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New IgE immediate hypersensitivity reactions on reintroduction of food restricted for treatment of eosinophilic esophagitis



Eosinophilic esophagitis (EoE) is a chronic immune-mediated disease. Because EoE is largely food driven, elimination diet (ED) is 1 of the 2 primary modalities used to treat EoE^{1,2}. Options include empiric EDs (6, 4, or 2 food EDs) or targeted EDs based on food allergy testing.^{3,4} Recently, children with EoE have been reported to develop immediate hypersensitivity reactions with reintroduction of previously immunoglobulin E (IgE) tolerated milk.^{5–8} Herein, anaphylaxis to previously tolerated wheat in an adult with EoE, and diffuse urticaria from soy reintroduction in a teen with EoE are presented.

A 65-year-old woman with a 5-year history of dysphagia, previously dilated 5 times, had esophageal rings and 210 eosinophils per high-power field (eos/hpf) in the mid-esophagus and 180 distally despite omeprazole 40 mg twice daily. Allergy tests were positive to wheat (4-mm wheal, wheat IgE 8.61 kU/L) and other grains. Biopsy off grains and empiric milk elimination had 0 eosinophils. Sixteen months after grains were eliminated, the patient ingested a hamburger on a seedless bun. Twenty minutes later, palmar itching, flushing, generalized pruritus, lip swelling, stridor, and hypotension occurred, responding to epinephrine, antihistamines, and steroids without dual-phase reaction. Alpha-gal IgE was normal. Three months post-reaction, wheat skin prick test (SPT) had a 4-mm wheal; wheat IgE was 7.44 kU/L.

A 13-year-old boy with a 2-year history of dysphagia, had food impaction twice. On high-dose proton pump inhibitor, esophagogastroduodenoscopy showed rings, exudates, and furrows, and the biopsy specimen had more than 100 eos/hpf. Allergy testing was positive for milk, egg, wheat, soy (7-mm wheal), peanut, nuts, legumes, and meats. Six food plus meat ED resulted in a decrease to 40 eos/hpf. Budesonide slurry was started, and diet was to be liberalized. Because the anaphylactic reaction of case 1 had occurred just weeks earlier, and the patient was known to have a soy wheal of 7 mm, despite previous IgE soy tolerance, an in-office open graded food challenge (OFC) with soy was performed after 6 months' avoidance. Forty minutes after ingesting a total of 240 mL soy milk over 105 minutes, generalized urticaria developed. The patient responded to epinephrine and cetirizine. Eight weeks later, postreaction soy PST was a 6-mm wheal (soy IgE was

declined). Neither patient had ever had a previous allergic reaction to foods or medicines.

Very few reports have been made of EoE patients developing immediate hypersensitivity reactions to reintroduction of foods avoided for EoE. In 2015, Hill reported development of oropharyngeal edema from milk 2.5 years after its avoidance for EoE.⁵ Milk PST converted from normal to 10-mm wheal. Alsalamah et al⁶ observed milk causing hives, vomiting, and respiratory symptoms after 1 year of avoidance, with PST converting from nonreactive to 24-mm wheal. Soller et al⁷ reported a 15-year-old with milk allergy as a toddler, with subsequent tolerance for years, who developed angioedema, vomiting, dyspnea, and lightheadedness on accidental exposure 4 months after avoidance. Milk SPT was 10 mm, and milk IgE was 8.99 kU/L. Most recently, Ho and Chehade⁸ reported 5 patients with new milk IgE hypersensitivity after avoidance for their eosinophilic gastrointestinal disease. Two infants developed urticaria and oropharyngeal pruritus. All had previous normal milk SPT. Postreaction, all had SPT or milk IgE tests with strong positive predictive values (PPV) for failing an OFC. Three patients, including 1 adult, had no exposure, and OFC was deferred because of SPT/milk IgE of high PPV.

These cases add to the increasing number of reports of IgE tolerated foods, restricted as treatment of EoE, causing urticaria/anaphylaxis on reintroduction. The presented cases are notable because these are the first non-milk reactions, having occurred to wheat and soy. This is also the first report of an adult with a documented clinical reaction, in contrast to sensitization without definitive clinical reactivity, as in Ho and Chehade's report. Additionally, the reaction to soy was during an in-office, supervised oral food challenge, leading to no other conclusion than newly developed soy allergy. Finally, SPT or IgE to the causative foods were not to the degree associated with high PPVs.

These 2 case reports raise several questions. First, how often is this occurring? Ho's retrospective chart review showed that 2.3% of patients younger than 18 years and 2.1% of adults developed immediate reactions to avoided foods on re-exposure.⁸ Chang et al⁹ reported 13.6% of children with food-triggered atopic dermatitis developed new immediate hypersensitivity on re-exposure to the avoided food.⁹ With increased attention, this issue may be seen to have been underreported.

Second, can we predict who may be at increased risk? Tests for food-specific IgE confer some increased risk of reaction. However,

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they have low specificity and with no history of prior reaction usually reflects asymptomatic sensitization, as they did initially in our patients. In studies of certain high-risk pediatric populations (atopic dermatitis, anaphylaxis), 95% PPV cutoff values exist for predicting allergic reactions to milk, egg white, and peanut. Wheat and soy have performed less reliably, with 50% and 75% PPV, respectively.¹⁰ In an adult study, wheat-specific IgE PPV was 57%. Thus, performance characteristics may not be applicable between different populations (age, food, type of food allergy).

The previously reported milk reactions initially lacked IgE to milk, and post-reaction had milk IgE associated with high milk PPV in a different patient population; in contrast, our patients had evidence of wheat or soy IgE both initially and after their reaction, albeit levels associated with lower PPVs. Whether previously reported food-specific IgE/PST PPVs are applicable to children and adults with EoE reintroducing previously IgE tolerated foods remains to be seen.

Third, should all patients on a restricted diet for EoE be (re-) evaluated for specific IgE before reintroducing a food, or is this a phenomenon of just more “highly” allergenic foods? Fourth, who should be reexposed via in-office graded oral food challenge? Time, cost, and inconvenience become additional considerations. Finally, what is the mechanism by which, during food restriction, the immune response changes from non-IgE TH2 response to include an IgE response?

In discussing EDs and topical corticosteroids with patients and their families, the risks and benefits should be thoroughly detailed so that an informed decision can be made. A small, but real, risk of a more serious IgE-type food reaction developing in EoE patients after a period of restriction is apparent. Means to identify those at risk is needed and will help direct which patients should have in-office, physician-supervised, graded food challenges, continued restriction, or at-home food reintroduction. Further epidemiologic and immunologic studies are needed to gain insight into this increasingly recognized phenomenon.

A peripheral cause of asthma

Peripheral T-cell lymphoma

Peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS) is an aggressive subtype of T-cell non-Hodgkin's lymphoma. Despite the poor prognosis associated with PTCL, NOS, prompt diagnosis and treatment are critical to prevent further morbidity and mortality.¹ We report a case of new-onset asthma with peripheral eosinophilia, subsequently diagnosed with PTCL, highlighting the need to consider a broad differential in the setting of uncontrolled atypical respiratory symptoms.

A 49-year-old woman without significant medical history or known atopy was transferred from an outside hospital for new-onset asthma, peripheral eosinophilia, diffuse rash, recently diagnosed thymoma, and respiratory distress. Eight months before presentation, the patient developed a pruritic papulonodular rash to her upper chest and proximal upper extremities, which improved with steroid treatment. Two months later, the patient noted a new nonproductive cough and dyspnea after the completion of a marathon. She presented to an outside physician and received treatment for pneumonia, with improvement in symptoms. Four months later, her respiratory

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symptoms recurred, and the patient was referred to a pulmonologist, who performed pulmonary function testing notable for a forced expiratory volume in 1 second (FEV₁)/forced vital capacity ratio of 0.62, FEV₁ 36% of predicted, and a 24% improvement in FEV₁ after the administration of a bronchodilator. A methacholine challenge was also performed and was reportedly positive. She was diagnosed with new adult-onset asthma and treated with a short course of oral corticosteroids and eventually continued on inhaled corticosteroids with little improvement. A computed tomography (CT) scan of her chest demonstrated an anterior mediastinal mass that was consistent with a thymoma, and a complete blood count revealed peripheral eosinophilia. Given this constellation of symptoms, the patient underwent a bone marrow biopsy, which was negative for malignancy but did demonstrate 10% eosinophils. Before her thymoma could be evaluated further, the patient's respiratory symptoms worsened over the course of a month, and she was admitted to an outside hospital for worsening dyspnea, a cough productive of thick, string-like sputum (Fig 1A), new nasal congestion with a sensation of fullness in her nose, and progressive rash involving all 4 extremities.

On presentation to our hospital, her white blood cell count was 14,500 cells/ μ L, with a peak absolute eosinophil count of 1,312 cells/ μ L.