**Eosinophilic Granulomatosis with Polyangiitis Initially Diagnosed as Eosinophilic Gastroenteritis**

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**Abstract:**

We herein report two cases of eosinophilic granulomatosis with polyangiitis (EGPA) initially diagnosed as eosinophilic gastroenteritis (EGE) based solely on endoscopic biopsy results. One year after the EGE diagnosis, one patient presented with multiple purpura, and skin biopsy findings resulted in a change of the diagnosis to EGPA. In another patient, multiple skin and colonic ulcerations emerged eight years after the diagnosis of EGE, at which time histological examinations of endoscopic biopsy specimens revealed vasculitis, and the diagnosis was changed to EGPA. Physicians should be aware of the possible existence of EGPA in cases diagnosed as EGE.

**Key words:** eosinophilic granulomatosis with polyangiitis, eosinophilic gastroenteritis, endoscopic biopsy

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**Introduction**

Eosinophilic granulomatosis with polyangiitis (EGPA), previously known as Churg-Strauss syndrome, is a multisystem disorder that affects small- to medium-sized arteries or veins and is characterized by the presence of severe asthma as well as blood and tissue eosinophilia (1, 2). Characteristic histological findings include necrotizing vasculitis with infiltration mainly by eosinophils in vessels and surrounding tissues, with gastrointestinal (GI) manifestations reported to be seen in 37-62% of all cases (3). Although the detection of necrotizing vasculitis is important for the confirmation of a diagnosis of EGPA, detecting vasculitis in mucosal tissue samples obtained via an endoscopic biopsy is difficult.

EGPA can occur concomitantly with systemic eosinophilia in various organs, and the pathological findings of endoscopic biopsy specimens obtained from the GI tract may only demonstrate eosinophilic infiltration in the mucosa, which is generally diagnosed as eosinophilic gastroenteritis (EGE), based on dense eosinophil infiltration.

We herein report two cases of EGPA that were initially diagnosed as EGE based on the pathological examination of endoscopic biopsy specimens.

**Case Reports**

**Case 1**

A 28-year-old woman with a recent 3-year history of asthma visited a local clinic for frequent asthmatic attacks and persistent diarrhea with abdominal pain that had occurred for approximately 1 year. She was diagnosed with EGE, based on eosinophilic infiltration in the mucosa of the stomach [30 eosinophils/high-power field (HPF)] and duodenum (25 eosinophils/HPF) shown in endoscopic biopsy findings. At that time, no manifestation related to vasculitis in other organs was apparent. The abdominal symptoms were...
improved with oral prednisolone (PSL) at 25 mg once a day, although repeated exacerbation occurred when a gradual dose reduction was attempted. The patient was referred to our hospital and enrolled in food-elimination diet therapy for the treatment of EGE, as previously reported (4).

A physical examination revealed moderate tenderness in the left side of the abdomen, while several purpuric lesions on the back possibly related to EGPA were also noted. A dermatologist was consulted, and they advised us that the lesions were atypical for purpura of vasculitis and recommended performing follow-up observations. Laboratory results showed a white blood cell count (WBC) of 5,430/μL with 18.4% eosinophils, C-reactive protein (CRP) at 0.88 mg/dL, and immunoglobulin E (IgE) at 568 IU/mL. Antinuclear antibody (ANA) and anti-proteinase 3 anti-neutrophil cytoplasmic antibody (PR3-ANCA) tests were negative, whereas anti-myeloperoxidase ANCA (MPO-ANCA) was mildly positive at 3.8 U/mL.

Upper gastrointestinal endoscopy results revealed mild longitudinal linear furrows in the esophagus, while a biopsy sample obtained from the esophageal mucosa showed eosinophilic infiltration up to 24 eosinophils/HPF (Fig. 1a, b). No abnormal endoscopic or histological findings were obtained in an examination of the stomach and duodenum. However, antegrade balloon-assisted enteroscopy (BAE) demonstrated several areas of erosion in the jejunum, although eosinophilic infiltration was found to be only 13/HPF (Fig. 1c, d), possibly because of the oral PSL given prior to admission to our hospital. Computed tomography findings showed wall thickening in the small intestine and a low level of ascites in the pelvis.

Food-elimination diet therapy was started along with discontinuation of oral PSL. However, peripheral blood eosinophils and IgE were increased after two weeks, and the abdominal symptoms worsened. We decided that the diet therapy was not effective and discontinued it. Furthermore, the purpuric lesions on the back of the patient appeared at different sites and were increased in number compared to the findings obtained at admission (Fig. 2a). These findings were considered to be highly suggestive of EGPA. A skin biopsy procedure was performed, although the patient met the EGPA diagnostic criteria (1, 5). Histological examination results of the obtained specimens revealed leukocytoclastic vasculitis with fibrinoid necrosis and perivascular eosinophilic infiltrate (Fig. 3). Based on these findings, we made a diagnosis of EGPA and restarted oral PSL at 40 mg/
Thereafter, the abdominal symptoms and skin lesions showed gradual improvements, and the number of eosinophils and IgE were also decreased. Over time, the PSL dose was gradually decreased with no recurrence of symptoms.

**Case 2**

A 50-year-old woman with a 20-year history of asthma came to us suffering from diarrhea and abdominal pain. Plasma eosinophilia was noted, but biopsy results revealed prominent eosinophil infiltration in the duodenum (40 eosinophils/HPF) and jejunum (35 eosinophils/HPF). Eight years earlier, she had been diagnosed with EGE, although no manifestation caused by vasculitis in other organs had been seen at that time. Despite PSL administration at doses ranging from 2.5-10 mg/day, her abdominal symptoms were exacerbated approximately 1-2 times a year. She was therefore referred to our hospital for the treatment of steroid-dependent EGE, including food-elimination diet therapy.

Upon admission, the patient noted severe abdominal pain with persistent diarrhea and body weight loss, as her dietary intake had significantly decreased due to oral pain induced by ulcerative stomatitis. Furthermore, multiple skin ulcers appeared, which were highly suggestive of EGPA, although skin biopsy findings revealed only necrotic tissue. Laboratory results showed a WBC of 19,340/μL with 8.9% eosinophils, CRP at 8.45 mg/dL, IgE at 247 IU/mL, and serum albumin at 1.8 g/dL. ANA, MPO-ANCA, and PR3-ANCA tests were all negative. Colonoscopy examination results revealed multiple deep ulcers in the transverse colon to the sigmoid colon (Fig. 4), suggesting the presence of vasculitis.

In order to collect a large amount of submucosal tissue for testing, we obtained several biopsy samples from locations as deep as possible. Histological findings obtained from the transverse colon revealed inflammatory granulomas, as well as intravascular fibrin deposits and inflammatory cell infiltration in the submucosal layer (Fig. 5). Based on those findings we made a diagnosis of EGPA. After starting PSL at 30 mg/day, the abdominal symptoms and skin ulcers showed gradual improvement, while stomatitis completely disappeared, and the dietary intake recovered to a normal level. Thereafter, the dose of PSL was successfully tapered without relapse.
EGPA is a multisystem disorder that mainly affects the lungs, heart, nasal passages and sinuses, gastrointestinal tract, and skin (2, 3). The main characteristic feature of EGPA is asthma, which affects nearly 95% of diagnosed patients, and GI involvement is also quite common, being noted in 37-62% of reported cases (2, 3).

A diagnosis of EGPA is based on clinical parameters. At present, the clinical specific criteria developed for Churg-Strauss syndrome are used to distinguish EGPA from various possible vasculitides (5). However, to confirm an EGPA diagnosis, it is desirable to obtain histological evidence of vasculitis. For such a diagnosis, skin, nerve, and muscle biopsies have been reported to have a sensitivity of 67.4%, 65.7%, and 47.9%, respectively (6). However, the utility of specimens obtained via an endoscopic biopsy of the GI tract has not been systematically investigated, although several case reports have been published (7-10). In these reports, the histological findings have revealed eosinophilic infiltration in the mucosa, which is consistent with EGE.

EGE is defined by the presence of abdominal symptoms, including pain and diarrhea, as well as dense infiltration of eosinophils in the gastrointestinal mucosa (11, 12). In a nationwide survey of EGE in Japan reported in 2013, approximately half of affected patients had a history of allergic diseases, including bronchial asthma, allergic rhinitis, and atopic dermatitis, whereas multi-organ manifestations, such as purpura, skin ulcers, and mononeuritis multiplex caused by vasculitis, were not seen (11).

It has been proposed that the disease course of EGPA be divided into prodromal, eosinophilic, and vasculitic phases with regard to eosinophilia involving medium- and small-sized vessels (13). In the eosinophilic phase, it is possible for systemic eosinophilia, including asthma and EGE, to concomitantly appear. At that stage, it may be difficult to differentiate EGE from the GI involvement of EGPA when malformations other than GI lesions are not found. A GI manifestation of EGPA may thus precede or coincide with the vasculitic phase. This means that while a diagnosis of EGE during the eosinophilic phase of EGPA is possible, the existence of EGPA is not easily suspected when no manifestation caused by vasculitis in another organ is found. The present patients might have been in an eosinophilic phase of EGPA at the time of the initial EGE diagnosis. It is important for clinicians to be aware of the possibility of a GI manifestation of EGPA even in cases diagnosed as EGE.

Mucosal eosinophilic infiltration is easily identified in endoscopic biopsy specimens obtained from patients with EGPA. However, few reports have provided details regarding the histological confirmation of vasculitis in endoscopically obtained biopsy samples, possibly because of difficulties that may be encountered with the collection of adequate tissue samples including submucosal tissue with vessels. The histological identification of vasculitis in endoscopic biopsy specimens from the GI tract is generally not easy to confirm, so important diagnostic clues showing EGE in cases with possible EGE are related to manifestations in other organs, such as purpuric lesions, skin ulcers, and mononeuritis multiplex caused by vasculitis. Such lesions are usually not found in patients with EGE, who only have GI lesions with dense eosinophilic infiltration. In the present cases, multi-organ manifestations including skin lesions and deep GI ulcers prompted us to suspect the presence of vasculitis and provided clues for the subsequent diagnosis of EGPA. Physicians must therefore pay close attention to multi-organ manifestations based on the presence of vasculitis in order to distinguish between these conditions.

A diagnosis of EGPA might have been obtained earlier in the present cases if the attending physicians had taken note of the skin manifestations and consulted a dermatologist or rheumatologist. The possibility of multi-organ manifestations must be kept in mind when performing patient examinations. In addition, to obtain an accurate pathological diagno-

Figure 5. Case 2. (a) Endoscopic biopsy sample obtained from the transverse colon (low-power field). (b) HPF view of the area enclosed by a red square in (a) showing an inflammatory granuloma, intravascular fibrin deposition, and inflammatory cell infiltration in the submucosal layer. HPF: high-power field.
sis, gathering adequate and complete clinical information is vital.

In summary, we herein report two cases initially diagnosed as EGE based on pathological examinations of endoscopic biopsy specimens that were subsequently diagnosed as EGPA. Attending physicians should be aware of the difficulty in differentiating EGE from EGPA in patients with GI manifestations in an eosinophilic phase when the involvement of other organs is not detected. Furthermore, it is important to be aware of the difficulties in obtaining histological confirmation of vasculitis based on endoscopic biopsy specimen findings.

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

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