

# Lymphoid hyperplasia of the colon and its association with underlying allergic airway diseases

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## Abstract

**Purpose** The purpose of this study was to determine the prevalence of lymphoid hyperplasia in the lower gastrointestinal tract and its role in patients undergoing colonoscopic examinations, particularly focusing on any allergic predisposition.

**Methods** A database search performed at the Department of Gastroenterology at Onomichi Municipal Hospital identified seven patients with lymphoid hyperplasia in the large intestine (i.e., cecum, colon, and/or rectum). Data regarding the endoscopic, biological, and pathological examinations performed and the allergic histories for each patient were retrospectively reviewed from the clinical records.

**Results** Median age of the patients (four males, three females) was 50 years. Lymphoid hyperplasia was seen in the cecum ( $n=5$ ), ascending colon ( $n=2$ ), and transverse colon ( $n=1$ ). Six patients (85.7 %) had one of the allergic airway diseases: allergic rhinoconjunctivitis for pollen ( $n=3$ ), bronchial asthma ( $n=1$ ), infantile asthma ( $n=1$ ), or allergic bronchitis ( $n=1$ ). Drug allergy ( $n=3$ ) and urticaria ( $n=2$ ) were also found. All seven patients had one or more allergic diseases; however, none had a history of food allergy. Blood tests for allergens

revealed that six patients (85.7 %) had positive reactions to inherent allergens, whereas only one patient had a positive reaction to food allergens.

**Conclusions** Our results indicate that lymphoid hyperplasia in the large intestine may be associated with allergic airway diseases rather than with food allergies; thus, its presence may be useful to detect patients with underlying airway hyperreactivity.

**Keywords** Lymphoid hyperplasia · Colorectal disease · Colonoscopy · Food hypersensitivity · Seasonal allergic rhinitis

## Introduction

The lymphoid follicle is a physiological architecture composed of lymphocytes that form a spherical shape with a pale center known as the germinal center. This structure normally exists in the several areas of the gastrointestinal mucosa, such as Peyer's patches in the ileum. Numbers and sizes of lymphoid follicles are sometimes increased in association with physiological conditions or diseases, and this feature is known as lymphoid hyperplasia [1, 2]. Lymphoid hyperplasia can be seen in the lower gastrointestinal tract of patients with mucosal inflammation from infectious organisms, inflammatory bowel diseases, and colorectal carcinoma and can even occur in childhood as a normal variant [3]. Furthermore, lymphoid hyperplasia in the lower gastrointestinal tract has been reported to be one of the manifestations of food allergy [3–8]. However, because of limited research, the clinical significance of lymphoid hyperplasia in the large intestine has not been fully revealed.

This study aimed to determine the prevalence of lymphoid hyperplasia in the lower gastrointestinal tract and its role in patients undergoing colonoscopic examinations, particularly focusing on any allergic predisposition. Notably, in this study, allergic

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airway diseases and symptoms, rather than gastrointestinal diseases and symptoms, were more frequently found as underlying diseases in patients with lymphoid hyperplasia. A possible causal relationship between lymphoid hyperplasia in the large intestine and underlying allergic airway diseases is discussed.

## Methods

A database search of endoscopic examinations performed at the Department of Gastroenterology at Onomichi Municipal Hospital identified seven patients with lymphoid hyperplasia in the large intestine (i.e., cecum, colon, and/or rectum) between August 2013 and January 2015. As several previous studies have suggested a possible relationship between allergic diseases and lymphoid hyperplasia in the lower gastrointestinal tract, the seven patients were asked detailed questions after the colonoscopy examination regarding allergic diseases; food and drug allergies; medications; and symptoms of the gastrointestinal tract, rhinoconjunctival area, airways, and skin. Furthermore, the levels of allergen-specific IgE antibodies were measured to identify whether allergens were present in all patients, except for one patient. Chemiluminescence enzyme immunoassay with a multiple antigen simultaneous test 33 (MAST33; SRL Inc., Tokyo, Japan) was performed to determine 33 different allergen-specific IgEs, including 14 food antigens (wheat, buckwheat, peanut, soybean, rice, tuna, salmon, shrimp, crab, cheddar cheese, milk, beef, chicken meat, and egg albumen) and 19 inhalant antigens, i.e., pollen (Timothy grass [*Phleum pretense*], *Anthoxanthum odoratum*, orchard grass [*Dactylis glomerata*], ragweed [*Ambrosia artemisiifolia*], Japanese mugwort [*Artemisia princeps*], Japanese cedar [*Cryptomeria japonica*], Japanese cypress [*Chamaecyparis obtusa*], Japanese alder [*Alnus japonica*], and Japanese white birch [*Betula platyphylla* var. *japonica*]), microorganisms (Penicillium, Cladosporium, Candida, Alternaria, and Aspergillus), and environmental allergens (latex, American house dust mite [*Dermatophagoides farinae*], house dust, dog dander, and cat dander). In the remaining one patient, a radioallergosorbent test was performed for several possible allergens selected by the patient's attending physician.

Clinical data regarding past and present histories and endoscopic, biological, and pathological examinations performed were also obtained from retrospectively reviewed clinical records. This study was approved by the Ethical Committee of Onomichi Municipal Hospital and adhered to the Declaration of Helsinki.

## Results

Between August 2013 and January 2015, a total of 1810 colonoscopic examinations were performed in the Department of Gastroenterology at Onomichi Municipal

Hospital. A retrospective review of the endoscopy database revealed that lymphoid hyperplasia was found in the large intestines of seven patients, including four men and three women, ranging in age from 27 to 81 years (median 50 years). Clinical characteristics of the seven patients are shown in Table 1. One patient (case no. 1) presented with fever and diarrhea, which seemed to be associated with colonic inflammation, whereas the remaining six patients had no symptoms or only nonspecific symptoms, such as positive fecal occult blood, abdominal fullness, and narrow stools.

Lymphoid hyperplasia was observed as slightly elevated, round, whitish, tiny nodules with various densities, approximately measuring less than 1 mm in diameter (Figs. 1 and 2). Visualization of these tiny nodules was enhanced by chromoendoscopy with Indigo Carmine. Biopsy samples were obtained from the lymphoid hyperplasia area in all patients. Histopathological evaluation confirmed the diagnosis of benign lymphoid hyperplasia and did not show any neoplastic features such as lymphoma cell infiltration. Lymphoid hyperplasia was seen in the cecum ( $n=5$ ), ascending colon ( $n=2$ ), and transverse colon ( $n=1$ ). Both the cecum and ascending colon were affected in one patient (case no. 5), whereas lymphoid hyperplasia was found solely in one part of the colon in six of the seven patients. Terminal ileum was observed in all the patients, and multiple tiny nodules, which suggest the presence of lymph follicles within the mucosa, were also noted in the ileum in five patients (cases no. 1, 2, 3, 6, and 7). However, it was difficult to distinguish between lymphoid hyperplasia and physiological lymph follicles in these cases. Other colonoscopic features observed in these patients were hemorrhoids ( $n=2$ ) and colonic polyps ( $n=1$ ). None of the patients had erosions or ulcers.

All seven patients had one or more allergic diseases as past histories or underlying diseases. Notably, six of the seven patients (85.7 %) had one of the following allergic airway diseases: allergic rhinoconjunctivitis for pollen ( $n=3$ ), bronchial asthma ( $n=1$ ), infantile asthma ( $n=1$ ), and allergic bronchitis ( $n=1$ ). Drug allergy ( $n=3$ ) and urticaria ( $n=2$ ) were also found. Other underlying diseases include post-surgical resection of colon cancer (case no. 5) and irritable bowel syndrome (case no. 7). No patient reported a history of food allergy.

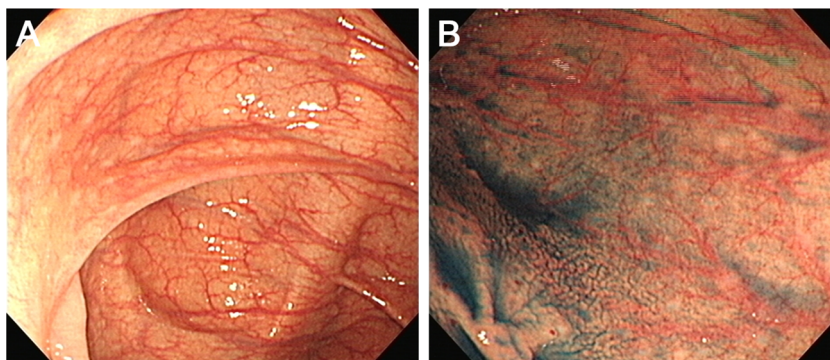
Blood tests revealed that C-reactive protein levels were within the normal range in all patients, suggesting the absence of active systemic inflammation. Elevations of the eosinophil count and IgE level were found in one patient. To identify specific allergens, one patient (case no. 1) underwent radioallergosorbent testing for multiple food allergens (egg white, milk, wheat, peanut, and soybean), wheat, shrimp, gluten, mugwort pollen, and Anisakis. This patient was positive for wheat, mugwort pollen, and multiple food allergens. The other six patients underwent MAST33. Five of these six patients were positive for inherent allergens, such as house dust, dust mite, and pollens but were negative for food allergens. The

**Table 1** Clinical characteristics of the patients

No.	Age	Sex	Symptoms	Location of lymphoid hyperplasia	Other endoscopic features	Known allergies/allergic diseases	Known food allergy	Other underlying diseases	CRP (mg/dL)	Eosinophils (/ $\mu$ L)	IgE (ng/mL)	Positive substances in RAST/MAST33
1	27	M	Fever, diarrhea	Cecum	None	Infantile asthma	None	None	0.01	100	1846	Multiple food allergens (egg white, milk, wheat, peanut, soybean), wheat, mugwort pollen
2	35	M	Abdominal fullness	Cecum	None	Allergic bronchitis (house dust allergy)	None	Dysgryphia	0.02	0	55	House dust, dust mite (Dermatophagoides farinae), cedar pollen
3	42	F	Narrow stools	Transverse colon	None	Allergic rhinoconjunctivitis (pollinosis), drug allergy (NSAIDs, quinolones)	None	Hypertension, diabetes, depression, sinusitis, post-enucleation of palatine tonsils	0.24	166	17	Cedar pollen, hinoki cypress pollen
4	50	F	Fecal occult blood	Cecum	None	Allergic rhinoconjunctivitis (pollinosis), drug allergy (NSAIDs, quinolones, histamine antagonists, dopamine receptor antagonists)	None	Hip replacement arthroplasty	0.02	1116	80	Cedar pollen, hinoki cypress pollen
5	81	M	None <sup>a</sup>	Cecum, ascending colon	Colonic polyps, hemorrhoids	Bronchial asthma, urticaria	None	Diabetes, dysgryphia, bladder cancer, post-surgical resection of colon cancer	0.17	216	56	None
6	66	M	Fecal occult blood	Ascending colon	Allergic rhinoconjunctivitis (pollinosis)	Allergic rhinoconjunctivitis (pollinosis)	None	None	0.02	168	10	Mugwort, cedar pollen
7	61	F	Fecal occult blood	Cecum	Hemorrhoids	Urticaria, drug allergy (tranexamic acid)	None	Irritable bowel syndrome, hyperlipidemia, glaucoma	0.03	0	45	Cedar pollen, hinoki cypress pollen

<sup>a</sup>NSAIDs nonsteroidal anti-inflammatory drugs, RAST radioallergosorbent test, MAST33 multiple antigen simultaneous test 33 (see main text)

**Fig. 1** Colonoscopy images (case 2, cecum). Slightly elevated, tiny nodules are seen in the cecum (a). Chromoendoscopy with Indigo Carmine spraying emphasizes lymphoid hyperplasia (b)



remaining one patient (case no. 5) had no positive result in MAST33 examinations despite his known allergic diseases of bronchial asthma and urticaria.

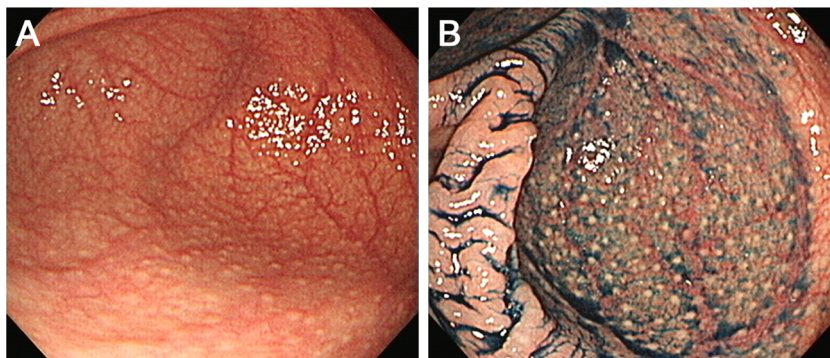
## Discussion

This study revealed, for the first time, that allergic airway diseases and symptoms, rather than gastrointestinal diseases, were more frequently found in patients with lymphoid hyperplasia of the large intestine. Patients with lymphoid hyperplasia also had positive reactions to inherent antigens rather than to food allergens. Krauss et al. investigated 302 consecutive adults and found that patients with untreated gastrointestinally mediated allergy had more lymphoid follicles in the terminal ileum ( $P < 0.001$ ) and cecum ( $P = 0.003$ ) compared with the control group [3]. They noted that increased numbers and sizes of lymphoid follicles might be an indicator of untreated gastrointestinally mediated allergy, since this might reflect an enhanced immunological mucosal response to antigenic stimulation [3, 5]. In addition to gastrointestinally mediated allergy, lymphoid hyperplasia has been reported in association with several diseases, such as bacterial and parasitic colorectal infections, inflammatory bowel disease, and colorectal carcinoma [3, 7, 9–11]. However, a high prevalence of airway hyperreactivity in patients with lymphoid hyperplasia of the colon has never been reported.

Several hypotheses have been proposed to explain why allergic airway diseases and positive reactions to inherent allergens were more prevalent in our patients. First, ingested inherent allergens might react with colonic mucosa and cause lymphoid hyperplasia via mucosal inflammation, while exposure to the same allergens by inhalation might provoke allergic airway disease. Second, lymphoid hyperplasia in individuals with allergic diatheses might be an endoscopic bystander indicating enhanced immunologic activity, including hyperreactivity of the airways and skin as well as of the gastrointestinal tract [5]. We believe that both speculations are probable; further investigations, such as challenge tests by direct administration of inherent allergens into the intestinal tract, should be conducted to prove which hypothesis is correct. Another hypothesis is that lymphoid hyperplasia is simply induced by food allergy in patients with accompanying allergic airway disease since both diseases sometimes coexist [12]. However, this is unlikely because our patients had no known history of food allergies and only one patient had high levels of food allergen-specific IgE.

Our study had several limitations. First, surveillance for multiple allergens was investigated by MAST33 or radioallergen sorbent tests. It has been reported that such allergen-specific serum IgE detection tests do not directly correlate with food-specific sensitization [13–17]. Food challenge tests and food exclusion diets are mandatory for precisely diagnosing food allergies; however, these were not performed in our patients because they had no previous history of hypersensitivity to

**Fig. 2** Colonoscopy images (case 4, cecum) with white light (a) and chromoendoscopy with Indigo Carmine (b). The degree of lymphoid hyperplasia is higher in this case compared with Fig. 1. The endoscopic features resemble “goose pimples”



foods. Second, the threshold to detect lymphoid hyperplasia could be different among the six endoscopists who performed colonoscopies during the study period. As a result, an underestimation of the prevalence of lymphoid hyperplasia may have occurred. Third, although lymphoid hyperplasia occurs in association with several diseases such as giardiasis, common variable immunodeficiency, and IgA deficiency, surveillance for these diseases was not performed in the enrolled patients. However, none of the patients reported any episodes or symptoms related to immunodeficiency and giardiasis. Fourth, only Japanese patients were enrolled in this study. Variability of allergic diseases among different ethnic groups and geographic areas likely affects the prevalence of lymphoid hyperplasia and/or underlying allergic diseases.

## Summary

In conclusion, we found seven patients with lymphoid hyperplasia in the large intestine. Most of the patients (6/7, 85.7 %) had a known history of allergic airway disease and a positive reaction to inherent allergens, whereas no patient (0 %) had a history of food allergy, and only one patient (14.3 %) had a positive reaction to food allergens. These results indicate that lymphoid hyperplasia in the large intestine may be associated with allergic airway diseases rather than with food allergies; thus, its presence may be useful to detect patients with underlying airway hyperreactivity.

**Author contributions** MI drafted and revised the manuscript. KT made the pathological diagnosis. SH, HO, YK, YM, and SK critically revised the manuscript for important intellectual content. KY gave the final approval for publication.

**Compliance with ethical standard** The study was evaluated and approved by the local ethics committee.

**Conflict of interest** The authors declare that they have no conflicts of interest.

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