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Complete Remission of Eosinophilic Esophagitis with Multi-aeroallergen Subcutaneous Immunotherapy – A Case Report

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Standard therapies for eosinophilic esophagitis (EoE) include proton pump inhibitors (PPIs), topical corticosteroids (tCS), and food elimination diets (FEDs). Though food allergens typically provoke immune responses in EoE, environmental aeroallergens may also be triggers.[1] Desensitization to aeroallergens via subcutaneous immunotherapy (SCIT) is effective for patients with allergic rhinitis, allergic asthma, and/or atopic dermatitis refractory to medications and avoidance measures.[2] SCIT also has been used in EoE as an adjunctive therapy in case reports of patients with comorbid allergic rhinitis and/or asthma.[3,4] Whether or not allergen SCIT monotherapy can induce and/or maintain clinicohistologic remission of EoE is unclear.

We report a case of multiallergen SCIT used as monotherapy in inducing and maintaining clinicohistologic remission of EoE in an adolescent with allergic rhinoconjunctivitis, shellfish allergy, and remote history of atopic dermatitis. A 14-year-old male presented with intermittent dysphagia and hours-long, self-resolving meat bolus impactions. After initial treatment with three months of omeprazole 20 mg twice daily, esophagoduodenoscopy (EGD) demonstrated mild narrowing, white plaques, edema, and rings, and esophageal

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Iglesia: Data collection; data interpretation; manuscript drafting; critical revision
Commins: Data interpretation; critical revision
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biopsy revealed a peak of 62 eosinophils per high-power field (eos/hpf) and microabscesses (Table 1). A 2FED eliminating dairy and wheat was then pursued, and omeprazole was stopped; he also avoided shellfish and fish due to previously known food allergy. Additionally, poorly controlled rhinoconjunctivitis prompted skin prick testing (Greer pick method) to environmental aeroallergens, which demonstrated sensitization to cat, dog, molds, tree pollens, grass pollens, and weed pollens (Table E1). He then started daily intranasal fluticasone 50 mcg 2 sprays each nostril and oral fexofenadine 180 mg. Neither the initial 2FED nor subsequent step-ups to 4FED (dairy, wheat, egg, soy) or 6FED (dairy, wheat, egg, soy, peanut/tree nuts, fish/shellfish) induced a clinicohistologic response, with worsening endoscopic features, strictures requiring dilation, and persistent esophageal eosinophilia (Table 1; Figure E1). He was next treated with two months of oral viscous budesonide (OVB) 1 mg twice daily, which induced clinicohistologic remission. With this response, the patient and family elected to stop tCS and start multiallergen SCIT for poorly controlled allergic rhinoconjunctivitis, guided by updated aeroallergen sensitizations via allergen-specific serum IgE (Table E1). The plan was to assess response to SCIT alone (Table 2). In the build-up phase, he received injections twice weekly per clinic protocol. Surveillance endoscopy after 3-months of SCIT demonstrated relapse with intraepithelial eosinophilia in the distal esophagus (Table 1). He reached the maintenance phase after six months. After three months of maintenance injections every 2 weeks, clinicohistologic remission was achieved. Five months later, surveillance endoscopy while on maintenance SCIT only (i.e., off tCS, FED, and PPI) continued to show complete clinicohistologic remission of his EoE, and his previously severe stricture had resolved. The patient continues to be symptom-free over one year since resolution of esophageal eosinophilia.

We present a case of clinicohistologic remission of EoE induced and maintained by multiallergen SCIT monotherapy. We feel that the combination of tCS cessation, relapse during the spring and summer seasons, previous incomplete responses to FEDs, and subsequent response to SCIT strongly support the role of targeting aeroallergen-mediated esophageal inflammation in this particular patient. In allergic respiratory disease, allergen desensitization is driven by promoting a deviation from T_H2 to T_H1 immune responses culminating in induction of T_{reg} cells, B_{reg} cells, and IgA, IgG, and IgG_4 blocking antibodies to culprit antigens.[5] It is less clear how aeroallergen sensitization interacts with EoE pathophysiology or how SCIT plays an adjunctive or primary role in reducing intraepithelial eosinophilia. Previously hypothesized mechanisms of aeroallergen-induced esophageal inflammation include swallowing postnasal secretions containing aeroallergens that act as triggers, as well as a local migration of eosinophils into the esophagus driven by a systemic immune response due to allergens encountered in the respiratory tract.[1] A single-center retrospective study did not identify worse efficacy or safety outcomes in patients with EoE treated with SCIT versus those without SCIT treatment, though the study was underpowered.[4] While FEDs did not induce remission in our patient, and thus might suggest that foods are not a trigger, we cannot exclude a contribution of cross-reactive antigens present in both pollens and foods. SCIT to house dust mite was used effectively as an adjunctive intervention in a child with EoE concurrently treated with tCS and PPI.[3] SCIT to environmental aeroallergens was reportedly effective as adjunctive therapy to FEDs, especially in the presence of sensitization to cross-reactive pollen-food aeroallergens, such

as Bet v 1 homologs (PR-10) or lipid transfer proteins (LTP, PR-14).[6,7] Multiallergen SCIT was also reportedly successful in an adult with indoor and outdoor aeroallergen sensitization who did not have a durable response to swallowed fluticasone for his EoE.[8]

In addition to case report limitations, it is uncertain if there were immunologic priming effects of initial treatments (PPI, tCS, FED) that allowed SCIT to induce and maintain clinicohistologic remission. Nonetheless, the patient demonstrated re-induction of and sustained clinicohistologic remission on maintenance SCIT, while not responding to PPI and FED and relapsing when tCS was stopped. We believe it would be unlikely that his EoE spontaneously remitted coincident with SCIT, given that EoE typically recurs without ongoing intervention, and considering the severity of his baseline EoE and stricture, which resolved post-SCIT without requiring another dilation. A possibility remains that remission was induced by desensitization to cross-reactive PR-10 allergens. While peanut, tree nuts, and soy were avoided during dietary elimination, empiric FEDs do not require eliminating cross-reactive PR-10 fruits and vegetables (e.g., apple, cherry, stone fruits, tomato, celery). To re-emphasize, allergic rhinoconjunctivitis was the indication for SCIT in this patient; EoE alone is currently not a SCIT indication. Additionally, EoE may even recur with SCIT.[9]

This report extends proof-of-principle that multi-aeroallergen SCIT to environmental aeroallergens may be a useful second-line therapy in EoE in patients and comorbid allergic rhinitis and/or allergic asthma. For this select subset of patients who incompletely respond to standard of care therapies for EoE, continuation of aeroallergen SCIT at maintenance doses –either as an adjunctive treatment or even monotherapy–might provide durable clinicohistologic remission in select patients. Future studies are needed to further characterize SCIT's efficacy and safety in EoE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Implications:

Multiallergen subcutaneous immunotherapy might be a safe and effective option for patients with eosinophilic esophagitis and comorbid allergic rhinitis and/or asthma who do not respond to standard therapies, though future controlled studies are needed.

Table 1.

Treatment Course

Treatment	Symptom response	EGD outcome (EREFS)	Eosinophil counts, proximal (eos/hpf)	Eosinophil counts, distal (eos/hpf)	Month of biopsy	Additional Notes
Omeprazole 20 mg twice daily x 12 weeks	No	Ex2, R1, E1, F1, S0 No dilation	62	21	March	
2FED* (dairy, wheat) x 8 weeks	No	Ex1, R2, E2, F1, S11 No dilation	90	45	August	
4FED (dairy, wheat, egg, soy) x 6 weeks	No	Ex1, R2, E1, F1, S9 Dilation (Savary to 11mm)	180	10	October	
6FED (dairy, wheat, egg, soy, peanuts/tree nuts, fish/shellfish) x 6 weeks	No	Ex1, R2, E1, F1, S9 Dilation (Savary to 12mm)	140	60	November	
Oral viscous budesonide (OVB) 1 mg twice daily x 8 weeks	yes	Ex0, R1, E0, F0, S16 Dilation (Savary to 17mm)	0	0	March	OVB subsequently stopped due to family preference in order to start SCIT and observe the response
Off OVB and on multiallergen SCIT (build-up phase) x 3 months	yes	Ex1, R1, E1, F1, S16 Dilation (Savary to 17mm)	0	48	August	
Multiallergen SCIT (maintenance phase) x 3 months	yes	Ex1, R0, E0, F1, S0	0	5	March	
Multiallergen SCIT (maintenance phase) x 8 months	yes	Ex0, R0, E0, F0, S0	0	2	August	Remains asymptomatic on 18+ months of maintenance SCIT; follow-up EGD deferred due to covid-19 pandemic

Table 2.

Allergen Subcutaneous Immunotherapy Prescription, Maintenance Concentrate[^]

Vial 1 – Mites, Trees, Grasses		
Percent Composition	**Major Antigen**	**Concentration**
25.00%	Standardized Mite Mix	5000 AU / mL
10.00%	Tree Mix 1 (Elm Mix, Hickory-Pecan Mix, Oak Mix)	1:20 w / v
10.00%	Tree Mix 2 (Ash Mix, Birch Mix, Maple Mix, Poplar, Sycamore)	1:20 w / v
5.00%	Walnut Pollen, Black	1:20 w / v
10.00%	Bahia Grass	1:20 w / v
20.00%	Standardized Bermuda	10,000 BAU / mL
5.00%	Standardized Timothy	100,000 BAU / mL
Total Percent of Antigen	85%	
Total Percent of Diluent	15.00%	
Glycerin Content	27.00%	
Vial 2 – Cat, Dog, Weeds, Molds		
20.00%	Standardized Cat Hair	10,000 BAU / mL
20.00%	Dog epithelia	1:10 w / v
10.00%	3-weed mix (Cocklebur, Lamb's Quarter, Rough/Redroot Pigweed)	1:20 w / v
10.00%	Plantain, English	1:20 w / v
10.00%	Ragweed, Short	1:20 w / v
10.00%	Mold Mix (*Alternaria alternate, Aspergillus niger, Bipolaris sorokiniana, Cladosporium sphaerospermum, Penicillium chrysogenum*)	1:20 w / v
Total Percent of Antigen	80.00%	
Total Percent of Diluent	20.00%	
Glycerin Content	19.00%	

[^]Contains Stallergenes Greer stock mixtures (Lenoir, NC)