

Systemic Contact Dermatitis

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Systemic exposure to allergens resulting in a cutaneous eruption is known as systemic contact dermatitis (SCD). Once sensitization occurs, varying exposures to antigens via multiple routes (including transepidermal routes, intravenous or intramuscular routes, inhalation, and ingestion) can result in systemic flare. This article highlights the different categories of common contactants, metals, medications, and plants, exposure to which leads to SCD. A comprehensive approach that takes into account all possible routes of exposure is essential in diagnosing SCD and in helping patients successfully avoid their allergens.

ALLERGIC CONTACT DERMATITIS (ACD) is a systemic disease defined as hapten-specific T-cell-mediated skin inflammation.¹ In the sensitization phase, the hapten penetrates the skin and reacts with self-proteins. The Langerhans' cells (LHCs), the antigen-presenting cells of the skin, take up the antigen (hapten and/or the hapten-protein complex) and express it on major histocompatibility complex (MHC) molecules on the cell surface. The LHCs then migrate via the lymphatic system to regional lymph nodes and present the antigen to naive T cells. The T cells are primed, undergo clonal expansion, acquire skin-specific homing antigens, and emigrate out of the lymph nodes into the circulation. These CD4⁺ and CD8⁺ T-cell clones are then able to act on target cells presenting the antigen in the future. The sensitization phase lasts approximately 10 to 15 days.¹

Subsequent exposure to the antigen leads to an elicitation phase.¹ Rechallenge can occur via numerous routes, including transepidermal routes, intravenous/intramuscular routes, inhalation, and ingestion. Langerhans' cells and keratinocytes take up and present the antigen, this time to the hapten-specific T cells patrolling the dermis. These cells then activate macrophages, release cytokines, and stimulate keratinocytes to release cytokines.² The inflammatory response is enhanced as monocytes migrate into the affected area and mature into macrophages, thereby attracting more T cells. Macrophages take up and present the antigen and release mediators of inflammation, amplifying the response. This

proinflammatory state results in the clinical picture of ACD.

Resolution of ACD is considered a passive process, and some T cells may remain at the affected site. Local skin memory may be secondary to the retention of T cells. Moed and colleagues investigated the mechanisms mediating T-cell retention. Twelve patients with known contact allergy were patch tested with their relevant allergen. The reactions were biopsied and analyzed for infiltrating cells and expression of various cytokines, including CCL-27, a CCR-10 targeting ligand. Clinically normal skin, up to 21 days after resolution of the inflammatory response was also biopsied and analyzed. The authors demonstrated that 21 days after patch testing the clinically normal skin CCL-27 expression persisted and there were an increased number of CCR10+ CD4+ T cells, thus recognizing the role of CCL-27 in local retention of T cells.³

These results provided a plausible explanation for the observation that rechallenge with an allergen can produce symptoms at the cutaneous site of exposure, at previously sensitized sites, or in previously unaffected areas. Since the ensuing dermatitic eruption can have a latency period for days after exposure, the temporal relationship with the eliciting allergen is often not associated. In 2002 Isaksson and Bruze published a landmark article on ACD in response to budesonide reactivated by inhalation of the allergen. The authors identified 15 patients with budesonide allergy. The subjects were patch-tested with budesonide and rechallenged at 6 weeks with inhalational budesonide or placebo. Four of seven patients had a positive reactivation at the site of budesonide patch testing, and several patients also had reactivations at the testing sites of other classes of corticosteroids. These results demonstrated the possibility of reactivations in the

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skin following systemic absorption, as well as the important cross-reactivities among the steroid classes.⁴

One decade ago, Kligman introduced the concept of subclinical patch-test reactions at the Jadassohn Centenary Congress.⁵ The concept was that local immunologic priming, such as the constitutive expression of a marker such as CCL-27, would allow for immune-cell trafficking to areas of sensitization. Along these lines, Hidsen and colleagues performed an experiment by patch-testing a group of patients with serial dilutions of nickel followed by an oral challenge. They found that a substantial number of patients flared at high-dilution (low-level allergen) sites, where there had previously been no reaction in the primary patch test, further supporting the concept of a nonvisible allergic phenomenon.⁶

The immune system's activation without a correlating cutaneous response (invisible phenomenon) explains the sensitization phase of ACD. Over time, the immune system becomes activated. With each subsequent challenge, the system creates more memory ($CD4^+$ and $CD8^+$ T cells). Traditionally, $CD4^+$ T cells acting as effector cells were considered responsible for mediating contact hypersensitivity. However, recent evidence has demonstrated that both $CD4^+$ and $CD8^+$ T cells may have effector function in these types of reactions.² In fact, in the past decade, many studies have shown $CD8^+$ T cells to be the main effector cells and $CD4^+$ T cells to behave as down-regulatory cells.^{2,7} In some cases, $CD4^+$ T cells can take on the role of effector in cases where there is a deficiency of $CD8^+$ T cells.² A complex interplay exists, and as suppressor activity yields to the effector function, a moderated or localized reaction at sites of prior sensitization results. Failure of the suppressor cells to maintain the effector cells in check subsequently leads to a systemic response, including a febrile state, general fatigue, flare-up of previously eczematous sites, flexural dermatosis, and erythroderma.⁸⁻¹⁰

Allergens That Cause Contact Dermatitis

Metals

A variety of metals have been found to cause systemic contact dermatitis (SCD) (Table 1). Exposure type, exposure duration, and environmental conditions (sweat, oxygen) in proximity to the metal are critical for mobilization of the ions inducing immune reactions. Transition metals (those elements in the "d block" of the periodic table) are electrophilic and can ionize and become

Table 1. Metals That Cause Systemic Contact Dermatitis

<i>Metal</i>	<i>Reference</i>
Cobalt	15
Copper	36
Chromium	37
Gold	20
Mercury	28
Nickel	6, 18
Zinc	8

reactive with proteins. The recognition and capture of these ion-protein complexes by dendritic cells leads to the contact sensitization.

Mercury

One of the more-studied metals that cause SCD is mercury. Cutaneous reactions to mercury vary from contact dermatitis and flare-up reactions to disseminated exanthema. The most common cause of systemically induced mercurial contact dermatitis relates to cases of mercury vapor inhalation from exposures to broken thermometers after previous sensitization to mercury compounds. In many cases, prior sensitization occurred by exposure to mercurials in vaccines, topical disinfectants, ophthalmologic preparations, and antiparasitic powders.^{11,12} Clinical cases of acute generalized exanthematous pustulosis (AGEP) and a symmetric flexural exanthem (symmetrical drug-related intertriginous and flexural exanthema [SDRIFE]), have both been reported as following systemic mercury exposure.^{10,13} In addition to a possible direct ability of systemic mercury to enhance the proliferation of lymphocytes, the excretion of mercury by the sweat glands may indirectly attract and localize activating and proliferating T cells in the flexural areas and account for the clinical appearance of mercury-induced SCD.^{13,14}

Nickel

Nickel allergy is common (second only to allergy to poison ivy and poison oak) and frequently causes contact dermatitis at localized sites in contact with the metal.¹⁵ The ubiquity of nickel, however, makes it a very difficult allergen to avoid. Nickel may be a component of many different types of metallic substances, such as white gold, silver, metal platings, and stainless steel. ACD due to nickel

arises from direct contact exposure to the skin, respiratory tract, and gastrointestinal tract. Reactivation of a previous dermatitis after oral challenge, on the other hand, is considered to be a specific indicator of SCD.⁶

Hindsen and colleagues studied flare-up reactions of positive nickel patch-test sites after oral challenge. All of their patients had positive reactions after the challenge dose, and all of the atopic patients had additional flares of previously eczematous sites after receiving the highest studied dose of oral nickel (3.0 mg).⁶ The clinical relevance of the normal daily intake of 0.5 mg of nickel in eliciting flare responses has been questioned, as it is significantly lower than the challenge doses required to elicit a response in study settings.¹⁶ This being said, peak intake of nickel in food sources may lead to flares. For example, electric kettles can release up to 1,000 µg of nickel into a liter of water, and two bags of airline peanuts can double the daily intake of nickel.¹⁶

Veien presented several examples of orally ingested nickel resulting in dermatitis. Twelve women with vesicular hand eczema ate high-nickel diets for 4 days. On the eleventh day, 10 of the 12 women had aggravated dermatitis. An increase in nickel absorption was confirmed by increased urinary nickel excretion.¹⁶ As nickel is ubiquitous, it may not be possible to completely remove it from the diet. Studies have reported some improvement in patients who follow low-nickel diets. Veien recommends this diet only to patients with treatment-refractory dermatitis.¹⁶

Most cases of nickel-induced SCD have been the result of oral exposure; however, reactions following transfusions and inhalation also occur. Implantation of metal medical devices and dental braces have been reported, in nickel-sensitive patients, to cause facial dermatitis and generalized pruritus.^{16,17} Since medical devices may contain nickel, it is important to consider systemic nickel allergy in the postoperative and postpartum stages, as exanthema in these situations is often attributed to cutaneous drug reactions.

Of interest, studies have shown that the frequency of nickel sensitivity is reduced if the ears are pierced after orthodontic treatment is begun, as compared to the converse.¹⁶ These data suggested that desensitization of patients via oral exposure to allergens might be effective. While some attempts to induce unresponsiveness to nickel in nickel-sensitized patients via oral exposure have been successful, flare-up reactions have also occurred in other individuals.^{16,18} The mechanism of this desensitization is not clearly established as lymphocyte reactivity is not known to change.¹⁶

Gold

The American Contact Dermatitis Society selected gold as Allergen of the Year in 2001. Gold had long been considered inert, but during the last 15 years, there have been numerous accounts of allergic reactions to gold, including jewelry contact dermatitis, eyelid dermatitis, and oral lichenoid lesions. Gold allergy can be a diagnostic challenge. Owing to the characteristic late reactions to challenge, patch tests with gold must be followed up for 3 weeks to minimize false-negative readings.¹⁹

The antiinflammatory properties of gold have led to its application in the treatment of rheumatoid arthritis via intramuscular injection.¹⁹ Delayed skin reactions have been seen in up to 50% of patients treated with gold for rheumatoid arthritis, as indicated by patch testing.¹⁹ Moller and colleagues demonstrated that patients who underwent systemic provocation with gold sodium thiomalate flared at previously involved sites and developed a transient high increase in body temperature.²⁰ Moller and colleagues have also done studies demonstrating increases in cytokines and acute phase reactants in cases of contact allergy to gold.²¹

Copper

Copper, although not used as a medicinal therapy, is commonly used in dentistry and fertility medicine (in intrauterine devices) and has been shown to produce SCD. Although the amount of copper released from dental devices is below that present in a normal diet, there are some cases of delayed contact stomatitis due to copper.²²

Cobalt

SCD from cobalt has been demonstrated and is of importance because this metal is the main component of vitamin B₁₂. Recall reactions at sites of vitamin B₁₂ injections following the oral ingestion of the vitamin have been described.¹⁵ Data have also shown that preexisting allergy to either cobalt or nickel can increase the development of allergy to the other metal. Cross-sensitization can also occur between nickel and palladium, as demonstrated by Hindsen and colleagues.⁹ This is of importance because the use of palladium is increasing in dental appliances, jewelry, and electrical appliances.

Medications

Cutaneous drug eruptions account for a significant percentage of adverse drug reactions and can range from

mild self-limited conditions to the rare life-threatening disease. Most of the immunologically mediated drug reactions are accounted for by T-cell-mediated (delayed type IV) hypersensitivity reactions.²³ While an in-depth review of systemic drug reactions is beyond the scope of this article, several specific reactions deserve mention.

The fixed drug eruption (FDE), for example, characteristically shows as asymmetrically distributed erythematous round patches or plaques that recur on rechallenge. Histologically, these lesions are rich in intraepidermal CD8⁺ T cells, phenotypically resembling effector memory T cells.²⁴ In contrast, as the name implies, drug reaction with eosinophilia and systemic symptoms (DRESS) exhibits a generalized symmetrical morbilliform rash, eosinophilia, and systemic symptoms such as fever.¹⁰ Also, in AGEP, patients present with an acute febrile episode of sterile pustules on a background of erythematous-edematous skin.¹⁰ It has been suggested that in AGEP, drug-specific T cells are responsible for the release of neutrophil-activating cytokines, leading to the accumulation of neutrophils within the lesions.¹⁰

SCD has been reported as being secondary to a wide range of medicinal therapeutics⁵ (Table 2). In the case of drug-induced SCD, the clinical picture is frequently that of SDRIFE (Table 3). This syndrome has been considered to be a specific cutaneous symptom of SCD²⁵ and was originally called baboon syndrome (a term introduced over 20 years ago), as the patient presents with a diffuse and symmetric erythematous morbilliform eruption of the

Table 2. Medications That Induce Systemic Contact Dermatitis

<i>Medication</i>	<i>Reference</i>
Miconazole, terbinafine	38
Neomycin, gentamicin	10, 41
Erythromycin	41
Pseudoephedrine,	10, 41
ethylenediamine, hydroxyzine	
Cinchocaine, benzocaine,	10, 41
tetracaine	
Oxycodone	10, 26
Corticosteroids	10, 41
IVIg (0.4 g/kg)	10
Aminopenicillins	10, 26
5-Aminosalicylic acid	39
Naproxen	26
Allopurinol	40
Mitomycin C, 5-fluorouracil	41
Suxamethonium, doxepin cream	41

IVIg = intravenous immunoglobulin.

Table 3. Criteria for Symmetrical Drug-Related Intertriginous and Flexural Exanthema (SDRIFE)

1. Exposure to systemic drug at first or repeated dose (contact allergens excluded)
2. Erythema of gluteal/perianal area and/or V-shaped erythema of the inguinal/perianal area
3. Involvement of at least one other intertriginous/flexural localization
4. Symmetry of affected areas
5. Absence of systemic signs and symptoms

Adapted from Hausermann et al.¹⁰

buttocks (resembling the dark red gluteal areas of baboons) and flexural areas, forming a V-shaped pattern on the medial thighs¹³ (Fig 1).

Hausermann and colleagues reviewed the history of baboon syndrome and its causes and discovered that the terminology was problematic because it is not specific to the characteristic intertriginous and flexural exanthem related to systemic drug reactions that can occur after the first or repeated dose of medication.¹⁰ The authors proposed a new term, SDRIFE, to be added to the repertoire of acronyms for specific drug eruptions. SDRIFE requires five diagnostic criteria (see Table 3). In contrast to other drug eruptions (FDE, AGEP, and DRESS), SDRIFE is a distinct type of response that is mediated by a type IV hypersensitivity immune response akin to SCD.¹⁰

Wolf and colleagues challenged the idea of baboon syndrome as a subset of SCD, reporting on 11 cases of intertriginous eruptions due to drugs.²⁶ These authors



Figure 1. V-shaped pattern on the medial thighs in a case of symmetrical drug-related intertriginous and flexural exanthema (SDRIFE). Reprinted with permission, photo by Alison Young, MD, Dermatlas; <http://www.dermatlas.org>.

attributed the eruptions to a “recall phenomenon,” indicating that the response that occurred after drug exposure was determined by preexisting dermatitis at the same location. They suggested that these drug-related eruptions may fall under the category of “isotopic response,” the occurrence of a new skin disorder at the site of another, unrelated, and already-healed skin disease, after they coined this term in 1985.²⁷ A differentiating factor in these intertriginous dermatitides from SCD was the absence of positive patch-test results in four of the patients.

Another plausible explanation for intertriginous dermatitis resulting from systemic medications is the possibility that the drugs are excreted via the sweat glands. As studies have shown that mercury is excreted by sweat glands, Lerch and Bircher hypothesized that this may contribute to the immune response occurring in flexural areas.¹³

Plants

A variety of plants and foods have allergenic potential that may lead to SCD (Table 4). As alternative medicine gains popularity within Western culture and more patients are turning to herbal preparations and homeopathy, physicians must be aware of the potential adverse effects of these remedies. Many plants and botanical extracts are constituents of topical preparations and cosmetics and could ultimately sensitize patients to these allergens.

The family Compositae (Asteraceae), also known as the “daisy family,” is composed of thousands of species worldwide. Members of this family are increasingly being used as herbal remedies and medicinal therapeutics.²⁸ Additionally, Compositae plant extracts are present in a

variety of cosmetics and personal hygiene products (eg, shampoos and soaps). This plant family encompasses flowers, herbs, vegetables, and weeds (eg, ragweed, chamomile, feverfew, *Arnica*, marigold, mugwort, and *Echinacea*). Sesquiterpene lactones (SLs) are the main allergens in these plants and can result in Compositae-induced ACD and SCD.

Chamomile is frequently ingested in the form of tea. Paulsen described two cases of SCD attributable to chamomile tea, in which minimal amounts of SLs caused reactions. These cases provided evidence of severe systemic reactions after the ingestion of chamomile.²⁸ It is well known that chamomile and mugwort cross-react serologically, and this cross-reactivity has clinical significance as sensitization to mugwort may be a risk factor for the future development of a reaction to ingested chamomile.^{28,29}

Tanacetum parthenium, also known as feverfew, has gained popularity in the prevention of migraines.³⁰ The leaves of the plant are taken orally and are known to cause irritant-type reactions of the mouth, tongue, and lips.³¹ Additionally, patients frequently develop oral ulcers, which are systemically and immunologically induced.³² *Parthenium hysterophorus* (“parthenium weed”) is a common cause of ACD throughout India and is known to sensitize occupationally exposed individuals.³³ Mahajan and colleagues presented a case of a male office worker with a 2-year history of episodes of widespread erythematous pruritic rash with associated painless lymphadenopathy. The patient’s condition improved while he was staying in a *Parthenium*-free region. Because the clinical picture did not agree with the classic pattern of airborne contact dermatitis, the patient was asked to inhale from a polythene bag containing *P. hysterophorus* (to confirm the hypothesis that his allergy was due to inhalation and not to direct contact). As suspected, 8 to 10 hours after inhalation, the patient developed widespread pruritus and dermatitis over the lower extremities, in the absence of nasobronchial symptoms.³³ Handa and colleagues attempted to hyposensitize their patients orally with this plant, and up to 30% of their patients experienced exacerbation of their dermatitis.³⁴

Many foods and spices are capable of causing cutaneous reactions. In addition to irritant contact dermatitis and ACD, SCD can occur after topical sensitization with the allergen. Flavoring agents, such as cinnamon oil, vanilla oil, balsam of Peru oil, spices, garlic, and raw cashew nuts have the potential to cause SCD. Additionally, there is a causal relation between balsam of Peru allergy and allergy to various flavoring agents and spices.³⁵ The “low balsam diet” restricting these agents and

Table 4. Plants and Herbals That Induce Systemic Contact Dermatitis

Plant/Herbal	Reference
Compositae (daisy family)	28
Ragweed	
Chamomile	
Feverfew (<i>Parthenium</i>)	
<i>Arnica</i>	
Marigold	
<i>Echinacea</i>	
Mugwort	
Cinnamon oil	34
Vanilla oil	34
Balsam of Peru	34, 35

spices has improved the dermatitis of sensitized persons in specific patient populations.³⁶ Whether a fully restrictive diet is necessary or whether the targeted elimination of some foods is sufficient is still to be determined.

Discussion

Contact dermatitis is a systemic disease that demonstrates the inherent role of the skin as an immunologic organ; systemic exposure to antigens can result in dermatologic effects. The integument can play an integral role in the capture and recognition of chemicals in our environment and in the sensitization to those chemicals, as well as in the recalling that a process occurred and in the activation of an immune cascade in response to rechallenge. T cells serve as the skin's inherent checks-and-balances system. This interplay between the effector and suppressor cells leads to either an expression of ACD, a nonvisible allergic phenomenon, or tolerance. The army of activated T cells that remains in the skin following sensitization plays an integral role in local skin memory, which leads to cutaneous symptoms upon rechallenge. Localization of this response demonstrates the skin's ability to perform a suppressive T-cell function and quiet the response. In the event that the suppressor function is inadequate, systemic administration of an allergen can lead to a full-blown effector response, SCD, with the potential for an erythrodermic state.

Once a patient is diagnosed as being sensitized to a given allergen, care should be taken to educate the patient about all potential exposures. Historically, patients are taught to avoid contact between allergens and their skin. However, evidence of systemically induced hypersensitivity requires patients to be cognizant of all the mechanisms by which they may experience exposure to an allergen. While generalized avoidance is more likely to result in decreased compliance, especially since the hypersensitivity can be quite delayed, the importance of minimizing exposures must be emphasized, and patient education is a key factor in preventing flares.

While daily avoidance is the patient's responsibility, physicians have a responsibility to maintain an interdisciplinary approach to contact dermatitis. Patients may be taking medications prescribed by other specialists that can affect their skin, they may be exposed at the hands of their dentist or surgeon, or they may be subscribing to alternative medical treatments that can cause dermatitides. Physicians must inquire not only about topical products, but also whether a patient is ingesting any form of

alternative (botanical) medicinal treatment. Ultimately, since elements of allergic hypersensitivity are indeed invisible, a high index of suspicion is the most direct path leading to diagnosis.

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