

Systematized Contact Dermatitis and Montelukast in an Atopic Boy

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Abstract: Upon ingestion, the artificial sweetener, aspartame is metabolized to formaldehyde in the body and has been reportedly associated with systemic contact dermatitis in patients exquisitely sensitive to formaldehyde. We present a case of a 9-year-old Caucasian boy with a history of mild atopic dermatitis that experienced severe systematized dermatitis after being started on montelukast chewable tablets containing aspartame. Patch testing revealed multiple chemical sensitivities which included a positive reaction to formaldehyde. Notably, resolution of his systemic dermatitis only occurred with discontinuation of the montelukast chewables.

CASE REPORT

We present a case of a 9-year-old Caucasian boy with a history of mild atopic dermatitis (stable on topical tacrolimus ointment 0.03%), mild intermittent asthma and known food and environmental allergies diagnosed by prick testing (egg, soy, and peanut) at 3 years of age, and wheat at age 8. Ten months prior to presentation in our dermatology clinic, he had experienced a severe exacerbation of his asthma triggered by smoke from burning sugar cane for which he was given oral corticosteroids and started on montelukast sodium (Singulair®, Merck & Co, Inc., Whitehouse Station, NJ, USA) 5 mg chewable tablet by mouth daily.

Three months after starting montelukast sodium, he experienced a severe systematized flare of his atopic

dermatitis. This required treatment with oral steroids and oral antibiotics. On oral steroids, the patient improved, however, with weaning doses, he continued to experience severe systematized dermatitis flares. Because of this, the patient missed 30 days of school and had to cease all sports activities for the academic year.

The patient was then referred to our pediatric dermatology clinic for evaluation of the increased frequency and severity of his presumed atopic dermatitis flares. On exam, there were generalized red and pink lichenified plaques with overlying excoriations involving 85% of his body surface area. Because notable fissuring was seen involving the eyelids, neck folds, and ears (see Fig. 1) the diagnosis of allergic contact dermatitis (ACD) was entertained (1). An initial laboratory work-up was done which demonstrated a significant elevation of his IgE

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Figure 1. Systemic flare in patient before patch testing.

level of 37,143 mg/dL (second draw retest confirmed) and an absolute eosinophil count of 1,395 cells/ μ L. A complete blood count, complete metabolic panel, zinc level, IgG, IgM, and IgD levels were within normal limits.

Hydrocortisone butyrate 0.1% ointment topically, hydroxyzine (Atarax[®], Roerig Division of Pfizer, Belmont, WA, USA) 25 mg one to two tablets every night, and doxepin 5 mg as needed every night, were added for pruritus control, in addition to his maintenance medicament regimen that included fluticasone and salmeterol discus (Advair[®] 100/50, GlaxoSmithKline, Research Triangle Park, NC, USA) one puff twice a day, montelukast sodium (Singulair[®]) 5 mg tablet daily, cetirizine (Zyrtec[®], Pfizer Laboratories, New York, NY, USA) 10 mg daily, ranitidine (Zantac[®], Pfizer Consumer Healthcare, New York, NY) 75 mg BID, and mometasone furoate monohydrate (Nasonex[®], Schering Corporation, Kenilworth, NJ, USA) one spray to each nostril daily. Given the addition of these new medications, the patient was noted to moderately improve. However 3 months later he relapsed and had an erythrodermic systemic dermatitis flare which required hospitalization for intravenous antibiotics and intravenous corticosteroids. On admission laboratory analysis was done which demonstrated an IgE level of 26,600 mg/dL.

The patient was referred to University of Miami Pediatric Patch Test Clinic for evaluation. Given his erythrodermic state, patch testing was deferred and preemptive avoidance was attempted. Fragrances and formaldehyde were removed from the patient's personal hygiene regimen by providing the mother with a contact allergen replacement database list, C.A.R.D.

(2) (with these allergens removed from personal care products). In addition, his back was treated with potent topical steroids up until 2 weeks prior to patch testing as per previously reported protocol (3). This resulted in a 20% improvement in body surface area involvement. With this minimal improvement, a limited area of patch testable skin became available, therefore chemicals with a high index of suspicion (based on his current environmental history) were selected from the North American Contact Dermatitis Group Standard Series and the University of Miami Fragrance, Bakery, Vehicles, and Textile Series, and the patient was patch tested according to formerly described procedure (4).

Positive patch test reactions were noted to 17 chemicals, which were mainly in the fragrance and formaldehyde groups: Fragrance group: fragrance mix [+1], cinnamic aldehyde [+1], benzyl alcohol [+1], benzoic acid [+1], sodium benzoate [+1], jasmine absolute [+1], ylang-ylang oil [+1], lylal [+1]; Formaldehyde group: formaldehyde [+1], 2-bromo-2-nitropropane-1,3-diol (bronopol) [+1], quaternium-15 [+1], imidazolidinyl urea [+1], diazolidinyl urea [+1]; and Other: para-phenylenediamine [+1], potassium dichromate [+1], bacitracin [+1], and stearyl alcohol [+1].

The patient and mother (a registered nurse) were educated on the common and not so common locations of these allergens and provided with information sheets. In addition, they were given a second list of products to use that was cross-referenced to not contain these chemicals from the C.A.R.D. The patient was directed to follow avoidance of these chemicals, which at this point included a trial avoidance of aspartame (which is metabolized to formaldehyde in the body), as this has been reported to be a trigger in some formaldehyde allergic patients (5,6).

With this regimen, the patient moderately (40%) improved. At this point, all "known" sources of the allergens had been removed (which included a balsam of Peru, *Myroxylon pereirae*, restriction diet), and the team including the patient's mother began an in-depth search for potentially missed exposure sources of the patient's allergens. Having read that the package insert of the montelukast sodium listed aspartame as one of the chewable tablet ingredients, (0.842 mg of aspartame per 5 mg chewable tablet) the mother stopped the medication and brought it to the attention of the medical team. Two months later, patient's IgE levels were rechecked showing a drastic decrease to 677 mg/dL.

With continued strict avoidance of his allergens this patient has significantly improved and he has been free of systemic flares for the last 6 months. Currently he has



Figure 2. Patient after strict avoidance regimen of his identified allergens.

had mild intermittent flares of his atopy in the antecubital, popliteal fossae and face (not eyelids) which have easily been treated with emollients, tacrolimus ointment 0.1%, and low potency topical steroids. Furthermore and foremost, he has been able to resume his normal daily activities, school, and sports participation (see Fig. 2).

DISCUSSION

Allergic contact dermatitis is typically an eczematous pruritic eruption that occurs after cutaneous re-exposure to an allergen, or exposure to a cross-reacting chemical to which a person has been previously sensitized. There are two distinct phases in the development of ACD: the induction phase, or first contact with the allergen, and the elicitation phase. The elicitation phase can occur both after cutaneous contact and following systemic exposure, whether through the gastrointestinal, intravenous or subcutaneous route (7).

Many contact allergens are abundant components of cosmetics, styling products, common foods and medications. The most common contact allergens in children are nickel, thimerosal, formaldehyde and the formaldehyde releasing preservatives, cocamidopropyl betaine, cobalt, topical antibiotics, and fragrances (8). Formaldehyde and formaldehyde releasing preservatives are contained in a large number of personal care products and medicaments frequently used and made for children (9). In addition, they are found in many household sources such as fiberglass, carpets, plywood, permanent press fabrics, paper products, and some domestic cleansers, which explain why levels of formaldehyde are usually higher indoors than outdoors (10). Cigarettes and other tobacco products are also important sources of formaldehyde exposure (10). Moreover, formaldehyde textile resins can be used on cotton and/or rayon fibers (especially the ones with durable press finishes),

TABLE 1. Common Medications for Children that Contain Aspartame

Common medications for children that contain aspartame*

Singulair® (montelukast sodium) 4 mg or 5 mg chewable tablets, Merck
 Augmentin® (amoxicillin/clavulanate potassium) powder for oral suspension and chewable tablets, GlaxoSmithKline
 Amoxil® (amoxicillin) 200 mg or 400 mg chewable tablets, GlaxoSmithKline
 Zantac® 25 (ranitidine hydrochloride effervescent) EFFERdose® tablets, GlaxoSmithKline
 Centrum Kids® Complete Dora the Explorer™/Centrum Kids® Complete Rugrats™/Centrum Kids® Complete
 SpongeBob SquarePants™, Wyeth
 Children's Dimetapp® ND Non-Drowsy allergy tablets (loratadine 10 mg) orally disintegrating tablets, Wyeth
 Junior Strength Motrin® (ibuprofen 100 mg) chewable tablets, McNEIL-PPC, Inc.
 Children's Benadryl® (diphenhydramine HCl) allergy chewable tablets, McNEIL-PPC, Inc.

*Physicians' Desk Reference (PDR®). Montvale, NJ; Thomson Healthcare: 2007.

“wrinkle-free” garments, and shrink-proof wool and twill (11). Additionally, certain very stiff fabrics such as upholstery, draperies, school and working uniforms, and lab coats, are usually heavily finished with formaldehyde-releasing resins (11).

Aspartame has been associated with systemic contact dermatitis in patients exquisitely sensitive to formaldehyde (5,6). Hill and Belsito were the first to describe the possibility that formaldehyde from aspartame breakdown could trigger a systemic contact dermatitis in formaldehyde sensitive patients (5). In their report, a 60-year-old woman with a history of multiple allergies including formaldehyde had persistent eyelid dermatitis that was temporally linked to aspartame ingestion. Complete remission occurred upon discontinuation of the artificial sweetener.

We present this case to draw attention to the potential role of aspartame in this patient's exacerbation of his atopic/allergic contact dermatitis. This patient was known to have had many exposure sources of aspartame from chewing gum, soda, yogurt, soft drinks, and children's vitamins; however these had all been discontinued after the postpatch testing counseling session. The presence of aspartame in the patient's medication was an oversight by the medical team and led us to investigate other medicament sources of aspartame (12) (see Table 1). There was a direct temporal relationship between the discontinuation of montelukast and our patient experiencing improvement of his dermatitis, and a significant reduction in his IgE level.

It is known that certain contact allergens such as nickel, can cause both type I (immediate; IgE mediated), and type IV (delayed; T-cell mediated)

hypersensitivity reactions (13). IgE-mediated hypersensitivity reactions to formaldehyde while rare, are reported (14–18). Previous reports describe certain characteristic features of type I allergy to formaldehyde, for example, manifestation of severe symptoms (angioedema, urticaria, or anaphylaxis), that often appeared a few hours later than with the usual causes of anaphylaxis (0.5 to 12 hours). In addition, the patients tended to have significantly high levels of anti-formaldehyde IgE (14,15,17).

Allergens are known to trigger cutaneous inflammation and aggravate underlying atopic dermatitis through both IgE-dependent and cell mediated mechanisms (19). Both clinically occurring simultaneously to formaldehyde however is not previously described. The severity of our patient's condition, in the context of the positive patch tests and the extremely elevated IgE levels led us to believe that he was simultaneously being triggered by both a type I and a type IV immune reaction. This clinical overlap would help to explain the resolution of his dermatitis flares and the drastic decline in IgE levels with avoidance of his allergen triggers.

The temporal relationship with improvement and cessation of the montelukast chewables suggest a contributory link. However, after 15 months of severe dermatitis, nine courses of oral steroids, 6 days of hospitalization, 30 days of lost schooling, and more than \$10,000 spent on therapy, the mother was not willing to reintroduce the montelukast or aspartame to prove a definite direct relationship between this medication, sweetener and her child's illness.

Of note, each 4 mg and 5 mg chewable tablet of montelukast (Singulair[®]) contains aspartame, however, the 10 mg tablet and the oral granule formulations do not. Aspartame is composed of methanol and two naturally occurring amino acids: aspartic acid and phenylalanine. Upon ingestion, aspartame is broken down into aspartic acid, aspartic acid methyl ester, and phenylalanine in the gut wall (20). The methyl ester is then converted to methanol in the small intestine by chymotrypsin (21). Approximately ten percent by weight of aspartame is released as methanol, which is finally oxidized to formaldehyde and formic acid and excreted (22). Formaldehyde has been shown to form adducts with nucleic acids and proteins in animal models. These adducts are more difficult to remove using normal metabolic pathways and accumulation may occur (22). This accumulation could explain why it took several months for our patient's dermatitis to completely clear.

It is known that in general normal healthy controls are unaffected by aspartame (23), however, formaldehyde allergic atopic patients may be different. We know from the extensive studies on nickel contact dermatitis that

exacerbation of atopic patients can be seen after oral ingestion (24). In fact, in one study, after an oral challenge with nickel, patients with atopic dermatitis showed a higher urinary excretion rate than non atopic controls as a measure of increased absorption (25). To date a study such as this on formaldehyde excretion has not been performed and further investigations are warranted.

Nonetheless, clinicians should be aware of the potential for hidden "inactive" or "vehicle" ingredients such as aspartame, in chewable and liquid medications and vitamins. It is important to recognize that oral ingestion of known contact allergens or a cross-reacting chemical can potentially induce a systemic flare of allergic contact dermatitis. This case also demonstrates the complexity of allergic contact/atopic dermatitis patients and the importance of a team approach, including the mother, in their management.

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