

Suspected food allergies in a septuagenarian with recurrent anaphylaxis

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ABSTRACT

Anaphylaxis is an acute, life-threatening reaction that can occur due to a variety of triggers. It is often associated with allergen exposure, such as food, venom, or medications; however, there are other less-common causes, and many patients are ultimately classified as idiopathic. In this report, we described a patient with recurrent reactions attributed to food exposure. Further evaluation revealed an alternative, less common diagnosis.

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CHIEF CONCERN

Allergic reactions.

HISTORY OF PRESENT ILLNESS

A 74-year-old man with a history of asthma, allergic rhinitis, and gastroesophageal reflux presented with a history of multiple episodes of facial warmth, erythema, swelling, and difficulty breathing. At the onset of symptoms, he would typically self-administer 50 mg of oral diphenhydramine and epinephrine autoinjectors, and call emergency medical services for transport to an emergency department (ED). Typically, symptoms would improve before arrival in the ED. He did not have documented urticaria, angioedema, or hypotension. He had not required intubation or hospital admission. These episodes occurred three to four times per year since early adulthood. Results of a previous skin test showed wheal and/or flare reaction to various foods, and these episodes were attributed to food-induced anaphylaxis. At the time of evaluation, he was avoiding many foods (Table 1).

The patient presented due to increased frequency of these episodes, without a clear association to a known food trigger. Two months before presentation, he had two reactions ~1 week apart. The first episode occurred 30 minutes after eating homemade tacos at a friend's

home. The friend had been provided a detailed list of foods to avoid and reported strict adherence to this list during food preparation. The patient experienced facial erythema and warmth, followed by shortness of breath. He took 50 mg of diphenhydramine, self-administered two epinephrine autoinjectors, and called emergency services. The ED physician noted a completely normal physical examination. The patient received albuterol *via* nebulization and was treated with oral steroids.

The second episode occurred 2 hours after eating a hamburger at a restaurant where he frequently dined. The patient had consumed the same menu item in the past. He developed facial erythema, warmth, and dyspnea. He took 50 mg of diphenhydramine, self-administered two epinephrine autoinjectors, and called emergency services. At this ED visit, the physician noted faint wheezing and facial erythema. He was given intravenous steroids and H₂ blockade therapy as well as albuterol *via* nebulization. For both episodes, the patient suspected a food allergen contamination or development of a new food allergy.

PHYSICAL EXAMINATION

At initial evaluation, vital signs included a temperature of 36.6°C, blood pressure of 151/73 mm Hg, and heart rate of 66 beats/minute. Results of the skin examination were unremarkable; the Darier's sign was not present. The lungs were clear to auscultation. Results of a cardiac examination demonstrated normal rate and rhythm. The abdomen showed no tenderness or visceromegaly.

INITIAL LABORATORY AND DIAGNOSTIC FINDINGS

Skin testing results demonstrated wheal-and-flare reactions to multiple foods and aeroallergens (Table 2).

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Table 1 List of all foods avoided by the patient at initial presentation

All tree nuts
Peanut and all legumes (including chickpeas)
All seeds (including poppy, sesame, caraway, sunflower)
All fish and shellfish
All squashes, zucchini and eggplant
All berries (including strawberry, blueberry, raspberry)
Buckwheat
Coconut
Avocado
Cantaloupe
Honeydew
Kiwi
Mango
Papaya
Rhubarb

Subsequent serologic immunoglobulin E (IgE) testing revealed no elevated serum-specific IgE to foods, including foods with sensitization on skin testing (Table 2). The total IgE level was 13.2 kU/L (reference range, <114 kU/L). Baseline tryptase was 15.2 $\mu\text{g/L}$ (reference range, <11 $\mu\text{g/L}$), and 12.0 $\mu\text{g/L}$ when repeated 1 week later. Galactose alpha-1,3-galactose IgE was <0.10 kU/L (reference range <0.10 kU/L). Latex IgE was <0.35 kU/L (reference range, <0.35 kU/L).

QUESTIONS

What Is the Differential Diagnosis?

Anaphylaxis is an acute, life-threatening reaction that can be triggered by food, Hymenoptera venom, medications, or other factors.¹ Unusual triggers, such as galactose alpha-1,3-galactose sensitivity, spice allergy, or food additive allergy merit consideration. Augmenting factors, such as exercise, heat or cold exposure, or increased nonsteroidal anti-inflammatory drug use can also play a role. When no clear trigger can be identified after thorough evaluation, patients are commonly diagnosed with idiopathic anaphylaxis. In such cases, mast cell disorders should be considered, particularly with hypotension in the absence of urticaria or angioedema.^{2,3} Given the broad clinical presentations of anaphylaxis, it is important to consider other possibilities, such as inducible laryngeal dysfunction or somatization disorder.⁴

What Additional Laboratory Data or Investigations Would Be Helpful in Arriving at a Diagnosis in This Patient?

Confirming a diagnosis of anaphylaxis requires a detailed physical examination that documents multi-

organ system involvement. Probable anaphylaxis has been described as involvement of two or more organ systems, including the respiratory and/or cardiovascular system.¹ Serologic testing can help confirm the diagnosis. Serum tryptase is a specific, although not sensitive, test to confirm mast cell degranulation suggestive of anaphylaxis.⁵ A baseline tryptase must first be established. Elevated basal tryptase levels are often indicative of clonal mast cell disorders.⁶ Postevent elevation of tryptase levels, specifically an elevation of 20% from baseline tryptase plus 2 ng/mL, is consistent with mast cell activation.⁷ Patients with evidence of mast cell activation may present with a variety of symptoms⁶; however, in our case, the multiorgan system involvement and respiratory compromise were consistent with anaphylactic events.

Once anaphylaxis is confirmed, a thorough evaluation to identify a possible cause is paramount. The clinical history and initial laboratory workup in our patient were not suggestive of medication, alpha-gal, stinging insect allergy, or exercise-induced anaphylaxis. Our case, however, was suggestive of possible food allergy. Oral food challenge is useful for confirming or ruling out a diagnosis of food allergy.⁸ If food allergy is ruled out, then a mast cell disorder may be present. Apart from tryptase level evaluation, peripheral blood *KIT D816V* mutation testing can provide further support for the presence of a mast cell disorder.⁹ If this mutation is present, or if the suspicion for mast cell disorder remains, then a bone marrow biopsy is indicated.¹

CLINICAL COURSE

The patient was given clear instructions to request a serum tryptase level during his next episode. He had three subsequent episodes of facial swelling, erythema, and difficulty breathing. These episodes began 1–2 hours after consumption of food. The events prompted self-administration of epinephrine and ED treatment. The patient continued to attribute his symptoms to food allergy, although there was no clear food allergen exposure. During one event, his tryptase level was obtained within 4 hours after symptom onset and was elevated at 43 $\mu\text{g/L}$ (reference range, <11 $\mu\text{g/L}$). A repeated baseline serum tryptase evaluation after the event was 13.5 $\mu\text{g/L}$. This tryptase elevation, paired with ED physician documentation of wheezing and flushing on examination, confirmed the diagnosis of anaphylaxis. We proceeded to further evaluate food as a possible cause. He underwent oral challenge to shrimp, tuna fish, strawberry, flaxseed, coriander, cumin, and fennel without adverse reaction (Table 2). These foods were previously identified by the patient as triggers of anaphylaxis; with negative food challenge results, we

Table 2 Skin testing, serologic IgE testing, and oral challenge results*

Allergen	Wheal/Flare Diameter, mm	Serum IgE, kU/L (normal, <0.35 kU/L)	Oral Challenge
Saline solution control	0/0		
Histamine control	12/45		
Legumes			
Peanut	4/5	<0.35	
Soybean	3/4	<0.35	
Tree nuts			
Almond	6/20	<0.35	
Brazil nut	2/3	<0.35	
Coconut	0/0	0.45	
Hazelnut	20/40	0.63	
Pecan	8/18	<0.35	
Pistachio	8/35	<0.35	
Walnut, black	10/30	1.01	
Walnut, English	5/10		
Fish and shellfish			
Shrimp	0/0		Passed
Catfish	4/5	<0.35	
Codfish	4/5	<0.35	
Mackerel	3/5	<0.35	
Perch	3/5	<0.35	
Salmon	10/20	<0.35	
Trout, lake	4/20	<0.35	
Tuna	0/0		Passed
Fruits and vegetables			
Cantaloupe	3/25	<0.35	
Strawberry	4/5		Passed
Squash	3/4		
Seeds, spices, and grains			
Buckwheat	3/6		Passed
Coriander (slurry)	2/3		Passed
Cumin seed (slurry)	3/4		Passed
Fennel seed (slurry)	3/5		Passed
Milled brown flaxseed (slurry)	4/6		Passed
Sesame	25/45	0.69	
Sunflower	3/6	<0.35	

IgE = Immunoglobulin E.

*Skin testing and/or serologic results were negative for the following foods: chickpea, cashew, crab, lobster, eggplant, honey dew, kiwi, mango, raspberry, rhubarb, zucchini, poppyseed, pumpkin seed.

concluded that his reactions were not due to an allergic food trigger.

We considered the diagnosis of mast cell disorder, and obtained serum *KIT D816V* mutation analysis; the result was positive. Results of a bone marrow biopsy were consistent with systemic mastocytosis with an associated hematologic non-mast cell lineage disease (SM-AHNMD). His bone marrow analysis demonstrated >25% of mast cells, with an atypical or spindle-shaped morphology, as well as aberrant CD25 expression. In addition, he was found to have monoclonal B-

cell lymphocytosis positive for CD5 and lymphoid enhancer binding factor 1 (LEF1), and negative for surface immunoglobulin light chains.

DISCUSSION

Food allergy is common, with a prevalence of 10.8% in U.S. adults, and may account for up to 30% of anaphylaxis cases.^{10,11} Despite this high prevalence, diagnosing true food allergy is difficult because the positive predictive value of food skin testing is only

~50%.⁸ Our patient had positive skin test results to many foods. For these reasons, it was not surprising that his anaphylactic episodes were attributed to food allergy. However, his episodes repeatedly occurred without consistent exposure to a food trigger and often occurred hours after consumption of any food, which is not wholly consistent with a diagnosis of food allergy. Our case highlights the importance of critical appraisal of the history and comprehensive evaluation, including oral food challenge.

Beyond food allergy, there are many causes of anaphylaxis. When a further workup is unrevealing, it is important to consider uncommon diagnoses, *e.g.*, mastocytosis, which may underlie unexplained anaphylaxis. Gülen *et al.*¹² evaluated 30 patients diagnosed with unexplained anaphylaxis referred to a mastocytosis center after undergoing extensive allergy/immunology evaluation. Fourteen (47%) were diagnosed with a clonal mast cell disorder (10 with systemic mastocytosis, 4 with monoclonal mast cell activation syndrome).¹² A minor diagnostic criterion of systemic mastocytosis is a baseline tryptase level >20 ng/mL; however, mast cell disorders can manifest with lower baseline tryptase levels.^{12,13} Two of the 10 patients diagnosed with systemic mastocytosis had baseline tryptase levels >11.4 ng/mL but <20 ng/mL, as did our patient.¹² This, paired with his clinical history, prompted further evaluation for a *KIT D816V* mutation, which was suggestive of a monoclonal mast cell disorder. Results of a subsequent bone marrow biopsy confirmed his diagnosis of SM-AHNMD.

Our patient's disease would be considered symptomatically indolent, despite frequent and severe anaphylactic reactions. Aggressive systemic mastocytosis requires evidence of organopathy.⁷ He had no significant cytopenias, impairment of liver function, skeletal involvement, splenomegaly, or evidence of malabsorption. Even with a lack of target organ involvement, the diagnosis of SM-AHNMD is associated with worse survival outcomes and may warrant consideration of cytoreductive therapy.¹⁴ Most data with regard to the use of cytoreductive therapy in SM-AHNMD involve myeloid neoplasias, whereas our case involves a monoclonal B lymphocytosis. Nevertheless, we discussed the option of midostaurin, a broad-spectrum tyrosine kinase inhibitor that has activity against *KIT D816V*, approved for aggressive systemic mastocytosis.¹⁵ After consideration of the potential for benefit *vis-à-vis* harm and/or burden, and consultation with a hematology specialist, the patient declined cytoreductive therapy. Whether midostaurin might be useful in patients with recurrent refractory anaphylaxis associated with SM-AHNMD when the associated hematologic non-mast cell lineage is not of myeloid-lineage origin merits further study.

Treatment focused on symptomatic control with H₁ antihistamine (four times the standard dose), H₂ antihistamine, and antileukotriene therapy. He has remained free of anaphylactic episodes for 6 months. If the patient demonstrated continued episodes of anaphylaxis, one could consider the off-label use of omalizumab. There is previous evidence that omalizumab reduces mast cell-related symptoms in patients with systemic mastocytosis, although the U.S. Food and Drug Administration indications are limited to allergic asthma and chronic urticaria.^{16,17}

FINAL DIAGNOSIS

The patient was diagnosed with systemic mastocytosis with an associated hematologic non-mast cell lineage disease.

CONCLUSION

We reported a case of a patient with recurrent anaphylaxis due to SM-AHNMD, previously attributed to food allergy. Food allergy is a common cause of anaphylaxis; however, when anaphylaxis continues to occur despite avoidance, further investigation is warranted. When a cause is not identified, before accepting a diagnosis of idiopathic anaphylaxis, careful consideration of a mast cell disorder is warranted.

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