

CASE REPORT

Cryptal lymphocytic coloproctitis: a new phenotype of lymphocytic colitis?

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Background/Aims: Lymphocytic colitis is a clinicopathological entity characterised by protracted watery diarrhoea and an increased number of intraepithelial lymphocytes (IELs) in the surface epithelium of the colonic mucosa. This report describes two patients with symptoms similar to those of lymphocytic colitis and an increased number of IELs, but within the cryptal epithelium.

Methods: The numbers of IELs were assessed in colorectal biopsies from the two patients. Sections were stained immunohistochemically for CD3, CD8, CD20, and TIA1.

Results: The colorectal biopsies had an abnormally high number of IELs in the epithelium of the crypts but not in the surface epithelium. The IELs in the crypts were CD3+++ , CD8+ , TIA1+ , and CD20–.

Conclusions: The histological diagnosis in these two patients was cryptal lymphocytic coloproctitis. Patients with similar symptoms and an increased number of IELs in the surface epithelium are now filed at this department as having surface lymphocytic coloproctitis. Immunohistochemistry showed that the cryptal IELs were cytotoxic suppressor T cells. Interestingly, a case of cryptal lymphocytic colitis was recently recorded in a non-human primate dying after years of protracted chronic diarrhoea. It is possible that antigens present in the lumen of the crypts elicit a lymphocytic reaction within the cryptal cells.

In 1980, Read *et al* noted a small increase in the number of inflammatory cells on colonic or rectal biopsy in eight of 27 patients with severe chronic diarrhoea of unknown origin.¹ Because of the normal sigmoidoscopic and barium enema appearances, the mild inflammation in those eight cases was called “microscopic colitis”. Later, that denomination was considered too ambiguous and in 1993 Levinson *et al* suggested microscopic colitis² as an umbrella terminology to cover cases with normal endoscopic or radiological findings but showing at histology collagenous colitis, allergic/eosinophilic colitis, and inflammatory disease of indeterminate type.

In 1989, Lazenby *et al* showed that an increased number of colonic intraepithelial lymphocytes (IELs) was the major distinguishing feature in many patients with microscopic colitis.³ Those authors proposed the term “lymphocytic colitis” to identify that subgroup.

In recent years, the number of published reports on lymphocytic colitis has increased rapidly,^{4–7} reflecting the increased histological detection of the disease.

While investigating various types of chronic colitis in non-human primates,⁸ we recently found an abnormally high number of IELs, not in the surface columnar epithelium of the colon, but in the epithelium of the colonic crypts,⁹ in a baboon that had died after protracted chronic diarrhoea.

More recently, while reporting colonic biopsies from patients with protracted watery diarrhoea we noticed an abnormally

high number of lymphocytes, not in the surface columnar epithelium, but within the epithelium of the crypts. Being aware of the phenomenon, we soon detected a second case.

The purpose of this report is to describe the clinical history in those two patients and to illustrate the histological features in colonoscopic biopsies.

CASE REPORTS

Patient 1

GD is a 52 years old married woman, mother of two children, treated for “coeliac disease”. For the past 22 years she has suffered 10 episodes of watery diarrhoea during each day and four during each night. She complained of abdominal pains, but no weight loss, and at palpation tenderness was found in the epigastrium.

Laboratory examinations revealed normal IgG antibodies against EuroD *Helicobacter pylori*, S-IgA-gliadin, S-IgA (3.0 g/litre), and no S-IgA-endomysium (1/10). A contrast x ray showed colon dehaustation and increased thickness of the colonic wall. Gastroduodenoscopy revealed no abnormalities. Biopsies revealed mild chronic gastritis. No *H pylori* could be detected.

A colonoscopic examination was done at a private clinic. The distal ileum, the right colon, and the transverse colon were apparently normal, but the sigmoid colon and the rectum were red and bled during the examination. Two biopsies were taken from the sigmoid colon and two from the rectum; they were initially reported as chronic coloproctitis at a private histopathology laboratory. The patient was subsequently referred to this hospital for treatment.

The histological re-evaluation here—in connection with a clinical pathological conference—disclosed many IELs in the crypts (fig 1). The mean number of IELs, assessed in five consecutive colonic crypts, was 46 IELs/100 cryptal epithelial cells (range, 32–55). In contrast, the mean number recorded in the surface columnar cells was 7 IELs/100 surface columnar cells (range, 0–13). The surface epithelial cells were columnar; flattened surface epithelial cells were not recorded.

Special stains (van Gieson, Masson trichrome) revealed a normal basement membrane underneath the surface epithelium. Immunohistochemistry showed that the IELs were CD3+++ (fig 2), CD8+ (fig 3), TIA1+ and CD20–.

CD3 reacts with the intracytoplasmic portion of the CD3 antigen expressed by T cells. The anti-CD8 antibody stains cytotoxic/suppressor T cells. CD20 is an antibody directed against an antigen present in most B cells. TIA1 is a mononuclear antibody that reacts with a 15 kDa cytoplasmic granule associated protein, expressed in lymphocytes possessing cytolytic potential.

This patient was treated with vitamin B12, omeprazol, loperamid, clomethiazol, neuroleptica, and antidepressive drugs.

Abbreviations: IELs, intraepithelial lymphocytes

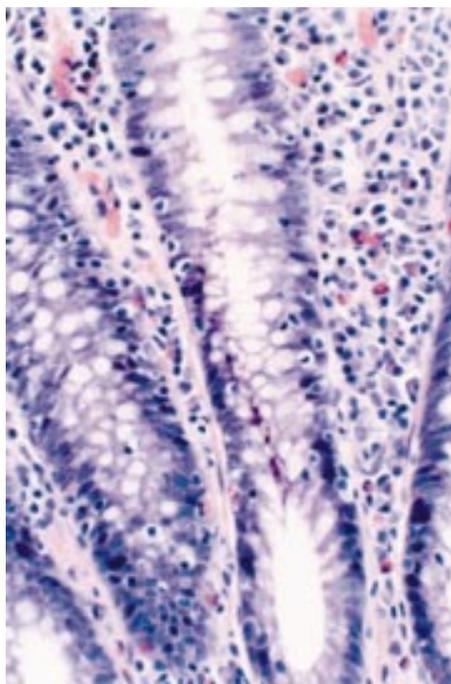


Figure 1 Colonic mucosa with many “in halo” cryptal intraepithelial lymphocytes. Cryptal intraepithelial lymphocytes appear somewhat “hidden” in the haematoxylin and eosin stain. (haematoxylin and eosin; original magnification, $\times 41.5$).

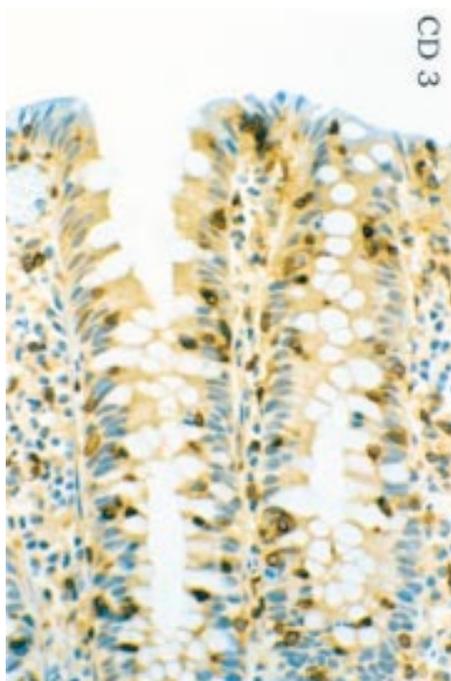


Figure 2 Colonic mucosa with many CD3+ cryptal intraepithelial lymphocytes. Note the occasional CD3+ superficial intraepithelial lymphocytes in the surface columnar epithelium. (CD3 immunostaining; original magnification, $\times 41.5$).

She received antibiotics on several occasions. Non-steroidal anti-inflammatory drugs were not administered.

Patient 2

CH is a 22 year old single woman who has had abdominal pains followed by watery diarrhoea for the past two years. Those symptoms were unrelated to meals. She was on preven-

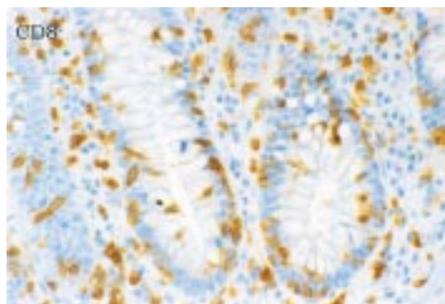


Figure 3 Colonic mucosa with many CD8+ cryptal intraepithelial lymphocytes (CD8 immunostaining; original magnification, $\times 41.5$).

tive pills (estradiol). A laparoscopy done five months previously showed no abnormalities. The night before the last consultation she awoke with abdominal pains, which were followed by watery diarrhoea. Tenderness in the right lower quadrant was found at palpation. A colonoscopy, performed at a private clinic, showed normal mucosa in the distal ileum, colon, and rectum. Biopsies were taken from the caecum; the right, the transverse, and the left colon; the sigmoid colon; and the rectum. The biopsies were initially reported as diagnostic for lymphocytic colitis at a private laboratory.

A thin basement membrane underneath the surface epithelium was demonstrated with van Gieson and Masson trichrome stains.

A recent duodenal biopsy showed normal histology. The patient was subsequently referred to our hospital for treatment.

The histological re-evaluation here—done in connection with a clinical pathological conference—disclosed an increased number of IELs in the colorectal crypts. The number of IELs, assessed in five consecutive crypts, showed a mean of 39 IELs/100 cryptal epithelial cells (range, 33–43). In contrast, the mean number of IELs recorded in the surface columnar cells was 8/100 surface columnar cells (range, 1–14).

The superficial cells were columnar; no flattened epithelial cells were detected. Immunohistochemistry showed that the IELs were CD3 + + +, CD8 + +, TIA1 +, and CD20–, suggesting that they were cytotoxic suppressor T cells. The patient was treated with antibiotics without success. Non-steroidal anti-inflammatory drugs were not administered.

DISCUSSION

These two patients had long periods of diarrhoea of unknown aetiology. Patient 1, with diarrhoea nearly “around the clock” for the past 22 years, was initially diagnosed as having coeliac disease. However, that diagnosis was not proved by either laboratory tests or duodenal and jejunal biopsies.

Normally, none to occasional IELs are found in the epithelium of the colorectal crypts, whereas the colorectal biopsies in our two patients showed an exceptionally high number of IELs in the crypts. In fact, the mean number of IELs in the crypt epithelium was 46 and 39 in the two patients, respectively. In the surface columnar epithelium, however, the mean number of IELs was only 11 and 12 IELs/100 surface cells in the two patients, respectively.

According to Lazenby *et al* the mean (SD) number of IELs in normal colonic mucosa is only 4.6/100 (1.5/100) epithelial cells.³ However, Wang *et al* claim that only cases with at least 15 IELs/100 surface columnar epithelial cells should be diagnosed as lymphocytic colitis,¹⁰ and Baert *et al* think that the number of IELs should exceed 20/100 epithelial cells.⁷ Thus, according to these two reports, the number of IELs in the surface epithelium in our two cases was not pathologically increased. In addition, no signs of surface epithelial injury (mucin depletion, epithelial cells with cuboidal configuration,

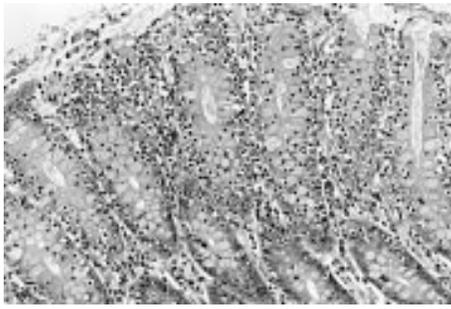


Figure 4 Cryptal lymphocytic colitis in a baboon. Note occasional intraepithelial lymphocytes in the surface columnar epithelium (haematoxylin and eosin; original magnification, $\times 15$).

or mucin-depleted flattened epithelial cells) reported to occur in lymphocytic colitis¹⁰ were found.

Recently, we reviewed colonoscopic biopsies from 10 cases filed as lymphocytic colitis. Those patients had watery diarrhoea, but their \times rays and colonoscopic examinations had been normal. In those 10 cases, the mean number of IELs in the surface epithelium was 28.4 (range, 21–37). The number of IELs in the crypts ranged from none to occasional.

In the two cases reported here, the absence of increased IELs in the surface epithelium, and of epithelial injury, strongly suggests that these two cases were not “classic” cases of lymphocytic (surface) colitis. In this respect, Wang *et al* think that lymphocytic colitis is a heterogeneous entity, which includes classic and “atypical” cases.¹⁰ In the atypical group, minimal endoscopic abnormalities and even macroscopic signs of colitis may be present at endoscopic examination.¹⁰ In agreement with this, abnormal radiological and endoscopic findings were seen in our case 1. Future studies (in a large number of cases) will elucidate whether classic and atypical subtypes also occur in cryptal lymphocytic coloproctitis.

There was no indication that these two patients suffered from coeliac disease or from lymphocytic colitis, collagenous colitis, infectious colitis, or parasitic colitis.

In the absence of an alternative diagnosis and because of an exceptionally high number of IELs in the epithelium of the crypts, the histological diagnosis was cryptal lymphocytic coloproctitis. The immunohistochemical pattern suggested that the IELs are cytotoxic suppressor T cells.

The treatment so far administered to those two patients has been unable to abrogate the intraepithelial lymphocytosis in the cryptal epithelium.

“A case of cryptal lymphocytic colitis was recently found in a non-human primate”

From these studies it would appear that two subphenotypes of IEL infiltration of the colorectal mucosa may be envisaged: one infiltrating the surface epithelium exclusively, and the other infiltrating the cryptal epithelium predominantly. The former subtype is being filed at this hospital as surface lymphocytic coloproctitis and the latter as cryptal lymphocytic

Take home messages

- There appears to be two subphenotypes of IEL infiltration of the colorectal mucosa
- One infiltrates the surface epithelium exclusively, and the other infiltrates the cryptal epithelium predominantly

coloproctitis. Interestingly, a case of cryptal lymphocytic colitis was recently found in a non-human primate⁹ (fig 4) that dyed after years of protracted chronic diarrhoea.

The cause(s) of the massive infiltration of cryptal colorectal cells by lymphocytes remains elusive. However, it is possible that in this condition the IELs are attracted by antigens present in the lumen of the crypts, whereas in surface lymphocytic colitis, the IELs are attracted by antigens present in the lumen of the organ. Differences between non-adherent mucins in the lumen of the crypts and adherent mucins and glycocalyx on the surface epithelium might have influenced the selection of the various antigens presented to the colorectal mucosa in susceptible individuals.

ADDENDUM

Since this paper was sent for publication, four new cases of cryptal lymphocytic colitis were histologically diagnosed in colonoscopic biopsies at this department.

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