

cause because it is often given with cyclophosphamide. Although the positive and negative predictive values of skin testing for cyclophosphamide and mesna are not well defined, it may still be worth pursuing, particularly when the culprit medication is uncertain. A 12-step desensitization protocol can be successfully implemented if there are limited options for treatment, including the pediatric population with underlying autoimmune and renal disease.

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Annatto seed hypersensitivity in a pediatric patient



Food allergy is of increasing concern and prevalence, particularly in children younger than 5 years who reside in urbanized areas of developed countries.¹ In response to this trend, The Food Allergy Labeling and Consumer Protection Act of 2004 (Public Law 108-282, Title II) was passed, requiring that the 10 most common food allergens be listed on nutrition labels. This legislation, although progressive, does not capture other allergens such as food additives that can cause near-fatal reactions.¹

Food additives are used for coloring, preservation, emulsification, flavoring, and nutrition.² They may be derived from natural sources (plants and minerals) or they may be synthesized in a laboratory. IgE-mediated reactions to food additives are thought to be rare, estimated at 2.0% in adults and up to 0.2% in children.^{3,4} Natural flavoring and artificial color are exempt from the US Food and Drug Administration labeling law (21 CFR 70.25) and are often disregarded entities on nutrition facts and ingredient labels. Several ingredients included in the category of natural flavorings and colors are associated with life-threatening anaphylactic reactions, specifically vegetable powder, oil, fruit juices, vitamins, and coloring agents derived from carbohydrates, vegetables, and seeds, including annatto (*Bixa orellana*).⁵ Annatto seed is derived from the achiote or lipstick tree (Fig 1). It is a deep yellow or orange food coloring that can be found in cheese, condiments, sausage, juice, ice cream, seasoning, and cosmetics.⁶ The coloring agents within annatto seed, bixin and norbixin, are carotenoids. We present a pediatric case of annatto seed hypersensitivity documented by immediate skin prick tests (SPTs).

A 5-year-old girl with a history of allergic rhinitis (SPT positive to ragweed and mountain cedar) and mild intermittent asthma presented with 2 episodes of generalized urticaria. The first episode occurred after eating macaroni and cheese at a popular North American chicken wings restaurant, despite having tolerated other exposures to macaroni and cheese at home. She again developed hives accompanied by angioedema after eating a new brand of chocolate chip ice cream sandwiches. She had urticaria on 3 other

occasions, with food ingestion including pasteurized cheese (Velveeta), a cheeseburger dinner helper (Hamburger Helper), and chocolate frozen yogurt (Tutti Frutti). Individual ingredients of chocolate, peanut, hazelnut, milk, wheat, and egg were tolerated on multiple occasions after her initial reactions. Review of macaroni and cheese and ice cream sandwich labels identified annatto seed as the common ingredient. The cheeseburger dinner helper ingredients listed “natural flavors and coloring” but neither sesame nor annatto seed specifically.

Physical examination revealed findings of allergic rhinitis with boggy turbinates without eczema, hives, or angioedema. Skin testing to tree nuts (almond, brazil nut, cashew, hazelnut, pecan, walnut) and sesame seed and traditional aeroallergen testing were performed (Table 1). The patient had marked dermatographia on testing, but SPTs revealed sensitivity to walnut and annatto by published guidelines for SPT measurement. Prick-to-prick testing of annatto seed was performed using a half teaspoon (2.33 g) of annatto seed powder reconstituted in 5 mL of normal saline solution, and the results were positive (Table 1). The same annatto seed SPT produced a nonirritating result in known non-annatto allergic individuals. Serum specific IgE and basophil activation testing and oral challenge were refused.

The patient received an automatic injectable epinephrine pen prescription, and her caregiver was instructed on epinephrine and antihistamine use and was given a food allergy action plan for guidance with unintentional exposures. Education regarding reading of nutrition labels and food avoidance of walnuts (all tree nuts with concern for cross-contamination), sesame seed, and annatto seed was provided.

Young et al⁷ reported the prevalence of annatto seed reactions in adults with chronic urticaria orally challenged with combination food additives as 0.01% to 0.07%. Because confirmatory testing was not performed for the single additive annatto, these data are inconclusive. Annatto seed allergy has been reported in 3 adults and a 2-year-old child.^{5,7,8} Food exposures included cheddar cheese, Gouda cheese, and a fiber cereal (Fiber One). Anaphylaxis reported in 3 cases included nonfacial angioedema, wheezing, and



Food

Cheese (American, Velveeta, Scottish cheddar, Cheshire and Red Leicester, Gloucester), Fiber One, Butter, Margarine, Mayonnaise, Sauces, Mustard, Sausage, Soup, Juice, Ice Cream, Bakery Products, Packaged Macaroni and Cheese

Spices

Saffron, Sazon, Paprika

Cosmetics

Makeup, Sunscreen, Dye

Other Coloring

"Natural Coloring," Color additive exempt from certification

Figure 1. Annatto seed use in the United States. Reddish annatto seeds found in dried fruit pod when split open (left). Sources of annatto in the United States' commercial products (right). Data from Ebo et al.⁵

hypotension. Annatto seed SPTs and specific IgE immunoblotting confirmed hypersensitivity in 2 of the adult cases.^{5,9} No allergic diagnostic testing was performed for the solitary pediatric case, and annatto seed hypersensitivity was presumed by clinical history.⁶ Our report documents annatto seed hypersensitivity by SPT but is limited by an inability to confirm this by oral challenge or serologic testing (eg, basophil activation test).

With the popular culture movement toward consumption of organic foods, we suggest that there may be an increase in human exposure to natural additives such as annatto.¹⁰ This may precipitate inadvertent reactions that are never identified because seeds (mustard, sesame, annatto) are not included in US labeling. Other countries (Australia, New Zealand, Canada, the 28 constituent member states of the European Union, and Kuwait) include the mandatory disclosure of some seed allergens in prepackaged foods.¹¹

Although the literature suggests that anaphylaxis triggered by annatto seed and other natural flavorings is rare, we suggest that these conditions are likely underreported because affected individuals may be unaware of exposure. Increased exposure to natural flavorings in organic foods and the lack of awareness regarding nut and natural flavoring hypersensitivity for the

community set the stage for unexplained anaphylaxis. To improve education, we encourage development of educational materials that detail the potential for seed reactivity. Allergists in practice should consider seed (annatto and sesame) hypersensitivity in patients with unexplained anaphylaxis.

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Table 1

Skin Prick Testing for Sesame Seed, Walnut, and Achiote (Performed With Individual Skin Test System Available Commercially as Hollister-Stier QuinTip)

Allergen	Wheal/flare, mm ^a
Control positive skin prick test result	12/38
Control negative skin prick test result	5/9
Sesame seed 208 (1:20)	7/30 P
Walnut 229 (1:20)	8/30 P
Achiote	8/30 P

Abbreviation: P, pseudopod formation.

^aMeasurements represent the mean of 2 diameters. Test results to hazelnut, almond, brazil nut, cashew, and pecan were negative (data not shown).

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Systemic mastocytosis presenting as occupational IgE-mediated anaphylaxis to pine processionary caterpillar



Mastocytosis is characterized by the accumulation of clonal mast cells (MCs) in organs such as skin, bone marrow (BM), and the gastrointestinal tract. Patients with systemic mastocytosis often have symptoms related to the mediator release of MCs, including anaphylaxis in 22% to 49% of the cases.^{1,2} The frequency of anaphylaxis among patients with indolent systemic mastocytosis without skin lesions (ISMs[−]) is higher than that found in patients with skin involvement (ISMs⁺).^{2–4}

The most common trigger for anaphylaxis in patients with ISMs[−] is Hymenoptera venom sting.^{3,4} These patients are predominantly males who present with severe systemic reactions to Hymenoptera venom characterized by cardiovascular collapse in the absence of pruritus, urticaria, or angioedema, remaining otherwise asymptomatic. They typically have a low BM MC burden together with low (even normal) serum baseline tryptase levels.^{3,4} In contrast to the well-known association between Hymenoptera venom anaphylaxis and systemic mastocytosis, anaphylaxis caused by other insects has been rarely described in patients with mastocytosis.⁴ We report a case of occupational IgE-mediated severe anaphylaxis attributable to pine processionary caterpillar (PPC) as the clinical presentation of an underlying ISMs[−].

A 54-year-old, male pine-resin worker was treated at the emergency department for local pruritus and erythema, dyspnea, wheezing, dizziness, loss of consciousness, and sphincter relaxation 10 minutes after direct skin contact on his neck with 1 PPC during work, which required parenteral epinephrine, corticosteroids, and dexchlorpheniramine. Foods, drugs, and other potential triggers for anaphylaxis were ruled out on an exhaustive anamnesis. Physical examination did not reveal urticaria pigmentosa, adenopathy, or organomegaly. A complete blood cell count, biochemical analyses, thyroid function tests, serum immunoglobulin levels, antinuclear antibody levels, and complement were normal. Initial allergy workup revealed the following: serum baseline tryptase (ImmunoCAP Tryptase, Thermo Fisher Scientific, Uppsala, Sweden), 37.1 µg/L; total serum IgE, 72 kU/L; positive skin prick test (SPT) results for a whole-body PPC extract (Laboratorios Bial-Aristegui, Bilbao, Spain⁵; wheal, 4 × 3 mm; erythema, 7 × 5 mm; histamine, 3 × 3 mm); and negative SPT results for a battery of common food extracts, together with no detectable (<0.35 kU/L) serum specific IgE antibodies to *Anisakis simplex*, *Ascaris lumbricoides*, and *Echinococcus granulosus*. The SPT result for whole-body PPC extract was negative in 30 controls (atopic and nonatopic).

The Spanish Network on Mastocytosis (REMA) score was applied, resulting into a score of +4 (ie, male [+1], syncope [+3], pruritus [−2], and serum baseline tryptase >25 µg/L [+2]), which translated a high probability of systemic mastocytosis.^{3,4} In view of these results, the patient was referred to the Instituto de Estudios de Mastocitosis de Castilla La Mancha for a complete BM study,

which included cytomorphologic and histologic evaluation, flow cytometry immunophenotyping of BM MCs, and molecular analysis of the D816V *c-KIT* mutation on fluorescence-activated cell sorting–purified hematopoietic cell lines, including MCs, eosinophils, and CD34⁺ progenitor cells. This study revealed an increase of MCs in BM smears and sections with the presence of more than 15 MC aggregates. These cells accounted for 0.675% of all BM nucleated cells and revealed an aberrant CD25⁺/CD2⁺ immunophenotype. The D816V *c-KIT* mutation was detected in fluorescence-activated cell sorting–purified BM MCs and tested negative in other BM hematopoietic cells. Abdominal ultrasonography and dual-energy X-ray absorptiometry scan revealed mild hepatic steatosis and osteopenia in the lumbar spine and femoral neck, respectively.

The patient was diagnosed as having ISMs[−] associated with anaphylaxis attributable to sensitization to PPC. Although the reaction occurred immediately after direct skin contact with PPC, because of the high risk of reexposure because of his job, the patient was warned to carry an epinephrine autoinjector and to use adequate protective equipment at work to minimize the probability of future skin/inhaled contacts with PPC.

Nine months later, after the aforementioned job security instructions, no further anaphylaxis had been observed and the serum baseline tryptase level remained high (40.2 µg/L). At that time, additional allergy studies using whole-body PPC extracts

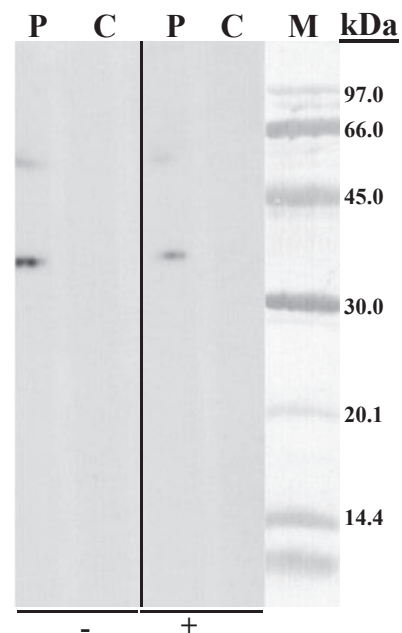


Figure 1. Sodium dodecyl sulfate–polyacrylamide gel electrophoresis immunoblotting assay (without and with 2-mercaptoethanol) revealing 2 IgE-binding proteins. Lane P, patient serum; lane C, control serum; lane M, molecular mass marker; plus sign, positive; and minus sign, negative.

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