



Contact dermatitis as a systemic disease

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Abstract Systemic contact dermatitis (SCD) is a condition occurring in previously sensitized individuals after systemic re-exposure to the same or cross-reacting substance. Systemic route of administration means uptake of an allergen via percutaneous, transmucosal, oral, intravenous, intramuscular, and inhalational routes, as well as through implants. The intimate mechanisms behind SCD are not yet fully understood, but it is thought to be a T-cell mediated delayed type hypersensitivity reaction. The most common allergens recognized to date are nickel, aminoglycoside antibiotics, corticosteroids, balsam of Peru, and plants from the Anacardiaceae and Compositae families. The most typical presentation of SCD, known as *baboon syndrome*, includes diffuse erythema of the buttocks, the upper inner surface of the thighs, and the axillary folds. Cases with the classical baboon pattern of distribution elicited by systemically introduced drugs without previous sensitization are encompassed by the acronym SDRIFE (Symmetric Drug-related Intertriginous and Flexural Exanthema). Interestingly, corticosteroids, although widely applied for anaphylaxis and other allergic conditions, can produce sensitization, and they are commonly mentioned as triggers of SCD.

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Introduction

Systemic contact dermatitis (SCD) is a condition occurring in previously sensitized individuals after systemic re-exposure to the same or cross-reacting substance. Systemic route of administration means uptake of an allergen via percutaneous, transmucosal, oral, intravenous, intramuscular, and inhalational routes, as well as through implants.^{1–3} The intimate mechanisms behind SCD are not yet fully understood, but it is thought to be a T-cell mediated delayed type hypersensitivity reaction.⁴ The most common allergens recognized so far are nickel, aminoglycoside antibiotics, corticosteroids, balsam of Peru, and plants from the Anacardiaceae and Compositae families. The most typical presentation of SCD includes diffuse erythema of the buttocks, the upper inner surface of the thighs and the axillary folds, also known as baboon syndrome.

Definition

Contact dermatitis by definition is an inflammatory skin reaction, caused either by allergens (allergic contact dermatitis; ACD) or irritants (irritant contact dermatitis; ICD).

The mechanism behind ACD is a delayed, cell-mediated hypersensitivity reaction induced by exposure to an allergen to which the patient has already been previously sensitized. The clinical picture of ACD varies according to the severity, location, and duration of the inflammation. In the acute form, the exudative lesions predominate, consisting of well-demarcated erythema, on which closely grouped vesicles and/or papules are situated. In the subacute and chronic forms, scaling and lichenification predominate.

ICD, on the other hand, is a toxic phenomenon, characterized by a nonspecific inflammatory response of the skin to direct chemical damage. It can be subdivided into two forms. The acute form occurs after a single exposure to the offending substance; it is concentration dependent and develops in every exposed individual. Lesions may vary in severity, ranging from mild erythema

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and vesiculation, to caustic burns and necrosis. The chronic form is triggered by repeated cumulative exposure to mild irritants and is often accompanied by disturbance of the barrier function of the skin manifested clinically by dryness, hyperkeratosis and scaling, fissures, and crusting on a mildly erythematous base. In severe cases of ACD, the pathological process is no longer confined to a single skin area but can encompass large body surfaces leading to erythroderma/exfoliative dermatitis.

The usual route of administration of the allergen, in patients with ACD, is through the skin; however, there are cases in which the allergen or a cross-reacting molecule may enter the organism via the bloodstream of previously sensitized individuals, thus reaching the skin and producing varying skin changes. Such alterations include a flare of eczema and/or a patch test reaction, vasculitis-like lesions, pompholyx or a generalized eruption, and also a specific exanthema, consisting of an acute eruptions, localized in the major flexures and the anogenital area with the catchy name *baboon syndrome* (BS). Systemic routes of administration mentioned in the literature include oral, transmucosal (including transrectal), intravenous, intramuscular, inhalational, and implants.⁵

There are many terms applied for this condition, among which are internal-external contact-type hypersensitivity,⁶ mercury exanthema,⁷ baboon syndrome,⁸ nonpigmenting fixed drug eruption (Comment: A proposed term for cutaneous eruptions related to or imitating the baboon syndrome. We think they mean a distinct entity and not fixed drug eruption, although the terms seem similar),⁹ drug-induced intertrigo,¹⁰ systemic contact dermatitis (SCD),² paraptotic eczema,¹¹ symmetric psychotropic and nonpigmenting fixed drug eruption,¹² flexural drug eruption,¹³ and symmetric drug-related intertriginous and flexural exanthema.¹⁴

In 1983, researchers described 15 cases of an exanthema developing after inhalation of mercury vapor from crushed thermometers in previously sensitized individuals, the so-called "mercury exanthema."⁷ A paper from 1984 described three different cases with ampicillin, nickel, and mercury as allergens and introduced the term *baboon syndrome* (BS), due to the characteristic clinical presentation resembling the gluteal region of a baboon and in an attempt to make the entity memorable.⁸ Ten years later, the umbrella term *systemic contact dermatitis* (SCD) was introduced, which included BS and other types of dermatitis from systemically administered substances with or without previous topical exposure.² Later, the term ACDS (allergic contact dermatitis syndrome) was proposed for patients with prior cutaneous sensitization to distinguish them from other cutaneous allergic dermatitis reactions without the background of a previous skin sensitization.¹⁵

Other researchers introduced a new acronym, SDRIFE (Symmetric Drug-related Intertriginous and Flexural Exanthema). According to them, since the first description of the BS, about 100 cases have been published in the literature, in which systemic drugs have been recognized as the causative

agents of the skin changes; however, for most of these medications, previous cutaneous or cross-sensitization has not been discovered. As a result, these researchers proposed that cases with the classical baboon pattern of distribution elicited by systemically introduced drugs without previous sensitization be encompassed by the more politically correct term SDRIFE.¹⁴

In this paper, we shall use the term SCD, which we find is a broad enough and contemporary designation to encompass the variety of triggers and patterns of reaction in previously sensitized individuals, who are systemically exposed to the same contact allergen or a cross-reacting molecule. From our point of view, SDRIFE should be reserved for cases elicited by systemically administered drugs without prior sensitization and with the characteristic distribution pattern. SDRIFE should supersede the colorful term *baboon syndrome*.

The most common triggers of SCD can be divided into three major groups: metals, drugs, and plant products.¹⁻³

Metals

Metals are ubiquitous in our environment, especially after the industrialization of modern society, thus making skin and systemic exposure easy and inconspicuous. Higher exposure levels lead to an increase in the percentage of allergies towards metals.

Metal ions are haptens, which need to be bonded to protein molecules to form antigenic complexes that can be further recognized by dendritic cells that allow sensitization to occur. The most common metals reported in the literature that elicit ACD and SCD are nickel, mercury, cobalt, chromium, zinc, and gold.

Nickel, by far, is the most common contact allergen. Nickel sensitization is observed in up to 17% of women and 3% of men. The higher percentage among women can be explained with the specific consumer demands. Many alloys, foods, jewelry, and everyday items contain nickel, thus the route of exposure varies significantly, including surgical implants.^{16,17} The clinical manifestation can vary dramatically. In previously sensitized individuals, nickel can elicit pompholyx after oral provocation.¹⁸ Recently, a case of SCD to nickel occurred in a 14-year-old boy after intake of cocoa¹⁹ and also another challenging case of a patient with long-standing therapy resistant pruritus and turned out to be an allergy case due to ingestion of peanut butter, which has high nickel content.²⁰ The previous recommendation of a nickel-free diet for nickel-sensitized individuals is of decreasing popularity and controversial among dermatologists.²¹

Cobalt and chromium (more specifically hexavalent chromium) sensitization is estimated to be 1% to 3% in the general population.⁴ Cobalt is used in the production of paints, jewelry, prosthetics, and various everyday objects. Concomitant allergy between cobalt and nickel has been researched and proves to be on the basis of cosensitization, rather than due to cross-reactivity.²²



Fig. 1 Systemic contact dermatitis 24 hrs after an oral provocation test with hydrocortisone with confluent macular papular erythema. The patient had a history of ACD due to a prednisolone-containing topical eye ointment. The patch test reaction to prednisolone 1.0%/pet. was ? at 48 hrs and + at 72 hrs.

Chromium is an important alloying material for the production of steel (stainless steel) due to its corrosion resistant properties. It is also used in the dye and pigment industry, as a wood preservative, in the tanning of leather, the production of polyethylene, and in environments like blast furnaces, cement kilns, molds for the firing of bricks, and as foundry sands for the casting of metals. Chromium can be found in water, soil, and foods. This availability of the element makes it easy for individuals to be sensitized to it or to be reexposed. There are cases in the literature describing dermatitis associated with chromium after knee arthroplasty,²³ dermatitis to a chromium dental plate,²⁴ and SCD due to ingestion of multivitamin tablets or different types of food supplements, containing the element.^{25,26}

Mercury and its compounds have been used in medicine in dental amalgams, as a preservative in vaccines, and in antiseptic preparations for topical use. Because light was shed on its toxic properties, its use has significantly declined, but mercury is still used in some parts of the world. This element is also used for the production of chlorine and caustic soda, in thermometers, fluorescent lamps, in make-up products (such as mascara), and also some foods that have higher mercury content (seafood). SCD to mercury has been reported in a patient using a skin-lightening cream,²⁷ in metal workers,^{7,28} in a patient with a dental amalgam,²⁹ and after exposure to mercury vapor.³⁰

Zinc is an essential element in many physiologic processes. It is also used for dental restoration, as an anticorrosion agent, in batteries, alloys, in paints, and for other industrial purposes. A case of a severe SCD due to zinc allergy has been reported.³¹ Two other cases have been found in the literature in patients who developed SCD due to dental fillings with zinc.^{32,33}

Gold has been used since ancient times for the production of jewelry and coins, as well as in medicine and dentistry. It can also be found in some foods and beverages. The first proven case of contact allergy to gold induced after systemic administration of sodium aurothiomalate in a rheumatoid

arthritis patient was described in 1988.³⁴ Since then, a growing number of cases on the subject have been published.³⁵⁻³⁸ An interesting case of SCD induced by gold was reported in a patient using a homeopathic drug containing the metal. The patient had been previously exposed to it through her gold earrings and a dental gold crown.³⁹

Drugs

The second most common group causing SCD is drugs. Medications can be applied both topically and systemically, which increases the risk of developing allergic reactions. In the past, local application of antibiotics was a popular treatment modality that nowadays is avoided in part due to the high sensitization potential of some drugs, such as neomycin and bacitracin.⁴⁰ In previously sensitized individuals to neomycin, the systemic application of gentamycin may induce SCD.⁴¹ There is a case of SCD in a patient who underwent knee replacement with an implant containing gentamycin.⁴² Research shows that half of patients allergic to neomycin will react to gentamycin.⁴¹ There is also a case of SCD to ampicillin due to systemic absorption of the drug.

Interestingly, corticosteroids, although widely applied for anaphylaxis and other allergic conditions, can produce sensitization, and they are commonly mentioned as triggers of SCD. Cross-reactivity is often present among them⁴³⁻⁴⁵ and might even occur between different classes of corticosteroids.⁴⁶ Elaborate skin testing followed by subsequent provocation tests are essential in such cases in an attempt to differentiate cross-reacting from alternative compatible drugs (Figures 1 and 2). In our case, a SCD developed 24 hours after an oral provocation test with hydrocortisone with



Fig. 2 The same patient 24 hrs after oral provocation test with triamcinolone (group B), which belongs to a different group of corticosteroids than prednisone and hydrocortisone (group A) (Coopmann et al.⁴⁶); however, the patch test to triamcinolone acetoneide 0.1%/pet. was negative both at 48 and at 72 hrs. The patient finally tolerated dexamethasone (group C).

a previous history of ACD to a prednisolon-containing topical eye ointment. The same patient developed SCD after an oral provocation test with triamcinolone, which belongs to a different group of corticosteroids; however, the patch test to triamcinolone acetonide 0,1% in petrolatum was negative both at 48 hours and 72 hours.

Other medications that can induce SCD are anesthetics, antihistamines, aminophylline,^{47,48} 5-aminosalicylic acid,⁴⁹ and buprenorphine (systemic absorption through anal application).⁵⁰ The list of drugs that can elicit SDRIFE also includes a wide range of medications, amoxicillin being the most common, followed by mitomycin.¹⁴

Plants

Plants are ubiquitous in our everyday life, being used as food, medications, and decoration. The most common adverse reaction caused by plants is ACD. Previous sensitization can easily occur, which also increases the risk for the development of SCD. This group includes Balsam of Peru (*Myroxylon balsamum* Pereira), garlic (diallyl disulfide), sesquiterpene lactones (*Compositae/Asteracea* family), and urushiol (*Anacardiaceae*).⁵¹⁻⁵⁴

Balsam of Peru is an aromatic resin used in various fields, including medicine and pharmacy due to its excellent antiseptic properties, and in food and perfume industry due to its scent, reminiscent of vanilla and green olives. It is well known for its potential to elicit ACD.

The chemical composition of Balsam of Peru consists of benzylcinnamate and benzyl benzoate, cinnamoin; styrene, vanillin, and coumarin. Some of these are encountered in various foods and beverages, which facilitates their systemic administration; hence, the chance of provoking SCD.^{55,56}

Another well-known contact allergen is propolis or “bee glue.” It consists of various resins, depending on the geographic area in which the beehive is situated, and is famous for its antiseptic properties. The main sensitizers identified in propolis are 3-methyl-2-butenyl caffeate and phenylethyl caffeate. Propolis can be found in cosmetic products, syrups, lozenges, tablets, etc; however, its growing use has led to an increase in ACD cases. In 2011 the first case of SCD due to propolis was reported.⁵⁷

Diagnosis and management

SCD has a vast spectrum of differential diagnoses, ranging from infections to bullous diseases. In pediatric patients viral exanthems, such as infectious exanthema,⁵⁸ bacterial infections-impetigo, and perianal cellulitis, should be excluded, and if there are systemic symptoms, staphylococcal scalded skin syndrome (SSSS) should be ruled out.

Other dermatoses, which have similar localization, to be considered are Hailey-Hailey disease, pemphigus vegetans,

inverse psoriasis, candidosis, tinea cruris, acute generalized exanthematous pustulosis (AGEP), and SDRIFE, as well as common ICD and ACD.

Flexural allergic and irritant contact dermatitis should be ruled out on the basis of the clinical presentation and patient's history. Proving or excluding previous sensitization can be performed with the help of the epicutaneous patch test and exposure/provocation test. Patch testing is often necessary to differentiate between SCD and other drug-induced eruptions without previous sensitization, especially, from the pattern specific entity SDRIFE.¹⁴ Epicutaneous patch testing can be performed with a standard series panel and/or with a customized one, depending on the suspected allergen. It is thought to be the gold standard in detecting contact allergy. The results obtained serve not only for elucidation of the triggering factor but also as a recommendation, showing which allergens and cross-reacting substances should be avoided in the future. It must be performed in a disease-free stage to prevent the so called “angry back” syndrome with false-positive reactions.

Another diagnostic tool is the exposure/provocation test, which rechallenges the patient with the suspected allergen via systemic route of administration; however, it is not as safe as patch testing, leading in many instances to a flare-up of the previous eczematous condition.

The most obvious way of treatment of any allergic condition, including SCD, is the avoidance of the causative allergen. Most of the substances causing SCD are ubiquitous, so this often proves to be a difficult or almost an impossible task. In professional settings, patients should be encouraged to seek requalification as means of allergen avoidance. In everyday life, an appropriate diet should be established to avoid or diminish allergen contact. Triggering medications and cross-reacting molecules should be avoided.

Another management strategy, although yet at an experimental level, that may prove useful for patients with nickel allergy is oral hyposensitization.⁵⁹ Depending on the severity of the skin inflammation, topical steroids with different potency can be applied. In severe cases, systemic use of corticosteroids or immunosuppressants may be necessary.

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