies performed in the 41 adult patients in this subgroup was 163 (mean 3.97 colonoscopies/adult patient).
- *Adults patients without granulomas at colonoscopy.* Of the 233 adult patients with CD (table 2), 192 (82.4%) had no granulomas in colonoscopic biopsy specimens. The total number of colonoscopies performed in the 192 adult patients in this subgroup was 661 (mean 3.44 colonoscopies/adult patient).

The difference between the numbers of paediatric and adult patients having granulomas in one or more colonoscopy specimens was significant ($p < 0.05$). On the other hand, the difference between the numbers of paediatric and adult patients with granulomas at initial colonoscopy as well as the

Table 2 Adult patients with Crohn's disease (n = 233) with and without granulomas at colonoscopy

No. of colonoscopies performed/patient	No. patients with granulomas	No. patients with granulomas at 1st colonoscopy	No. patients without granulomas
1	3	3	39
2	12	10	60
3	10	6	28
4	5	3	17
5	5	2	23
6	2	1	4
7	2	2	5
8	1	–	3
9	–	–	1
10	–	–	5
11	–	–	–
12	–	–	2
13	–	–	3
14	–	–	–
15	1	1	2
Total	41	27	192

mean number of colonoscopies of paediatric and adult patients with granulomas, was non-significant ($p > 0.6$).

Patients requiring surgical treatment

- *Paediatric patients with granulomas at colonoscopy requiring surgical treatment.* Of the 64 paediatric patients with CD having granulomas at previous colonoscopy, 6.3% (4 patients) received surgical treatment. Granulomas were present in 50% (2/4) of the specimens.
- *Paediatric patients without granulomas at colonoscopy requiring surgical treatment.* Of the 55 paediatric CD patients without granulomas at colonoscopy, 14.5% (8 patients) received surgical treatment. Granulomas were present in 37.5% (3/8) of the specimens. Of the 8 surgically treated patients, 2 underwent surgery twice (25%). Granulomas were found in one of the surgical specimens but not in the other.
- *Adults patients with granulomas at colonoscopy requiring surgical treatment.* Of the 41 adult patients with granulomas at previous colonoscopy, 26.8% (11 patients) were subsequently surgically treated. Granulomas were also found in 63.6% (7/11) of the surgical specimens.
- *Adults patients without granulomas at colonoscopy requiring surgical treatment.* Of the 192 adult patients without granulomas in previous colonoscopies 24.5% (47 patients) underwent surgery. Granulomas were also present in 29.8% (14/47) of the surgical specimens. Of the 47 surgically treated patients, 5 underwent surgery twice (10.6%). Granulomas were found in one of the surgical specimens but not in the other.

The proportion of surgical specimens with granulomas was higher in paediatric patients having granulomas in previous colonoscopy specimens than in those without granulomas, but the difference was non-significant ($p > 0.6$). In adults, the proportion of surgical specimens with granulomas was significantly higher in patients having granulomas in previous colonoscopy specimens (63.6%) than in those without granulomas in previous colonoscopy specimens (29.8%) ($p < 0.05$).

DISCUSSION

The results of the present investigation showed that the frequency of granulomas in colonoscopic biopsy specimens from patients with Crohn's colitis was significantly higher in

children than in adults. The higher frequency of granulomas in children than in adults with Crohn's colitis (53.8% vs 17.6%) was not due to a higher number of examinations performed in the former group, as the mean number of colonoscopies in children was lower than in adults. These results contrast with those of Heresbach *et al*¹³. These authors found that epithelioid granuloma detection in CD increased with the number of endoscopic sampling procedures. In that work, however, the results obtained were based not only on biopsies from the colon and rectum, but also from various organs in the gastrointestinal tract such as the oesophagus, stomach, duodenum and ileum. We showed that the number of paediatric and adult patients with Crohn's colitis showing granulomas, increased in those having up to three colonoscopic examinations but not for those having ≥ 4 colonoscopies.

Table 3 shows that the frequency of granulomas present in tissue sections varies in different publications, from 7%²⁷ to 100%.¹⁹ One confounding factor for this variation may be that some series include only children,^{23–27} others both children and adolescents,²⁶ others both children and adults,^{13–18, 24, 25, 28, 29} and others only adults.^{10, 19, 20, 30, 31} However, from table 3, it may be deduced that in some series, the frequency of granulomas in CD was higher in adults than in children. Another confounding factor may be differences in the quantity of tissue investigated by the various pathologists: some series include only rectal biopsies,^{20, 21, 27, 28} others recto-sigmoidoscopic biopsies,²⁶ other colonoscopic biopsies,^{10, 12, 13, 23, 28} and others only sections from surgical specimens.^{14–19, 25, 29, 31} The possibility to detect epithelioid cell granulomas at histology should be greater in larger tissue sections from surgical specimens than in tissue sections from tiny biopsies obtained at colonoscopy. However, the absence of granulomas in surgical specimens from children and adults having granulomas in previous colonoscopic biopsies in this work, militates against the notion that the presence of epithelioid cell granulomas is directly related to the quantity of colorectal tissue available for histological examination.

The clinical and prognostic significance of epithelioid cell granulomas in CD is uncertain. For some workers,^{10, 13, 15, 18, 26} granulomas are indicative of severe disease with intestinal and extraintestinal complications, whereas for others,^{22, 30, 31} granulomas are unrelated to the biological behaviour of the disease. Glass and Baker¹⁷ found that the recurrence rate for non-granulomatous disease was double that of granulomatous disease. Markowitz *et al*²⁶ found that granulomas at initial rectosigmoid biopsies were associated with a poor prognosis, with more extensive small bowel and colonic CD involvement, more perianal disease and requiring surgery more often than CD children without granulomas. Ramzan *et al*³⁰ found no differences between patients with granulomas and fistulisation, perianal disease, oral aphthous ulcers, disease severity, arthralgia, episcleritis, uveitis, erythema nodosum, or pyoderma gangrenosum. Wolfson *et al*²² postulated that granulomas found in resected specimens from CD patients have no independent influence on the rate of postoperative recurrences. Heiman *et al*²⁵ noticed that the occurrence of granulomas at initial rectosigmoid biopsy did not protect patients from a more aggressive disease.

In the present work, surgical treatment was undertaken in 26% of the adult patients having granulomas at colonoscopy, and 24.5% of those having no granulomas at colonoscopy. In children, surgery was required in 6.3% of the patients with granulomas at colonoscopic biopsy, and 14.5% of those without granulomas at colonoscopic biopsy. The latter results suggest that the presence of granulomas at colonoscopic biopsy protected some children with CD from future surgical intervention. However, the number of operated paediatric cases was too small to allow a positive statement. Thus, the present work

Table 3 Frequency of epithelioid cell granulomas in the colon and/or rectum in patients with Crohn's disease reported in the literature

Reference	Rectal biopsy	Age	Rectal and colonoscopic biopsy	Age	Colonoscopic biopsy	Age	Surgical specimens	Age
Molnar <i>et al</i> ¹⁰					10/18 (55.6%)	Adults		
Schmitz-Moormann <i>et al</i> ¹¹			34/249 (13.6%)	11–>40				
Heresbach <i>et al</i> ¹³					25/98 (26%)	6–85 y		
Farmer <i>et al</i> ¹⁴							48/87 (55.2%)	≤20 y
From <i>et al</i> ¹⁵							29/62 (46.7%)	3–68 y
Assarsson and Räf ¹⁶							34/147 (23.1%)	0–79 y
Glass and Baker ¹⁷							60/90 (66.7%)	11–79 y
Anselme <i>et al</i> ¹⁸							71/130 (54.6%)	13–77 y
Chambers and Morson ¹⁹							79/79 (100%)	Adults
Suravics <i>et al</i> ²⁰	25/90 (28%)	Adults						
Petri <i>et al</i> ²¹	11/39 (28%)							
Wolfson <i>et al</i> ²²							9/17 (53%)	Not given
Chong ²³					21/58 (36%)	4–14 y		
Chardavoyne <i>et al</i> ²⁴							71/187 (45.2%)	8–78 y
Heimann <i>et al</i> ²⁵							22/44 (50%)	16–57 y
Markowitz <i>et al</i> ²⁶	19/56* (33.9%)	Children/adolescents						
Keller <i>et al</i> ²⁷	37/528 (7.0%)	Children						
Schmitz-Moormann and Schäg ²⁸	42/120 (28.6%)				58/265 (21.9%)	2–24 y		
Morpurgo <i>et al</i> ²⁹							39/92 (42.3%)	8–76 y
Ramzan <i>et al</i> ³⁰							21/82 (25.6%)	Adults
Pierik <i>et al</i> ³¹							111/161 (68.9%)	Adults

*Rectosigmoidoscopy.

provides no evidence that the occurrence of granulomas at colonoscopy will predict which patients will require surgical intervention at follow-up.

We found in patients with granulomas in the colonoscopic series and surgical intervention, that 50% of the children and 64% of the adults also had granulomas in surgical specimens. These results also imply that the remaining 50% of paediatric patients and 36% of adult patients had no granulomas in multiple sections from surgical specimens, despite the presence of granulomas in preceding colonoscopic biopsy specimens. The possibility that granulomas found earlier in tiny colonoscopic biopsy specimens were overlooked by the same pathologist while reading much larger, multiple tissue sections from surgical specimens, appears unlikely.

Rationally, two possibilities might be at stake: (i) that granulomas develop at a particular stage during the course of the disease in susceptible individuals; and (ii) that granulomas are able to regress in some patients.

Why are the results of the frequency and significance of granulomas in CD so different in the various series? To compare the reported series is difficult, not only because of differences in age (an important confounding factor as shown here), but also because many reports date from the time when patients received different therapeutic regimens. In this context, Schmitz-Moormann and Shag²⁸ and Geboes and Dalle³² found that the frequency of epithelioid cell granulomas decreased under the influence of therapy. Modern medication (steroids, azathioprine, infliximab) has diminished the number of complications and the number of patients requiring surgery.³² All these confounding factors, added to the recently reported changing pattern of the disease in paediatric patients³³ may partly explain some of the conflicting results in the literature regarding frequency and significance of epithelioid cell granulomas in CD.

However, it remains enigmatic why granulomas develop in some but not in all patients with CD. In this respect, Hara *et al*³⁴ found that granuloma formation in CD was coupled to antigen presentation via the B7-1/B7-2-CD28 pathway.

Holdstock *et al*³⁵ reported that the number of granulomas in non-HLA B8 patients with CD was significantly higher than in

HLA B8 positive patients. But despite those differences, the clinical manifestations and disease course of the two groups of patients was similar,³⁵ suggesting that neither the presence of HLA B8 nor the development of granuloma directly influenced the course of the disease. Matsumoto *et al*³⁶ postulated that granulomas in CD may play a crucial role as antigen-presenting sites to memory type T cells, which leads to activation and proliferation of T cells. Particular tissue response in susceptible individuals, perhaps associated with the severity of the inflammatory process, might trigger the development of granulomas in CD.

In conclusion, we found no evidence that granulomas recorded in entry and/or in subsequent colonoscopic biopsy specimens in patients with colorectal CD can predict the need for subsequent surgical intervention. The fact that the frequency of granulomas was significantly higher in children

Take-home messages

- The significance of granulomas as markers of a more aggressive clinical behaviour was studied in 1117 colonoscopy specimens.
- Granulomas at colonoscopy were found more frequently in children than in adults ($p < 0.05$).
- Although granulomas were present at colonoscopy, they were not found in the subsequent surgical specimens in 50% of the paediatric patients and 36% of the adult patients.
- Granulomas at colonoscopy did not predict the need for future surgical intervention.
- Granulomas in Crohn's colitis seem to evolve or regress at different time intervals during the course of the disease. This behaviour would reflect a particular immunological reaction, an epiphenomenon from immature tissues—as those in children—when challenged by the so far elusive aetiological agent responsible for Crohn's disease.

than in adults with Crohn's colitis (despite a higher mean number of colonoscopic biopsies in adults) and that granulomas were present in colonoscopic biopsy specimens but not in the subsequent surgical specimens from 50% of the paediatric and 36% of the adult patients, strengthens the conviction that granulomas in Crohn's colitis might evolve or regress at different time intervals during the course of the disease. This behaviour would reflect a particular immunological reaction, an epiphenomenon from immature tissues—as those in children—when challenged by the so far elusive aetiological agent responsible for Crohn's disease.

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