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【 CASE REPORT 】

Eosinophilic Gastroenteritis in an Ulcerative Colitis Patient During Treatment with Tumor Necrosis Factor-alpha Antagonist

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Abstract:
A 45-year-old man with steroid-dependent ulcerative pancolitis was hospitalized with frequent diarrhea, abdominal pain and distension 3 months after induction of golimumab, a tumor necrosis factor-alpha antagonist. Computed tomography showed wall thickening from the stomach to the colon and massive ascites. Peripheral blood test revealed eosinophilia. A large number of eosinophils were observed in the ascites fluid. Although esophagogastroduodenoscopy showed no abnormal findings and colonoscopy showed ulcerative colitis with a Mayo endoscopic subscore of 1, eosinophil infiltration was histologically observed. Based on these findings, we diagnosed him with eosinophilic gastroenteritis and started prednisolone. Consequently, his eosinophil counts and abdominal symptoms dramatically improved.

Key words: eosinophilic gastroenteritis, ulcerative colitis, tumor necrosis factor-alpha antagonist, ascites, prednisolone

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Introduction

Eosinophilic gastroenteritis (EGE) is a rare digestive disorder characterized by eosinophilic infiltration of the gastrointestinal tract wall. In 1937, Kaijser et al. reported this disorder for the first time (1). Since EGE lacks specific gastrointestinal symptoms and endoscopic findings, its exact epidemiology is not well known. In a recent report from a population-based database in the United States, the prevalence of EGE was estimated at 5.1 per 100,000 people (2). In a Japanese survey of eosinophilic gastrointestinal disorders from 2004 to 2009, EGE was frequently observed in middle-aged persons, and approximately half of the patients had a history of allergic diseases (3). Recent studies have shown that Th2-type immune responses are associated with the pathogenesis of EGE (4).

We herein report a case EGE in an ulcerative colitis patient during treatment with a tumor necrosis factor (TNF)-alpha antagonist.

Case Report

A 45-year old Japanese man had been admitted to our hospital with ulcerative pancolitis 10 years before presentation. Colonoscopy revealed typical features of moderate ulcerative colitis with a Mayo endoscopic subscore of 2 (Fig. 1). A histological examination of biopsy specimens revealed diffuse inflammatory cell infiltration in the mucosal layer, crypt abscess, and goblet cell depletion. He had been treated initially with 5-aminosalicylic acid (5-ASA) and prednisolone. Since the induction of remission with prednisolone, he had been treated only with 5-ASA to maintain remission. However, he eventually developed a relapse and re-

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quired golimumab, a TNF-alpha antagonist, to maintain remission six months before presentation.

The patient then began to have frequent diarrhea (over 10 times a day), heartburn, abdominal pain, and distension 3 months after starting golimumab. The laboratory data showed no elevation of inflammatory response, with the following findings: C-reactive protein, 0.14 ng/mL, and erythrocyte sedimentation rate, 5 mm/h. Peripheral blood tests showed elevated white blood cells (19,000/μL), with eosinophilia (40% eosinophils, total count 7,600/μL). He had no history of food or drug allergies and no concomitant atopic disorder. Regarding the laboratory tests performed when starting golimumab, the eosinophil counts were in the normal range of 250/μL. A stool culture was negative for common pathogens and *Clostridium difficile* toxins A and B. Cytomegalovirus antigenemia tests were negative. Examinations of stool ova and parasites were negative. Serum immunoglobulin E levels were normal (14.6 KU/L). The results of the drug-induced lymphocyte stimulation test for 5-ASA and golimumab were both negative (5-ASA: 73 cpm with a stimulation index of 1.0%; golimumab: 100 cpm with a stimulation index of 1.5%). Contrast-enhanced computed tomography revealed edematous bowel wall thickening from the stomach to the colon with massive ascites (Fig. 2). Abdominal paracentesis revealed a large number of white cells that were predominantly eosinophils (over 95%). Esophagogastroduodenoscopy showed no specific findings (Fig. 3A, B). However, biopsy specimens obtained from the esophagus, stomach, and duodenum revealed eosinophilic infiltration at 10-15 cells/high -power field (Fig. 4A, B). Colonoscopy revealed rough mucosa, erythema, and friability, continuously from the terminal ileum to rectum, evaluated as a Mayo endoscopic subscore of 1 (Fig. 3C, D). Biopsy specimens obtained from the terminal ileum to the rectum revealed eosinophil infiltration at 30-100 cells/high-power field (Fig. 4C, D).

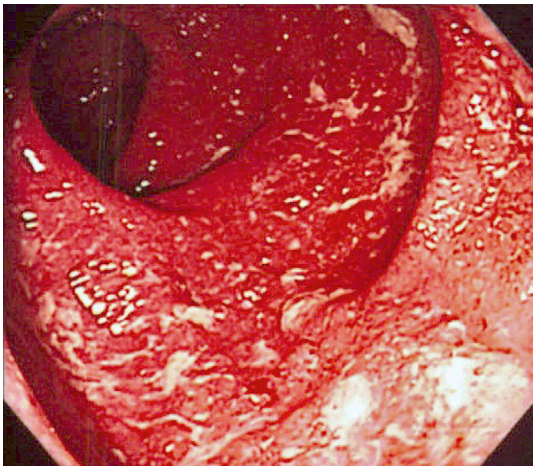

Figure 1. Endoscopic findings at the first visit. Colonoscopy showed loss of vascular pattern, erythema, erosions, friability, and easily bleeding mucosa and evaluated as moderate ulcerative pancolitis with a Mayo endoscopic subscore of 2.

Based on these findings, the patient was diagnosed with EGE with ulcerative colitis. He started prednisolone 40 mg/day (Fig. 5). His abdominal symptoms dramatically improved, and the ascites disappeared. Eosinophil counts immediately improved to normal by three days later. The dose of prednisolone was gradually tapered over the subsequent 2 weeks, and 5 mg of prednisolone was continued for maintenance therapy.

Discussion

TNF-alpha antagonists are commonly used to treat rheumatoid arthritis, psoriasis, and inflammatory bowel diseases. In Japanese clinical practice guidelines for inflammatory bowel disease, TNF-alpha antagonists are standard therapy for steroid-refractory or steroid-dependent moderate to severe ulcerative colitis (5). Common side effects of TNF-alpha antagonists are injection site reactions, infusion reactions, neutropenia, and upper respiratory tract infections. However, eosinophilia is a rare adverse event during treat-

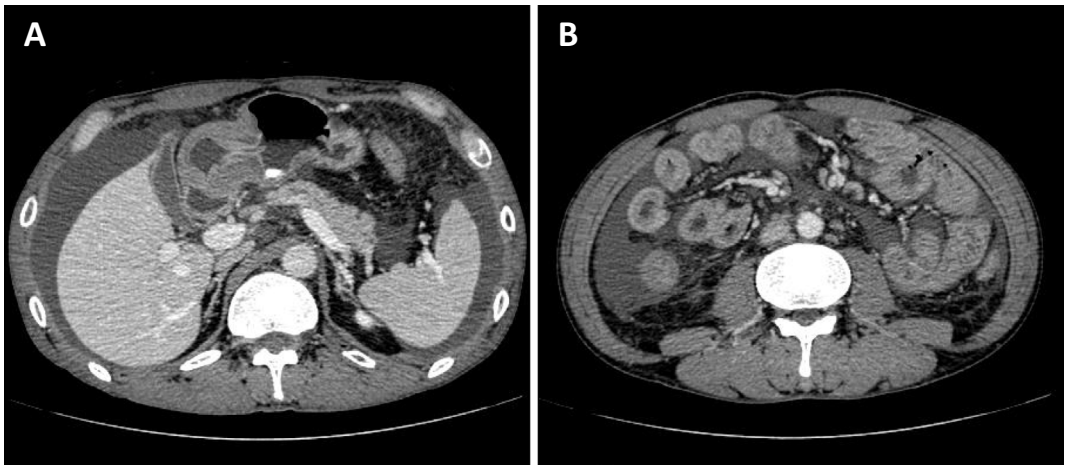

Figure 2. Contrast-enhanced computed tomography revealing bowel wall thickening continuously from the stomach to the colon, as well as massive ascites.

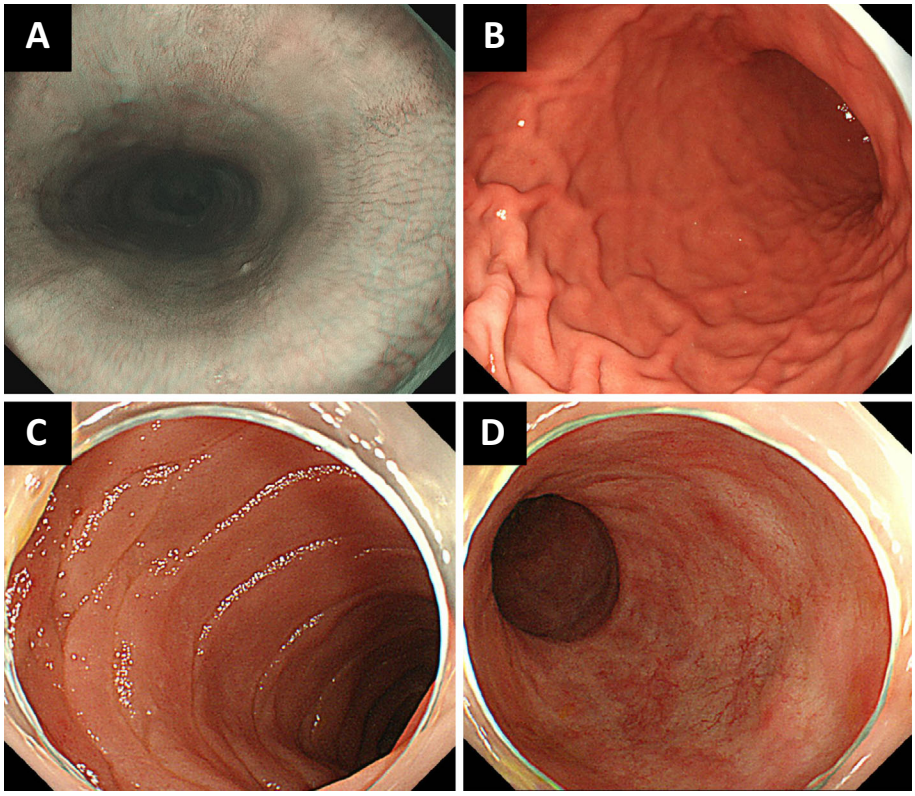

Figure 3. **Endoscopic findings. A: esophagus; B: stomach; C: terminal ileum; D: rectum. Esophagogastroduodenoscopy showed no abnormal findings. Colonoscopy revealed a decreased vascular pattern and was evaluated as a Mayo endoscopic subscore of 1.**

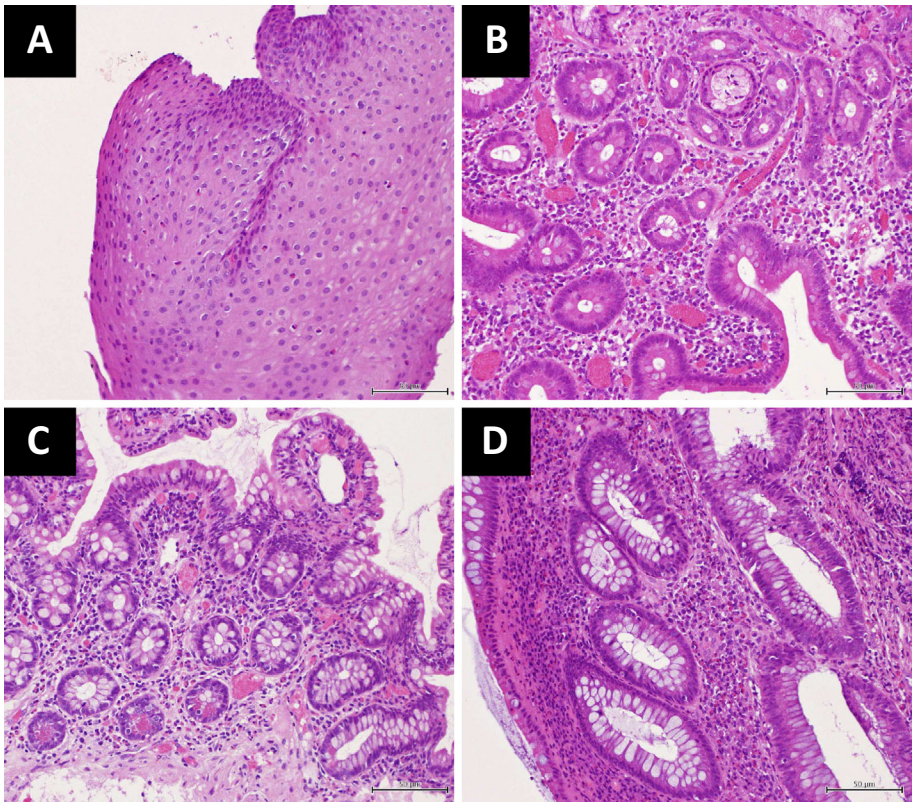

Figure 4. **Histological findings of the biopsy specimens revealing eosinophilic infiltration (Hematoxylin and Eosin staining, original magnification ×400). A: esophagus; B: stomach; C: terminal ileum; D: rectum.**

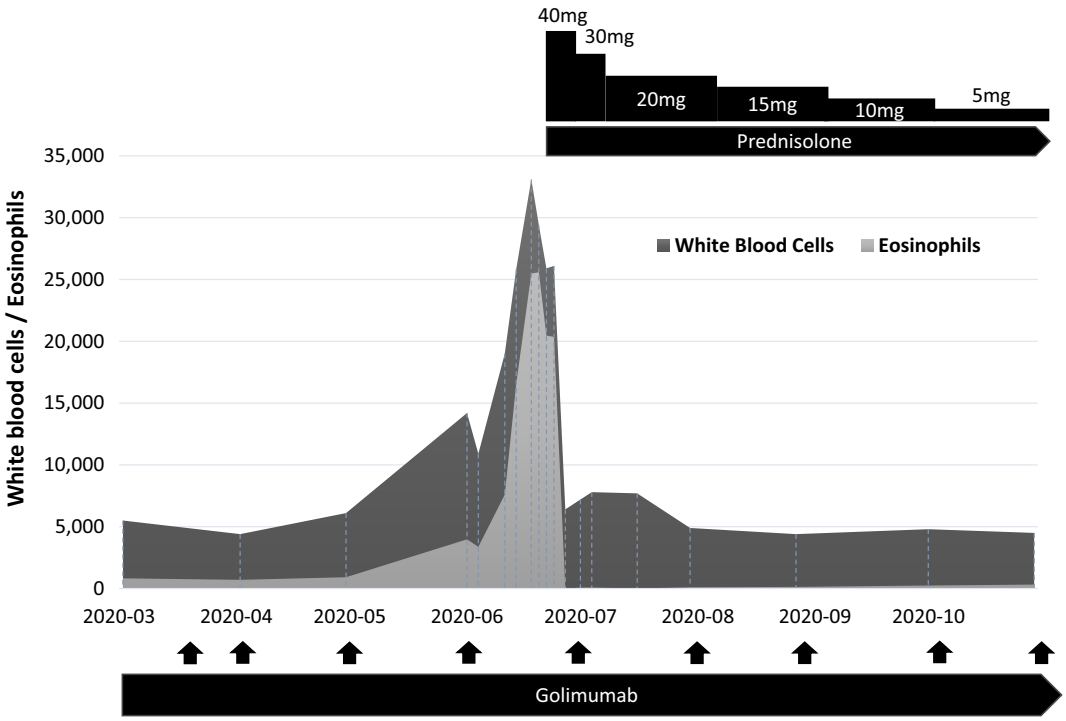

Figure 5. **White blood cell and eosinophil levels during the patient's clinical course.**

ment of TNF-alpha antagonists. According to the eHealthMe database, eosinophilia was observed during golimumab treatment in 0.02% of patients, adalimumab treatment in 0.03%, etanercept treatment in 0.02%, and infliximab treatment in 0.06% (6). Several cases of eosinophilia associated with TNF-alpha antagonist use have been reported (7-9). Nevertheless, there have been no reports of EGE during TNF-alpha antagonist for ulcerative colitis.

Interestingly, Muir et al. reported a patient with Crohn's disease that developed severe EGE after treatment with infliximab or adalimumab (10). EGE occurred three months after induction of golimumab in our case. Muir et al. reported that eosinophilia in peripheral blood and worsening of abdominal symptoms appeared six months to one year after induction of TNF-alpha antagonist. Reports of psoriasis also showed that eosinophilia developed about three months after induction of TNF-alpha inhibitors (11). Although the mechanism underlying eosinophilia induced by TNF-alpha antagonists remains unknown, both ulcerative colitis and Crohn's disease were significantly associated with Th1 or Th17 cytokines (12). TNF-alpha antagonists cause a shift from Th1 cytokine activity to Th2 activity, leading to elevated levels of Th2 cytokines (IL-4, IL-5, IL-13) and eotaxin, subsequently resulting in eosinophilic infiltration (11, 13-16). Quaglino et al. showed in psoriasis patients treated with etanercept that the response to TNF-alpha antagonist led to the reversal of the Th1/Th17 activation and a concomitant upregulation of Th2 and regulatory T cell subsets (17). Taken together, these findings suggest that initiation of golimumab for ulcerative colitis might be associated with the development of EGE.

Klein et al. proposed classifying EGE into three patterns according to the depth of eosinophilic infiltration: mucosal, muscular, and serosal patterns (18). The mucosal pattern is the most common subtype of EGE, presenting mainly with abdominal pain, nausea, vomiting, diarrhea, anemia, and weight loss. The muscular pattern is the second-most common subtype, characterized by bowel wall thickening and narrowing of the gastrointestinal tract and resulting in symptoms of intestinal obstruction. The serosal pattern is the rarest subtype, typically presenting with diarrhea, vomiting, and in some cases ascites. The serosal type has a better response to corticosteroids than the other types (19). In the present case, intestinal wall thickening and ascites were observed, suggesting that our case was EGE of the predominantly serosal type.

There are no specific endoscopic features of EGE; however, erythema, white specks, focal erosion, ulcerations, fold thickening, polyp, nodules, and friability have been reported (20). The histology of gastrointestinal mucosal biopsies is the gold standard for the diagnosis of EGE. Biopsies from both normally and abnormally appearing mucosa should be taken, as a large number of eosinophils might be observed even in mucosal sites that appear normal. At present, the number of eosinophils needed to diagnose EGE is unclear. In Japan, it is suggested that eosinophil infiltration of ≥20 per high-power field across several biopsies is needed to diagnose EGE. However, in a serosal type, like the present case, in which eosinophil infiltration was observed only in the deep part of the gastrointestinal tract, it is often difficult to confirm the diagnosis using endoscopy alone. As in the present case, the presence of eosinophilic ascites strongly suggests EGE.

Prednisolone is first-line treatment for the induction of re-

mission of EGE as well as for the treatment of ulcerative colitis (21). Initially, we started prednisolone because we believed EGE to be a complication of ulcerative colitis. Indeed, the eosinophil count and abdominal symptoms improved dramatically after starting prednisolone. However, approximately 20% of patients with EGE have steroid-dependent disease, and low-dose prednisolone may be required to maintain remission (22). If the development of EGE is actually an adverse reaction to the TNF-alpha antagonist, golimumab should be changed to another agent to avoid future flares. However, a previous case report of Crohn's disease reported that switching between TNF-alpha antagonists was not effective (10). Therefore, it might be desirable to switch to tofacitinib, a Janus kinase (JAK) inhibitor. Tofacitinib preferentially inhibits JAK1 and JAK3, thereby blocking and downregulating the exaggerated Th2 immune response. This approach was shown to be effective in the treatment of ulcerative colitis (23).

In summary, we report the case of a patient with ulcerative colitis who developed EGE after the introduction of golimumab. The administration of TNF-alpha antagonist for ulcerative colitis might induce EGE.

The authors state that they have no Conflict of Interest (COI).

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