Crohn's Disease Associated with Diffuse Lymphoid Hyperplasia of the Large Intestine: A Possible Role of the Lymph Follicle in HLA-DR Antigen Expression on Epithelium

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A 14-year-old girl diagnosed as Crohn's disease had lymphoid hyperplasia throughout the large bowel. Biopsy specimens from the lymphoid hyperplasia demonstrated non-caseous granulomas within the lymph follicles. An immuno-histochemical study of biopsy specimens showed that HLA-DR antigens were expressed on epithelium close to the lymph follicle, which was observed in all specimens containing the lymph follicle. This case provides evidence for the importance of the lymph follicle in the etiopathogenesis of Crohn's disease by demonstration of non-caseous granulomas within the lymph follicle and expression of HLA-DR antigens on epithelium close to the lymph follicle.

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Key words: intestinal (colonic) epithelium, red ring sign, non-caseous granuloma, class II antigens

Introduction

We report a child with Crohn's disease associated with diffuse lymphoid hyperplasia in the large bowel. An important role of the lymph follicle in the etiopathogenesis of Crohn's disease was implicated from immunohistochemical studies on epithelial class II antigens.

Case Report

A 14-year-old girl was referred to our department on July 27, 1989 because of fever, bloody diarrhoea, emaciation and a sore throat. An air-contrast barium enema performed on August 4 showed skip lesions, longitudinal ulcers, ragged ulcers, aphthoid ulcers, a cobblestone-like mucosal pattern, eccentric involvement, the disappearance of haustration, and a discontinuous irregularity of the wall (Fig. 1a). However, distensibility of the rectosigmoid was normal.

Colonoscopy revealed ulcers, including longitudinal and aphthoid ulcers, nodules, redness, and pseudopolyps in the colon. Intervening mucosa between lesions showed a normal vascular pattern. Most of mucosa in the rectosigmoid showed a clear vascular pattern, except for a few aphthoid ulcers in the lower part of the rectum and in the proximal sigmoid colon. Biopsy specimens from ulcer

margins showed distortion of the gland tubular pattern, and a plasma cell and lymphocytic infiltration with occasional non-caseous granulomas. The red ring sign (1) was observed at the rectosigmoid junction (Fig. 2a). Dye-spraying endoscopy using indigocarmine (2) visualised diffuse multiple round nodules with a central umbilication (Figs. 2b and 2c). A red ring encircling the border of the nodule was found (Fig. 2c). A biopsy specimen from the area showing the red ring sign revealed a lymph follicle (Fig. 3a), within which a non-caseous granuloma was found (Fig. 3b). The surrounding mucosa was completely normal; neither goblet cell depletion in the colonic epithelium, nor cell infiltration in the lamina propria was observed (Figs. 3a and 3b). A non-caseous granuloma within the lymph follicle was found in two other biopsy specimens taken from the nodules.

The diagnosis of Crohn's colitis was made.

1. Clinical course

The patient responded markedly to a sequential treatment of total parenteral nutrition (TPN), elemental diet (ED), and home elemental enteral hyperalimentation (HEEH) (3). She had clinical remission, and was discharged on September 27, 1989.

Air-contrast barium enema performed on discharge showed a picture of the remission (Fig. 1b), and that

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Fig. 1. X-ray films of air-contrast barium enema examinations performed on August 4, 1989 (1a) and September 12, 1989 (1b, 1c). The first examination demonstrated skip lesions, longitudinal ulcer (white arrows), ragged ulcers (black arrows), aphthoid ulcers (black arrow head), a cobblestone-like mucosal pattern (white arrow head) (1a), a discontinuous irregularity of the wall and disappearance of haustration. The irregularity of the wall had become smooth by the second examination (1b). Lymphoid hyperplasia is demonstrated throughout the large bowel (1b, 1c).

performed about four months later (January, 1990) showed restoration of haustration. Diffuse lymphoid hyperplasia was clearly demonstrated on X-ray film taken on discharge (Figs. 1b and 1c).

Endoscopy performed on discharge, and about three and a half months later, revealed the disappearance of the active findings seen on admission, except for two aphthoid ulcers in the cecum and a longitudinal ulcer at the hepatic flexure. However, the size of the longitudinal ulcer had decreased. Lymphoid hyperplasia was apparent in both occasions, as on admission, by indigocarmine-

spraying endoscopy (Figs. 2d, 2e and 2f).

2. Immunohistochemical study (Table 1)

Eleven biopsy specimens were obtained on the three occasions of colonoscopy; admission, discharge and about three and a half months after discharge. Class II antigens (HLA-DR, -DP, and -DQ antigens) were identified by the indirect immunoperoxidase staining method as previously described (4, 5). Anti-HLA-DR (Becton Dickinson, Mountain View, CA, USA) (6) and Nu-Ia (Nichirei, Tokyo, Japan) (7) were used as

Discussion

In the present case, diffuse colonic lymphoid hyperplasia was observed almost throughout the entire large intestine. The frequency with which lymphoid hyperplasia is found by barium enema or endoscopy differs among reports (9–16). Lymphoid hyperplasia is more easily detected by air-contrast barium enema than by conventional barium enema without air-contrast (11), and more easily detected by dye endoscopy than by routine endoscopy (2). It is reported that the younger the patients, the higher the frequency of occurrence of lymphoid hyperplasia (11, 14, 15, 17), with infants being the most frequently affected followed by children, adults, and the aged in that order. By air-contrast barium enema studies, Theander and Trägårdh (11) detected lymphoid hyperplasia in 5 of 53 cases (9.4%) in the 12 to 14-year age group, while it was prospectively detected in 4 of 11 cases (36.4%) in the 10 to 14-year age group by Riddleberger and Lebenthal (14).

Lymphoid hyperplasia can be classified into two groups; one being of no clinical significance and the other being disease associated. Even when lymphoid hyperplasia is of no clinical significance, it is thought to result from a wide variety of stimuli to the large bowel (9, 13, 14). Diseases associated with lymphoid hyperplasia include milk allergy (9), bacterial and viral infection (9, 18, 19), Crohn's disease (12, 13, 15, 16), ulcerative colitis (15, 16), colorectal cancer (16, 17), sarcoidosis (19), and immunoglobulin deficiency (20). In these instances, the lymphoid nodules tend to be greater than 2 mm in diameter in childhood (12) and greater than 4 mm in adults (13, 16). In sarcoidosis, noncaseating granulomatous inflammation, consistent with sarcoidosis, has been demonstrated in biopsy specimens from the lymphoid nodules (19). In Crohn's disease, granulomas were sometimes found within lymphoid follicles (21).

Recently, Kimura et al (1) reported an association between a red ring sign and Crohn's disease; of 15 patients with Crohn's disease, 5 (33%) showed the red ring sign. The sign was observed in an endoscopically normal area in the large bowel, and was microscopically identified to be the lymph follicle. In the present case, red ring signs were observed as part of lymphoid hyperplasia in the rectosigmoid, and were microscopically determined to be lymph follicles. Importantly, noncaseous granulomas were found within such lymph follicles. These observations lead to the conclusion that, in the present case, diffuse lymphoid hyperplasia was associated with Crohn's disease rather than being of no clinical significance.

Class II antigens (HLA-DR, -DP, and -DQ antigens) have been shown to be required for antigen presentation and various immunoregulatory mechanisms. Mayer et al (22) recently claimed that HLA-DR and -DP antigens could be identified on normal colonic epithelium using an avidin-biotin-peroxidase technique. However, some

of their results using this technique conflict with those from other investigators (23–25) including ours (4, 5). HLA-DR antigens are not expressed on normal, large intestinal epithelium by our technique (4, 5) and by others (23, 24). We previously described HLA-DR antigen expression on large intestinal epithelium in Crohn's disease (4). In the active stage, HLA-DR antigens were very frequently expressed even in the macroscopically uninvolved areas, whereas they were always expressed in macroscopically involved areas. This finding suggested that HLA-DR antigens are not merely expressed as a non-specific response to inflammation, but may be expressed as a primary change which results in macroscopic lesions (4). Some results in the present case are consistent with our previous reports (4, 5). Namely, HLA-DR antigens were expressed on the colonic epithelium in specimens taken from uninvolved areas by routine endoscopy (4). With regard to the intensity and extent of class II antigens on colonic epithelium, HLA-DR antigens were the most strongly expressed, followed by HLA-DP expression (5). A new finding is that HLA-DR antigen expression was observed on epithelium close to the lymph follicle. Spencer et al (26), studying normal intestinal tissue, noticed HLA-DR expression on the epithelium directly adjacent to the lymphoid tissue including the lymph follicle, and suggested a role of the lymphoid tissue in the expression. Our preliminary study showed a difference between patients with Crohn's disease and those with diseases other than Crohn's disease in the extent of HLA-DR expression on epithelium close to the lymph follicle. In the latter, HLA-DR antigens were rarely expressed, but when expressed, the extent was extremely limited around the lymph follicle (Chiba M, et al: manuscript in preparation).

The mechanism of induction of class II antigens on colonic epithelium is unknown. However, cytokines such as γ -interferon (27–29), tumor necrosis factor (29), interleukin 4 (30), and unknown agents (31) have been shown to induce expression of HLA-DR or -DQ antigens on various human cells including intestinal epithelium *in vitro*. Therefore, it would be of interest to determine whether the lymph follicle also produces such cytokines.

Since an aphthoid ulcer, which has been recognized as an early finding of Crohn's disease, is an inflammation of the lymph follicle (21, 32), it is quite natural to speculate that lymphoid hyperplasia has a very important role in the etiopathogenesis in Crohn's disease. In the present case, non-caseous granulomas were found in the lymph follicle and HLA-DR antigens were expressed on the epithelium close to the lymph follicle. Further microbiological, histological, and immunological studies of the lymph follicle may provide clues to the etiopathogenesis of Crohn's disease.

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