Int Surg 2017;**102:**210–215
DOI: 10.9738/INTSURG-D-16-00160.1

A Clinicopathologic Study of Small Intestinal Perforations in Patients With Eosinophilic Granulomatosis With Polyangiitis: A Series of 3 Patients

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Eosinophilic granulomatosis with polyangiitis (EGPA) is a vascular disorder of unknown etiology characterized by severe asthma, eosinophilia, and granulomatous vasculitis. It is sometimes associated with gastrointestinal lesions, although perforations are uncommon. Corticosteroids are commonly used in the treatment of patients with EGPA; however, they may impair tissue repair and induce fibrotic changes in the vascular intima, which can lead to vascular occlusion, ischemia, and perforation. The anti-inflammatory properties of corticosteroids may mask symptoms of gastroduodenal ulcers or other intra-abdominal conditions, which can lead to a delay in diagnosis. From January 1, 2001 to December 31, 2014, 71 patients underwent surgery for small intestinal perforations. Of these, 4 operations were performed on 3 patients with EGPA who were receiving corticosteroids. We retrospectively reviewed the clinical and pathologic features of these patients. All 3 patients with EGPA were men, with a mean age of 56 years. The length of resected intestine ranged from 10 to 60 cm. Histopathologic

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examination revealed ulcers and perforations of the small intestine associated with vasculitis, compatible with EGPA. All patients had an uneventful postoperative course. Patients with EGPA presenting with abdominal pain must be carefully evaluated for possible intestinal perforation, especially those receiving corticosteroid therapy.

Key words: Churg-Strauss syndrome; ANCA-associated vasculitis; Small intestinal perforation; Abdominal symptoms

Eosinophilic granulomatosis with polyangiitis (EGPA), or Churg-Strauss syndrome, first described by Churg and Strauss in 1951, is characterized by disseminated necrotizing vasculitis with extravascular granulomas occurring exclusively in patients with asthma and tissue eosinophilia.[1] There is no significant sex difference, with a mean age at onset of 38 to 54 years.[2,3] Characteristic histopathologic features include necrotizing vasculitis in arteries or veins with an infiltrate consisting mainly of eosinophils in vessels and surrounding tissues.[4]

Gastrointestinal manifestations are frequent in patients with EGPA (20% to 50%)[5] with a variety of symptoms including abdominal pain, diarrhea, nausea, and vomiting to more severe symptoms such as bleeding, pancreatitis, bowel perforation, ischemia, and cholecystitis.[6–8] However, severe gastrointestinal involvement is rare.[9] Corticosteroids remain the cornerstone of the initial treatment of EGPA.[10] Corticosteroids impair tissue repair and induce fibrotic changes in the vascular intima, resulting in intestinal perforation due to vascular occlusion and ischemia.[11] We report 3 patients with EGPA who developed small intestinal perforations due to angiitis while undergoing corticosteroid treatment.

Case Presentation

From January 1, 2001 to December 31, 2014, 71 patients underwent surgery for small bowel perforations at Jichi Medical University Hospital. Of these, 3 patients were diagnosed with EGPA. These 3 patients required hospitalization due to comorbidities of progressive neuropathy. One patient underwent 2 operations for recurrent perforations. Clinical, surgical, pathologic, and outcome data were collected retrospectively.

All 3 patients with EGPA in this series were men, with a mean age of 56 years. The length of resected intestine ranged from 10 to 60 cm. Histopathologic examination revealed ulcers and perforations of the small intestine associated with vasculitis, compatible with EGPA. Only 1 of the 3 patients with EGPA was positive for myeloperoxidase-antineutrophil cytoplasmic antibody. All patients had an unevent-

Table 1 Summary of 3 patients with EGPA

Patient	Age (y)	Sex	Classification criteria[a]	Corticosteroid (mg)[b]	WBC (/mm^3)[c]	MPO-ANCA (U/mL) (highest)[d]
1	63	Male	Bronchial asthma; eosinophilia; mononeuropathy	40	10,500	2744
1				40	10,400	
2	49	Male	Bronchial asthma; eosinophilia; multiple mononeuropathies; paranasal sinus abnormality	50	13,300	<1.3
3	56	Male	Bronchial asthma; eosinophilia; polyneuropathy; pulmonary infiltrates	60	22,900	<1.3

Patient 1 underwent a second surgery for the recurrent peritonitis within a month. NA, not applicable.

[a]American College of Rheumatology classification criteria

[b]Amount of corticosteroid at the onset.

[c]WBC at the time of perforation.

[d]ANCA and [e]Eosino shows the highest point before treatment and at the time of perforation, respectively.

ful postoperative course, although the first patient had a recurrent intestinal perforation. All 3 patients were undergoing corticosteroid therapy at the time of presentation. A summary of the clinical features of these patients is shown in Table 1.

Figure 1 shows the preoperative clinical course of these patients. Laboratory data obtained preoperatively, including white blood cell count, C-reactive protein level, and percent of eosinophils did not suggest the presence of peritonitis (Fig. 1). All patients had severe abdominal pain and fever, which suggested intestinal perforation.

The first patient underwent resection of 55 cm of small intestine repaired with a primary anastomosis. An 8-mm perforation with a 2.5-cm ulcer (Fig. 2A) and multiple small ulcers were found in the resected ileum macroscopically. Histopathologic examination revealed active angiitis with granuloma, surrounded by slight eosinophilic infiltration in the mesenteric fat (Fig. 2B). A tear in the internal elastic membrane of a small artery was detected by Elastica van Giesen stain (Fig. 2C). The pathologic findings of the resected intestine from the second operation were similar to the findings from the first resection.

Patient 2 was explored laparoscopically, and a 5-mm perforation in the ileum with purulent exudate was identified. This area of the ileum was resected (Fig. 2D). Histopathologic examination showed necrotizing vasculitis of small vessels, with luminal obstruction (Fig. 2E), as well as destruction of the internal elastic membrane (Fig. 2F).

Patient 3 had several perforations 8 to 10 mm in size with multiple ulcers in the resected ileum measuring 58 cm in length (Fig. 2G). Histopathologic examination showed fibrinoid necrosis of small arteries surrounded by a pronounced inflammatory infiltrate consisting of eosinophils in the mesentery (Fig. 2H) and destruction of the internal elastic membrane (Fig. 2I).

Discussion

EGPA is a rare vasculitis that affects small- to medium-sized vessels and is associated with asthma and eosinophilia.[3] The etiology of EGPA is unclear, but outcomes are generally good.[12] Factors such as renal disease, gastrointestinal involvement, cardiomyopathy, and central nervous system involvement predict a poor prognosis in patients with EGPA.[13] Gastrointestinal perforations are responsible for approximately 10% of deaths associated with systemic necrotizing vasculitis.[14]

Gastrointestinal involvement occurs in up to 50% of patients with EGPA, and the small intestine is the most common site.[15] In contrast, colonic perforations are relatively uncommon.[15] Corticosteroids are used for the initial management of patients with EGPA.[10] However, corticosteroids enhance fibrotic changes in the vascular intima, which can lead to vascular occlusion, ischemia, and perforation.[16] Even if treatment with corticosteroids is stopped, fibrosis and organized thrombus formation persist once these changes occur.[11] As is well-known among

Table 1 Extended

MPO-ANCA (U/mL) (on set)[e]	Eosino (%) (highest)	Eosino (%) (on set)	Site of perforation	Length of resected intestine (cm)	Operation	Anastomosis	Outcome
670	39.2	0.5	Ileum	50	Partial resection	End to end	Alive
		1	Ileum	10	Partial resection	End to end	Alive
NA	25.2	0	Ileum	15	Partial resection	Functional end to end	Alive
NA	51.4	0.2	Ileum	60	Partial resection	– (ileostomy)	Alive

Fig. 1 Schematic representation of the hospital course of 3 patients. Data for white blood cell count, serum C-reactive protein level, and percentage of eosinophils did not suggest intestinal perforation. Elevation of body temperature suggested a serious complication in 2 of the 3 patients.

surgeons, the anti-inflammatory properties of corticosteroids may mask symptoms of gastroduodenal ulcers or other intra-abdominal conditions, and this may lead to a delay in diagnosis.[17]

The first patient in this series underwent reoperation due to a second small bowel perforation. Corticosteroids may increase the risk of postoperative complications, such as anastomotic leak.[11] We

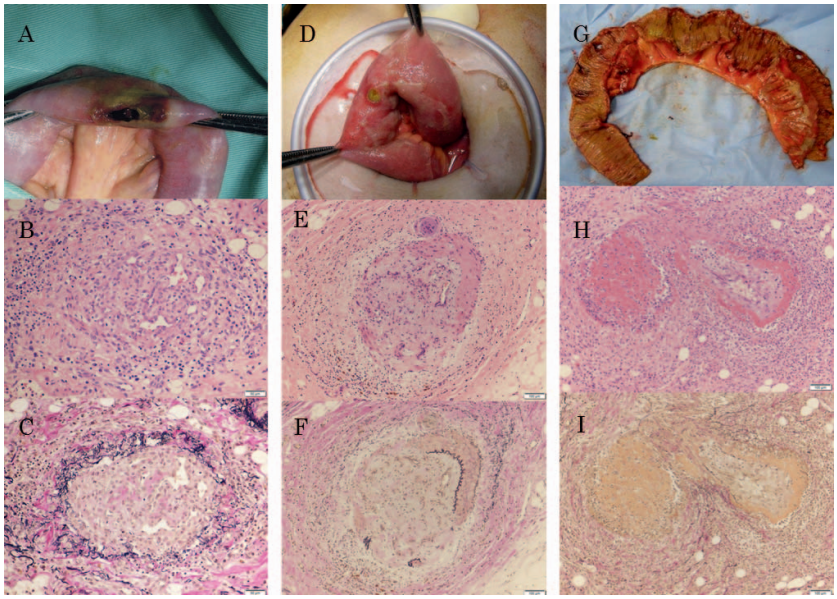

Fig. 2 Macroscopic and microscopic findings. Patient 1: An 8-mm perforation was found in the ileum (A). Histopathologic examination revealed active angiitis with granuloma surrounded by slight eosinophilic infiltration in the mesenteric fat (B) (hematoxylin and eosin stain, 400×). The internal elastic membrane of the small artery was torn, as shown by elastica von gieson stain (400×) (C). Patient 2: A 5-mm ileal perforation with purulent discharge was found (C). Histopathologic findings showed necrotizing vasculitis of small vessels (D) (hematoxylin and eosin stain, 400×), with luminal obstruction and destruction of the internal elastic membrane (E) (elastica von gieson stain, 400×). Patient 3: Perforations and multiple ulcers are in the resected ileum (F). Histologic examination showed fibrinoid necrosis of small arteries with a pronounced inflammatory eosinophilic infiltrate in the mesentery (G) (hematoxylin and eosin stain, 400×) and destruction of the internal elastic membrane (I) (elastica von gieson stain, 400×).

did not perform an anastomosis in patient 3 because this patient was receiving high-dose corticosteroids at that time (Table 1). A previous report suggested changing the therapy to immunosuppressive agents. This may be considered when gastrointestinal involvement is suspected based on symptoms and may reduce the incidence of perforation.[16]

Performing an anastomosis is associated with an increased risk of anastomotic leaks in patients receiving high-dose corticosteroid therapy.[18] Patients must be carefully evaluated for the development of such complications in the postoperative period, with appropriate workup as indicated.

Investigating the entire length of the small intestine can be difficult. Recently, the use of double balloon endoscopy[19] and capsule endoscopy[20] have been reported in patients with EGPA. These techniques allow the identification of multiple ulcers in the small intestine that could lead to perforation. In patients with abdominal symptoms and no definite evidence of perforation, these techniques may be useful to evaluate the entire length of the small intestine, although the risks associated with these evaluations must also be considered.

Patients with EGPA who present with abdominal symptoms must be evaluated carefully, considering the possibility of intestinal perforation, especially in patients undergoing treatment with corticosteroids.

Acknowledgments

The authors have no competing interests. All authors in this manuscript contributed to the design of the study, analysis/ interpretation of data, and drafting of this manuscript. SS collected and interpreted the data. AL helped in drafting the manuscript and interpretation of data. All authors have read and approved the final manuscript for publication. This study was approved by the Institutional Review Board of Jichi Medical University, and authors obtained written informed consent for the case presentations to be published. The

authors declare no conflicts of interests regarding the publication of this paper.

References

1. Greco A, Rizzo MI, De Virgilio A, Gallo A, Fusconi M, Ruoppolo G *et al*. Churg-Strauss syndrome. *Autoimmun Rev* 2015;**14**(4):341–348
2. Kahn JE, Bletry O, Guillevin L. Hypereosinophilic syndromes. *Best Pract Res Clin Rheumatol* 2008;**22**(5):863–882
3. Abril A, Calamia KT, Cohen MD. The Churg Strauss Syndrome (allergic granulomatous angiitis): review and update. *Semin Arthritis Rheum* 2003;**33**(2):106–114
4. Franco DL, Ruff K, Mertz L, Lam-Himlin DM, Heigh R. Eosinophilic granulomatosis with polyangiitis and diffuse gastrointestinal involvement. *Case Rep Gastroenterol* 2014;**8**(3): 329–336
5. Singh R, Singh D, Abdou N. Churg-Strauss syndrome presenting as acute abdomen: are gastrointestinal manifestations an indicator of poor prognosis? *Int J Rheum Dis* 2009; **12**(2):161–165
6. Lanham JG, Elkon KB, Pusey CD, Hughes GR. Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg-Strauss syndrome. *Medicine (Baltimore)* 1984;**63**(2): 65–81
7. Pagnoux C, Mahr A, Cohen P, Guillevin L. Presentation and outcome of gastrointestinal involvement in systemic necrotizing vasculitides: analysis of 62 patients with polyarteritis nodosa, microscopic polyangiitis, Wegener granulomatosis, Churg-Strauss syndrome, or rheumatoid arthritis-associated vasculitis. *Medicine (Baltimore)* 2005;**84**(2):115–128
8. Guillevin L, Lhote F, Gayraud M, Cohen P, Jarrousse B, Lortholary O *et al*. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. *Medicine (Baltimore)* 1996;**75**(1):17–28
9. Hasegawa W, Yamauchi Y, Yasunaga H, Sunohara M, Jo T, Matsui H *et al*. Factors that predict in-hospital mortality in eosinophilic granulomatosis with polyangiitis. *Allergy* 2015; **70**(5):585–590
10. Sinico RA, Bottero P. Churg-Strauss angiitis. *Best Pract Res Clin Rheumatol* 2009;**23**(3):355–366
11. Nakamura Y, Sakurai Y, Matsubara T, Nagai T, Fukaya S, Imazu H *et al*. Multiple perforated ulcers of the small intestine associated with allergic granulomatous angiitis: report of a case. *Surg Today* 2002;**32**(6):541–546
12. Mouthon L, Dunogue B, Guillevin L. Diagnosis and classification of eosinophilic granulomatosis with polyangiitis (formerly named Churg-Strauss syndrome). *J Autoimmun* 2014;**48-49**:99–103
13. Guillevin L, Lhote F, Cohen P, Jarrousse B, Lortholary O, Genereau T *et al*. Corticosteroids plus pulse cyclophosphamide and plasma exchanges versus corticosteroids plus pulse cyclophosphamide alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome patients with factors predicting poor prognosis. A prospective, randomized trial in sixty-two patients. *Arthritis Rheum* 1995;**38**(11):1638–1645
14. Bourgarit A, Le Toumelin P, Pagnoux C, Cohen P, Mahr A, Le Guern V *et al*. Deaths occurring during the first year after treatment onset for polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: a retrospective analysis of causes and factors predictive of mortality based on 595 patients. *Medicine (Baltimore)* 2005;**84**(5):323–330
15. Cojocaru M, Cojocaru IM, Silosi I, Vrabie CD. Gastrointestinal manifestations in systemic autoimmune diseases. *Maedica (Buchar)* 2011;**6**(1):45–51
16. Venditti D, Valerio B, Ielpo B, Buonomo O, Petrella G. Bowel perforations in a patient affected by Churg-Strauss syndrome under high-dose steroid treatment: will alternative drugs reduce risk of surgery? *Rheumatol Int* 2011;**31**(9):1239–1241
17. Narum S, Westergren T, Klemp M. Corticosteroids and risk of gastrointestinal bleeding: a systematic review and meta-analysis. *BMJ Open* 2014;**4**(5):e004587
18. Eriksen TF, Lassen CB, Gogenur I. Treatment with corticosteroids and the risk of anastomotic leakage following lower gastrointestinal surgery: a literature survey. *Colorectal Dis* 2014;**16**(5):O154–O160
19. Suzuki T, Matsushima M, Arase Y, Fujisawa M, Okita I, Igarashi M *et al*. Double-balloon endoscopy-diagnosed multiple small intestinal ulcers in a Churg-Strauss syndrome patient. *World J Gastrointest Endosc* 2012;**4**(5):194–196
20. Beye B, Lesur G, Claude P, Martzolf L, Kieffer P, Sondag D. Small bowel involvement documented by capsule endoscopy in Churg-Strauss syndrome. *Pan Afr Med J* 2015;**22**:41