Eosinophils in the rectal mucosa

A simple method of predicting the outcome of ulcerative proctocolitis?

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SUMMARY One-hundred-and-thirteen rectal biopsies and 17 total colectomy specimens from 50 patients with ulcerative proctocolitis were examined. These patients had been followed for periods up to 220 months, mean 70 months. The histological changes were compared with the clinical features of the disease. Patients with relatively benign disease which responded to treatment had significantly raised eosinophil counts in the mucosa examined, compared with patients who had aggressive disease which failed to respond to medical treatment ($P < 0.001$). Tissue eosinophilia in the rectal mucosa may provide a simple method for predicting the clinical course of patients with ulcerative proctocolitis.

Ulcerative proctocolitis follows a very variable clinical course ranging between the extremes of an acute fulminating disease to a relatively benign, apparently self-limiting one. In between there may be chronic progressive ill-health or alternatively intermittent relapses and remissions of unpredictable severity at varied intervals of time. Because of this, treatment is largely empirical, and is usually confined to treatment of symptomatic disease; in some cases, the widespread application of prophylactic treatment is not only expensive, but also inconvenient and sometimes unpleasant for the patient.

This variable and unpredictable pattern of illness is important in the management of patients with ulcerative proctocolitis. Although both the acute and chronic manifestations of this disease are responsive to treatment in most patients, some are incapacitated by the disease, and may require radical surgery. Because there is no satisfactory means of predicting the clinical outcome in these patients, most are given long-term treatment with drug therapy which is often associated with unpleasant side-effects, and with which many patients probably fail to comply.

In this study 113 rectal biopsies and 17 total colectomy specimens from 50 patients with acute and chronic ulcerative proctocolitis have been examined. The histological appearances have been correlated with a clinical assessment of the extent of the disease and its eventual outcome.

Methods

PATIENTS

The case notes of patients with ulcerative proctocolitis at present under review in the Nottingham area were examined. Those with well-documented clinical histories, together with biopsy and radiological evidence of disease, were selected for study. The majority of our cases were obtained at random from this source but a small number were taken from pathological cases (surgical resections) obtained from the files of the Pathology Department, General Hospital, Nottingham. Patients who developed systemic complications or carcinoma of the colon and were treated surgically because of these complications were excluded. All patients (except one who had a total colectomy at presentation) had one rectal biopsy taken at the initial presentation of the disease and in 34 cases subsequent biopsies (up to six in some cases) were taken during the clinical course of the disease.

An assessment of the clinical activity of the disease, and the treatment the patient was receiving was noted on each occasion that histological material was available for study. Activity of the disease was described as inactive, mildly active, moderately active, and severely active, on the basis of the patient's symptoms (Binder and Hvidberg, 1972), blood parameters, and sigmoidoscopic examination (Heatley *et al.*, 1975). The extent of the disease was assessed by radiology together with endoscopic and pathological—in resected specimens— examination,

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when available, and recorded as proctitis—confined to the rectum—distal colitis—distal to the hepatic flexure—and total colitis when the entire colon and rectum were involved (Powell-Tuck *et al.*, 1977).

The patients were divided into four groups according to the clinical outcome of the disease.

Group a: 12 patients

These were patients who had experienced one or more attacks of symptoms followed by an apparently complete remission, for which treatment was no longer required. In this group all patients (except two with distal colitis) had proctitis.

Group b: 13 patients

These were similar to group a, except that they required continuous treatment (most commonly sulphasalazine) and/or topical steroids to maintain remission of the disease. All patients had proctitis at initial presentation (except two with distal colitis and one with total colitis). Three patients who presented with proctitis later developed more extensive disease, one patient developing distal colitis, and two total colitis.

Group c: 13 patients

These were patients with unremitting symptoms which failed to respond to medical treatment. All but two were eventually subjected to elective proctocolectomy. Three of the patients undergoing surgery had total colitis at presentation, two distal colitis, and the remainder proctitis, of whom seven later developed total colitis and one distal colitis.

Group d: 12 patients

All of these patients underwent emergency proctocolectomy for acute fulminating disease and were found to have total colonic disease, four had preceding proctitis, the remainder having only a short history of bowel disturbance before presentation.

Twenty-five of the patients studied were male. The mean age at presentation was 42 years (range 19–72 years). The age and sex distribution of the patients in groups a and d were similar. The overall follow-up periods ranged between a few days in some of the

patients with acute fulminating disease, to 220 months in those with chronic disease, mean 70 months. The follow-up period in group a was 30–200 months, mean 97 months; group b 30–220 months, mean 104 months; group c 20–130 months, mean 64 months; group d 0–30 months, mean 11 months.

PATHOLOGICAL STUDY

The blocks of 113 rectal biopsies and 17 total colectomy specimens from the 50 patients studied were retrieved from the files of the General and City Hospitals, Nottingham, and reviewed without knowledge of the clinical course of the patients. The Table gives details of the numbers of biopsies and colectomy specimens available for examination in each of the clinical groups. Blocks were taken from the most distal ends of colectomy specimens so as to be anatomically comparable with rectal biopsies.

Five μ paraffin sections were stained with Harris haematoxylin and eosin, by the periodic acid Schiff reaction, and with carbol chromotrope. The following features were looked for in each section: epithelial atrophy, mucus depletion, chronic inflammatory cell infiltrate in the lamina propria, acute inflammatory cells around dilated mucosal blood vessels and infiltrating the glandular epithelium, crypt abscess formation, and mucosal ulceration. Each feature when present was roughly graded, but the degree of epithelial atrophy and mucus depletion was not found helpful, as a variable degree of epithelial atrophy was present in all cases and mucus depletion was present whenever there was active disease.

Each section examined was placed into one of two pathological grades: (1) those showing inactive disease, characterised by an atrophic epithelium with a normal or increased number of chronic inflammatory cells in the lamina propria but no evidence of acute inflammation; (2) those showing active disease with acute inflammatory cells in the lamina propria which infiltrated the glandular epithelium, formed crypt abscesses, and were associated in some cases with mucosal ulceration.

The eosinophils in the lamina propria in each of the 130 sections were counted using a net micro-

Table Numbers of rectal biopsies and colectomy specimens examined from 50 patients with ulcerative proctocolitis giving details of numbers showing active disease

Clinical group	Number of patients	Total number of rectal biopsies	Range of biopsies per patient	Biopsies showing active disease	No. of colectomy specimens	Colectomies showing active disease
A	12	26	1–4	16	0	0
B	13	34	1–7	24	0	0
C	13	39	1–6	28	5	4
D	12	14	0–3*	14	12	8

* In one patient no rectal biopsy was available before colectomy.

meter disc mounted in a $\times 10$ widefield eyepiece of a Zeiss standard 18 microscope at a $\times 40$ objective magnification. At this magnification each grid covered an area of the biopsy 0.06 sq. mm. The total number of eosinophils in 20 squares was counted and an average count per square taken for every section. The fields counted were taken at random and no attempt was made to correct for the area covered by epithelium. Statistical comparisons were made using Student's *t* test.

Results

There were no apparent histological differences between sections examined from patients with proctitis and those with extensive colitis. Similarly, there were no histological differences detected in those patients who presented with distal disease and subsequently developed proximal extension of the disease. The most striking feature observed was the marked tissue eosinophilia in sections showing active inflammation in patients who subsequently

achieved apparent complete remission of disease. In contrast, those patients who required surgery had relatively few eosinophils. The tissue eosinophil counts are illustrated in Fig. 1. In group a the counts ranged between 14–36, mean 23, and in group b 12–44, mean 24. There was no significant difference between these values. However, the values obtained in both of these groups were significantly greater than those in group c, range 0–31, mean 15 ($P < 0.001$); and also group d, range 0–13, mean 4 ($P < 0.001$). Similarly, the differences between groups c and d are also significant ($P < 0.001$), as are the differences between the combined values of both group a and b, compared with the combined values of groups c and d ($P < 0.001$). These findings relate only to sections which showed evidence of active disease. In groups c and d there were no significant differences in the eosinophil counts in sections showing active (range 0–31, mean 11) or inactive disease (range 0–29, mean

Fig. 1 Eosinophil counts in rectal biopsies (four colectomy specimens are included in group c and eight in group d) showing active disease from 50 patients with ulcerative proctocolitis, who were divided into four clinical groups (see text). Patients in groups a and b had a benign self-limiting disease. Those in groups c and d had an aggressive clinical course, and failed to respond to medical treatment.

Fig. 2 Eosinophil counts in all the rectal biopsies from 25 patients with ulcerative proctocolitis who had a benign clinical course (groups a and b), during inactive and active disease.

7). There were no significant differences in eosinophil counts in sections showing inactive disease in any of the clinical groups. However, the tissue eosinophil counts in groups a and b were significantly raised ($P > 0.001$) in the presence of active inflammatory change (Fig. 2).

In group a patients, of 26 biopsies available for study, 16 showed acute inflammatory changes; the corresponding figures for other groups were: group b, 34 : 24; group c, 44 : 32 (includes four colectomy specimens); and group d, 26 : 22 (includes eight colectomy specimens). There were no significant differences in the eosinophil counts or histological grades of biopsies from patients with proctitis and those with colitis.

Retrospective comparison between disease activity that was assessed clinically and that assessed histologically proved difficult. There was, however, a good overall correlation between these parameters, the most common exception being that histological evidence of resolving disease activity was delayed when compared with the clinical assessment after acute exacerbations of colitis. Treatment appeared to have no specific effect upon the histological appearances of the biopsies.

Discussion

One of the major problems in the management of patients with ulcerative colitis is the unpredictable nature of the disease. Many patients will suffer only mild bowel disturbance and respond satisfactorily to drug therapy, whereas some will be afflicted with a life-threatening illness which may eventually require aggressive surgical treatment. Others have a long-standing intractable disease producing chronic ill-health and sometimes serious complications. At presentation there is no satisfactory means of predicting the eventual clinical outcome, and consequently patients tend to be treated expectantly. Fortunately, most patients with this condition will respond to medical treatment during the acute attack, and long-term treatment with sulphasalazine undoubtedly maintains clinical remission of the disease in the majority of patients. However, drug therapy for ulcerative colitis is not without complications and many patients are encouraged to endure long-term treatment with sulphasalazine which is not infrequently associated with complications such as skin rashes, nausea, vomiting, haemolysis, and leucopenia (Dick *et al.*, 1964).

The results of this study suggest that it is possible to predict histologically the clinical course of ulcerative proctocolitis in some patients. As there is overlap between the eosinophil counts from the different groups of patients, this finding will not, of course,

be applicable to all patients with colitis. The restriction of these findings to histological material showing acute inflammatory changes may also place limitations on the value of these results in clinical practice. Similarly, as this study is in part retrospective, some caution must be exercised in the interpretation of the results. Nevertheless, our findings may well have relevance in the possible future management of the disease. Large numbers of eosinophils in the rectal mucosa during active disease predict a benign course, whereas a paucity of eosinophils indicate a more aggressive disease. It may well be that long-term treatment should be confined to the latter group of patients. In the light of these findings there may be a need to re-evaluate the current drug treatment of colitis in further clinical trials. Patients who relapse on currently available treatment may be those with sparse tissue eosinophils. Although long-term administration of corticosteroids is of no value in maintaining remission of disease in a population of unselected colitic patients (Lennard-Jones *et al.*, 1965), it is possible that this form of treatment might be of value in a group of patients with scanty tissue eosinophils. It is of interest that sodium cromoglycate, which has recently been shown to be effective in the treatment of both acute and chronic ulcerative proctocolitis, appears to be most active in patients with tissue eosinophilia in rectal biopsies (Heatley *et al.*, 1975; Mani *et al.*, 1976; 1977). As this compound at present appears to be remarkably free of side-effects, it may prove of value in the symptomatic treatment of those patients with a good long-term prognosis.

The function of the eosinophil in acute inflammation has long been an enigma but recent evidence indicates that it plays a part in moderating acute inflammatory responses. Beeson (1977) has reviewed some of the evidence for this. Immune complexes attract eosinophils and are ingested by these cells. Mast cells release both histamine and an eosinophil chemotactic agent (ECF-A), which will attract eosinophils to sites where mast cells are present. Eosinophils inhibit the action of histamine by elaborating prostoglandins E_1 and E_2 . The slow release substance of anaphylaxis is also inactivated by arylsulphatase, a component of the eosinophil. Beeson suggests that the eosinophil is attracted to sites of IgE mediated responses and may moderate the actions of some of the products of the allergic inflammation. The relatively benign course of proctocolitis associated with a high tissue eosinophilia certainly supports this suggestion. The variable eosinophil counts in the four clinical groups studied indicates that there may be several different basic immunological mechanisms responsible for proctocolitis.

Rectal biopsy is now an established routine in the investigation of patients with inflammatory bowel disease. It is easily performed at sigmoidoscopy and complications are rare. The identification of eosinophils in chronic ulcerative proctocolitis has implications for the prognosis, treatment and possible pathogenesis of this disease. Their quantification in acutely inflamed rectal biopsies is simple.

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References

- Beeson, P. B. (1977). Role of the eosinophil. In *Immunology of the Gut*. Ciba Foundation Symposium, 46, (new series), pp. 203-213.
- Binder, V., and Hvidberg, E. (1967). Histamine content of rectal mucosa in ulcerative colitis. *Gut*, **8**, 24-28.
- Dick A. P., Grayson, M. J., Carpenter, R. G., and Petrie, A. (1964). Controlled trial of sulphasalazine in the treatment of ulcerative colitis. *Gut*, **5**, 437-442.
- Heatley, R. V., Calcraft, B. J., Rhodes, J., Owen, E., and Evans, B. K. (1975). Disodium cromoglycate in the treatment of chronic proctitis. *Gut*, **16**, 559-563.
- Lennard-Jones, J. E., Misiewicz, J. J., Connell, A. M., Baron, J. H., and Avery Jones, F. (1965). Prednisone as maintenance treatment for ulcerative colitis in remission, *Lancet*, **1**, 188-191.
- Mani, V., Lloyd, G., Green, F. H. Y., Fox, H., and Turnberg, L. A. (1976). Treatment of ulcerative colitis with disodium cromoglycate. *Lancet*, **1**, 439-441.
- Mani, V., Lloyd, G., Green, F. H. Y., Fox, H., and Turnberg, L. A. (1977). Morphological changes in the rectal mucosa in patients with ulcerative colitis treated with disodium cromoglycate. *Gastroenterology*, **72**, 1093.
- Powell-Tuck, J., Ritchie, J. K., and Lennard-Jones, J. E. (1977). The prognosis of idiopathic proctitis. *Scandinavian Journal of Gastroenterology*, **12**, 727-732.