

Clinical and pathological profile of eosinophilic gastroenteritis

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Background Eosinophilic gastroenteritis (EoGE) can be diagnosed on the basis of histologic criteria; however, the pathology is considered to be heterogeneous. There is no consensus on the management of this enigmatic disorder with an unknown etiology.

Patients and methods Data for patients diagnosed with EoGE and followed up over a 1-year period were analyzed. Their symptoms, patterns of flares, and type of treatment were documented. The shift in peripheral blood eosinophil levels was also examined.

Results A total of 10 (mean age, 44 years; range: 31–70 years; women, 5) patients were diagnosed with EoGE. The most frequent presenting symptom was abdominal pain, and eight patients were classified with mucosal type of EoGE. Chronic disease or multiple flares were observed in seven out of 10 (70.0%) patients, and all of them had a history of allergy. Four were corticosteroid dependent (three relapsed during corticosteroid tapering and one following corticosteroid withdrawal). One of them received anti-IL5 monoclonal antibody that enabled corticosteroid dose tapering. In four patients with highly elevated initial eosinophil levels at diagnosis, the peripheral eosinophil level correlated with the amelioration and deterioration of their symptoms. The remaining three patients had a single flare without relapse. Two had no history of allergy.

Conclusion EoGE is a unique disorder with a variable clinical course. Although further studies are required to confirm our observations, the presence of other allergic disorders is associated with chronicity or multiple flares. Peripheral eosinophil level may be an effective biomarker for recurrence in patients with severe systemic disorders at diagnosis. Eur J Gastroenterol Hepatol 00:000–000

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Introduction

Eosinophilic gastroenteritis (EoGE) is a rare, heterogeneous disorder characterized by gastrointestinal (GI) symptoms and eosinophilic infiltration in the GI tract [1,2]. The first description of this condition was reported by Kaiser [3]. Subsequently, Klein *et al.* [4] classified this disorder into three types as mucosal, muscular, or serosal disease on the basis of the depth of involvement. In this condition, eosinophil infiltration involves single or multiple segments extending from the stomach to the colon, with or without esophageal involvement [5]. EoGE is distinctly different from eosinophilic esophagitis (EoE), which is characterized by eosinophil infiltration localized in the esophagus [6]. The clinical manifestations of EoGE vary depending on the site of the affected GI tract and the depth of involvement, and include abdominal pain, nausea/vomiting, diarrhea, or bloating [1].

The clinical management of EoGE is difficult owing to its enigmatic nature and unknown etiology. Currently, it is not easy to differentiate patients with EoGE who need long-term or repeated therapy from those who may have a transient illness without relapse. Dietary elimination is reported to be effective in some patients with EoGE, which indicates that this condition, like EoE, is related to an allergic disorder [7]. Corticosteroids show a favorable response for EoGE [8,9], although it may be a double-edged sword owing to the risk of side-effects. Chronic corticosteroid use triggers diabetes, osteoporosis, and results in immunocompromise. Moreover, most reports on EoGE are case report based owing to its rarity; therefore, an overview of this disease is difficult to comprehend. Here, we attempted to identify the best strategy for the management of adult EoGE by analyzing its clinical course and response to treatment.

Patients and methods

Patients with EoGE who were treated since 2016, and followed up for more than 1 year, were analyzed. Their symptoms, history of allergy (asthma, allergic rhinitis, atopy, food allergy), patterns of flares (single flare-up, chronic disease, multiple flares), and type of treatment were recorded. ‘Chronic disease’ was defined as a disease condition needing persistent treatment for their chronic symptoms and ‘multiple flares’ was defined as a disease state of a recurrence of symptoms after a symptom-free interval that is medication free. Peripheral blood eosinophil

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levels were monitored and followed up. Other clinical data were retrospectively reviewed by a single operator on the basis of patient electronic medical records.

EoGE was diagnosed on the basis of the following criteria: (a) presence of GI symptoms; (b) histology showing eosinophilic infiltration [≥ 30 eosinophils (eos) per high-power field in one or more areas of the GI tract in a minimum of two specimens], or eosinophilic ascites; and (c) no evidence of parasitic or other causes of secondary eosinophilic infiltration [5]. The differential diagnosis between inflammatory bowel disease (IBD) is considered difficult because IBD can also include histological eosinophilia. In IBD, characteristic endoscopic and histological findings play an important role in diagnosis. Patients suspected of having EoGE with GI symptoms and unexplained peripheral eosinophilia were excluded from this study in the absence of histology-confirmed eosinophilia.

Patients with EoGE were classified into the following three groups on the basis of Klein's classification using endoscopic, radiographic, and histological findings: (a) mucosal type, defined as eosinophil infiltration of the mucosa and/or evidence of mucosal findings on endoscopy, and without evidence of GI obstruction, eosinophilic ascites, or histologic evidence of infiltration beyond the mucosal layer; (b) muscular type, defined as eosinophilic infiltration of the muscularis and/or documented complete or incomplete bowel obstruction, and without/minimal eosinophilic ascites; and (c) serosal type, defined by the presence of eosinophilic ascites with or without evidence of eosinophilic infiltration of the GI tract [4]. This study was approved by the local institutional review board (approval no. E16-16, 2416), and was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Results

Clinical presentation of eosinophilic gastroenteritis

A total of 10 patients (mean age, 44 years; range: 31–70 years; women, 5) were diagnosed with EoGE and were followed up. Allergy history was identified in eight patients [asthma, 3; rhinitis, 4; atopy, 1, food allergy: 5 (duplicate answers allowed)]. The cause of food allergy was eggs in 3, wheat in 2, and blue-fish, nuts, and soybean each in 1 (duplicate answers allowed). The main presenting symptoms were abdominal pain in 6, diarrhea in 3, and bloating in 1. Although lesions were distributed randomly from the esophagus to the colon, the duodenum and the large colon were the most affected segment (Fig. 1). On classifying patients on the basis of the depth of involvement, eight patients had the mucosal type (Fig. 2), and one each had the muscular type (Fig. 3) and the serosal type, respectively. The initial peripheral eosinophil level (normal range: 0.2–8.4%) was elevated [9.7–62.7% (448.0–10596.3 eos/ μ l)] in seven (70.0%) patients. Peripheral immunoglobulin E (IgE) level (normal range: ≤ 173 IU/ml) was elevated (279.4–4219.3) in six (60.0%) patients. Patient characteristics are presented in Table 1.

Clinical course of eosinophilic gastroenteritis

Chronic disease or multiple flares were observed in seven (70.0%) patients. All of them had an allergy history.

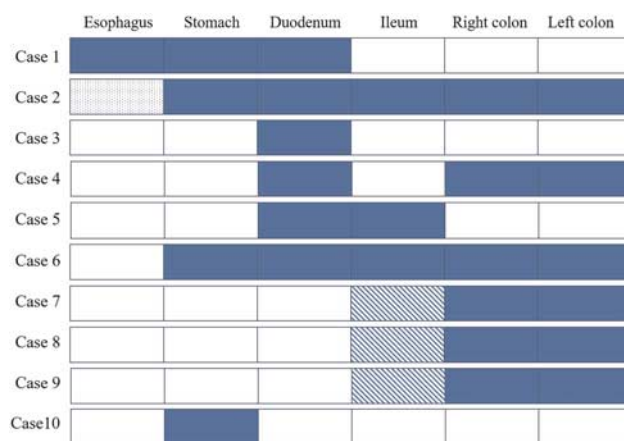


Fig. 1. Gastrointestinal (GI) tract segments showing eosinophilic infiltration (≥ 30 eos/high-power field). The duodenum and the large colon were the most affected GI segment, although the disease randomly affected the GI tract from the esophagus to the colon. The dotted box (case 2) indicates that the presence of esophageal trachealization and luminal compression (Fig. 3a) is considered to be indicative of the muscular type of eosinophilic gastroenteritis (EoGE), wherein it is not possible to include the muscular layer histology in an endoscopic biopsy. The diagonal-lined boxes (cases 7–9) indicate that ileal reddening and erosion, as seen on capsule endoscopy, are considered to be EoGE related, although mucosal biopsy was not available.

Among these patients, four were deemed corticosteroid dependent; three developed relapse during corticosteroid tapering (chronic disease), and one had corticosteroid withdrawal (multiple flares). The remaining three patients did not need corticosteroid therapy because their symptoms were not severe. The clinical details of these patients are summarized in Fig. 4. These seven patients received maintenance therapy, four with corticosteroids, two with dietary elimination and proton pump inhibitor (rabeprazole), and one with a leukotriene receptor antagonists (montelukast). One corticosteroid-dependent patient responded to anti-IL5 monoclonal antibody (mepolizumab) treatment, which enabled a reduction of his corticosteroid dosage (Fig. 4b). In addition, in patients with highly elevated initial eosinophil levels at diagnosis [25.3–48.2% (1351.0–5061.0 eos/ μ l)], the peripheral eosinophil level correlated with the amelioration and deterioration of their symptoms (Fig. 4).

Three patients had a single flare-up without relapse. Two of the three had no allergy history, and one had a history of food allergy. These three patients were treated only with intravenous drip infusion, a pain-killer, or an antispasmodic agent.

Discussion

Currently, there are no accepted guidelines for the diagnosis and treatment of EoGE. The difficulty with using histology alone for establishing the diagnosis is because of the distribution of eosinophils in a healthy GI tract, which increases progressively from the stomach to the right colon [12,13]. Therefore, a clear cut-off value of eosinophil counts for EoGE cannot be defined, further necessitating an individualized approach to the different sites of the GI tract. On the basis of the results of our study, and a previous study, multiple biopsies that include the duodenum are highly recommended for achieving a histological diagnosis with gastroscopic examination [14]. Second, in

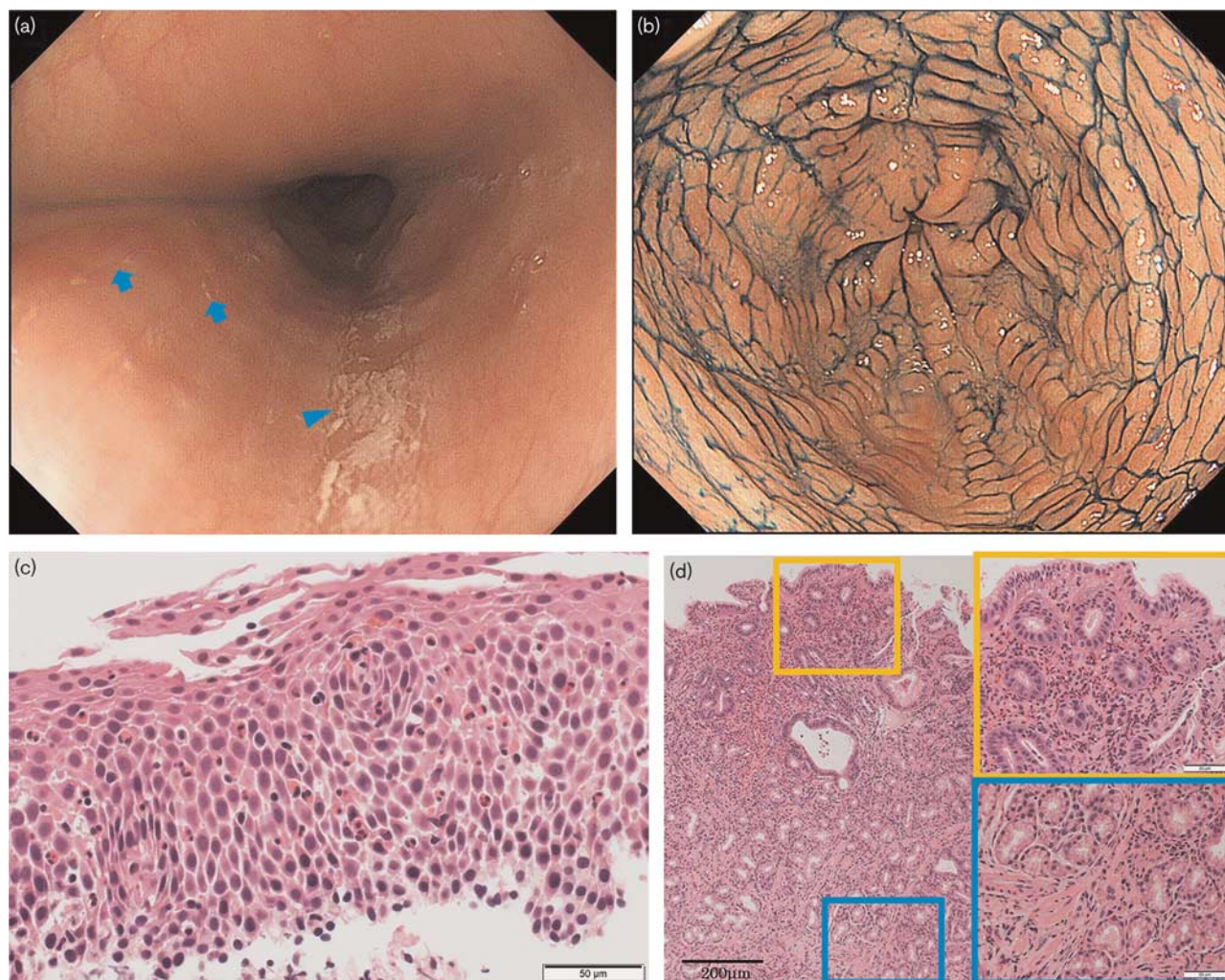


Fig. 2. Endoscopic and histological findings of the esophagus and the stomach in case 1. (a) In the esophagus, longitudinal furrows (blue arrow) and white plaques (blue arrowhead) are observed on endoscopy, compatible with the endoscopic description of eosinophilic esophagitis. (b) Chromoendoscopy with indigo carmine reveals an edematous antral wall. (c) Esophageal histology shows eosinophil infiltration in the epithelium (maximum, 52 eos/high-power field) compatible with an esophageal lesion of eosinophilic gastroenteritis (magnification, $\times 400$). (d) Gastric antral biopsy shows severe eosinophil infiltration (maximum, 201 eos/high-power field) in the superficial stroma of the pyloric gland mucosa (inset magnification, $\times 400$).

terms of its pathology, EoGE is a heterogeneous disorder. Caldwell *et al.* [15] reported that the respective disease transcriptomes were divergent in more than 90% of patients with histology-confirmed EoGE. In this study, we excluded patients suspected of having EoGE with peripheral eosinophilia alone. Only those patients who were found to exceed the high cut-off value of 30 eos/high-power field on histology were included. Nonetheless, several clinical patterns (single flare, chronic disease, and multiple flares) were observed in this study. Patients with single flare without relapse did not have any extra-GI allergic disorders (asthma, allergic rhinitis, atopy). One of them had concomitant food allergy, and had to be followed up carefully. Although further studies are required to confirm this observation, it is our opinion that in these patients, a single flare may be representative of a non-allergic, or at the most, a transient allergic response concomitant with histological eosinophilia. Further, Pineton de Chambrun *et al.* [16] reported that about 40% of the patients with EoGE recovered spontaneously, and more patients with the serosal type had a single flare,

in agreement with the results of this study. Thus, in the absence of severe symptoms, watchful waiting may be a potential strategy even in patients with histology-confirmed EoGE.

For patients with severe symptoms, multiple flares, or chronic disease, induction therapy should be performed with systemic steroids, which may be tapered gradually to maintenance dosage, or withdrawn if possible. In histological EoGE with multiple flares or chronic disease, the chronicity of co-existing allergy disorders may explain or be related to the chronicity of the EoGE. The anti-IL5 monoclonal antibody is considered an effective maintenance therapy for patients with EoGE with peripheral eosinophilia and those who are corticosteroid dependent [17,18]. However, in Japan, although anti-IL5 therapy is approved for severe asthma, it is not yet an approved treatment for EoGE. For patients with mild symptoms, leukotriene receptor antagonists can be an alternative, although it is uncertain whether it alleviates disease activity [19]. Proton pump inhibitor is considered partly effective for esophageal eosinophilia concomitant with

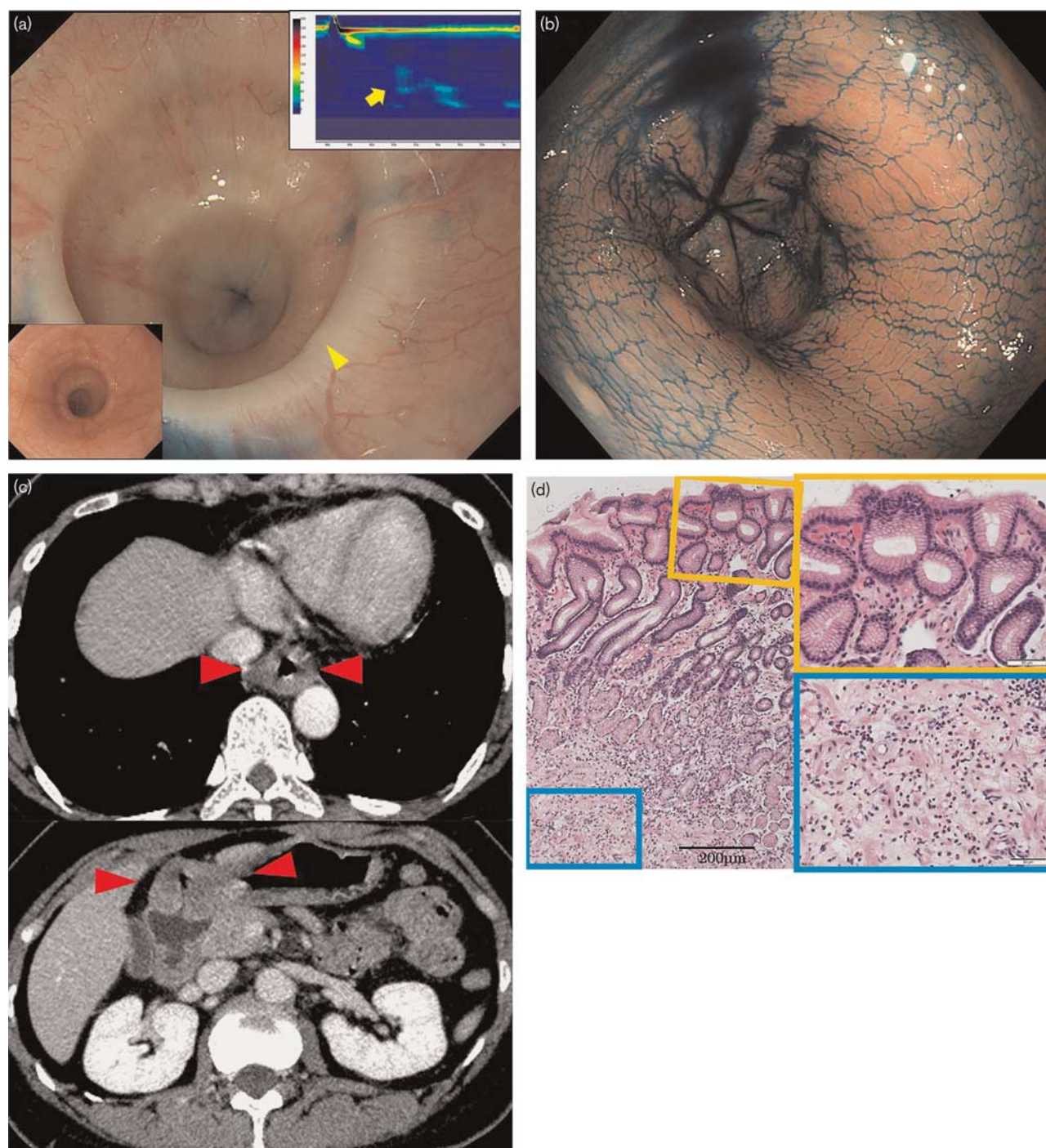


Fig. 3. Endoscopic, radiographic, and histological findings of the esophagus and the stomach in case 2 identifying it as muscular type of eosinophilic gastroenteritis. (a) In the esophagus, endoscopy shows luminal compression with findings of esophageal 'trachealization' (yellow arrowhead) or 'corkscrew' esophagus (left lower inset), which are the findings of eosinophilic infiltration in the muscle layer [10,11]. High-resolution manometry identifies highly disrupted peristalsis (yellow arrow, right upper inset). (b) Chromoendoscopy shows a stretched and flattened gastric areal pattern in the antrum. (c) Computed tomography shows thickened esophageal and gastric antral walls. (d) Antral biopsy shows severe eosinophilic infiltration (maximum, 77 eos/high-power field) predominantly involving the deep mucosa (inset magnification, $\times 400$).

EoGE, or for isolated EoGE, possibly owing to its direct anti-inflammatory effect by blockade of IL-4e-stimulated and IL-13e-stimulated secretion of eotaxin-3 [20,21]. Another issue for the treatment of this disorder is goal-setting. In our opinion, through this study, symptom resolution means histological improvement, and repeated endoscopy with biopsy to confirm the histological remission

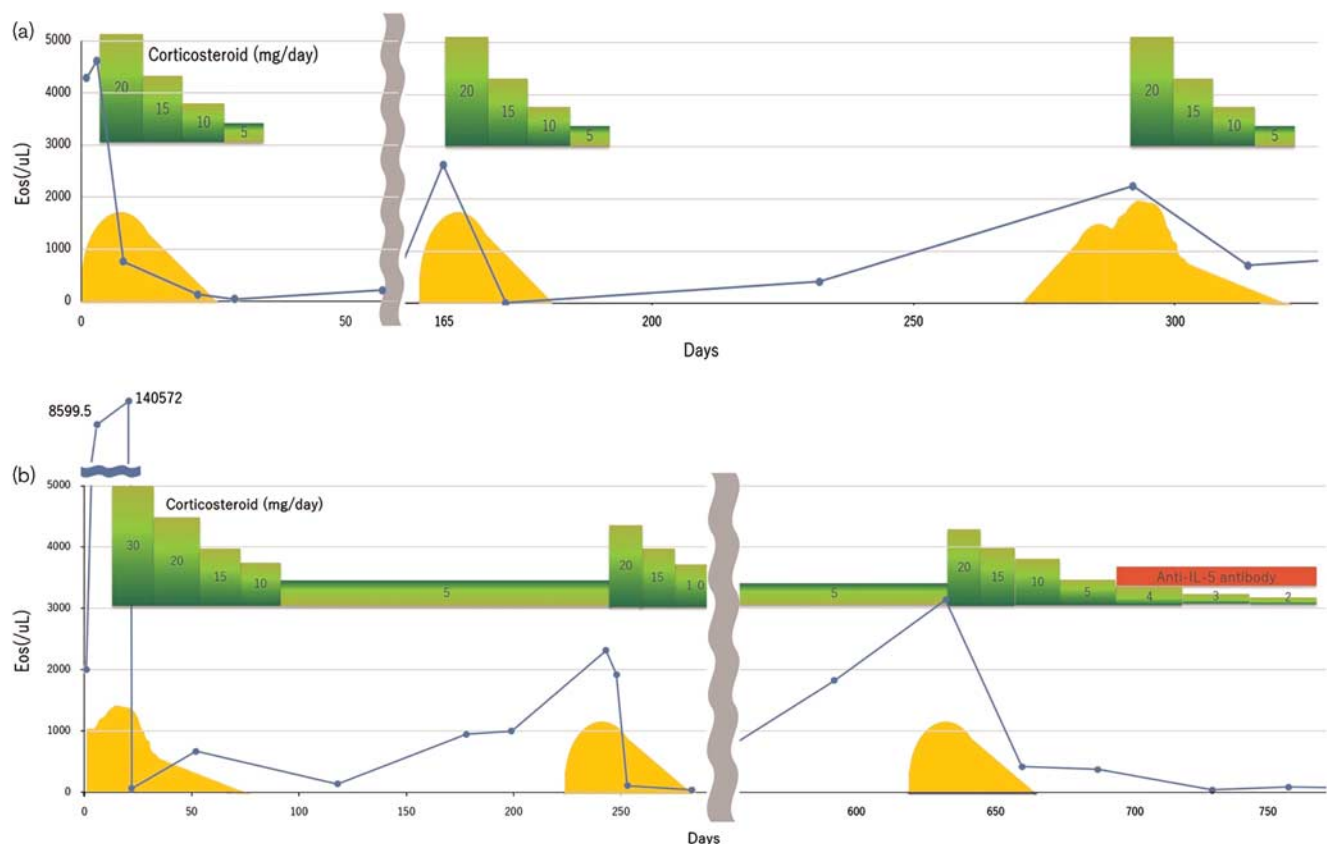
is not necessarily important in cases with symptom improvement.

The initial peripheral eosinophil level was elevated in 70.0% of the patients, in agreement with the results of a previous study in Japanese patients [22]. In patients with EoGE with highly elevated peripheral eosinophilia at diagnosis, its repeated elevation reflects recurrence of

Table 1. Summary of case series of eosinophilic gastroenteritis (*n* = 10)

	Age (years)	Sex	Allergy history ^a	Symptoms ^b	Peripheral eosinophil/ μ l (%) ^c	Serum immunoglobulin E (IU/ml) ^d	Depth of involvement	Clinical course	Treatment
Case 1	34	Female	-/+ / +/+	<u>A</u> /V	1351.0 (25.3)	714.0	Mucosal type	Chronic disease	Dietary elimination Proton pump inhibitor
Case 2	47	Female	-/+ / -/+	<u>A</u> /S/D	4284.0 (40.8)	161.9	Muscular type	Recurrent disease	Corticosteroid
Case 3	70	Male	+ / + / - / -	<u>A</u>	8599.5 (44.1)	1748.8	Mucosal type	Chronic disease	Corticosteroid Anti-IL5 antibody
Case 4	55	Female	- / + / - / +	<u>A</u> /D	5061.0 (48.2)	279.4	Mucosal type	Chronic disease	Corticosteroid
Case 5	40	Male	- / - / - / -	B/D	908.9 (8.3)	250.0	Serosal type	Single flare	Spontaneous remission
Case 6	52	Male	- / - / - / +	<u>D</u>	10596.3 (62.7)	4219.3	Mucosal type	Single flare	Spontaneous remission
Case 7	31	Female	+ / + / - / -	<u>D</u>	448.0 (11.2)	63.6	Mucosal type	Chronic disease	Leukotriene receptor antagonist
Case 8	53	Male	- / + / - / -	<u>A</u>	210.7 (4.3)	NA	Mucosal type	Chronic disease	Corticosteroid
Case 9	33	Male	- / - / - / -	<u>D</u>	598.5 (9.7)	18.7	Mucosal type	Single flare	Spontaneous remission
Case 10	41	Female	- / - / - / +	<u>A</u>	161.7 (3.0)	436.0	Mucosal type	Chronic disease	Dietary elimination Proton pump inhibitor

+, positive; -, negative.

^aAsthma/allergic rhinitis/atopy/food allergy.^bA, abdominal pain; D, diarrhea; V, vomiting; B, abdominal bloating; S, swallowing difficulty (dysphagia). Underlined items represent the main symptoms.^cNormal range 0.2–8.4%.^dNormal range ≤ 173 IU/ml; NA, data not available.**Fig. 4.** Clinical course of case 2 (a) and case 3 (b). Case 2 was treated with corticosteroids, and her symptoms (yellow enclosure) resolved immediately. Although a symptom-free period was observed following corticosteroid tapering and withdrawal, multiple flares were observed (recurring disease). (b) Case 3 was steroid dependent and had chronic disease. Following corticosteroid tapering, there was a flare. Anti-IL5 monoclonal antibody enabled corticosteroid dose tapering. In both cases, the peripheral eosinophil levels correlated with exacerbation of flares.

symptoms [15]. Therefore, the peripheral eosinophil level can be used as a biomarker in selected patients. However, in our study, we could not conclude that patients with highly elevated eosinophilia were significantly associated with clinical relapse as reported by a previous study [16]. The peripheral IgE levels may also be a useful indicator, although

we could not investigate its role in all our patients. In EoE, which is a similar GI allergic disorder, the pathogenesis is described as being non-IgE mediated [23]. It is possible that EoGE may be IgE mediated only in a few patients. Further, we should exercise caution when interpreting high IgE levels in these patients as these may only be a reflection of an

allergy-sensitized condition for antigens [24]. Other serum biomarkers for the diagnosis of EoGE or for monitoring its disease activity have not been identified [25].

The current study is more similar to a case series. Although prospective data collection was carried out in all cases during the observation period, there are other issues that may have to be highlighted, such as the lack of a clear protocol for treatment as this condition is very rare.

Conclusion

EoGE is a unique disorder with variable clinical presentations. Although further studies are required to confirm our observations, the presence of concomitant extra-GI allergies is associated with chronicity and multiple flares. Peripheral eosinophil level may be an effective biomarker for recurrence in patients with highly elevated eosinophilia at diagnosis.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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