

# Importance of cryptolytic lesions and pericryptal granulomas in inflammatory bowel disease

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## Abstract

**Aims**—To explore the diagnostic importance of pericryptal granulomas associated with epithelial lysis in colorectal biopsy specimens (cryptolytic colitis).

**Methods**—A series of patients with suspected inflammatory bowel disease and colorectal biopsy specimens showing either isolated pericryptal granulomas (14 cases) or non-granulomatous pericryptal inflammation (eight cases) were followed. A diagnosis of Crohn's disease was established if subsequent biopsy specimens or intestinal resections showed unequivocal non-crypt related granulomas, or if there was evidence of significant small bowel disease.

**Results**—Of the 14 patients with pericryptal granulomas and biopsy specimens, 10 were subsequently found to have Crohn's disease; of the eight patients with pericryptal inflammation only, one developed Crohn's disease. The former group also had a much higher instance of morbidity and required surgical intervention more often.

**Conclusions**—The presence of cryptolytic granulomas in a colorectal biopsy specimen otherwise showing only non-specific inflammatory changes should always raise suspicion of Crohn's disease, especially if surgery or ileo-anal pouch formation is contemplated.

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The diagnosis of inflammatory bowel disease (IBD), and the distinction between Crohn's disease and ulcerative colitis relies heavily upon the histopathological assessment of colorectal biopsy specimens, to which immunocytochemistry and molecular techniques have yet to make a significant impact. In the great majority of cases, a biopsy specimen of this kind consists mainly of mucosa and lamina muscularis mucosae, and seldom includes more than a thin rim of superficial submucosa. Assessment has thus to be based on mucosal alterations which are often non-specific.

In patients with colitis undergoing total colectomy, it is of great importance to distinguish between Crohn's disease and ulcerative colitis preoperatively so that the appropriate surgical procedure may be planned. For example, in patients with Crohn's colitis, the opera-

tion of choice is a proctocolectomy and ileostomy, or an ileorectal anastomosis if the rectum is spared. However, in those patients with ulcerative colitis, a pouch procedure may be performed to retain faecal continence.

Histological changes regarded as characteristic of ulcerative colitis, such as goblet cell depletion, crypt abscess formation, crypt irregularity, and thickening of the lamina muscularis, may all be seen to a lesser or greater degree in Crohn's disease. Only the presence of a discrete epithelioid granuloma in the lamina propria or in lymphoid aggregates can be relied upon to distinguish clearly Crohn's disease from ulcerative colitis, provided that no other cause of granulomatous disease is suspected (fig 1).<sup>1,2</sup>

In a large number of cases of putative IBD, discrete granulomas cannot be seen, but there may be foci of pericryptal inflammation (fig 2). In some cases, this pericryptal inflammation may be associated with distinct aggregates of epithelioid histiocytes and frank granuloma formation (fig 3). These pericryptal granulomas may occur in the absence of the discrete, non-crypt related epithelioid granulomas which are characteristic of Crohn's disease. They invariably cause segmental disruption of the epithelial lining of crypts (figs 4A and 4B). In the most advanced stages, there may be extensive crypt ablation (fig 5). We have used the term cryptolytic colitis to describe these appearances.

The importance of these lesions is unknown. They are usually considered to be a non-specific consequence of crypt damage. The term 'mucin granuloma' is sometimes applied to them, implying that they result from phagocytosis of mucin leaked from damaged crypts.

It is our experience that true pericryptal granulomas are histologically distinct from mucin granulomas which are characterised by the presence of giant cells with pale foamy cytoplasm and an absence of epithelioid histiocytes. We feel that pericryptal granulomas are a cause rather than a consequence of crypt lysis and that they may be as important as discrete granulomas.

The aim of this study was to investigate whether patients with pericryptal granulomas occurring in isolation have a high probability of subsequently developing Crohn's disease.

## Methods

Twenty two patients with symptoms and signs suggestive of IBD and biopsy specimens with the histological features of unspecified IBD

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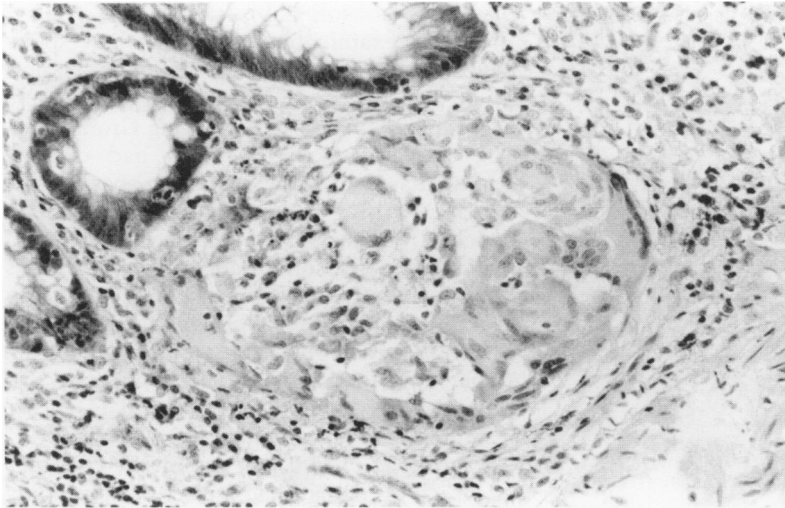


Figure 1 Discrete granuloma with giant cell formation in the lamina propria (haematoxylin and eosin; original magnification  $\times 150$ ).

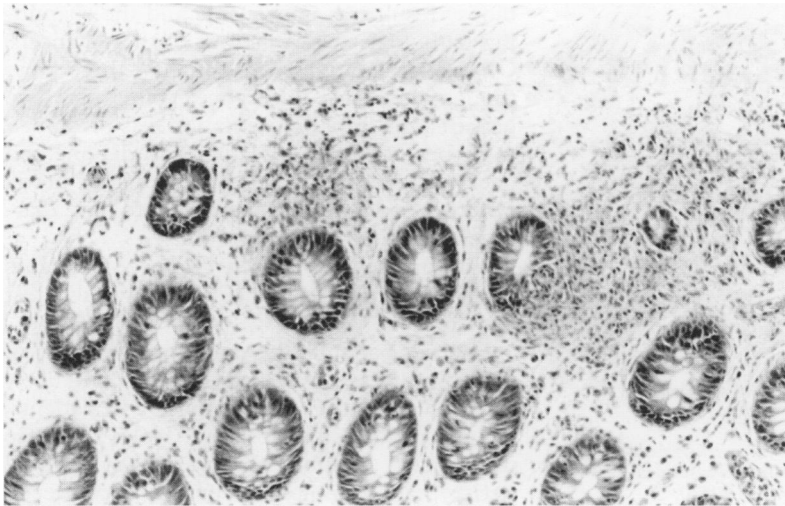


Figure 2 Colonic biopsy specimen showing pericryptal inflammation without convincing granuloma formation (haematoxylin and eosin; original magnification  $\times 100$ ).

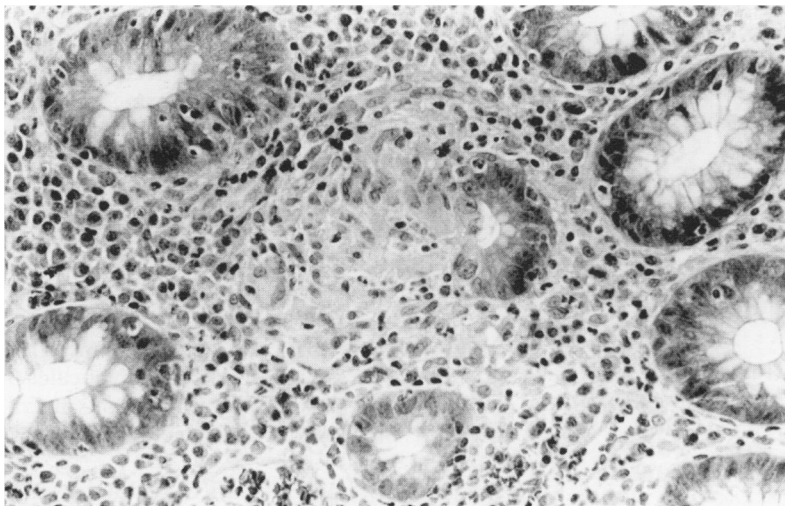


Figure 3 Pericryptal granuloma in a colonic biopsy specimen with early erosion of the crypt epithelium (haematoxylin and eosin; original magnification  $\times 280$ ).

were studied. The biopsy specimens all showed unexplained chronic inflammatory reaction in the lamina propria, with or without cryptitis or crypt abscess formation, but lacked any of the features which would enable a clear distinction to be made between ulcerative colitis and Crohn's disease. In particular, at the time of

inclusion into the study discrete epithelioid cell granulomas diagnostic of Crohn's disease were not seen. The examining pathologist was unaware of the subsequent definitive diagnosis. Patients were divided on the basis of histology into two groups.

Group A was comprised of patients with pericryptal granulomas identified on colorectal biopsy specimens. A pericryptal granuloma was defined as an aggregate of five or more epithelioid cells with or without Langhans giant cell formation arising in the vicinity of a crypt and associated with disruption of the epithelial lining (figs 4A and 4B).

Group B included patients with pericryptal inflammation on colorectal biopsy specimens. Pericryptal inflammation was defined as a collection of inflammatory cells without giant cells and with few (less than five) or no epithelioid cells associated with a crypt. These lesions were only occasionally associated with cryptitis (fig 2). This was in effect a control group to determine whether or not lesions of this kind might simply be a non-specific consequence of crypt damage and thus qualitatively similar to the lesions observed in group A.

The patients were selected from collections of colorectal biopsy specimens from the years 1978–88. This was to allow an adequate length of time for follow up of the patients.

#### HISTOLOGY

The biopsy specimens were processed routinely and 5  $\mu$ m sections were taken at multiple levels, and stained with haematoxylin and eosin. All slides were examined by an experienced pathologist and the presence of pericryptal granulomas was confirmed by using a standard immunohistochemical technique. The monoclonal antibodies directed against CD68 (Dako, High Wycombe, UK) for macrophages and epithelioid cells using the streptavidin-peroxidase method and broad spectrum cytokeratin (Dako) for epithelial cells using indirect immunoperoxidase methods were especially useful in this regard. Alcian blue/PAS stains were also used to demonstrate mucin and to help differentiate mucin granulomas from pericryptal granulomas. In all cases, the presence of intestinal pathogens was rigorously excluded by standard cultural methods. In addition, Ziehl-Neelsen stains were examined carefully but were negative for acid fast bacilli. All subsequent biopsy and resection specimens were also examined to detect the presence of discrete non-crypt related epithelioid granulomas characteristic of Crohn's disease, or features more suggestive of a diagnosis of ulcerative colitis.

The progress of the patients was reviewed to look for clinical or radiological evidence of small bowel involvement. All operative interventions, investigations, complications, and extraintestinal manifestations were recorded. Information about the patients' current status was obtained from outpatient consultations. A diagnosis of Crohn's disease was made in those patients with: (1) discrete non-crypt related epithelioid granulomas on subsequent biopsy or resection specimens; or (2) convincing

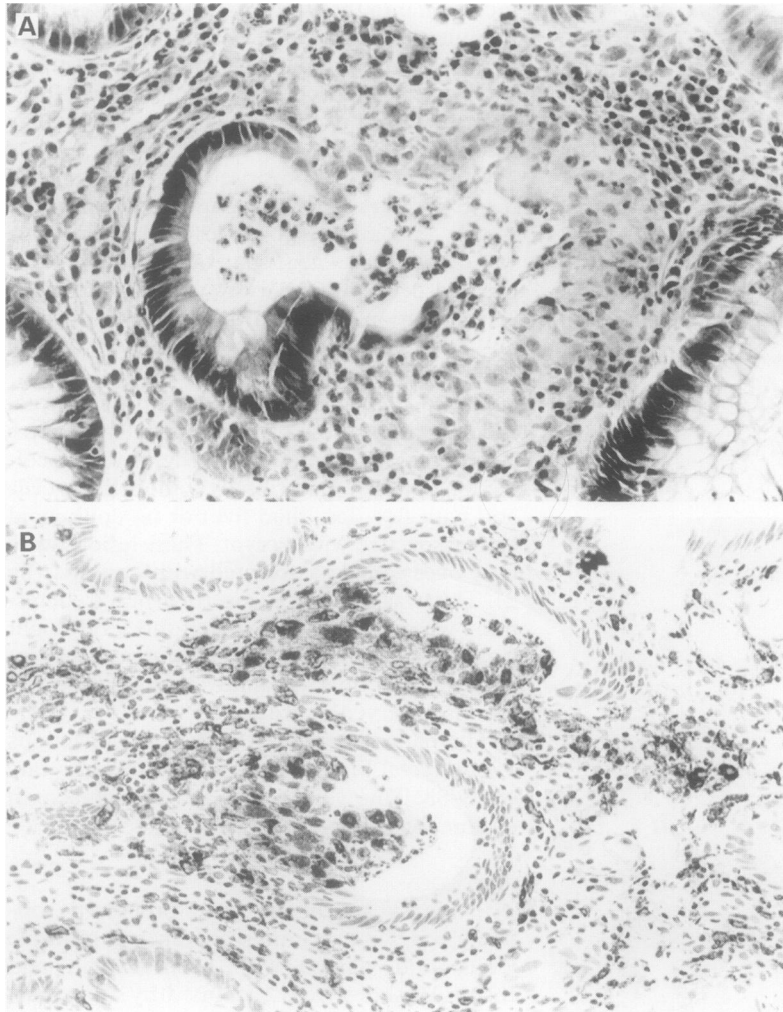


Figure 4 (A) Colonic biopsy specimen with pericryptal granuloma, extensive erosion of crypt epithelium and early crypt abscess formation. (B) Crypt granuloma stained with CD68 using the immunoperoxidase technique (original magnification  $\times 150$ ).

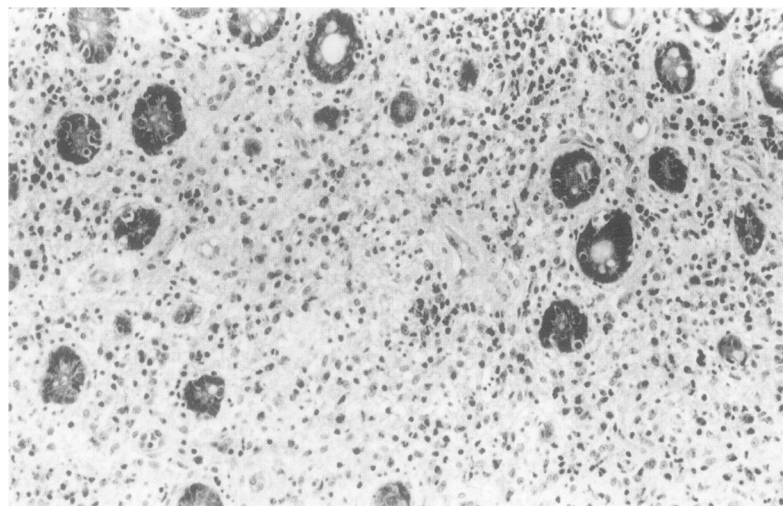


Figure 5 Colonic biopsy specimen showing extensive crypt ablation associated with a diffuse granulomatous process (haematoxylin and eosin; original magnification  $\times 130$ ).

evidence of small bowel involvement; or both (1) and (2).

Fischer's exact test was used for statistical analysis.

### Results

Of the 22 patients studied, 14 were assigned, on the basis of histology, to group A, and eight to group B.

### DIAGNOSIS OF CROHN'S DISEASE

Following examination of all histology specimens and review of the patients' clinical progress, 10 of the 14 patients in group A were subsequently diagnosed as having Crohn's disease (table 1). Nine patients had discrete granulomas seen on subsequent biopsy ( $n = 5$ ) or resection ( $n = 4$ ) specimens. Of these nine patients, four also had evidence of small bowel involvement. In one patient with Crohn's disease, discrete granulomas were not seen on histology at any stage, although the patient had recurrent small bowel strictures requiring surgery. Of the remaining four patients, two had probable ulcerative colitis and two were being treated for irritable bowel syndrome.

In group B, one of eight patients had Crohn's disease. This patient had a discrete granuloma seen on review of a rectal biopsy specimen taken at a previous presentation four years earlier. At the time of inclusion in the study, this biopsy result was unavailable and the examining pathologist was unaware of the diagnosis. Of the remaining seven patients, three were thought to have ulcerative colitis. In two patients, the initial presentation was presumed to be because of an infective episode; one had been diagnosed as having irritable bowel syndrome and another continued to have diarrhoea secondary to alcohol abuse.

The difference between groups A and B is statistically significant (Fischer's exact test  $p < 0.05$ ).

In most patients, the definitive diagnosis of Crohn's disease was made after a relatively short follow up period. In eight of 10 patients, an unequivocal diagnosis of Crohn's disease was made within three years of finding pericryptal granulomas on the colorectal biopsy specimen.

### SURGICAL INTERVENTIONS

In group A, six of 14 patients required surgical interventions. All of these patients had Crohn's disease. Colectomies or proctocolectomies with ileostomy formation were performed in four patients, two patients had eight hemicolectomies, and two had small bowel resections for stricture formation. None of the eight patients in group B required surgery.

### NUTRITIONAL PROBLEMS

Nutritional problems developed over the course of their illness in six patients with Crohn's disease in group A. These included anaemia, hypoalbuminaemia and hypocalcaemia. Two patients required intravenous nutrition and one had enteral feeding with an elemental diet.

In group B, only one patient had nutritional problems. This was a man who was disabled as a result of a childhood hemiplegia and who also

Table 1 Diagnosis of Crohn's Disease

	Group A	Group B
Total number	14	8
Crohn's disease	10	1
Discrete granulomas	9	1
Small bowel involvement	5	0
Both	4	0

had probable ulcerative colitis. He had hypoalbuminaemia and low folic acid concentrations and was treated with enteral feeding.

#### FOLLOW UP

The length of follow up in group A from the time of inclusion into the study ranged from three to 17 years, with a mean follow up of 8.7 years and a median follow up of nine years. Four patients in group A died after follow up periods of three, four, eight, and nine years, respectively. Three of these patients had Crohn's disease and one had probable ulcerative colitis.

Length of follow up in group B ranged from two to eight years, with a mean follow up of 6.6 years and a median follow up of seven years. One patient in group B died two years after inclusion into the study and thus had a relatively short follow up period. This patient had probable ulcerative colitis and died of an unrelated cause.

#### Discussion

We have shown that isolated pericryptal granulomas when found on colorectal biopsy specimens are associated with a high probability of the subsequent development of Crohn's disease. Ten of 14 patients in group A had an unequivocal diagnosis of Crohn's disease which was supported by the objective findings of discrete non-crypt related epithelioid granulomas or small bowel complications, or both. Eight of 10 patients were diagnosed within three years of inclusion in the study.

The large number of patients in group A who required surgical interventions undoubtedly contributed to the early diagnosis of Crohn's disease. In four cases, the definitive diagnosis was reached following histological examination of resection specimens.

Many patients in group A also had nutritional problems. This is not surprising considering the high percentage of patients with small bowel involvement and also the number of surgical resections performed. Overall, group A had a much higher morbidity than group B. This reflects the larger number of patients with Crohn's disease in group A and also suggests that most patients had relatively severe disease.

Of the four patients in group A who were not subsequently diagnosed as having Crohn's disease, two had probable ulcerative colitis and two were being treated for irritable bowel syndrome. Of the two thought to have ulcerative colitis, both had distal colitis on endoscopic examination and subsequent biopsy specimens had shown no diagnostic features of Crohn's disease. Only one of these patients had had small bowel radiology. One patient died of cardiac problems after a follow up period of eight years, and the other patient has gone abroad.

Of the two patients with irritable bowel syndrome, one had had no subsequent rectal biopsies, but had been a frequent attender at an outpatient clinic for nine years. The other patient had a subsequent rectal biopsy performed which was normal, and has been followed up for seven years so far. The reason why these patients had pericryptal granulomas

on their initial rectal biopsy specimen is unclear. It is possible that both patients had an episode of acute self-limiting colitis which resolved and then subsequently developed irritable bowel syndrome.

In our study, pericryptal inflammation was associated with a low probability of developing Crohn's disease: only one of eight patients in group B. All patients had a relatively long period of follow up, seven to eight years, except for one who died two years after the date of inclusion in the study. In group A, most of patients were diagnosed as having Crohn's disease within three years. Therefore, it is unlikely that further follow up of the group B patients would result in many more having a diagnosis of Crohn's disease. There were no surgical interventions and few complications in group B. This suggests that these patients had relatively benign and self-limiting disease, in contrast to the patients in group A.

Pericryptal inflammation was associated with a variety of different clinical outcomes. Three patients were thought to have ulcerative colitis and of these, one had died of an unrelated cause after a follow up period of two years. Another had been treated with oral sulphasalazine and steroid enemas at the time of initial presentation and had only had mild intermittent symptoms since then. The third patient had distal colitis on endoscopy at presentation and had remained symptomatic; this patient had never had small bowel radiology. In two patients, it is likely that the pericryptal inflammation resulted from an episode of acute self-limiting colitis triggered by an enteric infection. Both patients had no recurrence of their symptoms for many years and remained well on no medication.

It seems that pericryptal inflammation is in most cases a mild, transient and self-limiting phenomenon which as many different causes. It usually has a good prognosis and is not associated with progressive or debilitating disease.

#### SIGNIFICANCE OF PERICRYPTAL GRANULOMAS

Granulomatous lesions arising in the vicinity of mucosal crypts have always presented difficulties in the interpretation of colorectal biopsy specimens. In many studies, relatively little emphasis has been given to such lesions. In a recent publication concerning the discriminatory values of 41 biopsy features in IBD, there is no specific mention of pericryptal granulomas.<sup>3</sup> In a similar previous study, reference is made to 'basal histiocytic cryptitis' as a feature of IBD and Crohn's disease in particular, but it is not certain whether this lesion can be equated with the pericryptal granuloma as defined in the present study.<sup>4</sup> Another publication warns that granulomas restricted to the edges of ruptured crypts are not specific for Crohn's disease as they may be seen in other inflammatory conditions, particularly in infections.<sup>5</sup> It is of course certainly true that tuberculosis, syphilis<sup>6</sup> and chlamydial<sup>7</sup> infection can be associated with microgranuloma formation and that this might be pericryptal in location. It has also been shown recently that pericryptal granulomas might be a feature of

diverticular colitis.<sup>8</sup> In a recent study by Surawicz *et al*, pericryptal granulomas were referred to as 'granulomatous crypt abscesses' and were equated with mucin granulomas, implying that they may be a result of mucin leakage from damaged crypts and that the aetiology and significance is different from that of a discrete granuloma.<sup>9</sup> However, there are earlier references to granulomas within crypts having a similar significance as granulomas elsewhere in the mucosa.<sup>10</sup>

In our study, special stains have, for the most part, failed to demonstrate mucin in pericryptal granulomas, and in any case it is unlikely that the presence of epithelioid histocytes could be explained solely on the basis of mucin leakage. The analysis of multiple sections of the colorectal biopsy specimens included in this study strongly suggests that crypts are being damaged or eroded as a consequence of granuloma formation in the lamina propria, and that this process may lead to widespread crypt ablation. This phenomenon is well recognised by histopathologists in other contexts. Tuberculous granulomas arising in the endometrium frequently erode glands, and provoke neutrophil migration into gland lamina.<sup>11</sup> A similar phenomenon may also be observed in relation to renal tubules. It is possible that this may also take place in the colonic mucosa in Crohn's disease.

The results of our study thus suggest that the presence of pericryptal granulomas in a colorectal biopsy specimen should initiate an intensive search for unequivocal granulomas elsewhere in the gastrointestinal tract. We

would also recommend that the patient has close follow up, be screened for nutritional deficiencies and have small bowel radiology and other investigations as necessary. Finally, as these patients are very likely to develop Crohn's disease in the near future, the presence of pericryptal granulomas should signal a warning to surgeons that ileoanal pouch construction might have unwelcome consequences.

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