CASE REPORT

Microscopic Colitis with Granuloma Which Responded to Steroid Therapy

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Abstract

We present a patient with chronic watery diarrhea and weight loss, in whom colonoscopic findings were consistent with microscopic colitis, but histopathological examination revealed granulomatous inflammation. A 67-year-old Japanese female with a several year history of chronic watery diarrhea and body weight loss was admitted to our hospital. Her laboratory data showed hypoalbuminemia and high levels of serum immunoglobulin G and C-reactive protein. Colonoscopic findings were grossly normal. Histopathology showed inflammatory cell infiltrates with non-necrotizing granulomas and multinucleated giant cells, indicating that this was not conventional microscopic colitis, lymphocytic colitis or collagenous colitis. After treatment with prednisolone her symptoms and laboratory data improved dramatically, and she went into remission without the necessity of further steroid treatment.

Key words: microscopic colitis, granuloma, multinucleated giant cells, steroid

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Introduction

Microscopic colitis (MC) was originally described by Lindstrom as “collagenous colitis” in 1976 (1). In 1980, Reed et al first defined the term of MC, describing it as a clinical entity with inflammation in colon biopsy specimens of patients with chronic diarrhea and normal findings on sigmoidoscopy and barium enema (2). This term is now used as an umbrella term that encompasses both collagenous colitis and lymphocytic colitis (3). Both entities have a similar clinical presentation including chronic watery diarrhea, and normal colonoscopic findings, but they differ histologically. Lymphocytic colitis is characterized by an increase in intraepithelial lymphocytes and collagenous colitis by an increase in subepithelial collagen. It remains unclear whether these conditions are separate disease entities, or are parts of a single disease spectrum.

MC generally does not show granulomas histologically, however Saurine et al. reported four cases in which the clinical and endoscopic findings were consistent with MC, but the inflammatory infiltrate included a conspicuous granulomatous reaction (4). We report a case in which the clinical and colonoscopic findings were consistent with microscopic colitis, but histopathological examination revealed granulomatous inflammation, which was successfully treated with steroids.

Case Report

A 67-year-old Japanese female suffered from chronic diarrhea (more than 2 bowel movements/day) without blood or mucus for about 4.5 years. She lost 6 kg of body weight per 6 months during the course of these symptoms. She had a history of type II diabetes mellitus (DM) and asthma for many years. On the first hospital day, there was no abnormal finding on gastroduodenoscopy, abdominal ultrasonography, computed tomography or magnetic resonance cholangiopancreatography. Although CA19-9 and elastase were slightly elevated (56 U/ml and 646 ng/dl, respectively),...
which is often observed in patients with chronic pancreatitis, radiological investigations did not show any abnormalities of her pancreas. Her chronic watery diarrhea was treated with 3 g albumin tannate, 2 mg loperamide hydrochloride, 36 mg lactobacillus bifidus and 22.5 mg mepenzolate bromide daily. Her symptoms had improved for three years, but the loss of appetite and watery diarrhea (more than 6 bowel movements/day) recurred. After four months she experienced nausea, epigastralgia and difficulties with dietary intake, and she was admitted to our hospital.

Laboratory data on admission are shown in Table 1 and Fig. 1. Hemoglobin was 10.8 g/dl and white blood cell count was 8000/mm³. C-reactive protein (CRP) was 1.04 mg/dl. Serum total protein and albumin (ALB) concentrations were 6.7 g/dl and 2.0 g/dl, respectively. Total cholesterol and triglyceride were 82 mg/dl and 50 mg/dl, respectively. Serum immunoglobulin (Ig) G level was high (2600 mg/dl). No remarkable malabsorption was detected with the D-xylose test or Sudan III staining of stools. α1-antitrypsin clearance was 26.2 ml/day. This result indicated mild protein leakage, but a protein leakage 125-I-labeled albumin test was normal. Stool cultures and anti-Yersinia enterocolitica antibody were negative. Total colonoscopic examination was performed on the 3rd hospital day, which did not show any erosions, ulcers, mucosal edema or other macroscopic abnormalities (Fig. 2).

Biopsy specimens of the colon revealed a diffuse infiltrate of inflammatory cells with multinucleated giant cells (Fig. 3A) and non-necrotizing epithelioid granulomas. Both cryptolytic and pericryptal granulomas were seen (Fig. 3B and 3C). Immunohistochemistry showed that these granulomas were positively stained by anti-CD68 monoclonal antibody, which is a marker of macrophages (Fig. 3D). Because the concentration of lymphocyte infiltrates was less than 10 lymphocytes/100 epithelial cells and no subepithelial collagenous band was seen, this patient was diagnosed as neither lymphocytic colitis nor collagenous colitis. Amyloid deposits were not evident (data not shown). Interestingly, duodenal biopsy showed inflammation with small foci of histiocyte aggregation (mirogranulomas) (Fig. 3E).

She was managed with total parenteral nutrition and albu-

![Figure 1. Clinical course of this case. TPN, total parenteral nutrition; PSL, prednisolone; ALB, albumin; Ig, immunoglobulin.](image-url)
min infusion for 20 days, but her ALB concentration only increased slightly from 2.0 g/dl to 2.4 g/dl, and the watery diarrhea was unchanged. Intravenous administration of 30 mg/day of prednisolone (PSL) was started on the 55th hospital day because the histopathological findings supported active inflammation of the lower intestine. The watery diarrhea improved rapidly until she was passing one formed stool every five days. PSL was tapered to 10 mg/day at discharge (the 90th hospital day). Serum ALB improved to 3.4 g/dl and serum IgG level decreased to 1610 mg/dl (Fig. 1 and Table 1). Colonoscopy was repeated before discharge. Histopathological examination of the colon showed that the inflammation had been reduced, and no granulomas were observed (data not shown).

Discussion

We presented a case in which the clinical and endoscopic findings were consistent with MC, but histological findings revealed inflammation with granulomas. The histopathology of MC is characterized by intraepithelial lymphocytosis and mixed inflammatory infiltrate of the lamina propria, and in the collagenous variant, thickening of the subepithelial band of collagen. The presence of intraepithelial lymphocytosis with more than 10 lymphocytes/100 epithelial cells has been classified as lymphocytic colitis. The presence of inflammatory response in the lamina propria with detachment of the epithelium and thickening of the subepithelial collagen band has been classified as the collagenous variant of MC, collagenous colitis.

Although mucosal granulomas are uncommon in MC, Saurine et al. reported four cases of microscopic colitis with inflammatory infiltrate including a conspicuous granulomatous reaction (4) (Table 2). Granulomas usually consist of epithelioid cells, multinucleated giant cells and lymphocytes. The epithelioid cells and giant cells in granulomas are thought to be macrophage lineage cells. Although the detailed mechanism of granuloma formation remains unknown, it has been reported that the epithelioid and giant cells in the granuloma simultaneously express class II molecules and co-stimulatory molecules which are indispensable to antigen specific activation of T cells (5). Multinucleated giant cells and epithelioid cells in the granulomas strongly express CD 80/86 molecules, especially in Crohn’s disease (6). Granulomas in the intestinal mucosa are therefore evidence of some immune reaction in the mucosa. Granulomas of the gastrointestinal tract are seen in sarcoidosis, infectious diseases, foreign body reactions and drug reactions, as well as in Crohn’s disease. In the upper gastrointestinal tract, the most common cause of granulomatous gastritis is Crohn’s disease (7, 8). In the colon, mucosal granulomas are associated with a number of conditions including Crohn’s disease, tuberculosis, diversion colitis and drug reactions (9, 10). As in the four cases reported by Saurine et al, the present case had
diffuse non-necrotizing granulomas and giant cells, with inflammatory cell infiltration in the colonic mucosa. The lymphocyte infiltration and collagen band were not significant compared with typical lymphocytic colitis and collagenous colitis. This patient did not have a past history of tuberculosis, sarcoidosis or other chronic inflammatory disorders complicated by granulomas. Colonoscopic findings did not reveal inflammatory bowel disease, infection or tuberculosis. Interestingly, all of the five cases of MC with granuloma (the present case and the four previously reported cases, Table 2) are female, and four of the five patients were more than 60 years old. Although a female preponderance has

Figure 3. Histology of colonic biopsy and duodenal biopsy specimens. Infiltration of inflammatory cells with a multinucleated giant cell (A), a non-necrotizing cryptolytic granuloma (B), and a granuloma in the lamina propria, positively stained by anti-CD68 monoclonal antibody (C,D). Duodenal biopsy showed inflammation with small foci of histiocyte aggregation (miicrogranulomas) (E).

Table 2. Cases of MC with Granulome

<table>
<thead>
<tr>
<th>Age and Sex</th>
<th>Complications</th>
<th>Medications</th>
<th>Final Treatment for Colitis</th>
</tr>
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<tbody>
<tr>
<td>Saurina TJ et al. (ref. 4)</td>
<td>61 y/o female</td>
<td>type2 DM, Hashimoto disease,</td>
<td>-</td>
</tr>
<tr>
<td>35 y/o female</td>
<td>-</td>
<td>-</td>
<td>PSL enema</td>
</tr>
<tr>
<td>76 y/o female</td>
<td>IHD, hypertension</td>
<td>aspirin, allopurinol simvastatin, metprolol</td>
<td>PSL</td>
</tr>
<tr>
<td>74 y/o female</td>
<td>type2 DM, hypertension,</td>
<td>aspirin, allopurinol</td>
<td>discontinue allopurinol</td>
</tr>
<tr>
<td>present case</td>
<td>67 y/o female</td>
<td>type2 DM, hyperglobulinemia</td>
<td>-</td>
</tr>
</tbody>
</table>
been reported in MC, especially in collagenous colitis, (11-14), recent reports show that this remains controversial (3). Zins et al reported no significant gender differences for collagenous colitis or lymphocytic colitis (15). The female preponderance in these five cases suggests that they might have a common pathophysiology.

The granulomatous inflammatory reaction could be a drug reaction (16). Two of the four cases reported by Saurine et al had taken allopurinol and nonsteroidal anti-inflammatory drugs (Table 2). However, the present patient had not taken any medication that could cause a granulomatous inflammatory reaction in the colon. In our case and the previous four cases, Crohn’s disease was excluded on clinical grounds and by endoscopic examination. Interestingly, our case had type II DM, as did two of the four cases reported by Saurine et al. The present case was also complicated by hyperglobulinemia (IgG 2600 mg/dl) which suggests the possibility of an autoimmune background, and treatment with prednisolone was effective. Serum IgG decreased to 1610 mg/dl at the same time that clinical symptoms improved.

Furthermore, interestingly, we found histiocye infiltration in the duodenum, which suggests that chronic inflammation may also involve the upper gastrointestinal tract. It is an important issue whether or not the upper gastrointestinal tract including the small intestine was involved in the present case. In the other four cases reported by Saurine et al, it is unclear whether histopathological examination of the upper gastrointestinal tract was performed. Zuckerman et al reported a case of idiopathic granulomatous gastritis which also involved the sigmoid colon and esophagus (17). Therefore, in the present case, we cannot deny the possibility that microscopic lesions extended to the small intestine and duodenum, and affected protein loosing from the small intestine. Because the endoscopic techniques for the small intestine have progressed in recent years, we should screen small intestinal lesions in MC patients to establish the new entity “microscopic enterocolitis”.

Treatment for MC with granulomas has not been well established. 5-aminosalicylates and steroids are used to treat conventional MC, lymphocytic colitis and collagenous colitis (3). In the present case, prednisolone rapidly induced clinical remission and improved laboratory markers including ALB, CRP and IgG, while the efficacy of steroids in the previous four cases was unclear (4).

In summary, we present a variant case of MC, characterized by inflammation with granulomas that responded to steroid therapy. Although clinical symptoms and endoscopic findings were consistent with MC, histology was not typical for lymphocytic colitis or collagenous colitis. Considered together with the previous cases, our report suggests that we should identify a new entity, which shows histological inflammation and granulomas of the colon with normal endoscopic findings, as a variant of MC.

References