

Key words

Allergic contact dermatitis • Cell-mediated delayed hypersensitivity reaction • Metals • Cosmetics • Dyes • Drugs • Antihistamines • Corticosteroids

Allergic contact dermatitis

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Summary

Allergic contact dermatitis (ACD) is a cutaneous inflammatory disease very frequent in developed countries, therefore representing an issue of great impact in terms of public health. A large array of agents is responsible of DAC, including metals, cosmetics, dyes, fragrances, and drugs. DAC is sustained by a cell-mediated, delayed hypersensitivity mechanism. The clinical and morphologic features of point of ACD are characterized by eruptive polymorphism (multiple different lesions occurring simultaneously) as well as evolutive polymorphism (lesions changing over time), itching representing the pivotal subjective symptom. Diagnosis of ACD relies on patient history (assessing patient lifestyle, habits, hobbies, use of clothing and accessories, personal hygiene products, cosmetics and household detergents), clinico-morphological features and allergy testing, including patch tests and provocative use tests. The main objective of ACD therapy is to mitigate the acute phase inflammation, to oppose the subacute and chronic phases xerosis and to improve pruritus, which is present in all three phases. Most used therapeutic agents are sodium hypochlorite wet compresses, 1% phenicated fuchsin and 1% gentian violet stains in acute exudative phase, while subacute and chronic ACD benefit from systemic antihistamines and from alternated use of topical corticosteroids and emollients/moisturizers. Oral corticosteroids or systemic immunosuppressants are indicated in diffuse, erythrodermic and non-responsive ACD forms. Indeed, the major factor in the management is the avoidance of the offending agent(s) and the adoption of appropriate preventive measures.

Introduction

Allergic contact dermatitis is a cutaneous inflammatory disease which is really frequent in industrialised countries, and is known to be one of the most common professional diseases, therefore representing an issue of great impact in terms of public sanity ^{1 2}. Depending on the pathophysiological mechanisms involved, there are two main forms of contact dermatitis:

- irritant contact dermatitis (ICD), expression of the chemical-physical irritant effect of a substance, able

to activate the skin innate immune system;

- allergic contact dermatitis (ACD), induced by an antigen which, in predisposed subjects, activates the acquired specific immunity by involving T lymphocytes, which mediate skin inflammation ².

Definition

ACD, or allergic contact eczema, is characterized by itchy and sometimes polymorphic cutaneous manifestations, which start in the seat of contact with virtually sensitiz-

ing substances. Depending on the evolving phase, acute, subacute or chronic-relapsing, the affection shows erythematous, edematous and vesicular lesions, erosive and secreting lesions, or sometimes infiltrate lesions ³.

Epidemiology

In the last years the epidemiology of ACD has been evaluated in different studies ⁴⁻⁶, although the results obtained from different study groups are difficult to compare, for performing patch tests with aptens which often vary depending on geographic and cultural differences of the interested population ⁴. The prevalence of ACD is different among the various countries, depending on climate characteristics, cultural abitudes, working activity and legislation which regulates the content of specific aptens (nichel, for example) in the artefact ⁷. However, it's clear that contact dermatitis represents a very common disease in daily practice, with an estimated prevalence, in all of its clinical forms, between 1% and 10% in general population ⁴. Approximately 10% of subjects has at least one episode of contact dermatitis in life ⁸. In the context of contact dermatitis, 80% is represented by irritant contact forms, while 20% are of allergic origin ⁹. Cohort studies conducted in general population in Europe have shown a prevalence rate between 0.7% and 18.6% for ACD, therefore representing a very frequent clinical event in the fields of both professional and outside work ⁹. Women are more frequently susceptible to the development of ACD compared to men, most likely because of the increased exposure to allergens (jewelry, cosmetics). Moreover, a different distribution of sensitization relatively to age and gender has been observed: women are more exposed in young age (20-30 years), while men in adulthood (50-60 years) ⁴.

Etiology

METAL-INDUCED ACD

The prevalence of allergy from metals in general population is high: it is estimated that 17-24% of women and 3-4% of men are allergic from nickel and that 1-3% manifests allergy from cobalt and chromium ^{10 11}. Although non-occupational environmental exposure to metals represent the predominant cause of ACD, due to contact with jewelry,

accessories, clothing, dentures and dental materials, cell phones (according to recent reports) and leather, the importance of exposure to such haptens in a professional environment must not be underestimated (Table I).

Nickel

In 2008, nickel, which is ubiquitous and highly resistant to corrosion and high temperatures, has been called "Contact Allergen of the Year" by the American Contact Dermatitis Society for its global importance as a hapten responsible for ACD ¹². Nickel is, indeed, among contact allergens, the most frequently implicated in the etiology of ACD over the past 30 years, with a growth trend which continues to increase in North America, amounting to 19% in 2006 ¹³. In Europe, on the contrary, the introduction of laws that regulate and limit the content of nickel and its release from metallic objects allowed, particularly in adolescents, a reduction in sensitization to the metal ¹¹. A recent Italian study conducted on a population of more than 15,000 subjects showed a different sensitization to nickel in both sexes (31.6% in women and 10% in men) and a higher prevalence compared to other European countries, presumably correlated to the delay in the application of the European directive in Italy ¹⁴. Nickel typically induces micropapulovesicular on a poorly erythematous base lesions, most often isolated or confluent in nummular patches. When introduced systemically in individuals already skin sensitized, nickel can cause systemic contact dermatitis. The occurrence of gastrointestinal allergy with or without associated cutaneous manifestations seems also possible ¹⁵.

Chrome

Hexavalent Chromium salts are responsible for ACD mainly in subjects occupationally exposed to cement. For this reason, the frequency of ACD from Chromium is higher in males, but during the recent years there has been a marked reduction in sensitization induced by this metal in a professional environment. Although mainly used for the realization of metal alloys, Chromium is also used in the textile industry and in the tanning of skins, this resulting in a relatively high incidence of contact allergy in extraprofessional environment ¹⁶.

Cobalt

Sensitization to cobalt, the prevalence of which is about 10.2%, is frequent among workers employed in the tex-

Tab. I. Haptens most frequently associated to ACD: objects/food as carriers and potentially exposed occupational categories.

Apteni	Objects	Food	Exposed occupational categories
Nickel	Metal clothing accessories: bra hooks, watchbands and watchcases, buckles, buttons Other personal use objects: keys, lighters, necklaces, earrings, glasses side pieces, kitchen utensils, coins, detergents, cosmetics Medical tools: infusion cannulas, surgical clips, dental prostheses and materials, cardiac stents	Nuts, legumes (peas, beans, lentils, soy), cocoa, herrings, oysters, prunes, peanuts, asparagus, spinach, corn, tea, mushrooms, pears, almonds, flour	Nickel platers, metalworkers, hairdressers, cooks, housewives, health workers, dentists, cashiers, goldsmiths
Chromium	Leather clothes and accessories, fur coats Personal use objects: soaps, perfumes, antiperspirants, shoe wax Other objects: chromed objects, concrete, varnishes, inks, detergents, adhesives, bleachers, oxidants, caustics, anti-rust, mineral oils, plastic materials, galvanic and chromed metals, lithography fixatives, chrome glues, matchsticks	Minimal quantities: potatoes, mushrooms, onions, apples, watercress, frozen peas, plums and prunes, boxed cereals and legumes, whole wheat, egg, spices, tea, beets, wine, cocoa, chocolate, meat, fish, dairy products	Construction workers, leather workers, textile workers, cleaners, metalworkers, typographers, dairy workers
Cobalt	Personal use objects: fashion jewelry, detergents, antiperspirants, cosmetics, hair dyes, tattoos pigments Other objects: concrete, metal alloys in prostheses, varnishes, inks, adhesives, lubricating oils and fats, pottery and glass dyes, polyester, fabrics	Beans, fava beans, beets, cauliflowers, apricots, nuts, liver, whole wheat, coffee, cocoa, tea, bear, vitamins and mineral salts supplements	Construction workers, textile workers, cleaners, typographers, hairdressers
Balsam of Peru	Personal use objects: as fragrance in soaps, cosmetics, lotions, perfumes; as antiseptic in topical medications, cough syrups and pills, patches	Oranges and lemons peel, candies, ice creams, drinks (Coca-Cola, orange soda), cocktails, chocolate, chewing-gum, sweets	
Parabens	Personal use objects: cosmetics, bandages, adhesives, detergents, shoe wax, shampoos, soaps, sun screens, topical medicaments	Drinks, fruit juice, long life food	
Paraphenylenediamine	Dark colored clothes, leathers and furs Personal use objects: cosmetics, permanent or semi-permanent hair dyes (dark blue), dark colored cosmetics Other objects: black rubber, printing ink, photo developing agents		Hairdressers, typographers, textile workers

tile industry, construction and working of leather, in the cleaners and hairdressers ¹⁵. It is possible, moreover, a contamination of products used for personal house hygiene. It is common to find a simultaneous sensitization to cobalt, nickel and chromium.

ACD INDUCED BY FRAGRANCES, COSMETICS AND DYES

Fragrance mix

Fragrances are the most common cause of allergy to cosmetics, with an incidence of 10.4% ⁹. They are rather complex, and fragrance substances can contain different chemical components often difficult to identify.

Balsam of Peru (Myroxylon pereirae)

It is a flavoring and perfuming substance, responsible for direct skin contact allergy. The balsam of Peru, also, for its antiseptic properties, is also contained in topical medications (ointments, cough syrups). In recent years, the prevalence of sensitization to this hapten has increased (11.9%) ¹³, especially among adult females ⁴.

Parabens (parahydroxybenzoic acid's methyl, ethyl, propyl and butyl esters)

They represent the most common preservatives in cosmetics, although their antibacterial and antifungal properties make them useful also in food and pharmaceutical industries. The risk of sensitization to parabens is greater in the case of use on wounds of the skin, rather than healthy skin.

Paraphenylenediamine

It is an aromatic amine which turns black for a process of oxidation. This dye is most frequently involved in ACD of hairdressers, as well as in subjects who dye their hair. Paraphenylenediamine is also used for coloring garments (furs, fabrics), cosmetics, rubber, inks and resins. It presents cross-reactivity with other derivatives of the "para" group (sulfonamide, benzocaine) and with an antioxidant used in rubber production (N-isopropyl-N'-phenyl-paraphenylenediamine).

DRUG-INDUCED ACD

The most frequently responsible drugs for ACD are antibiotics for topical use and especially neomycin (10%), contained in creams, lotions, ointments, eye and ear drops. Neomycin cross-reacts with gentamicin, kanamycin, streptomycin, and tobramycin. Among local anesthetics,

the benzoic acid its derivatives (benzocaine, procaine, dibucaine) are responsible for contact sensitization with antiemorrhoid creams, eye drops and mouthwashes. The non-steroidal anti-inflammatory drugs for topical use most frequently induce photosensitivity. Topical corticosteroids are also potentially sensitizing, with possible cross-reactivity between the various groups of different power ¹⁷.

Pathogenesis

ACD develops with a mechanism of delayed type IV hypersensitivity (cell-mediated) according to the classification of Gell and Coombs ¹⁸. Any substance is potentially capable of inducing contact allergy even if the capacity of sensitization is really variable depending on the structure of the substance itself ¹⁹. Generally it is a low molecular weight chemical which binds to epidermal proteins to become an antigenic determinant capable of eliciting the immune reaction ⁹.

GENETIC ASPECTS

The immunogenic activity of the various haptens is linked to the interaction between external factors (environmental, cultural, occupational, geographical and local) and individual predisposing moments. From a genetic point of view, both genes that encode protective cutaneous factors and genes involved in the mechanism of oxidative stress and inflammation seem to be particularly important in the genesis of ACD. The role of mutations of genes coding for the filaggrin (FLG) is very studied. The identification of a significant association between sensitization to nickel and some polymorphisms in the same gene is recent ²⁰: the sensitization has been put in relation with the deficiency in the skin of FLG, a strong nickel chelator. The role of genetic polymorphisms in determining the susceptibility to sensitization of the skin has also been studied for many genes encoding for some cytokines, such as TNF- α , IL-1 β , IL-1RA and IL-6 ²¹. Only the carrier TFA-308 seems to be more frequent among polysensitized subjects, while no effect was shown for other cytokines. In particular, it seems that TFA-308 is associated with an increased risk of sensitization to paraphenylenediamine ²² and chromium ²³ in builders, while some studies have shown the same carrier associated with ACD without antigen specificity ²⁴. More recently it

has been shown an increased risk of sensitization also associated with the polymorphism of the gene coding for IL-16 (IL-16-295* C/C)²⁵. Most contact allergens require metabolic activation on the skin to become immunogenic, although for some of them this process seems to be rather a mechanism of detoxification. For this reason, the association between polymorphisms of N-acetyltransferase (NAT) of the skin has been evaluated²⁶⁻²⁸. Those with NAT2*4 are rapid acetylators, while NAT1*10 is associated with slow acetylators²⁷. In one study it was shown association between NAT2 phenotypes slow acetylation and ACD in a case of sensitization to trichloroethylene²⁸.

IMMUNOLOGICAL MECHANISMS

Sensitization

It is likely that other factors besides genetic ones (atopic constitution, age, sex, race), such as environmental and local cutaneous (erosions, ulcers, wounds), are responsible for a easier allergic sensitization to certain haptens⁴. Once penetrated into the epidermis, these are captured by antigen-presenting cells (APC) and presented to T lymphocytes for the induction of specific sensitization. Two modes of antigen presentation are known. In the first one the hapten, to become a complete antigen, binds directly to MHC proteins (presentation process independent). While in the second one, the hapten binds in a first step to cystein or histidine residues of soluble or membrane-bound proteins: the modified protein is then internalized by the APC, processed and presented to T lymphocytes as metal-protein complex on MHC class II molecules. During the process of antigen-presenting, APC cells are activated and migrate to regional lymph nodes. During this phase some membrane proteins are upregulated (e.g., MHC or costimulatory molecules) and other are downregulated (e.g. E-cadherin): activation aspects which are very similar to those induced by common inflammatory processes. In the case of allergic sensitization the process is mediated mainly by activation of p38 MAPK and there are data on the involvement of activation of transcriptional actors such as NF-kappaB, ATF-2 and CREB²⁹. It is interesting to note that the activation process is dependent, for many aspects, on the type of sensitizing hapten. Indeed it has been demonstrated how both the NiSO₄ and CoCl₂ in dendritic cells induce expression of CD86, CD83, HLA-DR and CD40 and the production of IL-6, while

K₂Cr₂O₇ induces only a modest upregulation of CD86. Furthermore, there are observations that only NiSO₄ is able to induce production of IL-12p40 and, like CoCl₂, activation of MAPK and transcription factor NFkB: these activations, instead, don't follow the antigenic stimulation with K₂Cr₂O₇³⁰.

Elicitation and damage

With the presentation of antigenic determinants, T cells (especially CD8 and also CD4) generate hapten-specific cell clones (memory cells) that recirculate in the skin both in the epidermis (CD8 > CD4) and in the dermis. The patient is sensitized, and a subsequent contact with the allergen will lead to a further activation and expansion of both CD8 and CD4 T-cell clones. The activated CD8 cytotoxic cells directly attack keratinocytes and, in association with CD4 (both Th1 and Th2) induce, through the production of cytokines (IFN- γ , TNF- α , GM-CSF, IL-2, IL-4, IL-5 IL-10 IL-13) an amplification of the inflammatory process characterized by synthesis of additional pro-inflammatory cytokines (overall TNF-alpha and GM-CSF) and chemokines (IP-10, Mig, I-TAC, MCP-1 and RANTES) by keratinocytes themselves with the activation of the expression of adhesion molecules (ICAM-1). The result is a massive recruitment of T lymphocytes and their permanence in the epidermis. At this level, the activation of MHC class II molecules facilitates direct cytotoxicity on keratinocytes by Th1 lymphocytes, and the upregulation of MHC class I molecules (induced by IFN- γ) exponentially facilitates cytotoxicity mediated by lymphocytes CD8. Recent data have shown that the initiation process also involves other components of the immune system, such as the adaptive system, in particular NK cells and complement. Experimentally, the initiation process is activated in 30 minutes from the secondary stimulation with antigen³¹ and appears to be due to the production of IgM induced early during the phase of immunization³². The formed immune complexes lead to activation of complement via the classical pathway with local generation of C5a³¹. As a result, there is a local activation of mast cells and platelets^{33 34} with release of serotonin and TNF- α ³¹. These mediators increase vascular permeability and induce the expression of ICAM-1, which participates in the recruitment and activation of additional T-cell clones specific for the antigen. Few minutes after immunization there is also the activation of NKT³⁵ cells, which are able to produce, in

addition to INF- α and INF- γ , IL-4 that is also required for the activation of B-1 lymphocytes through ILRR STAT6 for the production of antibodies ³⁶. As a result of the inflammatory process, the skin shows characteristics eczematous lesions, with infiltration of mononuclear cells in the dermis and epidermis, intercellular edema between the keratinocytes (the characteristic spongiosis) and cellular damage of the keratinocytes themselves (7-).

Resolution phase of the process

The resolution of the immunoreaction is not simply a passive moment in the absence of an antigenic stimulus. Probably this process involves T-cells secreting IL-10, which counteracts the function of dendritic cells and T-cells ^{37 38}. IL-10-producing cells, regulatory T-cells (Treg) are essential also in control of allergic sensitization. Indeed, infiltrations of these cells into cutaneous sites of application of hapten in healthy subjects are described, whereas CD8 lymphocytes are the characteristic cells infiltrating the same sites in allergic subjects ³⁹. Treg cells are also involved in modulating the severity of cutaneous inflammatory reaction, which in part has also been reported to exhaustion/apoptosis of effector T cells. Treg cells are characteristically a subset of CD4+ cells, producing IL-10 and characterized by the coexpression of receptors CD25 and FOXP3, even if CD8 cells with suppressive/regulatory activity have also been identified, whose characteristics, however, are still not fully defined. Many authors postulate that there is an exaggerated response of effector-specific CD8 T-lymphocytes due to an inefficient T-lymphocyte regulation at the basis of allergic sensitization ⁴⁰.

Symptoms

From a clinico-morphologic point of view, ACD is characterized by eruptive polymorphism (multiple different lesions occurring simultaneously) as well as evolutive polymorphism (lesions changing over time) ⁴¹⁻⁴³. Itching represents the fundamental subjective symptom; it may vary in intensity depending on dermatitis extension and other individual factors.

ACUTE ACD

The dermatitis presents with erythemato-edemato-vesicular aspects. Erythema is rose-red or bright-red and shows

indistinct margins. Edema has variable intensity, more pronounced in case of palpebral, hands, feet and genitals involvement. Vesicles are pinhead-sized and contain clear serum; they easily rupture evolving into exudative erosions. Bullae may also be present in this phase.

SUBACUTE ACD

It is characterized by minute crusting and furfuraceous desquamation. Erythema and exudation decrease.

CHRONIC ACD

In this phase erythema is mild, no vesiculation can be observed and lesional margins are fairly well defined. Skin ridges and furrows are accentuated due to epidermal hyperplasia. Infiltrative plaques (lichenification) may appear, at times associated to hyperkeratosis. In cases of recrudescence, erythema and vesicles recur over the lichenified dermatitis

CLINICAL FORMS

ACD can less commonly manifest with other clinical forms:

- dry hand eczema. Palms and sometimes fingertips show dry and fine desquamating skin, overlying a mild erythema. This form is hardly differentiated from hand cumulative ICD;
- nummular ACD. Lesions are eczematous, rounded or ovalar, size 1-5 cm and show well defined borders.

Aeromediated ACD

In this form the environment dispersed offending agents reach the skin through air. These agents are mainly occupational and comprise vapors, fumes, driblets and solid particles. As they are air exposed, face (upper eyelids in particular), neck, décolleté and hands are the most commonly affected areas. In such a case differential diagnosis with contact photodermatitis is mandatory. Conversely, when driblets or solid particles are responsible, non-air exposed areas will also be involved, as these can impregnate and pass through clothing. Aeromediated contact can of course parallel direct skin contact: as a matter of fact the same substance can be air dispersed as well as directly manipulated.

Allergic contact photodermatitis

Sunlight, interacting with particular exogenous chemicals, can induce contact dermatitis at photo-exposed sites. The commonly involved substances absorb in

Tab. II. Clinical types of non eczematous contact dermatitis.

Erythema multiforme – like contact dermatitis
Lichenoid contact dermatitis
Pigmented contact dermatitis
Purpuric contact dermatitis
Lymphomatoid contact dermatitis
Bullous eruption
Granulomatous eruption
Pustular eruption
Erythematous-exfoliative eruption

the UVA range. The clinical traits are polymorphic, with erythematous-edematous-vesicular-bullous lesions. This form is itching, may involve covered areas and begins 24-48 hours after photo-exposition.

Contact erythrodermia

Skin in its entire extension is affected in this rare form. Eczematous erythrodermia can follow persistence of the offending agent, or rather as complication of topical drugs administered to treat a preexisting contact dermatitis. It represents a severe condition: the skin is dark-red, dry and extremely infiltrated and desquamating. Pruritus is intense and polyadenopathy is often noticeable. Respiratory and cardio-circulatory complications are possible. Differential diagnosis with erythrodermia of other etiologies is not straightforward.

Non eczematous ACD

ACD can fairly frequently present with non eczematous aspects (Table II), sometimes depending on particular haptens involved. Among the many, the most common forms are herein reported:

- erythema multiforme-like ACD. More commonly induced by drugs and plants. Diffuse lesions resembling erythema multiforme manifest far from the primary eczematous site, after a 1-2 weeks' time delay. Differential diagnosis is indeed against true erythema multiforme;
- purpuric ACD. Clinically similar to leukocytoclastic vasculitis, from which has to be set apart;
- lichenoid ACD. Characterized by a diffuse eruption of erythematous-papulous lesions. Differential diagnosis is against lichen ruber planus.

Systemic ACD

Dermatitis persistence, diffusion or recrudescence can be elicited by systemic introduction (pulmonary, gastroenteric, vesical, intravenous, intramuscular and prosthetic) of the offending agents or other chemically similar molecules. Systemic ACD presents as different entities and morphologies (hand dyshidrotic eczema, urticarial or erythematous-papulous exanthematous eruptions). Recurrence at positive patch test sites is also possible.

Diagnosis

Diagnosis of ACD relies on patient history, clinico-morphological features and allergy tests⁴³⁻⁴⁵.

PATIENT HISTORY AND CLINICO-MORPHOLOGICAL FEATURES

Patient history permits both clinical diagnosis and offending agent identification. Patient lifestyle, habits, hobbies, use of clothing and accessories, personal hygiene products, cosmetics and household detergents should always be assessed. Topical medicaments as well as systemic drug intake also have to be thoroughly investigated. A meticulous occupational history should be taken, ideally completed by a work place inspection to evaluate protective measures (gloves, masks, suits, safety footwear and barrier creams) and work environment conditions.

Lesions first localization, morphology, evolution and distribution can orientate towards the correct diagnosis. When multiple sites are involved, the firsts give a clue to identify the offending agent.

PATCH TESTS

Further than just a diagnostic tool, patch tests permit to recommend alternative preventive measures (therapy, cosmetics, gloves) which patients can benefit from. Several study groups have theorized the basis for the procedure standardization, which is today considered accurate, reproducible and easily managed. The traditional testing apparatus encompass the patch (support), the tape and the hapten, all of which are separately provided. Complete ready-to-use kits are however commercially available (Epiquick®, Rapid Patch Test® and TRUE TEST®)⁴⁶. Nowadays more than 3,000 contact allergens are known, and many other are continuously identified through predictive tests or during clinical practice. Optimal testing concentration is known for most haptens. A

series comprising ubiquitous and high allergenic potential haptens is usually employed. The current SIDAPA (Società Italiana di Dermatologia Allergologica, Professionale e Ambientale) standard series comprises of 25 substances (plus Vaseline), of which 23 in pet and 2 in water (formaldehyde and Kathon CG). Based on patient personal and occupational history as well as dermatitis localization, other set of substances can be tested. Regardless, the etiological diagnosis is often elusive. At times it is necessary to patch test substances and materials provided directly by the patient; this should be exclusively done in dedicated sanitary structures, specialized in allergological and occupational dermatology. Patch tests results should be read and interpreted by an experienced dermatologist. Hapten exposure time is usually 2 days. If a double test-reading appointment is feasible, it is useful to schedule it at 48 and 96 hours. In case of a single test-reading appointment, exposure can be prolonged up to 72 hours. Qualitative and quantitative assessment of patch tests response is based on a series of parameters established by SIDAPA⁴⁵. The fine morphologic structure of the allergic reaction, composed by minute vesicles and papules which can also be appreciated at palpation, should be homogeneously distributed over the test area. The reaction will tend to expand beyond the test site with ill-defined borders. Allergic reactions must further be interpreted according to clinical relevance⁴⁷. Dermatologist knowledge and experience are prime factors in such an interpretation. Patient history and clinical examination, in light of patch tests results, contribute in clarifying the issue in 80% of cases.

OPEN TESTS

They are indicated in ACD to define the etiological role of substances provided by patients, which could be irritant or possibly elicit systemic effects when put under occlusion. Compounds are diluted (max concentration 5%) in volatile solvents (such as alcohol, ether, acetone) or in water or directly tested (cosmetics, topical medicaments, food). Few drops (0,1-0,2 ml) of the solution or the original substances are directly applied over a 5x5 cm cutaneous area and removed by cotton or gauze 15 minutes after. Favorable test site are the scapular region and the forearm volar aspect. Test-reading is at 48-72 hours; positive reactions are erythematous-edematous-vesicular in morphology.

PROVOCATIVE USE TESTS

Provocative use test are convenient to assess the etiological relevance in cases of contact dermatitis with negative patch test to the suspected agent.

- **ROAT (*Repeated Open Application Test*)** - A minimum substance quantity (0,1 ml) (usually with the same concentration and vehicle used for patch test) is applied over a 5x5 cm area on the forearm volar aspect or antecubital area, twice a day until the reaction onsets and in any case no longer than 7 days.
- **Handling test** - The patient manipulates the suspected product for 15 minutes. Test-reading is at 48-72 hours.
- **Rubbing test** - The examined product is delicately rubbed against the forearm volar aspect for 15 minutes. Indications and test-reading times are the same as the handling test.

INTRADERMAL TESTS

Seldom used in clinical practice, they can be useful in cases of contact dermatitis with patient history and clinical aspects highly suggestive of contact allergy, but showing negative patch tests. Only non-irritant and saline solution-soluble haptens (metals in particular) can be used. 0.02-0.04 ml of solution with a 1:10.000 diluted hapten is injected. Test response becomes apparent, at 48-72 hours, as erythematous-papulo-nodular lesions, often accompanied by vesiculation and/or lymphangitis.

CHALLENGE TESTS

Contact dermatitis prompt resolution following withdrawal of the offending agent, alongside recurrence of the former after reintroduction of the latter, permits to identify the etiological agent when patch tests are negative. These tests do not discriminate between allergic and irritant contact reactions, must be executed in therapy free regimen and their results should be critically assessed.

Prognosis

Duration of contact allergy cannot be established in quantitative terms; therefore its prognosis in the general population is still unknown. Undoubtedly such prognosis has gotten better in recent years: the percentage of patch tests turning negative has reached values ranging from

18%-40%, meaning the dermatitis resolves in a third of all cases, even if after several years. ACD chronic course is influenced by many factors, especially the ubiquity of peculiar allergens, whose elimination is hardly feasible, and the lack of prevention rules application. Age at dermatitis onset and gender, on the other hand, do not seem to play a role. The higher tendency of hand dermatitis towards a chronic course in women would only be apparent, often dependent on the coexistence of contact irritation due to "wet" tasks. Personal skin atopy can certainly worsen ACD prognosis, whilst working activity changes would not seem relevant.

As relevant investigations have shown, ACD prognosis improves with patient education regarding preventing regulations; as a matter of fact patients should be seen every 1-2 years in order to optimize and update knowledge on their own dermatitis ⁴⁸⁻⁵³.

Therapy

The main objective of ACD therapy is to mitigate the acute phase inflammation, to oppose the subacute and chronic phases xerosis and to improve itching, which is present in all three phases.

Acute ACD, especially when exudative, must be treated with 1-3% sodium hypochlorite wet compresses (alternatively 0.5-1% silver nitrate or 0.1-0.2% potassium permanganate) twice to 4 times a day. 1% phenicated fuchsin and 1% gentian violet stains should be reserved to treat exudative skin folds. Subacute and chronic ACD benefit from systemic antihistamines and from the alternated use of topical corticosteroids and emollients/moisturizers. Oral corticosteroids or systemic immunosuppressants are indicated in diffuse, erythrodermic and non-responsive ACD forms. Nonetheless the fundamental factor in the therapeutic approach is the avoidance of the offending agent(s) and the adoption of appropriate preventive measures, such as: to use detergents free of potential allergic substances; to avoid to further irritate the skin with excessively frequent baths and the use of aggressive soaps; to wear white colored clothing and underwear, preferably made of cotton, silk or linen and lastly to regularly use creams with moisturizing, emollient and protective actions.

DETERSION

Toilet soaps, detergent milks and creams, fluid gels, shampoos, shower gels and bathing oils represent the most commonly used detergent products. These are frequently responsible of irritant reactions and, in certain cases, cause ACD due to substances they contain, such as preservatives, perfumes, colorants, metals and surfactants. In particular, epidemiological data demonstrate allergy to surfactants, which is caused by impurities, to be frequent ⁵⁴. Detergents free of potentially sensitizing substances should therefore be recommended to individuals affected by ACD; such products should nevertheless be used as infrequently as possible, water diluted and only applied in eczema-spared areas.

MOISTURIZING

Topical emollients and moisturizers represent the mainstay therapy for xerosis in the subacute and chronic phases of ACD. When applied several times a day, these products protect the skin against exogenous insults, improving the epidermis barrier function.

An emollient softens the skin through its action, which is primarily exercised on the stratum corneum. As such a product is applied, it distributes filling the lacunas among superficial keratinocytes, immediately soothing and giving relief ⁵⁵. What's more, emollients occlude the skin surface, thus impeding transepidermal water loss, making water accumulate in the outer layers of the stratum corneum ⁵⁶. Emollients exhibiting only occluding proprieties, such as vaseline, have a temporary action. Other substances with hygroscopic action, like glycerin and polyethylenglicole, reveal more useful as they attract water from the outer environment as well as from the vehicle carrying them ⁵⁷. Urea acts instead through an interaction between water and membrane proteins.

Emollients and moisturizers designed for individuals suffering from ACD should be simply formulated, and devoid of potentially sensitizing molecules, like perfumes or preservatives. For instance lanolin, a major emollient agent, must be avoided since it can produce an ACD.

CORTICOSTEROID THERAPY

Systemic corticosteroids are valuable only in diffuse and therapy resistant cases, or in the erythrodermic form. Dosage must be tapered after dermatitis remission until complete drug withdrawal. Sudden drug discontinuation

can indeed cause the “rebound” effect, with consequent dermatitis reactivation. Conversely topical corticosteroids, especially the non-fluorinated, are commonly employed in an alternated regimen alongside emollients and moisturizers. The different pharmaceutical formulations relate to the dermatitis clinical phase; creams are indicated in case of exudative lesions, ointments in case of dry or lichenified manifestations, while lotions and foams are suited for hairy skin sites. Topical steroids should not however be applied over vast cutaneous areas and for longer than 5-7 days, in order to avoid tachyphylaxis as well as systemic absorption with consequent potential adverse effects. Even if rarely, topical corticosteroids can prompt contact sensitization, which should be suspected when the dermatitis does not improve and possibly worsen when treated with these medicaments ⁵⁸.

ULTRAVIOLET RADIATIONS

Ultraviolet radiations (UV) act on lymphocytes, mast cells, keratinocytes and endothelial cells interfering with the release of certain inflammatory cytokines and with the expression of determined membrane receptors. They actually induce immunosuppression, many studies demonstrating the efficacy of both UVA and UVB therapy in the treatment of chronic ACD, especially when localized on the hands ⁵⁶.

ANTI-HISTAMINIC THERAPY

Antihistamines are used in ACD to control pruritus, which can at times be unbearable. First generation products cause central sedation, since they are lipophilic and show a marked sedative activity. Hydroxyzine is the H1-antagonist with the most pronounced anxiolytic, sedative and soporific effects. The sedation frequently outlasts the night and persists during the following morning, effectively reducing the cognitive functions in some individuals. Second and third generation H1-antagonist are instead lipophobic, thus they do not elicit central sedation. In severe ACD, the administration of a sedative antihistamine at night and a lipophobic one in the morning is advisable to better control the itching.

IMMUNOMODULATING THERAPY

Topical immunomodulators, such as tacrolimus and pimecrolimus, are currently authorized exclusively for the treatment of atopic dermatitis. However they represent a valid alternative therapy in ACD, especially indicated for certain skin areas as the periocular region, the face and

the neck. Tacrolimus and pimecrolimus block calcineurin-mediated T-lymphocytes activation processes, with ensuing inhibition of proinflammatory cytokines release. These drugs show efficacy comparable to topical corticosteroids, without the adverse effects (e.g. cutaneous atrophy) of the latter ⁵⁹. It must be noticed that topical immunomodulators can cause a transient skin burning sensation immediately following application. The association with the development of skin malignancies, which was initially fostered, seems to have finally receded ⁶⁰. Cyclosporine A is an option in diffuse and therapy unresponsive acute ACD, at the same dosage used in atopic dermatitis: 3 mg/kg/die ⁶¹.

RETINOID THERAPY

Alitretinoin, a vitamin A derived retinoid, has been shown effective in the treatment of adults affected by chronic hand eczema ⁶⁰. The drug is taken orally once a day for 3-6 months and determines significant symptoms decrease in 75% of cases. Already available in UK, Germany and Denmark and approved in other EU countries, it has also recently been introduced in Italy.

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