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Disease Resolution after Cessation of Treatment in Patients with Eosinophilic Esophagitis

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Abstract

Background and aims: Eosinophilic esophagitis (EoE) is a chronic inflammatory condition of the esophagus. EoE is triggered in most patients by dietary allergens and mediated by type 2 immune responses. Over the past 3 decades, substantial progresses have been made in understanding EoE pathogenesis, management, and natural history. EoE affects children and adults, and the incidence and prevalence have increased over time. Untreated EoE can lead to severe complications including food impaction, small caliber esophagus, esophageal stricture, and esophageal perforation. EoE can be managed by dietary elimination, swallowed steroids, proton pump inhibitor, and biologics to achieve both clinical and tissue remission. Patients' quality of life is significantly improved with effective EoE management. Thus far, reports on treatment-free remission in EoE patients without any treatment is rather scattered.

Methods: We identified 7 EoE patients at our Massachusetts General Hospital Food Allergy Center via routine clinical care with treatment-free remission. Clinical charts and EGD biopsy reports were reviewed and analyzed.

Results: We report 7 EoE patients who achieved treatment-free remission over time. In all 7 patients, their active EoEs were responsive to either diet elimination treatment or swallowed steroid treatment in both clinical symptoms and tissue eosinophilia of the esophagus for a variable period. The treatment-free status was achieved after their treatment was stopped for longer than 12 months in 4 of the 7 patients.

Conclusions: We have reported 7 EoE cases, in whom all achieved treatment-free disease resolution after cessation of previous management and the treatment-free disease resolution lasted 12 months or longer. The precise mechanism and rate of the treatment-free remission need further investigation.

Keywords: Eosinophils, Esophagitis, EoE, Remission

Introduction

Eosinophilic esophagitis (EoE) is a chronic inflammation of the esophagus, mediated by the immunity, and triggered primarily by dietary allergens [1]. It affects both children and adults [1]. The disease burden imposes a negative impact on patients' quality of life [2]. EoE is a clinicopathologic diagnosis; it requires the presence of both clinical symptoms and abnormal tissue eosinophilia of the esophagus mucosa [1].

The incidence and prevalence of EoE vary across North America and Europe and have increased over time [3,4]. Studies focusing on endoscopic outcomes have reported progression of significant fibrostenoses in most patients with over a decade of untreated EoE [4].

EoE is a chronic condition that frequently recurs in patient who discontinues treatment [5]. It is generally necessary to continue maintenance treatment, whether avoidance of dietary triggers or pharmacological, to maintain remission [5].

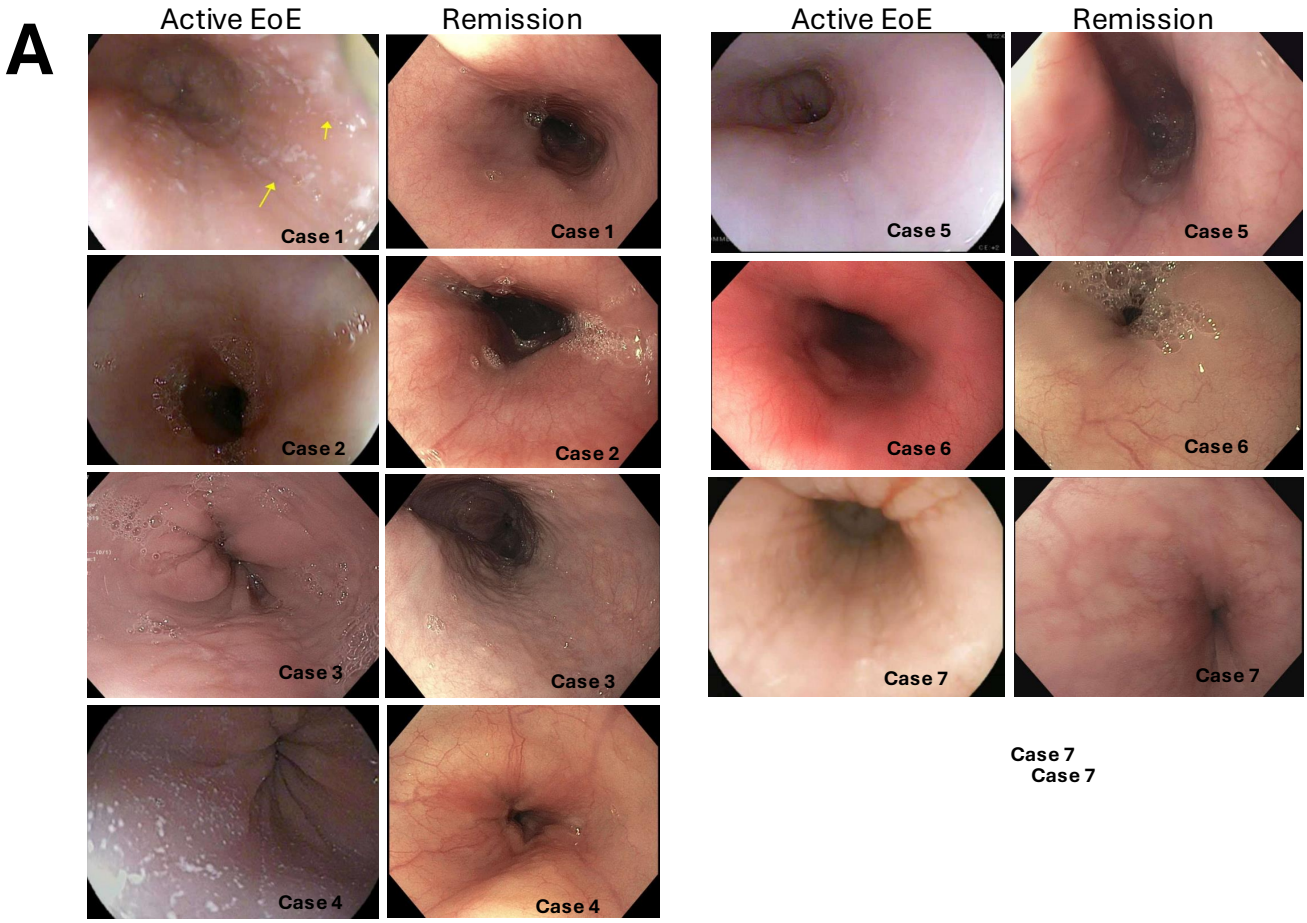
Treatment-free EoE remission is one of research focuses. It has been postulated that if it appears that a patient with EoE is likely to undergo spontaneous remission or experience

minor consequences, the risks of long-term therapy may outweigh the benefits [4]. There are scattered reports on treatment-free EoE remission, but they do not adequately and definitively address if EoE can spontaneously remit at the tissue level over time without treatment in a sustained fashion [6-8]. Spontaneous resolution of esophageal eosinophilia is generally considered uncommon in EoE, although the degree of eosinophilia may wane even in the absence of active therapy [4]. Therefore, better understanding the disease process and natural history will facilitate our management of EoE patients.

Case Reports

Here, we report 7 EoE patients whose EoE have achieved resolution after cessation of treatment. **Figure 1** depicts the endoscopic and histological appearances in active EoE and in remission for all 7 patients. **Tables 1** and **2** summarize the clinical and histological features of the cases. All 7 patients are identified through our routine clinical care, and they are all followed clinically at our hospital.

Case #1 is a 17-year-old male patient. His EoE was diagnosed when he was 8 years old, but his symptoms started when he was 2 years old with gastroesophageal reflux (GER) and difficulty swallowing. Dairy was identified as the sole trigger for his EoE. He tolerated baked dairy at 11 years and 4 months of age (3 years and 4 months post diagnosis), but he failed unbaked dairy trial at 11 years and 9 months of age (3 years and 9 months post diagnosis). His EoE was non-proton pump inhibitor (PPI)-responsive but responsive to swallowed budesonide, as proven by esophagogastroduodenoscopy (EGD) biopsies. He avoided unbaked dairy for 9 years, with clean repeat EGD biopsies. He took swallowed budesonide periodically during vacations when food avoidance was challenging. He re-trialed unbaked dairy at 17 years of age (9 years post EoE diagnosis), with daily consumption of unbaked



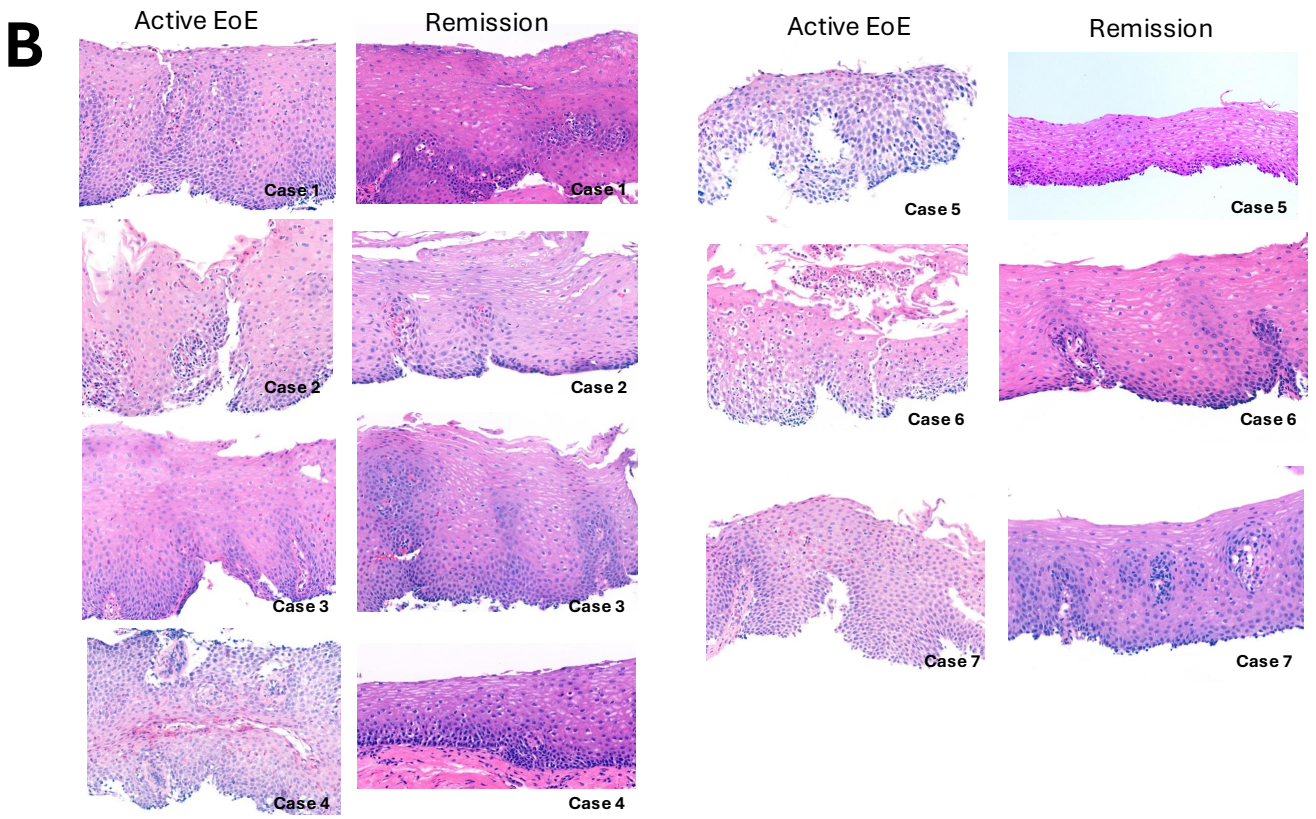


Figure 1. Endoscopic appearance and histology findings. **A.** Endoscopic appearance of all 7 cases in active EoE and in remission. **B.** Histology findings of all 7 cases in active EoE and in remission. Hematoxylin and eosin (H&E) staining of esophageal biopsies, 200x magnification.

Table 1. Clinical features of the 7 EoE patients.

Patients	Gender	Age of onset (yr)	Age of diagnosis (yr)	EoE trigger	EoE treatment	Age of EoE resolution (yr)	Duration of EoE (yr)
#1	M	2	8	dairy	dairy avoidance	17	15
#2	M	1	12	dairy	dairy avoidance	18	17
#3	M	7	13	dairy	dairy avoidance	17	6
#4	F	0.5	1.4	corn, pea, egg	Elemental diet	9	8.5
#5	M	1	8	unknown	Swallowed fluticasone	17	9
#6	M	5	5	unknown	6-food elimination	8	3
#7	M	12	1.5	dairy	dairy avoidance	11	9.5

M: Male, F: Female, Yr: Year(s)

Table 2. Esophageal biopsy results.

	Esophageal eosinophilia (eos/HPF) (D/M/P)		
Patients	**Initial**	**With treatment**	**Current, no treatment**
#1	>200/>200>200	0/0/0	0/0/0
#2	25/32/4	0/0/1	0/0/0
#3	50/30/15	0/0/9	0/0/3
#4	30/10/15	0/0/0	0/0/0
#5	24/24/>40	0/0/0	0/0/0
#6	>40/0 (D/P)	0/0/0	0/0/0
#7	>40/>40/20	3/0/5	0/0/0

D/M/P: Distal/Mid/Proximal Esophagus; eos: Eosinophils; HPF: High Power Field.

dairy for 3 months, without any clinical symptoms. Repeat EGD with biopsies showed remission of his EoE without any treatment.

Case #2 is an 18-year-old male patient. His EoE was diagnosed when he was 12 years old with presenting symptoms of food aversion started when he was 1-year-old. His EoE responded to a 4-food elimination diet (dairy, soy, wheat, and peanut). Sequential addition of soy and peanut, followed by wheat, then baked dairy did not provoke any clinical symptoms or tissue eosinophilia on repeated EGD biopsies. He was avoiding unbaked dairy for 6 years. At age of 18-year-old (6 years post diagnosis), he had a trial of unbaked dairy for 3 months with regular consumption (more than 5 days per week) without any symptoms, repeat EGD with biopsies showed remission of his EoE without any treatment. Of note, he received subcutaneous immunotherapy for environmental allergies for several years.

Case #3 is a 17-year-old male patient. His EoE was diagnosed when he was 13 years old, with presenting symptoms of vomiting and epigastric abdominal pain started when he was 7 years of age. His EoE was non-PPI responsive. Dairy was identified as the sole dietary trigger for his EoE, but he was unable to be compliant with the dairy-free diet. He was treated with swallowed budesonide, with biopsy-proven efficacy, for 4 years and continued consuming dairy in his diet. He self-stopped taking swallowed budesonide at 17 years of age and continued eating a regular diet including all dairy, without any clinical symptoms. Repeat EGD at 18 years of age (1 year without any swallowed budesonide) with biopsies showed remission of EoE without any treatment.

Case #4 is a 9-year-old female patient. She presented with gagging, choking, and coughing with eating and drinking when she was 6 months old. Her EoE was diagnosed at 1.4 years of age after an Emergency Room (ER) visit and hospitalization from a significant choking episode. Her EoE was non-PPI responsive, but responsive to elemental diet with clean esophageal biopsies. Subsequent diet trials with repeat EGDs identified corn, pea and egg as her EoE triggers. She was symptoms free and had clean EGD biopsies with elimination diet for 6 years. Due to developmental delay, Attention-deficit/hyperactivity disorder (ADHD) and slow weight gain, her parents decided to stop the elimination diet and let her to eat a regular diet without any restrictions. She was asymptomatic and gaining weight. Repeat EGD more than a year later (without any diet restrictions) with biopsies revealed remission of EoE.

Case #5 is a 20-year-old male patient. His presenting symptoms were gagging, choking, and GER when he was an infant. He was a very picky eater as a toddler. His EoE was diagnosed when he was 8-year-old. He was treated with swallowed fluticasone, and the efficacy was proven on repeat EGD biopsies. He avoided IgE allergic foods including peanut, tree nuts, egg, corn, coconut, and sea food. With the guidance from his allergist for oral food challenges, he has added corn, coconut, and baked egg back to his diet. He self-stopped taking swallowed fluticasone when he was 16 years old, without any clinical symptoms. His repeat EGD at 17 years of age showed clean esophagus on biopsies without any treatment.

Case #6 is a 9-year-old male patient. He presented with an acute onset of GER symptoms with vomiting at 5 years of age. He was treated with PPI and Pepcid but without improvement. His EGD revealed EoE. He was treated with oral swallowed steroid for 3 weeks because of persistent vomiting and weight loss and the steroid was weaned off. The PPI and Pepcid were stopped after the EGD. He was on an 8-food elimination diet (dairy, soy, wheat, egg, fish, shellfish, peanut, and tree nuts). He had a good clinical response without any vomiting. Repeat EGD with biopsies with the 8-food elimination diet showed a clean esophagus. Sequential diet expansion by adding back nuts and sea food, followed by soy and wheat, and finally dairy did not provoke any clinical symptoms and repeat EGD biopsies showed a clean esophagus. Follow-up EGD biopsies 12 months with a regular diet showed a clean esophagus.

Case #7 is a 12-year-old male patient. His presenting symptoms were vomiting, feeding difficulty, and slow weight gain. His EoE was diagnosed when he was 18 months old. His EoE was not PPI-responsive. Dairy was identified as the sole diet trigger of his EoE. A trial of baked dairy at 6 years of age caused worsening EoE on repeat EGD biopsies. At 11 years of age (9.5 years post diagnosis), his parents self-reintroduced dairy back to his diet and he did not have any clinical symptoms. He had a repeat EGD with eating dairy for 6 months and the esophageal biopsies were clean.

Discussion

Here, we presented evidence of resolution of EoE after cessation of treatment in 7 of our patients, identified through our routine clinical care. Our results suggest the possibility of treatment-free EoE resolution. Results from one study have shown that 25% patients achieved spontaneous remission off treatment with repeat EGD biopsies no earlier than 3 months [6]. But treatment-free disease resolution in EoE patients is still poorly understood.

The precise causes of the treatment-free EoE resolution are unclear. All 7 patients were in remission for variable amount of time with treatment (diet elimination or swallowed steroid) before they achieved the treatment-free disease resolution. It is possible that immune responses may have changed during the period when the EoE was in remission with treatment, and the potential changes of the immune responses either at the local tissue level or systematic level may have led to the final treatment-free remission.

Questions remain about the durability of the treatment-free remission. In our Cases #1 and #2, the duration of treatment-free (timing of the repeat EGDs) was 3 months but it was 6 months in Case #7, whereas in Cases #3, #4, #5, and #6, the treatment-free period was more than 12 months, suggesting that long-term treatment-free remission was present and achievable.

In our Case #2, the patient did receive subcutaneous immunotherapy for his environmental allergies, this may have impacted his immune responses, but it remains unclear if the immunotherapy could alter responses to EoE. He was in remission with 4-food diet elimination for his EoE prior to his subcutaneous immunotherapy, indicating that environmental allergens were unlikely his EoE triggers.

Large scale prospective study is needed to further definitively evaluate the rate of treatment-free disease resolution in EoE patients. This will undoubtedly have a significant impact on managing EoE patients, to potentially avoid long-term pharmacological treatment or diet elimination.

Authors' Contribution

QY: conceptualization, chart review, writing, review and editing the manuscript, WGS: supporting all aspects of the project, and review and editing the manuscript, JNG: pathology photos, review and editing the manuscript.

Conflict of Interest

None.

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