Surface epithelium related activation of complement differs in Crohn’s disease and ulcerative colitis

T S Halstensen, T E Mollnes, P Garred, O Fausa, P Brandtzæg

Abstract

IgG1 and activated complement are co-localised on the colonic epithelial brush border in active ulcerative colitis. To investigate whether such deposition is specific for ulcerative colitis, we examined ethanol fixed mucosal specimens from 18 patients with Crohn's colitis and 14 with terminal ileitis by indirect two colour immunofluorescence staining. Monoclonal antibodies to the IgG subclasses and to neoepitopes of activated complement C3b and the terminal complement complex were used in combination with rabbit antiserum to C1q, C4c or cytokeratin. Granular deposition of C3b and terminal complement complex were observed at the luminal face of the surface epithelium in 10 of 18 patients with Crohn's colitis. Specimens from eight of 14 patients with ileal involvement were intensely stained for activated complement (primarily C3b) within the surface mucus layer. No epithelial IgG, C1q or C4c deposition was observed. The results suggest that early and late phase complement activation takes place at the luminal face of the epithelium in Crohn's disease. The absence of co-localised IgG and complement components involved in the classical activation pathway (C1q and C4c), however, suggest that other immunopathological mechanisms (the alternative pathway?) are primarily involved in Crohn's disease in contrast with ulcerative colitis.

Crohn's disease is a chronic inflammatory bowel disease of unknown aetiology and pathogenesis.1 Immunohistochemical studies have revealed a strikingly increased local immunoglobulin G (IgG) production, particularly of the complement binding IgG1 subclass although Crohn's disease mucosa contains a higher percentage of IgG2 containing immunocytes than ulcerative colitis. The same result has been obtained by cultivation of mononuclear cells from the lesion.1 Patients with Crohn's disease are reported to have impaired C3b inactivation2 and increased complement C3 catabolism3 with raised serum concentrations of complement C3 activation split products.3,4,5 These findings suggest that complement activation takes place in the affected intestinal mucosa.

To address this issue we examined directly ethanol fixed as well as extensively pre-washed mucosal specimens from patients with Crohn's disease in the ileum and/or colon. Monoclonal antibody (mAb) to activation neoepitopes in the C3c (C3b) and late (terminal) complement complex complement activation pathway were used. The results showed deposition of both C3b and terminal complement complex in these deposits, however, in contrast with our previous observations in ulcerative colitis.6

Methods

Tissue specimens

Mucoosal tissue samples were immediately excised from surgically resected colon (n=56) or terminal ileum (n=26) from 21 patients with Crohn's disease (median age 29 yr, range 14–64). Three patients had only ileal involvement, one only colonic, whereas 17 had both segments affected (ileo biopsy available only in 11). The patients had been observed clinically for two to 13 years (median five years). Ulcerative colitis specimens (five) with epithelial complement and IgG1 deposits were selected from 23 previously reported patients.6 Control material was obtained from histologically normal colonic mucosa of 26 patients as described elsewhere7 and normal ileal mucosa (six).

All tissue specimens were placed in ice cold isotonic saline and brought to the laboratory within one hour for preparation in two alternative ways. Trimmed tissue blocks (about 2×4×5 mm) were either fixed directly in cold 96% ethanol for 18 hours to preserve soluble immune complexes (17 ileal and 33 colonic samples), or washed for 48 hours at 4°C in 0·01 M phosphate buffer (pH 7·5) containing 0·15 M NaCl (phosphate buffered saline to extract diffusible proteins before cold ethanol fixation (nine ileal and 23 colonic samples). All tissue samples were finally dehydrated in cold absolute ethanol, cleared in xylene, embedded in paraffin for three to four hours at 56°C, and stored at 4°C until sectioning.8

Staining procedures and immunological reagents

Dewaxed sections cut at 6 μm from directly fixed tissue were incubated for 20 hours at room temperature with monoclonal antibody to a C9 neoepitope of terminal complement complex (aE11; 2·5 mg/l)9 in combination with rabbit antiserum to S-protein/vitronectin (1:1500; kindly provided by B Dahlbäck, Department of Clinical Chemistry, Malmö General Hospital, Sweden).10 An alternative combination was monoclonal antibody to a C3b neoepitope in the C3c part of C3b/C3b (bH6, 7·5 mg/l)10 and rabbit antiserum to cytokeratin (1:100).11 Dewaxed sections of prewashed tissue were examined both for IgG deposits and complement activation products. Monoclonal antibodies to
C3b, TCC, IgG1 (clone 267, 1:800; HP 6070), IgG2 (clone GOM2, 1:800; HP6009), OgG3 (clone CBI-AH7, 1:800; HP6048) and IgG4 (clone RJ4, 1:8000; HP6011) were all used in combination with rabbit antiserum to C3c (1:500; Behring, Marburg, Germany) as previously described. Selected colonic (three) and ileal (two) specimens from five patients with Crohn’s disease and five with ulcerative colitis found to have apical complement deposition (see below) were, in addition, examined with rabbit antiserum to Clq (1:500; Dakopatts, Glostrup, Denmark); C3c (1:500; Behring) and C4c (1:500, Dakopatts) in combination with monoclonal antibody to C3b or terminal complement complex. Secondary reagents were biotinylated horse antimouse IgG (0.025 g/l; Vector Laboratories, Burlingame, CA, USA), followed either by swine antirabbit IgG (0.14 g/l; Dakopatts) conjugated with rhodamine in combination with fluorescein isothiocyanate (FITC) conjugated streptavidin (0.02 g/l; Boehringer Mannheim, Germany), or by fluorescein isothiocyanate conjugated swine antirabbit IgG (1:10, Dakopatts) combined with Streptavidin-Texas Red (0.0025 g/l; BRL, Gaithersburg, MD, USA). The reagents were applied in a three step two colour immunofluorescence staining method principally as described elsewhere. The selected prewashed specimens were also subjected to three colour staining in which monoclonal antibody to human IgG1 (murine IgG1) was combined with monoclonal antibody bH6 to C3b (IgG2a) or monoclonal antibody aE11 to terminal complement complex (IgG2a), and mixed with rabbit antiserum to C3c or C4c. Secondary reagents were biotinylated and fluorescein isothiocyanate conjugated subclass specific goat antimouse IgG2a and IgG1 (Southern Biotechnology, Birmingham, AL, USA) followed by 7-amino-4-methylcoumarin-3-acetic acid (conjugated goat antirabbit IgG (1:20, Vector Laboratories) in combination with Streptavidin-Texas Red (0.0025 g/l; BRL).

Selected colonic specimens (six) with C3b positive globular elements in the lamina propria (see later) were also examined for terminal complement complex and C3b deposition by immunoenzyme staining; the alkaline phosphatase antialkaline phosphatase and the avidin-biotin complex peroxidase methods were both applied, the latter according to the instructions given by the manufacturer (Dakopatts).

IMMUNOHISTOCHEMICAL EVALUATION, CONTROLS, AND STATISTICAL ANALYSIS

Immunofluorescence was examined in a Leitz Orthoplan microscope equipped with a Ploem type vertical illuminator for selective observation of red (Cy3 fluorescein isothiocyanate (FITC)) and green fluorescein isothiocyanate or blue 7-amino-4-methylcoumarin-3-acetic acid emission. For every immunofluorescence marker, each specimen was given a semiquantitative score ranging from no (−) to intense (3+) staining. Scoring of the unselected Crohn sections was done blind by the same investigator. Mucus associated and the strictly epithelium related complement deposits were scored separately. One section from every series was subjected to blind histopathological evaluation after haematoxylin and eosin staining; each specimen thereby received an arbitrary inflammation score from negative (−) to intense (3+) according to cellular infiltration and mucosal destruction.

Primary incubation with murine control ascites or normal rabbit serum, at dilutions similar to those used for monoclonal antibodies and rabbit antiserum, did not produce immunofluorescence.

The relation between mucus associated and/or epithelium related terminal complement complex/C3b deposits and inflammation was based on Kendall’s correlation analysis.

Results

ILEAL COMPLEMENT DEPOSITS

Staining for C3b-neo (monoclonal antibody bH6) was observed within the ileal surface mucus layer in directly fixed specimens from eight of 14 patients. Additional but weaker and scattered staining for terminal complement complex was observed in five of these patients. A distinct epithelium related apical staining for C3b was observed in seven patients, and four of them showed terminal complement complex at the same location (Table). C3b often dominated throughout the mucus layer whereas terminal complement complex appeared to be located closer to the epithelial surface and was then scored as epithelium related (Fig 1). Only the staining intensity of epithelium related and mucus associated terminal complement complex was significantly correlated with the topical degree of inflammation (Fig 2), although wide scatter was observed. Fine granular staining for terminal complement complex and S-protein was present in the basement membrane zone of five patients, whereas C3b was seen in only one. No epithelial deposition of Clq, C4c or any of the four IgG subclasses was detected in the prewashed specimens.

An approximately 100 µm broad zone of the mucosal wall surrounding ileal ulcers stained

![Figure 1: Intense C3b positivity (a) was noted in the mucus layer and apically on the epithelium, whereas terminal complement complex (TCC) (b) was selectively deposited on the epithelial surface. Broken line indicates the basement membrane zone. Paired immunofluorescence staining in section of directly ethanol fixed ileal mucosa from a patient with Crohn’s disease of the ileum.](image-url)
Clinicopathological information about the patients with Crohn’s disease of the colon and scoring of inflammation and epithelium related immune deposits

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* M=male, F=female, †S=salazopyrin, P=prednisone, ‡colon S=sigmoid colon, A=ascending colon, T=transverse colon, §BMZ=basement membrane zone, |patient received Imurel (azathioprin).

Diffusely for terminal complement complex, and numerous terminal complement complex positive globular elements were observed in the luminal content (not shown).

**Colonic Complements Deposits**

*Crohn’s disease*

Often granular and parallel positivity for C3b (Fig 3) and terminal complement complex was observed at the luminal face of the epithelium in 10 of 18 patients with Crohn’s disease of the colon (Table). The staining intensity for strictly epithelium-related (Fig 2b) C3b and terminal complement complex was better correlated with the topical degree of inflammation (Fig 2a) than the mucus associated. Granular terminal complement complex positivity in the basement membrane zone was often observed beneath intact epithelium in nine of the patients. The content in colonic fissures was, like that in crypt abscesses, often intensely positive for terminal complement complex but mostly negative for C3b. Globular elements with various combination of peripheral positivity for IgG subclasses (IgG2>IgG3>IgG1) and/or C3b were observed within the mucus associated content, whereas

**Figure 2:** Scatter diagram showing intensity of (a) epithelium related and (b) mucus associated complement related to the degree of inflammation in Crohn patients (controls not shown). Epithelium related and mucus associated terminal complement complex (but not C3b) correlated with the topical degree of ideal inflammation (r=0.33 and r=0.41, respectively; p<0.01), whereas both the epithelium-related C3b (r=0.45) and terminal complement complex (r=0.38) correlated with the degree of inflammation in the large bowel (p<0.0001). The mucus associated terminal complement complex (but not C3b) showed a weak correlation with the topical degree of colonic inflammation (r=0.27; p<0.005). Filled symbols represent C3b, open symbols TCC. Ileum, □ ○; caecum and ascending colon, △ △; transverse colon, ● ◇; descending and sigmoid colon, ■ ◊; rectum, ▼ ▼.
Surface epithelium related activation of complement differs in Crohn's disease and ulcerative colitis

terminal complement complex positivity was more diffuse (not shown). Similar C3b positive elements were observed attached to and/or located within the epithelium in nine patients. Aggregates of C3b positive globular elements were observed in the lamina propria in directly ethanol fixed specimens from six patients (Fig 4). These aggregates were apparently located within lymphatic vessels as visualised also with avidin biotin complex peroxidase (Fig 4C) and alkaline phosphatase antialkaline phosphatase staining technique in three patients examined.

No epithelial deposition of IgG, Clq, or C4c was observed in prewashed tissue samples from Crohn's disease (Fig 5).

Ulcerative colitis
All selected ulcerative colitis samples showed deposition of IgG1, C3b and terminal complement complex on the luminal face of individual enterocytes, only interrupted by goblet cells as previously reported.\textsuperscript{11} Crypt abscesses and luminal contents often stained for terminal complement complex but only weak and scattered C3b positivity was observed, contrasting the intense mucus-associated staining for C3b in Crohn's disease.

Epithelium related staining for C4c was observed in three of the five patients but it was less prominent than seen for C3c. Supraepithelial Clq was weak and observed only occasionally. Three colour staining for IgG1, C3b and C4c or Clq revealed that the IgG1 and C3b positive epithelial deposits often costained for C4c (though weaker than for C3b/C3c). Such deposits were observed in all three samples (Fig 6). C3b/terminal complement complex positive deposits in the absence of both IgG1 and C4c/Clq were also observed. The other two samples contained either epithelial C3b and terminal complement complex deposits in the absence of IgG1 and Clq/C4c, or only IgG1 in the absence of complement components.

C3b positive globular elements were often observed in the lumen and were attached to the surface epithelium in one of the ulcerative colitis samples.

VASCULAR COMPLEMENT
Submucosal blood vessels in both ileum and...
colon were intensely positive for terminal complement complex, and to a lesser extent for C3b, as previously reported. Some of the C3b positive submucosal blood vessels in both Crohn's disease and ulcerative colitis showed segmental costaining for Clq and C4c. Two colonic samples from Crohn's disease contained a submucosal blood vessel that stained for all complement components (Clq, C3b, C4c and terminal complement complex) in addition to some weak IgG1 positivity (not shown). Numerous cells with cytoplasmatic staining for C3c, C4c, Clq and occasionally also IgG1 were observed deep in the lamina propria and between the smooth muscular cells in inflamed sections (not shown).

**Discussion**

Our previous observation of epithelium related IgG1 and activated complements (C3b and terminal complement complex) in active ulcerative colitis reflected a potentially destructive immune reaction caused by autoantibodies to epithelial brush border associated protein(s). Here we report that luminal complement activation also occurs in Crohn's disease of the ileum and colon. Lack of IgG and classically complement activation components (Clq and C4c) within the epithelial C3b/terminal complement complex deposits, however, suggests that initiators of the alternative pathway are more important in Crohn's disease than in ulcerative colitis. In the latter disorder epithelial immune deposits often costain for IgG1 and C4c and also occasionally for Clq, strongly suggesting that IgG1 induces classical pathway activation. Epithelial immune deposits negative for IgG1, Clq and C4c are also observed, however, probably reflecting that alternative pathway activation also occurs in ulcerative colitis.

The two complement activation pathways are not strictly separate because antibodies and immune complexes may also activate the alternative pathway, and agents such as cardiolipin, C-reactive protein, and bacterial (Escherichia coli) surface antigens may initiate the classical pathway. In addition, C3b produced by classical activation may complex with factor B to generate the alternative pathway C3 convertase (C3bBb), resulting in increased C3 activation (alternative pathway amplification). It is therefore difficult to determine the main activation pathway on the basis of immunohistochemical staining for complement components in immune deposits. Nevertheless, codeposition of IgG1 in ulcerative colitis but not in Crohn's disease, strongly suggests that autoantibodies to the colonic epithelium are involved in the epithelial complement deposition only in the former disease. Also, patients with Crohn's disease have been found to have higher serum levels of the alternative pathway activation product Bb than patients with ulcerative colitis.

The subepithelial deposition of C3d, terminal complement complex and S-protein (presumably representing the soluble form of terminal complement complex, SC5b-9) observed in affected ileum and colon might have represented fluid face complement activation secondary to epithelial destruction. Alternatively, soluble immune complexes generated in the basement membrane zone could have induced subepithelial complement activation and induced epithelial damage. These deposits, however, were mainly seen beneath intact epithelium in Crohn's disease, contrasting with ulcerative colitis where such deposits primarily were observed beneath or close to damaged epithelium.

Ahrenstedt et al recently reported that patients with Crohn's disease of the ileum have increased concentrations of C3 in jejunal lavage fluid. It was suggested that this finding reflected activated C3 because most was of a molecular size similar to the complement split product C3c. This does not seem to be a general small intestinal phenomenon, however, because C3b/C3c positivity (mAb bH6) was observed only in mucus of affected ileum.

The epithelial complement deposition in Crohn's colitis tended to be more granular than in ulcerative colitis. The globular elements positive for IgG1, IgG2, IgG3, and C3b observed in the mucosa, and the C3b positive elements on the epithelium and in the lamina propria, resembled surface staining of microorganisms. This sug-
gested an immune attack but the putative microorganisms might have bound C3b by complement receptor like structures as recently shown for Candida albicans.49 Such C3b coating does not afford opsonisation and the microorganisms may escape phagocytosis. In an electron microscopic study of Crohn’s disease, Thyberg et al.50 observed partly degraded bacteria in lamina propria macrophages and epithelial cells regardless of the severity of the lesion; and Aluwihare51 found intramural bacteria in six of 11 colonic specimens with intact epithelium and minimal inflammatory changes. Patients with Crohn’s disease have, in addition, higher serum concentrations of agglutinating antibodies to anaerobic cocoid rods (Eubacterium contaminantum, Coprococcus comes, Peptostreptococcus productus) than patients with ulcerative colitis.52 Furthermore, only Crohn affected mucosa contains 160-kDa, 120-kDa, and 110-kDa proteins that are exclusively precipitated by sera from patients,53 suggesting an immune response to foreign antigens selectively located in the Crohn lesion.

Taken together, these results support the suggestion that Crohn’s disease may be caused by immune responses to relatively non-pathogenic replicating microorganism(s). The actual lesion may be produced by an activated immune system rather than directly by the microorganism. Many microbial candidates have been suggested, including Mycobacteria, Spherooblats, and wall deficient Salmonella species, but their pathogenic significance remains obscure.14-15* This is also true for the C3b coated elements seen on the epithelium in our study, the same observation was made in six ulcerative colitis specimens. Conversely, the aggregates of C3b coated globular elements in the lamina propria have not been observed in ulcerative colitis despite severe epithelial damage. Their nature therefore needs further elucidation.

We have previously reported that patients with Crohn’s disease and ulcerative colitis have increased deposition of terminal complement complex54 and C3b55 in submucosal blood vessels, suggesting that vascular complement activation takes part in the pathogenesis. The vascular immune deposits do not generally contain detectable Ig components.56 In this limited study of prewashed tissue specimens, however, we observed that the vascular C3b deposits occasionally contained for C1q and C4c, suggesting classical complement activation. Furthermore, by three colour immunohistochemical staining, making it possible to focus on the relatively few terminal complement complex positive vessels containing both C3b and C4c, we observed some weak segmental IgG1 positively in submucosal vessels of two colonic specimens from Crohn’s disease. The nature of this observation needs further examination, but vascular complement activation may be involved in the multiple intestinal infarction that seems to be a feature of Crohn’s disease.57

Although activated T cells have been suggested to be particularly important in the pathogenesis of Crohn’s disease,58 local complement activation may contribute to the immunopathology. The absence of IgG, C1q, and C4c within the epithelium related immune deposits suggests that other immunopathological mechanisms operate in Crohn’s disease than in ulcerative colitis.

TSH is a research fellow of the Norwegian Cancer Society.
36 Graham DY, Marakesich DC, Yoshimura HH. Mycobacteria and inflammatory bowel disease result of culture. Gastroenterology 1987; 92: 436-42.
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Correction

Surface epithelium related activation of complement differs in Crohn's disease and ulcerative colitis by Halstensen et al, July 1992; 33: 902-8. We regret that an error occurred in this paper. The sentence on page 902 should read 'The results showed deposition of both C3b and terminal complement complex at the luminal surface. No IgG was colocalised in these deposits, however, in contrast with our previous observations in ulcerative colitis.'