Received: 31 October 2022 | Revised: 15 December 2022 | Accepted: 3 January 2023

DOI: 10.1002/ccr3.6885

CASE REPORT

Clinical Case Reports Open Access WILEY

Treatment of primary eosinophilic colitis using immunoglobulin/histamine complex

Hyuk Soon Kim[1,2] | **Geunwoong Noh**[3]

[1]Department of Biomedical Sciences, College of Natural Science, The Graduate School of Dong-A University, Busan, Korea

[2]Department of Health Sciences, The Graduate School of Dong-A University, Busan, Korea

[3]Department of Allergy and Clinical Immunology, Cheju Halla General Hospital, Jeju-si, Korea

Correspondence
Geunwoong Noh, Department of Allergy, Allergy and Clinical Immunology Center, Cheju Halla General Hospital, Doreongno 65, Jeju-si, Jeju Special Self-Governing Province 63127, Korea.
Email: admyth@naver.com

Abstract

Primary eosinophilic colitis (PEC) is a primary eosinophilic gastrointestinal disorder, and immunoglobulin/histamine complex (IHC) may be an effective therapeutic for PEC. IHC has a nonallergen-specific antinociceptive effect in the treatment of histamine-mediated pain.

KEYWORDS

abdominal pain, antinociceptive effects, immunoglobulin/histamine complex, monosodium glutamate, primary eosinophilic colitis

1 | INTRODUCTION

Primary eosinophilic colitis (PEC) is a primary eosinophilic gastrointestinal disorder, and its diagnosis is made by exclusion. The diagnosis is contingent upon histologic evidence of excessive eosinophilic infiltration of the colon without evidence of a helminthic infestation or any other underlying disease.[1] The treatment of PEC consists of diet therapy when food allergies are thought to be the cause; glucocorticoids; immunomodulatory drugs including azathioprine, leukotriene receptor antagonists, antihistamines, and mast cell stabilizers; and novel emerging therapeutics such as omalizumab and mepolizumab. However, there are currently no curative therapeutics.

Immunoglobulin/histamine complex (IHC) is an anti-allergy therapeutic, the main mechanism of which is histaminopexy. Antihistamine therapy has been reported to be effective in treating PEC,[2] and omalizumab has even been suggested as a new therapeutic for PEC.[3] Currently, antihistamines are used for symptomatic control, and omalizumab has been reported to be an effective drug for chronic spontaneous urticaria.[4,5] Recently, IHC was reported as a curative drug for chronic spontaneous urticaria,[6] atopic dermatitis,[7] and multiple other allergic diseases.[8] Based on this rationale and considering the pathologic and therapeutic characteristics of PEC, IHC therapy has been applied to PEC. Abdominal pain develops due to many medical and surgical conditions and is the presenting symptom of PEC.[1]

This report presents the case of a patient who initially presented with acute abdominal cramping pain with eosinophilia and then took corticosteroids for 9 years without a diagnosis being made and was ultimately diagnosed with PEC. The PEC remitted completely with IHC therapy, and monosodium glutamate (MSG) was strongly suspected to be the cause of the PEC in this patient.

2 | CASE PRESENTATION

A 49-year-old female Korean patient visited the Department of Allergy and Clinical Immunology, Cheju Halla General Hospital, due to itching and skin rash with rhinorrhoea, sneezing, eosinophilia, and abdominal pain. Weight loss and diarrhea were not present. Nine years ago, cramping abdominal pain developed suddenly, and she visited the local emergency center. Hemoperitoneum was suspected, with severe tenderness of the entire abdomen, and the patient was transferred to a high-grade hospital. On the basis of abdominal computed tomography (CT) and ultrasonography, ovarian rupture was suspected, and the patient was transferred again to a university hospital. However, only ascites was observed, and no medical or surgical problems were observed through laparoscopy. In her laboratory findings, only eosinophilia was observed in the previous three hospitals. Tests for parasitic infestation were all negative. She was initially treated with high-dose oral methylprednisolone (60 mg) as a high-dose steroid pulse therapy, and her abdominal pain disappeared. Thereafter, she took 2.5 mg methylprednisolone daily for 9 years. She frequently experienced sudden bouts of severe abdominal cramping pain.

She was a heavy alcohol drinker and smoked a half-pack of cigarettes per day for more than 10 years. She had experienced an anaphylactic reaction to contrast media 9 years prior. Urticaria and itching developed after taking diazepam 4 years prior because of a sleep disturbance. There was no history of intestinal obstruction, colonic perforation or surgery. There was no specific family history.

Owing to the presentation of allergic rhinitis, chronic urticaria, eosinophilia and abdominal pain of unknown cause, the patient underwent blood tests, including a complete blood count with differential and tests for serum eosinophil cationic protein, serum total IgE and IgE levels for specific allergens using a multiple allergosorbent test (MAST, Green Cross PD, Korea). Serum IgG, A. M, D, and IgG subclass levels were also checked as part of a basic immunologic evaluation.

In the MAST test, the specific IgEs for 41 allergens were evaluated, and results below 0.35 IU ml were negative (Table 1B). A skin prick test was also performed for 53 allergens (Table 1C) as described in a previous report.[6] Histamine hydrochloride (10 mg/ml) was used as a positive control, and physiologic saline was used as a negative control. The results were measured as the wheal size. Reactions were read after 15 min and described as negative (0, no reaction), 1+ (reaction greater than the control reaction but smaller than half the size of histamine), 2+ (equal to or more than half the size of histamine), 3+ (equal to or more than the size of histamine), and 4+ (equal to or more than twice the size of histamine). The minimum size of a positive reaction was 3 mm. To clarify the allergic causes, open food challenge tests for foods that were positive on the skin prick tests were performed as described in a previous report.[9]

The patient was also evaluated by a rheumatologist, and basic rheumatologic tests, including those for antinuclear antibody (ANA), anti-citrullinated peptide antibody, rheumatoid factor and C-reactive protein, were performed.

For the evaluation of parasitic infestation, routine stool examination and parasite antibodies against *Clonorchis sinensis*, *Paragonimus westermani*, *Cysticrcosis*, *Sparganum* and *Toxocara cannis* were tested in our hospital again.

A general psychiatric evaluation was performed for the patient's sleep disturbance and mood by a clinical psychologist at the Institute of Clinical Psychology using the Beck Depression Inventory (BDI-2) to evaluate depression, the State–Trait Anxiety Inventory (STAI) to evaluate anxiety and the Beck Hopelessness Scores to evaluate hopelessness.[10,11] The clinical severity of chronic spontaneous urticaria was evaluated using the Urticaria Severity Score by Jariwala et al., with a total score of 92 points.[12]

For the evaluation of abdominal pain, a gastroenterologist examined the patient. The first impression was alcoholic pancreatitis and allergic gastrointestinal disease. Duodenoscopy, colonoscopy, and abdominal CT were performed.

Her laboratory test results are described in Table 1A. In the allergic laboratory test, she showed eosinophilia, increased serum eosinophil cationic protein levels and increased serum IgE levels. In the immunologic laboratory tests, the serum IgA level was high, and the serum IgG1 and IgG3 levels were low. In the MAST test, she showed specific IgE only for the birch-elder mix (Table 1B). In the skin prick test, she showed polysensitization to many allergens, including food allergens (Table 1C). The rheumatologic and parasitological tests were negative. In the general psychological evaluation, the patient showed a moderate depressive mood and mild hopelessness. The initial clinical severity score for chronic urticaria was 22 points.

Through duodenoscopy, erosive gastritis, and reflux esophagitis were diagnosed. In the biopsy sample obtained by colonoscopy, mild chronic inflammation with scattered eosinophils (up to 20/high power field (HPF) in the ascending and descending biopsy samples, up to 10/HPF in the transverse colon sample and up to 25/HPF in the sigmoid colon sample) was observed (Figure 1A). On abdominal and pelvic CT, parenchymal liver disease with fatty changes and diffuse wall thickening of the gastric mucosa were observed.

TABLE 1 (A) The results of the laboratory tests and psychological evaluation. (B) The results of MAST. (C) The results of the skin prick test

(A)

Classification	Test items	Results (grade)	Normal range (unit)
Allergy	Blood eosinophil fraction	9.9	0–5 (%)
	Serum eosinophil cationic protein	66	0–24 (ng/ml)
	Serum total IgE	612	350 > = (IU/ml)
Immunology	Serum IgA	533.3	70–400 (mg/dl)
	Serum IgG	743.5	700–1600 (mg/dl)
	Serum IgG1	2958	3824–9286 (mg/L)
	Serum IgG2	3519	2418–7003 (mg/L)
	Serum IgG3	26	218–1760 (mg/L)
	Serum IgG4	314	39–864 (mg/L)
	Serum IgM	53.1	40–230 (mg/dl)
	Serum IgD	4.80	0.77–13.2 (mg/dl)
Rheumatology	Anti-nuclear Ab (ANA)	1:80	1:40>
	Anti-cyclic citrullinated peptide (CCP) Ab	8>	8 > (U/ml)
	Rheumatoid factor (RF)	–	
	C-reactive protein (CRP)	–	
Parasitology	Routine stool examination	No helminth ova or no protozoa cyst	
	IgG for Clonorchis sinensis	0.104	1.0 index >
	IgG for Paragonimus westermani	0.088	1.0 index >
	IgG for Cysticecosis	0.127	1.0 index >
	IgG for Sparganum	0.376	1.0 index >
	IgG for Toxocara canis	0.13	1.0 index >
Psychologic tests	Beck Depression Inventory (BDI) -2	22 (Moderate)	Normal ≤ 13, mild 14–19, moderate 20–28, and severe 29–63
	Beck Hopelessness Scores	6 (Mild)	Normal <4, mild 4–8, moderate 9–14, and severe 15–20
	State–Trait Anxiety Inventory (STAI) State	42 (Normal)	normal ≤ 51, mild 52–56, moderate 57–61, and severe 62–80
	State–Trait Anxiety Inventory (STAI) Trait	39 (Normal)	normal ≤ 53, mild 54–58, moderate 59–63, and severe 64–80

B. MAST (IU/ml)

MAST allergens	Result	Allergens	Result
Alternaria alternaria	0.35>	Reed	0.35>
Aspergillums fumigatus	0.35>	Japanese hop	0.35>
Penicillium notatum	0.35>	Acacia	0.35>
Cladosporium herbarum	0.35>	Pine	0.35>
Cockroach	0.35>	Poplar mix	0.35>
House dust mites	0.35>	Sycamore	0.35>
Dermatophatoides Pteronyssinus	0.35>	Ash mix	0.35>
Dermatophatoides farinae	0.35>	Oxeye daisy	0.35>
Dog	0.35>	Dandelion	0.35>
Cat	0.35>	Russian thistle	0.35>
Birch-Alder mix	1.39	Goldenrod	0.35>

(Continues)

TABLE 1 (Continued)

B. MAST (IU/ml)			
MAST allergens	**Result**	**Allergens**	**Result**
Mugwort	0.35>	Pigweed	0.35>
Short Ragweed	0.35>	Crab	0.35>
Sallow willow	0.35>	Shrimp	0.35>
Orchard grass	0.35>	Mackerel	0.35>
Bermuda grass	0.35>	Soybean	0.35>
Timothy grass	0.35>	Hazelnut	0.35>
Sweet vernal grass	0.35>	Peach	0.35>
Rye pollen	0.35>	Milk	0.35>
White oak	0.35>	Egg white	0.35>
Japanese cedar	0.35>		

C. Skin Prick Test (Grade)			
Allergens	**Result**	**Allergens**	**Result**
Alternaria alternaria	–	Beef	2
Aspergillums fumigatus	–	Pork	–
Aspergillus niger	2	Cod	2
Candida albicans	–	Oyster	2
Cladosporium	–	Salmon	–
Penicilium chrysogenum	–	Prawn	3
German cockroach	–	Mackerel	2
Dermatophatoides Pteronyssinus	–	Tuna	–
Dermatophatoides farinae	–	Almond	–
Dog	–	Peanut	2
Cat	–	Bean	–
Gray alder. Silver birch mix	3	Carrot	2
Grass mix	–	Cabbage	–
Mugwort	–	Walnut	–
Short Ragweed	2	Maize	–
Black willow pollen	2	Peach	–
Orchard	–	Tomato	2
Bermuda grass	–	Black pepper	1
Timothy	–	Spinach	–
English plantain	–	Wheat	–
English Rye gass	–	Rabbit	–
Holm oak	2	Kapok	–
Japanese cedar	–	Hop	2
Latex	–	F acacia	–
Milk	–	Pine	–
Egg	–	Poplar	–
Chicken	2		

Interestingly, her abdominal pain subsided within a day after the initiation of an elimination diet for chicken, beef, cod, oyster, prawn, mackerel, peanut, carrot, tomato and black pepper, which were positive on the skin prick test, along with artificial food additives. No food provoked any reactions in the open food challenge tests. Interestingly,

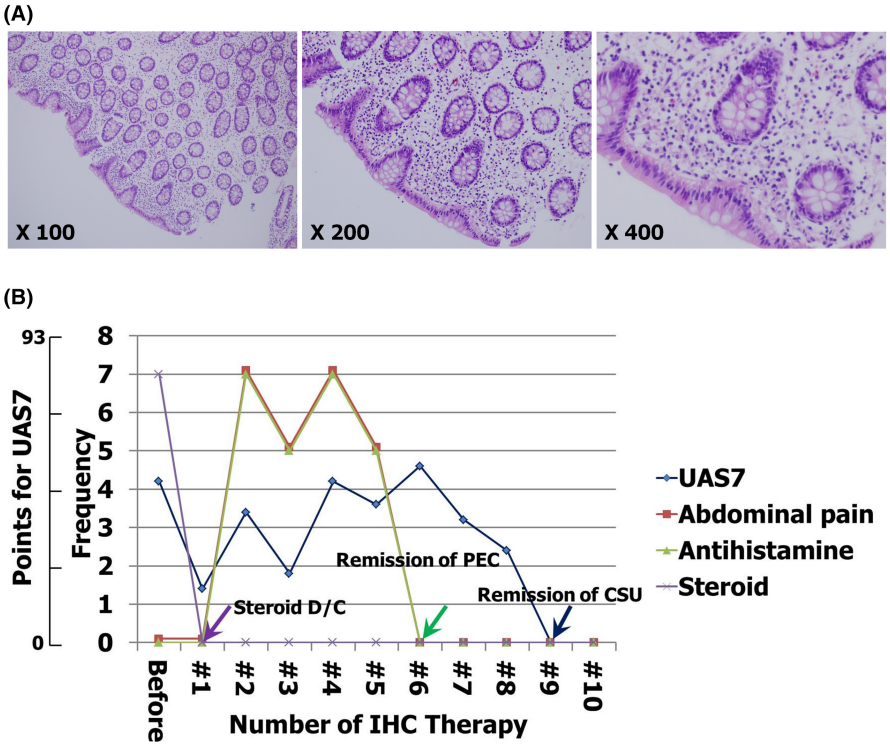

FIGURE 1 (A) Pathologic findings in a colonic biopsy sample. Sheets of eosinophils within the lamina propria extending into the muscularis mucosa were observed with a diagnosis of eosinophilic colitis (H&E ×100, ×200, ×400). (B) Clinical progression. The violet arrow indicates the point at which steroid intake was discontinued. The green arrow indicates the point of PEC remission. The blue arrow indicates the point of CSU remission. CSU, chronic spontaneous urticaria; PEC, primary eosinophilic colitis

only MSG provoked severe abdominal cramping pain within an hour, which was rapidly ameliorated with antihistamines.

For treatment of the PEC as well as the allergic rhinitis and chronic urticaria, IHC therapy was initiated. Histobulin™ (12 mg human immunoglobulin/0.15 μg histamine complex in a 2 ml ampule; Green Cross PD, Korea) was used as the IHC preparation. An ampule of Histobulin™ was injected subcutaneously into the deltoid area of the upper arm every week.

Daily steroid intake was ceased before the basic allergy tests, endoscopy, and IHC therapy (Figure 1B). In the first week after the discontinuation of steroids and the initiation of IHC therapy, her abdominal cramping pain appeared every day, but it was well-controlled by the intake of the second-generation H1 antihistamine levocetirizine (5 mg) within 30 minutes after the manifestation of pain. After 2 weeks of IHC therapy, her abdominal cramping pain was no longer well-controlled by an antihistamine. However, after 3 weeks of IHC therapy, her abdominal pain became well-controlled by the antihistamines again, and after 5 weeks of IHC therapy, she no longer experienced any abdominal pain. Her chronic urticaria was remitted after 8 weeks of IHC therapy, and her allergic rhinitis completely resolved after 9 weeks. She finished the IHC therapy after 10 weeks (10 injections of IHC). She did not show abdominal pain in challenges with MSG-seasoned foods, including chicken, after finishing IHC therapy through her last follow-up at 16 months.

3 | DISCUSSION

IHC therapy was effective in the treatment of this patient with PEC. The patient responded well to initial high-dose and low-dose steroids, which is consistent with other reports.[1,13] There is no known curative treatment for PEC. Steroids were also not curative for this patient, whereas IHC seemed to be curative.

Abdominal pain develops because of many surgical and medical conditions. This patient had no history of the intake of drugs such as clozapine, carbamazepine, rifampicin, gold, or naproxen, which can induce eosinophilic infiltration of the colon secondarily.[14-19] She had no history of tacrolimus intake, which is a risk factor for developing colonic eosinophilia in patients undergoing liver transplantation.[20] In the rheumatologist's evaluation, there was no evidence of ulcerative colitis, which induces a dense eosinophilic infiltrate mimicking PEC and implicates a pathogenic role for eosinophils in inflammatory bowel disease.[21] There was no neurologic manifestation of Tolosa Hunt syndrome, a rare neurologic disorder characterized by headaches, ophthalmoplegia, cranial nerve palsies, high serum IgE levels (1300 U/ml), and marked submucosal infiltration with eosinophils.[22] Thus, these possible conditions for eosinophilic inflammation of the colon were excluded for this patient. PEC is a diagnosis of exclusion, and its diagnosis depends upon pathologic evidence of eosinophilic infiltration of the colon and efforts to rule out other underlying diseases, including parasitic infestations.[1] Taking into account her allergy history,

abdominal pain, the pathologic finding of eosinophilic infiltration of the colon and the elimination of other possible underlying diseases, this patient was diagnosed with PEC.

The abdominal pain of this patient was well controlled by antihistamines. Histamine plays a central role in the pathogenesis of chronic spontaneous urticaria, for which omalizumab is the most recommended treatment.[5,23] Antihistamine and omalizumab have been reported to improve PEC.[1,3] In this respect, the therapeutic characteristics of PEC seem to be similar to those of chronic spontaneous urticaria. Recently, IHC was reported not only to be an effective therapeutic but also to induce complete remission in chronic spontaneous urticaria.[6] Considering its histaminopexy effects and remission induction in chronic spontaneous urticaria, IHC is a potential therapeutic for PEC and was thus tried on this patient. Her PEC completely clinically remitted after 5 weeks of treatment and has remained in remission since then. Moreover, abdominal pain developed after MSG challenge before but not after IHC therapy. The IHC therapy seemed not only to ameliorate the PEC but also to desensitize her MSG hypersensitivity.

With IHC therapy, the frequency of abdominal pain decreased simultaneously with a decrease in the frequency of antihistamine intake, and remission was achieved. The concepts of the intensity and/or frequency of allergy impact should be considered on the basis of the clinical progression. Eosinophilic infiltration is a delayed change and is not affected by antihistamines. It is possible that the eosinophilic infiltration of the gastrointestinal tract may be secondary to the immunologic situation of histamine release and the resulting pathologic changes. However, most studies on the mechanisms of drugs have concentrated on eosinophil control[13] because the representative and diagnostic pathological change is eosinophilic infiltration of the colon. IHC inhibits allergen-induced peritoneal accumulation of eosinophils in mice.[24] Considering the pathological change in eosinophilic infiltration in PEC, IHC seems to be the most appropriate treatment for PEC for the control of both histamine and eosinophilic inflammation.

The sudden onset of severe abdominal pain after the intake of MSG in this patient is similar to that of the clinical presentation of drug-induced anaphylaxis.[25] Abdominal pain is classified as a grade 1 systemic allergic reaction.[26] Thus, PEC may also be considered a separate allergic disease entity that involves only the gastrointestinal tract and is mediated by histamine, and it appears to be one of many clinical manifestations of anaphylaxis. Additionally, all symptoms and signs of anaphylaxis may become organ-specific in chronic conditions. Namely, individual clinical manifestations of anaphylaxis appear as a histamine-mediated chronic disease entity that involves a specific organ, such as chronic urticaria of the skin or PEC of the gastrointestinal tract.

Recently, depression and anxiety were successfully treated with IHC.[27] In that case, a histamine-mediated syndrome was suggested to have a psychologic manifestation of an allergic disease entity. These chronic conditions are all histamine-mediated syndromes, a group of separate disease entities that consist of all possible clinical manifestations of anaphylaxis, such as chronic urticaria and histamine-mediated psychiatric diseases. PEC may be added to this group as a histamine-mediated disease entity that involves the gastrointestinal tract.

The therapeutic protocol of IHC therapy is also an important issue because there is no currently established protocol for any disease due to the lack of clinical studies. Fortunately, a protocol of IHC therapy has begun to be established for treating chronic spontaneous urticaria, in which weekly injections are given until remission.[6] Weekly injections until remission should be considered an appropriate protocol for IHC therapy of PEC until additional clinical studies are performed.

IHC therapy was previously reported to decrease allergen-specific IgE and desensitize multiple food allergies simultaneously, and it was suggested to have potential for the desensitization of drug allergies.[8] MSG is an artificial food additive, and its clinical characteristics are similar to those of a drug.[25] In this patient, her allergy to MSG seemed to be desensitized by IHC and tolerance of MGS was obtained. From a therapeutic perspective, IHC therapy is a nonallergen-specific immunotherapy. IVIG therapy might be a type of nonallergen-specific immunotherapy for nonallergen-specific allergies.[8] Nonallergen-specific immunotherapy was also reported to have polydesensitization effects on atopic dermatitis when combined with allergen-specific immunotherapy using IFN-gamma.[28] IFN-γ also seems to have nonallergen-specific polydesensitization effects. IHC can thus be added to IVIG and IFN-gamma as treatments for inducing nonallergen-specific desensitization.

The elimination of MSG from this patient's diet was effective in ameliorating her abdominal pain, and MSG provoked abdominal pain when reintroduced. Clinically, MSG could not be determined as the cause of the patient's abdominal pain according to Goldmann's criteria.[29] A limitation to definitively identifying MSG as the cause of her PEC is that direct evidence of MSG causing the colon eosinophilic infiltration was not obtained. Therefore, MSG is described as a suspected cause. Allergies to food additives[30] are well known.[30] In particular, allergies to MSG[31] have been well described, including MSG-induced asthma.[32] In mice, food colorants, the most abundant food additives in the world, can trigger IBD-like colitis in mice

conditionally expressing IL-23.[33] The relationship between food additives and inflammatory bowel disease is well known.[34,35] Nevertheless, there have been no reports that food additives, including MSG, induce eosinophilic colitis. Eosinophil cationic protein was elevated in the laboratory tests of this patient, as previously reported in cases of PEC.[36] This may be the first report that food additives, especially MSG, can cause eosinophilic colitis mediated by histamine.

Moreover, following MSG intake, this patient immediately developed abdominal pain, which was well controlled by antihistamines. Therefore, one cannot help but deduce that MSG intake induced histamine release as an allergic response and that antihistamines ameliorated the histamine effects in this patient. The PEC of this patient seemed to be improved mainly through the histaminopexy effects of IHC. Consequently, histamine may be involved not only in the development of clinical manifestations but also in the pathogenesis of PEC.

Histamine seemed to be the cause of this patient's abdominal pain since the pain was immediately relieved by antihistamines. Histamine has been previously reported not only as a chemical mediator of cutaneous pain[37] but also as a mediator of pain in specific organs, such as in cystitis.[38] Antihistamines may thus be considered for pain relief in various organs and circumstances.[39,40] Additionally, in this context, IHC may be applicable for antinociceptive effects in various conditions.

4 | CONCLUSIONS

In this case, IHC was an effective treatment and induced the remission of PEC. Additionally, since histamine is related to the development and pathogenesis of abdominal pain in PEC, IHC may have an antinociceptive effect for histamine-mediated pain. PEC is considered a histamine-mediated gastrointestinal syndrome, which includes all chronic conditions of separate disease entities that present all possible clinical manifestations of anaphylaxis, such as chronic urticaria and histamine-mediated psychiatric diseases. Weekly injection until remission may be an appropriate clinical protocol for IHC therapy of PEC.

AUTHOR CONTRIBUTIONS

Hyuk Soon Kim: Conceptualization; investigation; validation. **Geunwoong Noh:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; supervision; validation; visualization; writing – original draft; writing – review and editing.

ACKNOWLEDGMENTS

This research was supported by the National Research Foundation of Korea (NRF) 252 grant funding by the Korean government (NRF-2020R1C1C1003676). Most of all, I thank my son (Chanyong Noh), my young daughters (Yeonseo Noh, Damseo Noh, Eunseo Noh), and my wife (Yea Hee Yoo) who contributed many things, along with psychological support, for this work to be completed.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

DATA AVAILABILITY STATEMENT

Not applicable.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

ORCID

Geunwoong Noh https://orcid.org/0000-0002-4083-6844

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How to cite this article: Kim HS, Noh G. Treatment of primary eosinophilic colitis using immunoglobulin/histamine complex. *Clin Case Rep*. 2023;11:e6885. doi:10.1002/ccr3.6885