CASE REPORT

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

Sho Hayashida¹, Shunsuke Sato¹, Yuji Shimada¹, Hironori Tsuzura¹, Yuji Ikeda¹, Sho Takahashi¹, Sho Sato¹, Nozomi Amano¹, Ayato Murata¹, Akihito Nagahara² and Takuya Genda¹

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

(Intern Med 59: 1977-1981, 2020)  
(DOI: 10.2169/internalmedicine.4554-20)

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-
quired golimumab, a TNF-alpha antagonist, to maintain re-
mission 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 fol-
lowing findings: C-reactive protein, 0.14 ng/mL, and eryth-
rocyte sedimentation rate, 5 mm/h. Peripheral blood tests
showed elevated white blood cells (19,000/μL), with eosino-
philia (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 nor-
mal range of 250/μL. A stool culture was negative for com-
mon pathogens and *Clostridium difficile* toxins A and B.
Cytomegalovirus antigenemia tests were negative. Examina-
tions of stool ova and parasites were negative. Serum immu-
noglobulin 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 to-
mography revealed edematous bowel wall thickening from
the stomach to the colon with massive ascites (Fig. 2). Ab-
dominal 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 in-
filtration at 10-15 cells/high-power field (Fig. 4A, B).
 Colonoscopy revealed rough mucosa, erythema, and friabi-
ity, continuously from the terminal ileum to rectum, evalu-
ated as a Mayo endoscopic subscore of 1 (Fig. 3C, D). Bi-
opsy specimens obtained from the terminal ileum to the rec-
tum revealed eosinophil infiltration at 30-100 cells/high-
power field (Fig. 4C, D).

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 im-
proved, and the ascites disappeared. Eosinophil counts im-
mediately 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 mainte-
nance therapy.

**Discussion**

TNF-alpha antagonists are commonly used to treat rheu-
matoid 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 se-
vere ulcerative colitis (5). Common side effects of TNF-
alpha antagonists are injection site reactions, infusion reac-
tions, neutropenia, and upper respiratory tract infections.
However, eosinophilia is a rare adverse event during treat-

**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 ulcer-
ative pancolitis with a Mayo endoscopic subscore of 2.

**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.
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-

![Figure 5. White blood cell and eosinophil levels during the patient’s clinical course.](image-url)
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).

References

1. Kaijser R. Zur Kenntnis der allergischen Affektionen des Verdauungskanals vom Standpunkt des Chirurgen aus. Arch Klin Chir 188: 36-64, 1937.
2. Mansoor E, Saleh MA, Cooper GS. Prevalence of eosinophilic gastroenteritis and colitis in a population-based study, from 2012 to 2017. Clin Gastroenterol Hepatol 15: 1733-1741, 2017.
3. Kinoshita Y, Furuta K, Ishimura N, et al. Clinical characteristics of Japanese patients with eosinophilic esophagitis and eosinophilic gastroenteritis. J Gastroenterol 48: 333-339, 2013.
4. Zhang M, Li Y. Eosinophilic gastroenteritis: a state-of-the-art review. J Gastroenterol Hepatol 32: 64-72, 2017.
5. Matsuoka K, Kobayashi T, Ueno F, et al. Evidence-based clinical practice guidelines for inflammatory bowel disease. J Gastroenterol 53: 305-353, 2018.
6. eHealthMe [Internet]. [cited 2020 Jan 18]. Available from: https://www.ehealthme.com/
7. Malisiewicz B, Murer C, Pachlopnik Schmid J, et al. Eosinophilia during psoriasis treatment with TNF antagonists. Dermatology 223: 311-315, 2011.
8. Boura P, Sarantopoulos A, Lefaki I, et al. Eosinophilic cellulitis (Wells’ syndrome) as a cutaneous reaction to the administration of adalimumab. Ann Rheum Dis 65: 839-840, 2006.
9. Vester K, Rüger RD, Harth W, Simon JC. Transient blood eosinophilia during treatment with adalimumab. J Eur Acad Dermatol Venereol 26: 924-925, 2012.
10. Muir A, Surrey L, Kriegermeier A, Shaikhkalil A, Piccoli DA. Severe eosinophilic gastroenteritis in a Crohn’s disease patient treated with infliximab and adalimumab. Am J Gastroenterol 111: 437-438, 2016.
11. Malisiewicz B, Murer C, Pachlopnik Schmid J, et al. Eosinophilia during psoriasis treatment with TNF antagonists. Dermatology 223: 311-315, 2011.
12. Kobayashi T, Okamoto S, Hisamatsu T, et al. IL-23 differentially regulates the Th1/Th17 balance in ulcerative colitis and Crohn’s disease. Gut 57: 1682-1689, 2008.
13. Mattes J, Foster PS. Regulation of eosinophil migration and Th2 cell function by IL-5 and eotaxin. Curr Drug Targets Inflamm Allergy 2: 169-174, 2003.
14. Kinoshita Y, Ishimura N, Oshima N, et al. Recent progress in the research of eosinophilic esophagitis and gastroenteritis. Digestion 93: 7-12, 2016.
15. Tugnet N, Youssef A, Whailet AJ. Wells’ syndrome (eosinophilic cellulitis) secondary to infliximab. Rheumatology (Oxford) 51: 195-196, 2012.
16. Boura P, Sarantopoulos A, Lefaki I, Skendros P, Papadopoulos P. Eosinophilic cellulitis (Wells’ syndrome) as a cutaneous reaction to the administration of adalimumab. Ann Rheum Dis 65: 839-840, 2006.
17. Quaglini P, Bergallo M, Ponti R, et al. Th1, Th2 and regulatory T cell pattern in psoriatic patients: modulation of cytokines and gene targets induced by etanercept treatment and correlation with clinical response. Dermatology 223: 57-67, 2011.
18. Klein NC, Hargrove RL, Sleisenger MH, Jeffries GH. Eosinophilic gastroenteritis. Medicine (Baltimore) 49: 299-319, 1970.
19. Khan S. Eosinophilic gastroenteritis. Best Pract Res Clin Gastroenterol 19: 177-198, 2005.
20. Sunkara T, Rawla P, Yarlagadda KS, Gaduputi V. Eosinophilic gastroenteritis: diagnosis and clinical perspectives. Clin Exp Gastroenterol 12: 239-253, 2019.
21. Walker MM, Potter M, Talley NJ. Eosinophilic gastroenteritis and other eosinophilic gut diseases distal to the oesophagus. Lancet Gastroenterol Hepatol 3: 271-280, 2018.
22. Reed C, Wooley JT, Dellon ES. Clinical characteristics, treatment outcomes, and resource utilization in children and adults with eosinophilic gastroenteritis. Dig Liver Dis 47: 197-201, 2015.
23. Sandborn WJ, Su C, Sands BE, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. N Engl J Med 376: 1723-1736, 2017.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).