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Systemic Contact Dermatitis to Foods: Nickel, BOP, and More

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Abstract Systemic contact dermatitis (SCD), a cutaneous reaction that is a direct manifestation of systemic exposure to a known allergen in a sensitized individual, has been increasingly recognized as a cause of persistent cutaneous contact dermatitis that is refractory to conventional therapies. While SCD in response to drugs has been described well in the literature, SCD to allergens in common foodstuffs is a less well-articulated phenomenon. Several foods that are universally consumed throughout the world contain potent allergens including nickel, balsam of Peru, trace metals, urushiol, and sesquiterpene lactones as well as a host of others that may cause a distinctive clinical picture. In this review article, the authors review the typical presentation and prevalence of SCD to foods, pathophysiology, the most common offensive ingestible food allergens, several appropriate diets, and effectiveness of dietary avoidance for situations in which SCD is suspected.

Keywords Systemic contact dermatitis · Allergic contact dermatitis · Allergens · Balsam of Peru · Nickel · Food hypersensitivity

Introduction

Systemic contact dermatitis (SCD) is defined as a cutaneous reaction that is a direct manifestation of systemic exposure to a known type IV, lymphocyte-mediated allergen in a sensitized individual. It is completely unrelated, both in pathophysiology and clinical manifestations, to type I, IgE-mediated food allergies. SCD can occur via oral, intravenous, percutaneous, or inhalational routes and may develop in response to exposure to a variety of allergens such as drugs, metals, preservatives, or herbal preparations. While some forms of SCD have been recognized, described phenomena in the literature for decades, SCD to foods has only recently gained recognition as a significant cause for treatment unresponsiveness in patients that may be unknowingly ingesting their allergens. In these patients, dietary avoidance and allergen removal may be the key treatment factor in improving their skin manifestations. In this article, the authors will detail the mechanism of SCD, patient presentation, and prevalence in the contact dermatitis population and review the key food allergens that have been identified in the most recent literature.

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When to Suspect SCD

SCD has been increasingly recognized as a confounding factor in patients being treated for refractory or persistent allergic contact dermatitis (ACD) who have been consciously avoiding any known topical allergens. This is the main situation in which the astute clinician should consider it—in a patient with a positive patch test to a known cause of SCD who has not been cleared with avoidance of cutaneous exposure.

Presentation

SCD can present with a number of specific cutaneous manifestations, with the most classic being a refractory vesicular hand dermatitis occurring with ingestion of allergenic metals such as nickel, cobalt, and chromium. Importantly, though, several other dietary agents such as balsam of Peru (BOP),

garlic, and food preservatives have also been implicated in the exacerbation of vesicular hand dermatitis [1]. Another much less well-known, but probably more common, presentation that is specific for SCD due to dietary metal is pruritic papules on the extensor surfaces on the elbows and/or knees [2]. Finally, recrudescence of prior sites of allergic contact dermatitis, including old patch test reaction sites, in the absence of known cutaneous exposure, should strongly suggest SCD.

Acral and anogenital erythemas are a commonly reported presentation which comes to mind when contemplating SCD, but which has not commonly been implicated from food-related ingestions and should be thought of as more likely to indicate drugs as a causative entity [3]. It has been difficult to distinguish some of these reports from the classically reported "baboon syndrome." More severe reactions such as urticaria, purpuric plaques, and erythema multiforme-like lesions have all also been detailed in rare instances [4]. Table 1 indicates that certain haptens in foodstuffs seem to be more related to certain cutaneous presentations such as vesicular hand eczema or erythema multiforme-like eruptions than others, though more information is needed, given the small numbers of case series and reports.

Systemic contact dermatitis syndromes may also include extracutaneous findings such headache, fever, fatigue, malaise, gastrointestinal, respiratory, and vasculitic disturbances [37]. In the author's experience, however, it is difficult to disprove the possibility that resolution of these symptoms with dietary allergen avoidance is not due to placebo effect. The most imperative element to bear in mind is to consider SCD in any patient with positive patch testing to allergens that may be included in dietary products and has a dermatitic eruption in anatomical areas that have not been exposed topically to those allergens.

Prevalence

The prevalence in the population of patients with ACD is largely unknown due to a lack of literature. In the most recent study, systemic nickel allergy syndrome (SNAS) alone was identified in up to 6 % of patients presenting to allergy clinics in Europe, implying that SCD may be underidentified in the SCD population [38]. Dose response studies have shown that between 1 and 10 % of patients who are nickel allergic are likely to have SCD with ingestion of normal dietary amounts of nickel. Smaller case series indicate that up to half of patients with ACD to allergens contained in foods, such as BOP, may react upon exposures to foods containing the allergen to which they have been sensitized to, and would improve accordingly with dietary restriction [13••].

Mechanism of Action

The exact mechanism of action for SCD is unknown, though several postulations have been reported in the literature. Similar to primary cutaneous ACD, SCD is in part a type IV T cell-mediated hypersensitivity reaction to a hapten that the affected individual has come into contact with. However, it is likely that a type III humoral, immune complex-mediated reaction may also play a role in SCD as hapten-albumin immune complexes have been found on biopsies of patients with nickel-related SCD, and both immediate and delayed responses have been identified, with patients developing cutaneous manifestations as soon as 30 min after ingestion of a hapten [39, 40]. Desensitization has also been shown to be effective in patients with SNAS with significant reductions in cutaneous manifestations by increasing the capacity of CD25+ T regulatory cells to modulate T cell responses to nickel [5].

Similar to atopic dermatitis, both nickel-induced systemic and primary cutaneous allergic contact dermatitides have been shown to demonstrate a T helper 2 (Th2) phenotype of immunologic response when challenged with nickel. In humans, a definite dose-dependent increase in blood levels of IL-5, a hallmark of the Th2 response, was shown when nickel-allergic subjects were exposed to oral nickel [6]. In mice, increased levels of serum IL-4 and IgE were found after sensitized mice were exposed to nickel continuously for a month, showing that the Th2 response is similar in both systemic and cutaneous nickel hypersensitivity reactions [7].

Specific Dietary Agents

Nickel

SCD to nickel has been the most commonly reported and described form of dietary SCD in the literature, which is compatible with the fact that it is the most common contact allergen that is ingestible. As mentioned, relapsing vesicular hand dermatitis is the most commonly described patient presentation for SCD due to nickel, although pruritic papules on the elbows have been at least as common in the author's practice.

Several systemic nickel avoidance diets have been well detailed in the literature with excellent response rates in the patient population when proper adherence is followed. The difficulty lies in the issue of adherence, with nickel being in a plethora of common foods, ranging from common grains such as rice and oats to protein sources like beans, lentils, and shellfish, spanning to some fruits, vegetables, and flavorings such as chocolate and coffee, making it impossible to eliminate nickel consumption completely [8]. Further complicating the picture is the fact that drinking water from different sources can have dramatically varying amounts of nickel

Table 1 comprehensive review of dietary agents proven to cause systemic contact dermatitis

Allergen	Foods implicated	Patient presentation	Food cross-reactors	Improvement with dietary avoidance	Ref.
Nickel	Beans, lentils and shellfish, chocolate, coffee, spinach, soy	Vesicular hand dermatitis and/or itchy papules on extensor surfaces; widespread symmetric maculopapular eruptions	Cobalt	40–78 %, diet alone ~50 %, chelation alone Up to 90 %, both interventions	[5–12, 13••, 14–19]
Chromate	Potatoes, meats, tea and coffee, grapes	Subacute eczematous dermatitis of lower legs, ankles, hands		Unknown	[20, 21]
Cobalt	Flaxseeds, chickpeas, chocolate, nuts	Generalized eczematous eruption	Nickel	Complete clearance (n=1)	[22•, 23]
BOP	Citrus fruits, tomatoes, liquors, spices, condiments	Anogenital, hand, and extremity dermatitides and pruritus	Garlic, propolis	~50 %	[24, 25]
PG	Salad dressing, snacks, cake mixes, beverages	Pruritic eczematous plaques on extremities		Complete clearance (n=3)	[26, 27, 28••]
Sesquiterpene lactone	Chamomile, chicory, lettuce, and Echinacea	Flare of baseline eczema; mucosal and anogenital pruritus		Complete clearance (n=2)	[29]
Formaldehyde	Aspartame	Vesicular hand eczema		Complete clearance (n=2)	[30•, 31]
Urushiol	Cashew, *Rhus* lacquer (Korea)	Erythematous maculopapular eruption; erythema multiforme-like reactions; erythroderma		Gradual improvement, inpatient admission needed in 1/3 of Rhus cases (n=32)	[32, 33]
Garlic	Garlic	Vesicular hand eczema	BOP	Complete clearance (n=2)	[34, 35]
Propolis	Propolis	Pruritic papules and patches; edema of the face, neck, arms, abdomen, and thighs	Possibly Compositae; BOP	Complete clearance (n=1)	[32, 33, 36]
Sorbic acid	Strawberry, prunes, and cheeses, packaged foods	Vesicular eczema		Complete clearance (n=2)	[34, 35]

and that cooking acidic foods in stainless steel cookware can increase the nickel content of food. Overall, the average dietary intake of nickel equates to approximately 300–600 μg daily, a level demonstrated to provoke vesicular hand eczema in sensitive patients in the literature [9]. In individuals consuming high-nickel foods regularly, daily ingestion can be several-fold higher, leading to increased frequency and severity of eruptions due to a dose-dependent response with worsening exacerbations of SCD correlating with higher amounts of dietary nickel [10].

Given the ubiquitous nature of nickel in trace amounts in foods across the world, the lowest nickel diets generally still contain at least 25–35 μg of daily nickel [11]. The response rates to these low-nickel diets without chelation therapy range from 40 to 78 % and may depend on the level of adherence, type of cutaneous manifestation of their SCD, and severity of reaction on patch test, with long-term remissions of SCD reported with continued dietary adherence [12, 13••, 14]. Strategies to attempt improving adherence such as using the more recently proposed simplified point-based low-nickel scoring diet may theoretically improve response rates [15].

Chelation therapy with disulfiram can be a helpful adjunct in those attempting nickel avoidance diets in order to expedite or enhance response rates. On its own, disulfiram therapy is likely not as effective as dietary nickel avoidance with response rates of about 50 % [16]. However, when disulfiram is used for 4–8 weeks while the low-nickel diet is being introduced, response rates of up to 90 % have been observed [17]. Patients will frequently experience a flare of their dermatitis or even systemic symptoms such as malaise, muscle aches, etc., over the first 2 weeks of disulfiram therapy, and in the authors' experience, either of these events predicts a good long-term response to disulfiram and low-nickel diet. It is thought that this occurs because chelation therapy leads to an initial increase in availability of nickel to the immune system as it is mobilized from tissue deposits. The most important concerning adverse effects to educate patients on are hepatotoxicity and transaminitis; however, these are mainly seen in treatment periods of 6 weeks or more [18]. Clearly, patients must be counseled on the absolute necessity of strict alcohol avoidance while on this therapy, even minute alcohol exposures in things like mouthwash and wine sauces.

BOP

BOP has also long been recognized as a common dietary cause of SCD. As a derivative of the *Myroxylon* tree in Central America, BOP is best known for its presence in fragrances, but it also has a number of cinnamates and vanillins in its natural resin which are used as sweetening agents in a plethora of food products [24]. Similarly, there are several other structurally related molecular compounds that are very prevalent in Western diets. While patients with a positive patch test to BOP are the most likely to have SCD to these compounds, those with positive patch tests to fragrance mix and negative patch tests to BOP can still have SCD from these types of food.

Similar to nickel, several diets restricting BOP intake have been put forward with good response rates with appropriate adherence. Patients are instructed to avoid a number of foods including citrus fruits, tomatoes, liquors, spicy condiments, and spices such as cinnamon, vanilla, cloves, anise, and ginger. About half of patients who reacted to fragrance or BOP but did not clear with avoidance of cutaneous exposure to fragrance are expected to improve on this diet in 6–8 weeks [25]. Similar to nickel restriction diets, low-BOP diets may be very difficult to adhere to because allergenic compounds exist in numerous common foods.

Other Trace Dietary Metals

Chromate, cobalt, and zinc can all be causative agents in SCD. Chromate is implicated in 2 % of all cases of ACD and is included in such foodstuffs such as potatoes, meats, tea and coffee, and grapes, and the absorbed amount may be increased by cooking foods in acidic environments, such as vinegar or lemon juice [20, 41]. Chromate and chromium in vitamins and nutritional supplements should also be avoided [21]. Cobalt is found in high amounts in foods such as flaxseeds, chickpeas, chocolate, and nuts, and low-cobalt diets have been introduced into the literature utilizing the daily point system in order to aid in adherence [22•].

Chamomile and Other Compositae Members

Plants in the Compositae family produce compounds known as sesquiterpene lactones. This group includes herbs, spices, foods, and flowers such as chamomile, chicory, lettuce, and Echinacea, many of which are commonly used in ingested preparations such as teas and supplements taken for holistic health properties as well as being common salad ingredients [29, 30•]. While most patients allergic to sesquiterpene lactones are able to tolerate these foods without difficulty, those who do react to them can have florid reactions with even small amounts of ingestion of these foods. Patients have been described to have had flaring of their long-standing eczema as well as mucocutaneous and anogenital pruritus [14].

Aspartame

Aspartame, an artificial sweetener, has been implicated in several pediatric and adult cases of SCD due to its conversion to formaldehyde, one of the most common contact allergens, in the liver as a step in its metabolism [31]. The vast majority of formaldehyde-allergic patients do not have any problem

with aspartame ingestion because it requires an enormous amount of daily aspartame consumption before the metabolic pathway is overwhelmed and the formaldehyde begins to accumulate. Thus, only patients with positive patch tests to formaldehyde who do not clear with avoidance of cutaneous exposure should be counseled to avoid this artificial sweetener [30•]. While there is no specific clinical pattern of dermatitis strongly associated with SCD to formaldehyde generated from aspartame, the literature describes a patient with refractory eyelid dermatitis who had complete clearance after avoidance of aspartame in diet beverages [31].

Sorbic Acid

Sorbic acid has been classically thought of as a contact allergen implicated in perioral contact dermatitis in response to dentifrices and other medicaments in which it is used as a preservative. It has also, however, been recently implicated in SCD, manifesting itself as vesicular eczema [42]. Sorbic acid is commonly found in foods such as strawberries, prunes, and cheeses [43]. In addition, many processed foods contain potassium sorbate as a "freshness protector" and this ingredient is chemically identical to sorbic acid and should be avoided.

Garlic

Garlic has also been known to be causative in SCD, of which the cases that have been described demonstrate a chronic vesicular hand eczema [34]. Allergy to BOP may also necessitate avoidance of garlic as these two entities may cross-react when ingested [35]. This may also need to be suspected in those taking garlic in the form of a dietary supplement.

Propolis

Propolis, a resinous mixture produced by honey bees, is used in a number of lotions and medications and has been implicated in 1–6 % of cases of ACD that necessitated patch testing [44]. Propolis has been more recently used as a holistic health therapy and was implicated in a case of SCD in the literature in which a patient presented with severely pruritic, erythematous papules and patches, as well as edema, of the face, neck, arms, abdomen, and thighs after eating a propolis syrup for health purposes [45]. Again, patients should be asked about any holistic or alternative syrups or treatments being used when being evaluated for SCD. Similar to garlic, allergy to BOP may also necessitate avoidance of propolis as these two entities may cross-react when ingested.

Cashew and Rhus

Cashews are an urushiol-containing legume that cross-reacts with poison ivy, poison oak, mango, and Japanese lacquer tree. These nuts contain much less allergen than poison ivy and poison oak, and heating of the nut decarboxylates the allergen to cardanols, further reducing their allergenicity, but still not eliminating it completely. A case was described in the literature of a patient who developed a rapid reaction after ingesting raw cashew pesto that manifested itself as pruritic, brightly erythematous papules and plaques distributed on the buttocks, medial thighs, and periaxillary skin, with sparing of the intertriginous creases [32]. Rhus lacquer, another member of this botanical family, is commonly eaten in Korea with chicken for its holistic properties and has been implicated in at least 31 cases of SCD, most commonly presenting with an erythematous maculopapular eruption, but also with erythema multiforme-like reactions and erythroderma [33].

Propylene Glycol

Propylene glycol (PG), a common culprit in ACD due to its common presence as a humectant and viscosity-adjusting agent in topical preparations, is also very commonly used as a thickening agent in foods such as dressings, snacks, baked goods, and beverages [46]. There have been reports of PG-related SCD presenting as pruritic eczematous plaques on the face, neck, and right hand [26]. Flares at sites of previous hand dermatitis and at patch testing sites after ingestion are also relatively common [27]. Just as with other common causes of SCD that are also common causes of cutaneous contact dermatitis, an avoidance diet should only be recommended to patients that do not improve after avoidance of cutaneous exposure.

Conclusion

SCD due to food ingestion has been an increasingly recognized entity and should be suspected in patients with a positive patch test reaction to an allergen known to cause SCD whose dermatitis does not resolve when they avoid cutaneous exposure to the allergen. Suspicion should be even greater if the patient has vesicular hand eczema or acral or flexural erythema. Although nickel and balsam of Peru have long been well-known causes of dietary SCD, several other agents that are well-known causes of primary cutaneous CD have recently been found to also cause SCD. The prevalence and mechanism of these reactions is not clear from the literature, and studied diets have not been put forward for each systemic allergen. However, there are guidelines that have been created to assist patients to avoid any systemic allergen in foods based

on already existent nutritional data, and the authors would recommend the utilization of these for some of the less common causes of food-related SCD [28••].

Compliance with Ethics Guidelines

Conflict of Interest Matthew J. Zirwas declares the receipt of consulting fees from Smart Practice, outside of the submitted work.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the authors.

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- •• Of major importance

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