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REVIEW

Allergic contact dermatitis: Immune system involvement and distinctive clinical cases

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Abstract The aim of this review is drawing the attention to the contact dermatitis, an inflammatory skin condition due to pro-inflammatory and toxic factors able to activate the skin innate immunity (irritant contact dermatitis) or caused by a T-cell- mediated hypersensitivity reaction (allergic contact dermatitis).

The immune system involvement and a variety of clinical pictures are described in order to better diagnose, prevent and treat allergic contact dermatitis.

Introduction

Contact dermatitis is an inflammatory skin condition induced by exposure to an environmental agent.

Two main types of contact dermatitis may be distinguished: irritant contact dermatitis, due to pro-inflammatory and toxic factors able to activate the skin innate immunity; and allergic contact dermatitis, which is a T-cell-mediated hypersensitivity reaction.[1,2]

Contact dermatitis is usually characterised by itching with erythema, vesicles and bullae in acute phase and by lichen with cracks and fissures in chronic phase.[2]

Epidemiology

Contact dermatitis is a highly frequent disease with a significant influence on the quality of life of the affected patients and a relevant socioeconomic impact.[3]

The occurrence of allergic contact dermatitis increases with age; prevalence rates of 13.3–24.5% have been reported, but the highest sensitisation rate has been found in children aged 0–3 years.[4]

However, many cases may pass unnoticed, so it is not simple to establish the frequency of this affection.

Age and sex do not represent risk factors, whereas the occupational activity is the main condition implicated in the onset of allergic contact dermatitis.

Pathogenesis

Chemically reactive small molecular compounds penetrating into the skin may determine a hapten-specific immune response that involves T cells, invariant Natural Killer T cells, Natural Killer, T regulatory cells, epidermal Langerhans cells and keratinocytes.[5] Most of the T-regulatory cells involved in this process are the IL-10-producing T cells, namely Tr1, and the CD4+CD25+ T-regulatory lymphocytes.[6]

Two temporally and spatially spaced phases are usually necessary to achieve a contact hypersensitivity reaction: the sensitisation and the elicitation phase.

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In the sensitisation phase, which occurs at the first contact of the skin with the hapten, the innate immunity induces inflammation and consequently the recruitment of dendritic cells, especially Langerhans cells, and leukocytes. Cutaneous haptens are processed by dendritic cells and are expressed in the groove of MHC classes I and II molecules on the cell surface. Hapten-bearing dendritic cells migrate to the draining lymph nodes; here they present the antigenic peptides to specific effector and regulatory T cells. Activated specific T cells leave the lymph nodes and circulate in blood, tissues, and secondary lymphatic organs. The sensitisation step lasts 10–15 days. This first step has no clinical consequence in the majority of cases. However a ''primary allergic contact dermatitis'' has been described; it is characterised by a hapten-specific skin inflammation 5–15 days after the initial skin contact. The persistence of the hapten in the skin for a long period of time allows the recruitment and activation in the skin of CD8+ T cells, which have been primed in the lymphoid organs a few days before.

Re-exposure of sensitised individuals with the same hapten induces the activation of specific T lymphocytes in the dermis and the epidermis and triggers the inflammatory process responsible for the appearance of cutaneous lesions within 24/72 h. The inflammatory reaction, determined by type 1 or type 17 cytokines, persists for only a few days; its rate decreases through the clearance of hapten from the skin and the activation of regulatory T cells.[7–9]

Human hapten-specific CD8+ T cells show a type 1 cytokine profile, whereas the cytokine released by CD4+ T cells are more variable, with a predominance of Th1 cells and a lower number of Th2 cells. Tr1 lymphocytes represent 7–10% of nickel-specific T-cell clones isolated from the affected skin or the blood of allergic individuals. These Tr1 cells, depending on IL-10, block the maturation of dendritic cells and release IL-12 to impair the activation of hapten-specific Th1 effector lymphocytes.[10,11]

The involvement of Th17 cells has been observed in some recent studies. For example, in patients with nickel contact dermatitis, our group reported an increase in serum levels of IL-22; one of the cytokines produced.[12]

Another study of ours showed an alteration of the redox homeostasis occurring in nickel allergic contact dermatitis and particularly in ''systemic nickel allergy syndrome'' (SNAS) through the measurement of serum levels of specific biomarkers of oxidative stress, such as protein carbonyl groups and nitrosylated proteins.[13]

Increased IL-18 serum levels have been found in patients with allergic contact dermatitis. This pro-inflammatory cytokine is involved in the Th1 response and immune cell infiltration into the tissues, so it probably has a role in the induction of contact dermatitis, together with IL-12 and IFN-gamma.[14]

Common and particular causes of allergic contact dermatitis: our experience

Allergic contact dermatitis may be caused by metals, cosmetics, skin care products, drugs, or plants.[1]

Nickel is the most common cause in women in almost all countries because of the frequent exposure to high-nickel content jewellery. Hand eczema is often of the dyshidrotic type.

Potassium dichromate is the most common contact allergen in men exposed to cement.

Regarding cosmetics, allergic contact dermatitis is caused by preservatives, perfumes, active or category-specific ingredients, excipients /emulsifiers, and sunscreens.[15]

Contact dermatitis to clothes is usually related to formaldehyde; disperse dyes[16]; accelerators; and antioxidants used in the production of synthetic rubber. It is often located in the axillae because of the action of sweat and friction.

Topical drugs, through their active principle, the vehicle or the preservatives, have been reported as responsible for allergic contact dermatitis. We described the case of a 26-year-old woman who presented an itchy erythematous reaction and oedema localised to the face after a topical acne treatment with a gel containing benzoyl peroxide.[17]

The most frequent allergic contact dermatitis caused by plants is related to sesquiterpene lactones found in plants belonging to Compositae family. A particular kind of finger dermatitis may be determined by the contact with plants from the Liliaceae and Alstroemeriaceae families. Moreover, we reported a particular case of allergic contact dermatitis due to *Zantedeschia aethiopica*. ''A 30-year-old non-atopic woman developed itching, redness, and swelling on her hands after cutting calla lily in her garden''. The manifestations appeared 2–3 h after the contact with the plant. We performed a Patch test with a piece of calla lily stem, which resulted positive after readings on Day 2 and Day 4.[18]

Another report by our group concerns a case of contact dermatitis that occurred in a 28-year-old man after prolonged contact with a carbon-fibre fishing rod.[19]

Protein contact dermatitis is a chronic or recurrent eczema caused by proteins deriving from fruits, vegetables, spices, plants, woods, animal proteins, grains and enzymes.[20] We reported protein contact dermatitis caused by *Anisakis simplex* in a 54-year-old woman, who worked in the fish industry. Prick test with the extract of *A. simplex* and Patch test with the larvae, prepared according to the method reported by Conde-Salazar et al., showed the sensitisation.[21,22]

Substances usually responsible for contact dermatitis have been related to other manifestations. For example, alginate paste used for dental impressions has been reported as a cause of fatal anaphylactic shock[23] and cadmium sulphate used in a denture wearer engendered a burning mouth syndrome.[24]

Diagnosis

Epicutaneous patch testing is the best method to diagnose an allergic contact dermatitis, reproducing its pathogenetic mechanism. The classic positive patch test reaction is a miniature form of the same dermatitis: erythema, oedema, and small, closely set vesicles, which often extend beyond the borders of the patch.[25]

Different patch test units are now commercially available, such as the Finn Chambers or van der Bend square chambers.[26] Patients should be informed about avoiding

excessive exercise, showers, etc. to keep the test system dry. The most frequently encountered contact allergens have been included in standard patch test series.[27] Most commercially available allergens supplied in syringes are incorporated in petrolatum.

The patch test system, applied on the upper half of the back, is usually removed after 48 h, as recommended by the International Contact Dermatitis Research Group,[28] and readings should be taken 20 min after removal of the strips, and after 72 or 96 h. For some test series it could be necessary to read the tests once more after 7 days, to avoid missing the late reactions.

Occasionally some severe reactions can cause itching and burning, so the patch test can be prematurely removed.

The interpretation method recommended by the International Contact Dermatitis Research group (ICDG[29]) is:

−: negative reaction
?+: faint erythema only: doubtful reaction
1+: nonvascular erythema, infiltration, possibly papules: weak positive reaction
2+: vesicular erythema, infiltration, papules: strong positive reaction
3+: intense erythema and infiltration, coalescing vesicles, bullous reaction: extreme positive reaction
IR: irritant reaction of different types

Irritant reactions are characterised by fine wrinkling, erythema and papules in follicular distribution, petechiae, pustules, bullae or even necrosis and with minimal infiltration.[3,30]

Sometimes, other tests may be useful to diagnose an allergic contact dermatitis. For example, ''open tests'' are used for testing poorly defined or unknown substances (gels, liquids or creams), brought by the patient and potential cause of irritant reactions if occluded. Cosmetics such as perfumes, aftershave lotions and hairsprays are tested in this manner. It is applied undiluted to the normal skin twice a day for at least two days. The test is read after 15–30 min to detect contact urticaria. A negative open test indicates that an occlusive patch test can be performed with the substance without expecting severe irritant reactions.

The ''provocative use tests'' are performed to confirm positive patch test reactions.[31]

''Photopatch testing'' should be used to investigate patients with clinically suspected photoallergic contact dermatitis, which is caused by photochemical conversion of a certain agent into a contact allergen, mainly induced by UVA. Plant derivatives, fragrances, antiseptics and sunscreen agents are known for photosensitisation.[32]

Treatment

Identifying the aetiological agent is necessary in order to avoid the possible sources of reactions in patients with diagnosed allergic contact dermatitis. The elimination of contact allergen is the best preventive measure. In presence of the cutaneous manifestations, topical steroids are used in the acute stage and are gradually replaced by ointments and cold creams.

In the event of widespread and severe allergic contact dermatitis, systemic corticosteroids may be used for a short period of time.[1] Antihistamines may be used to alleviate itching.

Conventional immunosuppressive treatment is not appropriate but new immunomodulating macrolactams have been successfully tested in clinical trials.[33,34] New classes of immunosuppressors, inhibitors of cellular metabolic activity, and inhibitors of cell adhesion molecules targeted skin application of regulatory cytokines and neutralisation of pro-inflammatory cytokines (antisense oligonucleotides, anticytokine antibodies, soluble cytokine receptors) have been considered as future approaches.

Conclusions

The conspicuous variety of clinical pictures requires more and more attention on the part of physicians, especially allergists and dermatologists, in order to better diagnose, prevent, and treat allergic contact dermatitis.

Conflict of interest

The authors have no conflict of interest to declare.

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