SYSTEMIC CONTACT DERMATITIS

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Allergic Contact Dermatitis (ACD) is an important disease that affects 14.5 million Americans each year.[1] The economic impact of this condition is high, whether measured by patient morbidity, health care expenditures, loss of income or lost time from school and work.[1] Once patch testing is performed and an allergen source has been identified, education becomes the critical intervention to ensure adherence to an avoidance regimen. With allergen avoidance, remission of the dermatitis ensues. Patients who are unable to comply with allergen avoidance are at risk for recurrent or sustained dermatitis or progression to a systematized presentation.[2,3] In fact, patient education often begins before the diagnostic patch tests are ever placed, to ensure that ACD patients have an appropriate understanding of potential outcomes and the central role patients play in both their disease and treatment.

During the initial consultation, patients are often taught about the delayed presentation of ACD and its relationship with the immune system (sensitization to a chemical and elicitation of a dermatitis with re-exposure). Furthermore, they are instructed that it may develop at any point in time, even to something that the patient has been using regularly for a short period of time or intermittently for years. In certain cases, other related disorders such as irritant contact dermatitis (ICD) and contact urticaria (CU) may be relevant; history, rather than patch testing, can point to these as the correct diagnosis for the patient. It is important to note that ICD, the most prevalent form of contact dermatitis, can, at times, precede or occur concomitantly with ACD.[4,5] Unlike ACD, ICD is not immune-mediated. It occurs secondary to contact with an irritating or abrasive substance. CU, on the other hand, represents the least prevalent form of ICD. The wheal and flare reaction of CU is an IgE- and mast cell-mediated immune phenomenon of immediate-type hypersensitivity. Although this form of contact reaction is rare, it is important to recognize because of its potential to produce serious anaphylactic-type reactions.[6–8]

This column highlights ACD, focusing on significant allergens, regional presentations of dermatitis and topic-based allergic manifestations and offers clinical tips for diagnosis and treatment. This month, we feature an uncommon but especially important category of allergic dermatitis — systemic contact dermatitis.

SYSTEMIC CONTACT DERMATITIS

Systemic contact dermatitis (SCD) is an interesting subset of ACD that may occur more often than clinically recognized. SCD refers to the development of dermatitis upon systemic exposure to an allergen in someone previously sensitized to that chemical through cutaneous contact. Since this process was first recognized, several terms other than

SCD have been suggested to describe it.[9–21] **See Table 1.**

Elicitation of dermatitis by allergen exposure through routes other than trans-cutaneous contact was first described by Jadassohn in 1895.[22] He reported that individuals topically sensitized to mercury developed dermatitis after systemic mercury exposure. During World War II, Park recognized cutaneous eruptions occurring in patients previously topically sensitized to sulfonamides when those antibiotics were administered orally.[23] In 1951, Leifer reported that ingestion of cinnamon oil precipitated a recurrence of hand eczema in a patient allergic to cinnamon.[24] In 1954, Sidi and Melki demonstrated flares of eczema in chromium-sensitive patients given an oral challenge of potassium dichromate.[25] Three years later, Pirila described both reactivation of a thiuram patch test and widespread dermatitis appearing in a patient given oral antabuse (tetraethylthiuram disulphide).[25] In 1958, Hjorth reported a girl sensitized to thiamine through occupational contact who developed dermatitis after ingesting the vitamin.[26] Similarly, after handling streptomycin while treating tuberculosis patients, nurses subsequently erupted with dermatitis when they received injections of the antibiotic.[27] Describing another instance of medication-induced SCD, Pirila detailed in 1960 the development of a widespread dermatitis from neomycin inadvertently administered orally to a patient with previous contact sensitization.[9] Over the decades since these early reports, the scope of allergens has broadened and the reported routes of exposure have multiplied.

Table 1. ALTERNATIVE NAMES FOR SYSTEMIC CONTACT DERMATITIS

Endogenic contact eczema[9]	Internal-external contact-type hypersensitivity[10]
Contact type dermatitis medicamentosa[11]	Mercury exanthem[12]
Hematogenous contact eczema[13]	Baboon syndrome[14]
Systemic contact-type dermatitis[15]	Paraptic eczema[16]
Systemically induced contact dermatitis[17]	Systemic reactivation of allergic contact dermatitis[19]
Symmetrical drug-related intertriginous and flexural exanthema[20]	Systemic allergic dermatitis[21]

Table 2. DIVERSE PRESENTATIONS OF SYSTEMIC CONTACT DERMATITIS

Reactivation of patch test site	Pompholyx (dyshidrotic eczema)
Aggravated local allergic contact dermatitis	Reactivation of a previously sensitized area (recall reaction)
Disseminated patchy dermatitis	Generalized erythroderma
Baboon syndrome (SDRIFE)	Vulvar pruritus or dermatitis
Pruritus ani	Cheilitis
Lichen planus of the lip	

CASE REPORT

A 13-year-old Asian female was referred for a fingerprint-like dermatitis covering her chest, abdomen and back present for 2 years. Her prominent nocturnal pruritus was only partially relieved by topical steroids. On exam, she had dozens of post-inflammatory hyperpigmented oval macules, as well as slightly scaly small plaques, pink in color and thin, covering her trunk but sparing her face, neck and extremities. Epicutaneous testing by the allergist revealed sensitivity to dust mites. Environmental modifications were undertaken to reduce dust mite exposure, but symptoms persisted. She was then instructed to avoid common contact allergens, including formaldehyde releasers and fabric resins, but she resisted eliminating her favorite perfumes. Biopsy showed perivascular lymphocytic infiltrate with prominent eosinophils. Patch tests were performed with a modified panel of 65 allergens and read at 48 and 96 hours. Positives were found for propylene glycol, disperse blue dyes 106 and 124, cocamidopropyl betaine, oleamidopropyl dimethylamine and vanillin. The patient changed her brand of acetaminophen after discovering propylene glycol among its ingredients. She was no longer wearing dance leotards, which may have been a source of previous exposure to azo dye. She continued use of her desoximetasone ointment and substitute shampoo, both free of her allergens. At follow-up visit, the patient reported that her symptoms and rash improved when she began to avoid her nightly vanilla ice cream; she flared if she resumed eating it.

PATHOPHYSIOLOGY OF ALLERGIC CONTACT DERMATITIS

The immunologic basis for SCD is not completely understood and may not be identical for all allergens. As reviewed recently by Jacob and Zapolanski,[28] during allergen sensitization, a hapten penetrates the skin and reacts with resident antigen-presenting dendritic cells that transfer the bound antigen to T lymphocytes. Once these cells are primed and reproduce, they return to the skin, ready to act on target cells when the antigen is encountered again. It seems that the immune system can be activated by allergen exposure as well through oral and other systemic routes, triggering the activated CD8+ effector T cells.[29]

DIVERSE PRESENTATIONS OF SYSTEMIC CONTACT DERMATITIS

Systemic provocation by allergen in the allergic patient can produce many different types of dermatitis. **See Table 2.** Reports often describe a reactivation or exacerbation at the original cutaneous location or acceleration to a more widespread dermatitis, occasionally a generalized erythroderma. Frequently, systemic exposure to a demonstrated

allergen incites reactivation of the relevant patch test site.[30,31] Recall of prior localized dermatitis has been described by Giordano-Labadie and colleagues when perianal dermatitis, previously produced by a cream that contained sorbic acid, was provoked in a patient by ingestion of sorbic acid-containing foods, such as strawberries, candies, margarine and cheeses.[32] Fisher described a woman who, after previously reacting to propylene glycol in vaginal lubricant jelly, later developed vulvar pruritus upon receiving intravenous diazepam containing propylene glycol.[33] Other authors have also reported pruritus ani[34,35] and vulvar dermatitis[34,36,37] as manifestations of SCD.

The most widely studied and reproducible manifestation of SCD is pompholyx, deep-seated vesicles of the palms and lateral fingers and, in some cases, feet. This so-called "dyshidrotic eczema" can be precipitated by oral administration of nickel, cobalt and chromium.[38–43] It may erupt after ingestion of spices[44] and can improve with reduction of dietary components of balsam of Peru.[3,45]

Perhaps the most unique presentation of SCD is the so-called baboon syndrome, with its demarcated erythema of the buttocks, axillae and upper inner thighs.[14] Many of these cases have been reported from exposure to mercury inhaled from broken thermometers or ingested in homeopathic preparations after presumed sensitization through topical application of mercurochrome.[46–48] Because this peculiar pattern is most often described as a drug reaction, rather than a consequence of systemic exposure to a prior contact allergen, some authors have proposed distinguishing symmetric drug-related intertriginous and flexural exanthema (SDRIFE)[20,49] from the baboon presentation of SCD.

Less common presentations of SCD include cheilitis,[50] lichen planus of the lip and oral mucosa,[51] perioral dermatitis[52] and eyelid dermatitis.[53]

ALLERGENS INGESTED ORALLY

A large number of allergens have now been described that produce dermatitis after oral ingestion. Hjorth was among the first to describe dermatitis induced by administered spices.[54] Veien also demonstrated provocation of dermatitis by an oral dose of balsam of Peru.[55] He studied this relationship further by demonstrating flares of eczema after oral challenge with graduated doses of nickel, cobalt, chromium and balsam of Peru in patch-test positive patients.[56] He proposed depletion diets to benefit individuals with positive patch tests to or history of aggravation by ingestion of these allergens. Jensen and colleagues were able to show a dose-dependent relationship between ingested nickel and flare of dermatitis.[38] Based on a subsequent meta-analysis, they concluded that normal daily consumption of nickel is sufficient to aggravate dermatitis in some sensitive individuals.[57] A low-nickel diet improved dermatitis after just 4 weeks in nearly two-thirds of 90 patients studied by Veien and colleagues, and after more than one year, 73% of respondents continuing the diet reported improvement.[58] Exacerbations of dermatitis in nickel-sensitive individuals may occur after seemingly benign intake of cocoa[59] and herbal vitamin or mineral supplements.[60]

Veien and colleagues also reported flare of dermatitis in cobalt-sensitive individuals after oral dosing with 1 mg cobalt sulfate.[39] Response to oral challenge in those patch-test positive to cobalt but not to nickel was useful for predicting which patients would subsequently benefit from a diet low in cobalt.[40] Stuckert and Nedorost have recently updated dietary cobalt guidelines by proposing an easy-to-use point system.[41]

Oral ingestion of metals may be especially likely to aggravate the pompholyx pattern of hand dermatitis. This was suggested in a double-blind trial of potassium dichromate versus placebo by Kaaber and Veien,[61] as well as a later placebo-controlled study dosing chromate-positive patch test patients orally.[62] In addition to normally occurring dietary chromium (eg, in black pepper, apple peel and brewer's yeast), the metal introduced through multivitamin and mineral supplements[63] or the nutritional additive chromium picolinate may cause patients to flare.[64]

Numerous reports of dermatitis exacerbated by ingestion of spices have been published since Hjorth first described an association between balsam of Peru patch test reactivity and sensitivity to aromatic spices and flavorings.[54] Balsam of Peru, a fragrant extract from the Latin American *Myroxilon pereirae tree*, is a composite of many sensitizing chemicals. It is used as an allergen in patch testing to detect fragrance sensitivity. Veien and colleagues have demonstrated dermatitis flares in patients orally challenged with the substance.[55] Ingestion of its component flavorings, including cinnamon, cloves and vanilla, has also been reported to instigate widespread SCD.[65] Observance of dietary restriction of balsam of Peru components may benefit many sensitive patients, including children.[3,45,52,66] In our clinic we recently evaluated a balsam of Peru patch-test positive woman whose hand and patchy dermatitis developed when she began to consume six or more cans of Dr. Pepper daily at her new job and subsided when she weaned herself from this spicy beverage.

More rarely reported are incidents of SCD related to ingestion of preservatives and excipients. Although many patients have contact sensitization to formaldehyde and formaldehyde releasers, food sources of formaldehyde are limited. Recent reports affirm that the artificial sweetener aspartame, which is metabolized in the body to formaldehyde, may induce SCD when ingested by formaldehyde-sensitive individuals.[53,67] Aspartame is not only commercially available as a sugar substitute, but it is an ingredient in innumerable foods, beverages and chewable or syrup forms of medications.

The parabens, para-hydroxybenzoate preservatives, have been widely utilized for decades, but they are currently employed in personal products in much lower concentrations than in the past.[68] Veien and colleagues were able to precipitate cutaneous flares in only a few of their 14 sensitive patients challenged orally,[69] but generalized dermatitis has been reported in sensitized individuals following ingestion of paraben-containing medicaments, including haloperidol[70] and a mucolytic.[71] Paraben-sensitive individuals seldom experience flare of dermatitis from consuming paraben-containing foods such as pro-

cessed tomato products, pickles, relishes and packaged meat products.[68]

Propylene glycol is a widely used humectant and solvent for foods as well as topical and systemic medicaments. Hannuksela and Forstrom demonstrated that oral propylene glycol caused eczema in some patients shown to have contact allergy to the chemical.[72] More recently, Lowther and colleagues[73] described a woman whose dermatitis improved with avoidance of numerous topical preparations that contained propylene glycol, to which her patch test showed questionable reactivity. Her dermatitis recurred, however, at previous locations and at the patch test site when she ate foods known to contain propylene glycol, such as sauces, dressings and snack foods. We have seen a propylene glycol patch test positive boy whose dermatitis cleared when his topical corticosteroid was changed to a propylene glycol-free alternative, but then flared each spring when, for respiratory allergies, he resumed his oral antihistamine pill containing propylene glycol.

Plants in the large *Compositae (Asteraceae)* family are common sensitizers through repeated contact. Recently, derivatives of many species, such as feverfew, calendula and *Arnica montana*, are being formulated into topical personal products. Dietary sources are even more plentiful and reports have been published of flares of *Compositae*-acquired dermatitis after eating lettuce, chicory and endive,[74,75] consuming chamomile tea[75,76] and ingesting *Echinacea*.[77]

Propolis, also known as beeswax or bee glue, is a hive cement and protectant generated by bees using substances collected from poplar resin and conifer buds. It is a potent sensitizer, as well as a potential cross-reactor with both *Compositae* and balsam of Peru. Not only is it found widely in cosmetics, lip balms, toothpastes, chewing gums and a host of other products, but it is also present in some coated oral pills, cough syrups and gummy vitamins. Consumption of these can elicit SCD.[78] Royal jelly and propolis-comprised "alternative" products for "immune enhancement" may precipitate generalized rashes in sensitized individuals.[79] Decades ago, Morrow and colleagues reported a similar aloe-positive patch test man with widespread eczematous patches perpetuated by chronic oral and topical aloe use.[80]

Table 3. REPORTED ROUTES OF SYSTEMIC EXPOSURE TO CONTACT ALLERGENS

Oral	Intravenous
Subconjunctival	Intraarticular
Intramuscular	Subcutaneous
Pulmonary inhalation	Intradermal
Intranasal	Dental
Intrauterine	Intratubal
Endocardial	Endovascular
Arthroplastic	

OTHER ROUTES OF ALLERGEN RE-EXPOSURE

Ingestion by mouth is just one of the many recorded routes of systemic exposure to cutaneously sensitized allergens. **See Table 3**. Intravenous administration of propylene glycol precipitated the related vulvar recall reaction mentioned above.[33] Aminophylline, a compound of theophylline and ethylenediamine, whether given intravenously or orally, has produced baboon syndrome and generalized exfoliative dermatitis in patients previously sensitized to ethylenediamine by topical application of a product containing it.[81–83] Because this amine is the parent compound of the hydroxyzine family of antihistamines, these drugs should also be avoided in sensitive patients.

Neomycin is a common contact allergen, with ubiquitous exposure in over-the-counter antiseptic preparations. Exposure to the antibiotic orally can trigger a flare at former sites of contact dermatitis or a widespread dermatitis.[13,84] Gentamicin, tobramycin and framycetin are very closely related to neomycin structurally and they have produced reactions as severe as erythroderma when administered to neomycin-sensitive patients either intravenously,[85] subconjunctivally[86] or intra-articularly in bone cement.[87] Although erythromycin is seldom a topical sensitizer, one patient is described in whom contact rash was followed by a generalized eczema after the antibiotic was prescribed orally.[88] Various reactions have been reported to acyclovir given orally or intravenously in patients previously sensitized through topical application of the ointment.[89]

Intramuscular injection of gold was a common treatment for rheumatoid arthritis in the past. In patients with contact allergy to gold, such injections can provoke severe skin reactions.[90] Although allergic reactions to subcutaneously injected insulin are only rarely due to the metacresol preservative and most of those reactions are local, one case of exfoliative erythroderma has been credited to SCD from this agent.[91]

Pulmonary inhalation of the corticosteroid budesonide has been reported to reactivate previously positive budesonide patch tests, provoke new distant skin lesions and display cross-sensitivity to other group B corticosteroids such as triamcinolone acetonide.[31] Other groups of corticosteroids and other routes of administration, such as oral, intravenous, intraarticular, intradermal and intranasal, have also been associated with SCD.[92–94] A study by Mahajan and colleagues demonstrated SCD caused by inhalation of plant material from the allergenic weed *Parthenium*.[95] Inhalation is also one route by which mercury has caused SCD,[12,47] although allergen exposure may also come from ophthalmologic preparations and dental amalgams.[96]

Whereas reactions to dental amalgam metals such as mercury, gold, nickel, palladium, copper, cobalt and chromate usually present as localized adjacent buccal lichenoid sores[97] and less commonly as SCD, nickel in dental braces has been reported to produce not only mucosal reactions, but also significant cutaneous dermatitis requiring appliance removal.[98–100]

Allergic dermatitis, although rarely reported from a copper intrauterine device, has been documented by posi-

tive patch test to copper sulfate and reversal after removal of the IUD.[101–105] Recently, a woman without prior recognized allergy developed generalized pruritus and nausea following insertion of an intratubal birth control device composed of a stainless steel coil covered by the nickel-titanium alloy nitinol. Patch tests were positive to nickel and nitinol and the patient had improvement of symptoms after prompt removal of the implant.[106]

In addition, nitinol composes the only presently approved device for percutaneous occlusion of patent foramen ovale. There are several case reports of severe systemic symptoms following placement and nickel allergy requiring explanation of the appliance.[107–110] Nickel is also thought to be responsible for a generalized eczematous dermatitis that developed in a patient after nitinol endograft placement for abdominal aortic aneurysm repair.[111]

A host of different metals are used regularly in arthroplastic surgery and cutaneous complications are rare. They can include, however, overlying or generalized dermatitis, with metal allergy sometimes being implicated.[112] The subject of hypersensitivity reactions to implanted metal was recently reviewed by Basko-Plluska and colleagues.[113] With the field of "bionic parts" burgeoning, the future may hold more reports of SCD related to implanted pulmonary, biliary, urologic and neurologic stents, shunts, stimulators and other devices.

ROLE OF PATCH TESTING

Patch testing is often necessary to diagnose SCD and distinguish it from atopic dermatitis, systemic drug eruption and non-compliance with allergen avoidance. Screening patch test arrays are available to search for reactions to the most common chemicals and generate clues for the provider as to potential sources. The North American Standard Series includes allergens from several different categories, and supplemental series, such as metal, are also available. The reason to test with supplemental allergens is to increase the chance of finding positive patch test reactions that prove relevant.[114]

TREATMENT GUIDELINES

Repeated exposure to allergens may occur before sensitization develops and days or years may pass before an allergic dermatitis erupts.[115] Exposures may be additive, eventually causing the immune system to cross a metaphorical "threshold," after which subsequent contact elicits a cutaneous response.[4] Just as repeated contact over time leads to the immune allergic response, persistent avoidance of exposure over time may be required to induce remission. Patients must be enlisted to become actively involved in the management of their dermatitis. It is helpful to provide them clear written instructions accompanied by verbal explanations. Thorough education is essential to clarify for the patient what products, foods and medications are allowable in order to prevent unnecessary invalidism.

Avoidance of specific allergens can be a painstaking task and discovering sources of systemic exposure can be an even more tedious process. There are programs available, however, to aid in this endeavor. Both the Contact Allergen Management Program (CAMP), a service offered through the American Contact Dermatitis Society (ACDS),[116] and the Contact Allergen Replacement Database (CARD), developed by Mayo Clinic,[117] provide information to help identify products in which specific allergens may be encountered. Both systems allow the provider to enter a patient's known contact allergens to generate a "shopping list" of products free of those particular chemicals and cross-reactors.

When systemic sources of relevant allergens are identified, they can usually be eliminated. Medications and personal products should be replaced by tolerated alternatives unrelated to the sensitizing chemical. Often a 6-week diet is recommended, restricting ingested sources of the allergen to evaluate improvement. In the few cases where removal of allergen is impossible, medical management of the allergic reaction can involve topical corticosteroids, the use of barrier devices, systemic antihistamines, calcineurin inhibitors, UVB, UVA and, sometimes, systemic immunosuppressants.[118] ■

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