

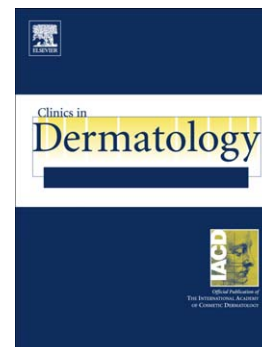
Accepted Manuscript

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PII: S0738-081X(16)30222-X
DOI: doi: [10.1016/j.clindermatol.2016.09.003](https://doi.org/10.1016/j.clindermatol.2016.09.003)
Reference: CID 7088

To appear in: *Clinics in Dermatology*



Please cite this article as: Bangash Haider K., Petronic-Rosic Vesna, Acral Manifestations of Contact Dermatitis, *Clinics in Dermatology* (2016), doi: [10.1016/j.clindermatol.2016.09.003](https://doi.org/10.1016/j.clindermatol.2016.09.003)

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Acral Manifestations of Contact Dermatitis

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ABSTRACT

Contact dermatitis is a broad term that encompasses both non-immunologic irritant contact dermatitis (ICD) and immunologically mediated allergic contact dermatitis (ACD). Both ICD and ACD can negatively affect a patient's quality of life and are a source of exorbitant medical and societal costs. Avoidance of inciting irritants and/or allergens and liberal use of emollients or humectants are the cornerstone of therapy. When an allergic cause is suspected, patch testing is highly encouraged. In this contribution, we highlight both the commonalities and differences of acral contact dermatitis as it relates to specific regions of the body. In addition, a review of the predisposing conditions, risk factors, and treatment options in the literature is presented to help with the care of these challenging patients.

List of abbreviations

Irritant contact dermatitis (ICD), allergic contact dermatitis (ACD), transepidermal water loss (TEWL), natural moisturizing factor" (NMF), stratum corneum (SC), atopic dermatitis (AD), Thin-Layer Rapid Use Epicutaneous Patch (T.R.U.E.), 2-hydroxyethyl methacrylate (HEMA), North American Contact Dermatitis Group (NACDG), methylchloroisothiazolinone/methylisothiazolinone (MCI/MI), methyldibromoglutaronitrile (MDBG), para-*tert*-butylphenol-formaldehyde resin (PTBPF), dimethylglyoxime (DMG), randomized controlled trial (RCT), Topical calcineurin inhibitors (TCI), 8-methoxypsoralen (8-MOP), ultraviolet B (UVB), psoralen with ultraviolet A (PUVA).

Introduction

Acral skin is that of the hands, feet, tip of the nose, and earlobes. There are unique features that are associated with contact dermatitis involving these sites. Acral skin protects us from the environment, while forming the basis of our interaction with it. Acral skin may facilitate transferring allergens to other parts of our body, most notably to the eyelids.

Acral contact dermatitis can broadly be divided into irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD). Other reactions include phototoxic and photo-contact dermatitis and contact urticaria.¹

Clinically, acral contact dermatitis initially presents with varying degrees of erythema and vesiculation that gradually progress to scaling, lichenification, and/or fissuring, as the dermatitis becomes chronic. Pruritus may be a prominent feature and can help differentiate it from mimickers.

Both ICD and ACD are dependent on a multitude of factors including climate, cultural practices, occupation, socio-economic status, geographic location, legislation, or availability of certain products or medications.

Acral dermatitis can result in significant effects on a patient's quality of life.² It may lead to substantial personal expenditure, loss of productivity, sick leave, and medical treatments. In addition, it may necessitate alternative occupations or even lead to unemployment. In a Danish study looking at sick leave and loss of job in occupational hand dermatitis, one-fifth of the patients (19.9%) required prolonged sick leave (> 5 weeks) and loss of employment over the previous year was reported in 22.9 % patients. Food related occupational hand dermatitis was the most frequent cause of prolonged sick leave and loss of employment.³ In a German study of 151 patients with hand dermatitis, this condition was associated with an average of 76.4 days (11 weeks) lost from work. This study also estimated "societal costs," including direct medical costs and indirect costs, approaching \$10,000 per patient.⁴ Interestingly, patients with hand dermatitis have been shown to develop alterations in their fingerprints that can lead to difficulty in recognition at fingerprint terminals, whether logging in at work⁵ or at security checkpoints.⁶

Histopathologic examination reveals the presence of the spongiotic reaction pattern. Both ICD and ACD may present with similar findings on pathology. The level of intraepidermal spongiosis can vary from mild to severe with variable amounts of dermal edema. Necrosis of individual keratinocytes may be present in ICD. Vesiculation, mild exocytosis and presence of eosinophils can be seen in ACD (Figure 1).

The reviewed literature was assessed for level of evidence and strength of recommendations, using the strength of recommendation taxonomy (SORT). With level 1 evidence, level 2 evidence and level 3 evidence, denoting high quality studies,

medium to lower quality studies and studies lacking sufficient quality, respectively. Similarly, the strength of recommendation was denoted by Grade A if based on consistent good quality evidence; Grade B if based on inconsistent or lower quality evidence, Grade C if it did not meet the aforementioned criteria.⁷

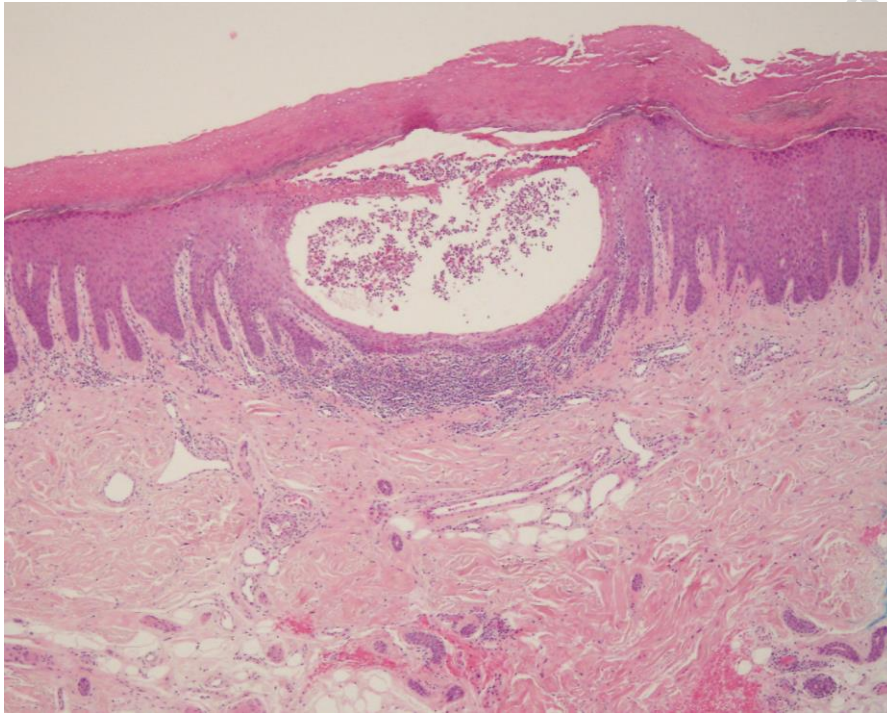


Figure 1: Contact dermatitis involving acral skin: compact hyperkeratosis, intraepidermal spongiosis, vesiculation, and presence of numerous eosinophils (H&E 4x)

Etiology, pathophysiology and risk factors

The stratum corneum (SC) forms the skin barrier, a two-way checkpoint that prevents transepidermal water loss (TEWL), as well as the entry of irritants or allergens. The individual corneocytes are packed in close approximation within the SC and have a complex layer of intercellular lipids including ceramides, cholesterol and free fatty acids. Corneocytes also contain “natural moisturizing factor” (NMF), which is a complex layer of lipids that enables them to retain moisture in the skin. The SC requires a slightly acidic environment to provide effective barrier function. Agents that interfere with the delicate acidic layer can result in alteration of normal lipid enzymatic metabolism, causing disruption of the skin barrier by alteration of sebaceous and eccrine secretions, and overgrowth of bacteria.⁸

ICD results from an imbalance of the regenerative capacity of skin and the constant barrage of irritants that break down this barrier. Wet work and detergents disrupt the lipid layer and NMF, and alter the pH of skin.⁹ The association of wet work or increasing frequency of hand hygiene with hand contact dermatitis can be appreciated as hand hygiene drives have been shown to increase the diagnosis of ICD in healthcare workers.¹⁰

Increasing evidence points to an unequivocal link of the filaggrin gene, located on chromosome 1q21, to atopic dermatitis (AD). In normal gene expression, pro-filaggrin molecules are converted to filaggrin monomers, which help with organizing keratin filaments within the epidermis. Additionally, its metabolites form NMF, which is essential in skin hydration. In one study from Denmark, 730 patients were selected through a questionnaire and then subsequently genotyped for the most common filaggrin loss of function mutations (R501X and 2282del4) via venous blood draws and utilizing polymerase chain reactions. Filaggrin null mutations were significantly associated with fissured hands and fingers but not with vesicular hand dermatitis. Interestingly, even though patients with null mutations were more prone to developing AD, hand dermatitis was independently associated with these mutations.¹¹ In other studies of patients with homozygous or heterozygous mutations of filaggrin, the presence of AD has been associated with persistent hand dermatitis and foot dermatitis.¹² Filaggrin null mutations have also been associated with the development of nickel sensitization. It has been hypothesized that filaggrin may help to chelate nickel ions. Ear piercings, therefore, may bypass this protective mechanism and allow nickel direct access to Langerhans cells in the dermis, causing sensitization in patients even without filaggrin mutations. This may explain why earlobe piercings are a greater risk factor for nickel sensitization than filaggrin mutations.¹³

History and clinical examination

A thorough and meticulous history is essential in teasing out the environmental, occupational, or social exposures that may be contributing to the dermatitis. A history of atopy should be sought.

Different scoring systems have been developed to assess the severity of hand dermatitis. The hand eczema severity index (HECSI) incorporates location and severity of the eruption and has shown good inter and intra-observer reliability.¹⁴ For occupational hand dermatitis, the Osnabrück Hand Eczema Severity Index (OHSI) and Manuscore systems were developed with good inter-observer reliability.¹⁵ In addition, a photographic guide has also been developed to assess hand dermatitis severity with good inter-observer reliability.¹⁶ These scoring systems are primarily used in epidemiologic and clinical studies and have limited utility in daily practice. We did not encounter any similar scoring systems for other acral sites in the literature.

Patch testing

Patch testing should be pursued for both adults and children with acute or chronic acral dermatitis, where an allergen is suspected of causing a delayed hypersensitivity reaction (Grade A recommendation). It is also recommended in treatment resistant acral dermatitis.

Different patch test panels are available in the USA and Europe. In the USA, patch testing is usually initiated with the standard 36 panel Thin-Layer Rapid Use

Epicutaneous Patch (T.R.U.E.) test (Table 1). The North American Contact Dermatitis Group (NACDG) has an 80-panel core allergen group that consists of 8 series in groups of ten. Series I-IV are similar to the composition of the T.R.U.E test, save for some minor exceptions. The other series (V-VIII) can be added on depending on the clinical presentation and patient exposures. For illustrative purposes, some allergens that are missing on the T.R.U.E test include fragrance mix II and iodopropnyl butylcarbamate, which were the 10th and 14th most common allergens respectively as reported in the NACDG patch test results from 2011-2012. That is one reason why a permutation of the NACDG 80 panel core allergen series can be pursued.¹⁷

All guidelines recommend multiple readings. The European Society of Contact Dermatitis guidelines recommend a minimum of 2 readings but preferably 3: on day 2, day 3 or 4, and near day 7.¹⁸ Day 3 or day 4 reading are deemed obligatory and the day 7 reading is preferred, as 7-30% of delayed reactions may be missed if the later readings are not performed. Common causes of delayed reactions include metals (gold, mercury, cobalt, palladium), topical antibiotics (gentamycin, neomycin, bacitracin), fragrances, preservatives, colophony, dyes (disperse blue), acrylates, methylchloroisothiazolinone / methylisothiazolinone (MCI/MI), *p*-phenyldiamine, diazolidinyl urea and corticosteroids.¹⁹ Expanded panels (e.g. cosmetic series)²⁰, can be utilized in patients with negative results and persistent symptoms or high clinical suspicion.²¹

There are limited scenarios, where patch testing should be deferred: if there is an active dermatitis at the site of application, if the patient is treated with significant amounts of immunosuppressive medications, if the area has recently been treated with topical corticosteroids, or if there has been ultraviolet light exposure to the area. Current treatments with topical corticosteroids, anti-histamines or even low levels of immunosuppression are not a contraindication to patch testing.

The utility of prick testing in patients with acral dermatitis is limited. It may be considered in patients with Ig-E contact urticaria from latex or other protein allergens.

T.R.U.E test panels		
Nickel sulfate	p-tert-Butylphenol formaldehyde resin	Diazolidinyl urea
Wool alcohols	Epoxy resin	Quinoline mix
Neomycin sulfate	Carba mix	Tixocortol-21-pivalate
Potassium dichromate	Black rubber mix	Gold sodium thiosulfate
Caine mix	Cl+Me- isothiazolinone (MCI/MI)	Imidazolidinyl urea
Fragrance mix	Quaternium-15	Budesonide
Colophony	Methyldibromo glutaronitrile	Hydrocortizone-17- butyrate
Paraben mix	p-Phenylenediamine	Mercaptobenzothiazole
Negative control	Formaldehyde	Bacitracin

Balsam of Peru	Mercapto mix	Parthenolide
Ethylenediamine dihydrochloride	Thiomerosal	Disperse blue 106
Cobalt dihydrochloride	Thiuram mix	2-Bromo-2-nitropropane-1,3-diol (Bronopol)

Table 1: Adapted from

<http://www.fda.gov/biologicsbloodvaccines/allergenics/ucm294326.htm> date of accession: 12/20/2015.

Common allergens and irritants to consider

According to the latest North American Contact Dermatitis Group Patch Testing results (2011-2012), 19.2% percent of individual with contact dermatitis had involvement of their hands and 3.9% had leg dermatitis. Overall 9.6% of patients were found to have contact dermatitis that was linked to their occupation.²² Close to two-thirds (63.8%) had shown polysensitization on patch testing. In this study the sites of involvement did not describe the allergens. Nevertheless, it may be useful to keep the most common culprits in mind when investigating a contact dermatitis for an acral site. Overall, the 15 most common allergens identified were; metals e.g. nickel (#1), Cobalt (#6); fragrances e.g. fragrance mix 1 (#2), fragrance mix 2 (#10), balsam of Peru (#4) and cinnamal (#15); preservatives e.g. formaldehyde (#7) quaternium-15 (#8), methylchloroisothiazolinone (#11), iodopropenyl butylcarbamate (#14), wool alcohols i.e. lanolin alcohol (#13), rubber chemicals e.g. carba mix (#12) and paraphenyldiamine (#9). When compared to the commonly utilized 36-panel T.R.U.E test, the sensitivity was estimated to be between 69.7% and 75.1%.

ACD is also observed in pediatric patients and patch testing can be utilized to detect potential allergens. According to a prospective Italian study (n=321; < 3years old) some commonly implicated allergens in pediatric patients included nickel sulfate (26.8%), potassium dichromate (9%), cocamidopropylbetaine (7.2%), cobalt chloride (6.2%), neomycin sulfate (5%) and methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) (4.4%). The prevalence for contact sensitivity was similar in patients with and without AD, 63% and 61.3% respectively.²³ Cocamidopropylbetaine is a detergent that is commonly found in shampoos, shower gels, and liquid soaps.²⁴

Hand dermatitis

The point prevalence of hand dermatitis is reported to be 4%, with the 1-year prevalence approaching 10%.²⁵ A recent review of the literature from North America and Western Europe identified nickel, fragrance mix, and thiomersol as the most common contact allergens affecting this site.²⁶

As with most contact dermatitis, ICD is more prevalent than ACD on the hands. Women were more prone to developing hand dermatitis, with highest rates reported in the 2nd and 3rd decades. AD was found to be the most important risk

factor for developing hand dermatitis, with one third of patients having a history of atopy. In some patients with atopy, hand dermatitis may be the only presenting feature.²⁵ Other risk factors reported were filaggrin mutations, nickel dermatitis, cigarette smoking, detergents, water and occupational exposures.²⁵ Nickel contact dermatitis has also been associated with hand dermatitis in women, with the prevalence of nickel allergy as high as 81.5% in some studies.²⁶ Common irritants for the hands include soap and water.

Occupational ICD has been shown to be more prevalent than ACD. Common irritants include wet work, gloves, mechanical trauma and oils.²⁷ ICD and pulpitis to acrylates or (methyl)acrylates have been reported in dentists, printers and fiberglass workers. Recently, acrylates have been identified as an important cause of ICD to artificial nails with nail technicians accounting for most of the cases. Screening via patch testing with 2-hydroxyethyl methacrylate (HEMA) has a sensitivity of 80.6%. Curiously, it is not a part of the T.R.U.E test. Suspicion of true acrylate allergy, thus, requires expanded patch testing.²⁸

Rubber gloves are a common cause of contact hand dermatitis in healthcare workers. The common sensitizers are changing in frequency as health care centers shift to latex-free alternative gloves. A recent study from Ireland looking into causes of contact dermatitis in the pharmaceutical industry identified thiurams in latex gloves as an allergen in 7 cases in addition to an unidentified allergen in nitrile gloves.²⁹ Another study identified rubber accelerators such as carbamates, thiurams, 2-mercaptobenzothiazole, and 1,3-diphenylguanidine (DPG), in decreasing order of frequency, as the most common sensitizers. Some alternative gloves that can be offered to patients include vinyl gloves, accelerator free nitrile gloves or neoprene gloves.³⁰

A recent cross-sectional, multicenter study from Italy identified food processing, health professions, craft and related trades (building, plumbing, electricians), hairdressing and beauty related work and handicrafts as the professions most commonly associated with chronic hand dermatitis.³¹ Workers in the pharmaceutical industry are also at risk for developing irritant and ICD.²⁹

Patients can present with varied clinical findings including scaling, hyperkeratosis, fissuring and vesiculation (Figures 2 and 3). A recent multicenter, cross-sectional, Danish study looking at the types of hand dermatitis classified 710 patients with hand dermatitis in 6 clinical groups: vesicular (rare and repeated eruptions), dry fissured, palmar hyperkeratotic, nummular, pulpitis and non-classifiable. They also examined the dynamics of the eruption and classified them as rare, recurrent, or permanent eruptions. In order of decreasing frequency the most commonly observed presentations were dry fissured (36.1%), vesicular with repeated eruptions (31.8%), non-classifiable (8.8%), nummular (7.9%), palmar hyperkeratotic (7.4%), vesicular with rare eruptions (5.9%) and pulpitis (2.2%). ICD was the most common etiology in dry fissured type (44.3%), pulpitis (41.7%) and nummular dermatitis (40.9%). ACD was the most common etiology in both the

vesicular subtypes (vesicular with repeated eruptions 35% and vesicular with rare eruptions 24.2%). Interestingly, no clear subtype was associated with AD even though 21.7% of the patients had a personal history of AD. A distinct clinical subtype that the authors identified was the hyperkeratotic palmar subtype, which was seen in older men and was not associated with ICD or ACD. Questionably, they differentiated this eruption from psoriasis by noting that these patients lacked the characteristic scaling of psoriasis and also did not exhibit psoriatic plaques on other sites.³²

A recently concluded retrospective study by the Danish Contact Dermatitis Group (DCDG) expanded on the work of Johansen *et al* and classified hand into 6 clinical subtypes: chronic fissured hand dermatitis, recurrent vesicular hand dermatitis, hyperkeratotic palmar dermatitis, pulpitis, interdigital dermatitis and nummular hand dermatitis. They identified nickel sulfate (18.8%) as the most common allergen on patch testing. Similar to the findings of elsewhere, recurrent vesicular hand dermatitis most frequently elicited positive patch-testing results. In contrast, hyperkeratotic palmar dermatitis and pulpitis subtypes were less likely to elicit positive reactions on patch testing. In contrast to the previously mentioned studies, a history of atopy was not associated with hand dermatitis. The most common allergens identified were metals (nickel sulfate, cobalt chloride), fragrances and preservatives (methylchloroisothiazoline /methylisothiazoline MCI/MI, methyldibromoglutaronitrile MDBG).³³

Non-inflammatory, clear vesicles and bullae located on the lateral digits, palms, and soles characterize pompholyx or dyshidrotic dermatitis. Although traditionally thought to be an endogenous condition, a recent prospective study from France identified a higher than expected prevalence of contact allergy in patients with pompholyx (67.5%). In this study, cosmetic or personal hygiene products e.g. shower gels, shampoos, fragrance etc., and metals, primarily nickel, accounted for 31.7% and 16.7% of the cases of “contact pompholyx”, respectively.³⁴ In light of these findings, patch testing may be advantageous in these patients as well.



Figure 2. Irritant contact dermatitis of the hand: superficial fissures and scaling involving the fingertips.



Figure 2. Allergic contact dermatitis of the hand: Deep fissures and thick hyperkeratotic scaling involving right hand.

Foot dermatitis

The prevalence of foot dermatitis varies widely and has been reported to be anywhere between 1.5% and 24%. Common culprits are shoe materials (leather, rubber, textiles, glues, and adhesives), hosiery, topical medications, and cosmetics (Table 2). Other factors that may exacerbate foot dermatitis include stasis dermatitis, occlusion, perspiration, heat and friction. A large retrospective review of over 10,000 patients identified 154 relevant ICD reactions with the North American Contact Dermatitis Group (NACDG) patch test panel. Rubber, adhesives and leather components were the most commonly implicated allergens. Overall, potassium

dichromate (31.5%) (Figure 4), para-*tert*-butylphenol-formaldehyde resin (PTBPFR) (17.1%) and cobalt chloride (12.9%) were the most common allergens in order of decreasing frequency of involvement.³⁵ In addition, colophonium, mercapto mix and mercaptobenzothiazole (MBT) have been implicated in causing allergic reactions.

In pediatric patients, a retrospective study identified MBT, mercapto mix, and potassium dichromate as the most commonly implicated allergens affecting the soles.³⁶

Potassium dichromate is used in the tanning/dyeing of leather shoes.³⁷ Glues and adhesives used in the shoemaking industry may contain PTBPFR and colophonium. Mercapto mix and MBT are used as accelerators for the vulcanization of rubber.²⁴ Remarkably, despite washing or boiling white cotton socks that have become contaminated with MBT, they can still elicit significant allergic contact reactions. It is logical to suggest that along with changing shoes patients should also be advised to change their socks.³⁸ Cobalt is a metal that is increasingly used in the leather dyeing industry and has been implicated in foot dermatitis.³⁹ Dimethyl fumarate (DMF) is a volatile powder that is utilized as a constituent of anti-humidity sachets in shoes and shoeboxes. It has been associated with severe contact dermatitis outbreaks in Europe and usually affects the dorsa of the feet and toes. Additionally, even if the sachets are physically removed, traces of DMF can remain imbedded in the packaged shoes for up to a year.⁴⁰ Commonly implicated rubber allergens include 4,4-dithiodimorpholine, thiuram mix and diphenylguanidine.⁴¹

Dyshidrotic dermatitis, tinea pedum, and psoriasis should be considered in the differential diagnosis of foot dermatitis.⁴² In the case of pediatric patients with dermatitis involving the soles, juvenile plantar dermatosis should also be considered.³⁶



Figure 4: Allergic contact dermatitis of the feet to potassium dichromate: hyperkeratotic plaques on the dorsum of the feet and toes.

Foot dermatitis		
Study	Allergens implicated	Comments
Landeck et al ⁴²	Potassium dichromate, <i>p</i> - <i>tert</i> -butylphenol-formaldehyde resin, colophonium, mercapto mix and mercaptobenzothiazole.	Reactions were more frequent in men. Products that elicited positive responses: shoes (27.5%), topical medications (24.4%) and cosmetics (16.8%)
Warshaw et al ³⁵	<i>p</i> - <i>tert</i> -butylphenol-formaldehyde resin, potassium dichromate, carba mix.	Common allergens included: rubber chemicals (40.4%), adhesives (32.5%), and leather components (20.1%).
Darling et al ³⁶	Mercaptobenzothiazole, mercapto mix, potassium dichromate, disperse blue106, Ethylene urea, Formaldehyde, glutaraldehyde, fragrance mix.	Reactions were more frequent in boys. Common allergens included: rubber accelerators and tanning chemicals.

Table 2: Commonly reported allergens in foot dermatitis.

Ear dermatitis

Metal jewelry is an important cause of contact dermatitis involving the ears (Figure 3). In particular, nickel allergy has been reported in close to 15% of adolescents.⁴³ It is also more frequently observed in women, as they have traditionally had higher rates of ear piercings. Ear piercings in adolescent girls has been associated with nickel sensitization and, interestingly, there is also an association with the number of ear piercings.^{43, 44} A study from San Francisco looking for the presence of nickel in low-priced earrings tested positive with dimethylglyoxime in 69% of purchases from local artists and 42.9% of tourist stores.⁴⁵ The dimethylglyoxime (DMG) test utilizes the property of this compound to change color to a bright red hue when it comes into contact with nickel salts (provided the release is $>0.5 \mu\text{g}/\text{cm}^2/\text{wk}$). False positive results have been reported with ferrous containing products. Furthermore, false negative reactions have been reported with cobalt containing products as the latter can bind to DMG and prevent it from reacting with nickel.⁴⁵ Substitute metals such as palladium and titanium may be used in patients with nickel allergy, as they have not been shown to elicit dermatitis.⁴⁶ Of note, limiting oral nickel intake in patients with nickel-induced earlobe ACD has not been shown to help with their

symptoms.⁴⁷ The European Union passed the nickel directive regulation in July 2001 as a method to limit the amount of nickel that is released from jewelry (no more than 0.5 μg nickel/cm²/week). Since that time the rates of ACD have decreased.³¹

Gold is a common irritant and was also named the allergen of the year in 2001. According to the North American Contact Group 9.5% of patients were reported to have a positive reaction to gold. It can cause localized contact dermatitis on the hands and ears, and is commonly seen with exposure to jewelry, with women more likely to elicit positive reactions. It is also seen in occupations where gold is mined, smelted or plated. The cutaneous reactions to gold may appear late and are also slow to subside once the allergen is removed. In addition, on patch testing, gold can often elicit delayed (up to 3 weeks later) and persistent reactions. Up to 31% of patients have been reported to have a positive reaction to the gold sodium thiosulfate hapten used in patch testing. Some authors have questioned the clinical relevance of these reactions, as patients may react to gold salts and not to gold foil or gold scrapings from jewelry. These factors make the interpretations of positive reactions to gold extremely challenging. In patients with a history of dental gold implants and relevant exposures it may be useful to consider testing for gold.²⁰



Figure 5. Allergic contact dermatitis of the earlobe to jewelry.

Treatment

There are several excellent guidelines available for the management of hand contact dermatitis.^{48, 49} Certain studies on hand dermatitis also include patients with foot dermatitis.; however, no specific guidelines exist for other acral sites and relevant literature is scant. Results from some of the well-conducted studies on hand dermatitis must thus be extrapolated to apply to other acral sites.

General measures

Physicians often counsel patients to avoid inciting allergens, either identified via history or confirmed by patch testing. Indeed, when compared to controls, patch testing and subsequent detailed individual counseling regarding avoiding relevant

allergens and adhering to gentle skin care recommendations (e.g. regular application of emollients, using cold or lukewarm water, minimizing wet work, using protective gloves, using disinfectants instead of detergents etc.) has been shown to improve hand eczema severity index in healthcare individuals with hand dermatitis.⁵⁰

In some cases, this advice may not be feasible, especially in patients with hand dermatitis, as they frequently have or can develop polysensitization to multiple allergens that is irrespective of AD status of the individual.⁵¹

Wet work should be limited and mild or gentle cleaners with a pH similar to the slightly acidic pH of the SC (5.5) should be used to prevent further degradation of the skin barrier.⁹ The mainstay of therapy is the liberal use of emollients and humectants (moisturizers) with or without occlusion. Emollients provide an occlusive layer that prevents TEWL. Humectants such as glycerol or urea help to retain water and moisturize the skin.⁵² Regular and liberal application of moisturizers may protect against developing ICD.⁵³ Thicker ointments are generally favored over creams, and bland petrolatum is less likely to cause sensitization as compared to the preservatives and emulsifiers found in creams. Individual moisturizers vary in the ability to prevent TEWL. In one randomized controlled trial (RCT), a “complex” 5% urea cream was shown to decrease TEWL as compared to a hydrocarbon containing cream. Furthermore, moisturizers are able to control the expression of different epidermal genes and affect the skin barrier directly.⁵⁴ A Cochrane review examined 4 RCTs (n=894) in individuals at risk for occupational ICD that were educated with gentle skin recommendations. Patients who were advised to apply barrier creams and moisturizers regularly, use gloves and follow other skin care recommendations did show a positive effect in the prevention of occupational ICD; however, this did not reach a level of statistical significance.⁵⁵

The use of gloves and personal protective equipment may be beneficial in cases of ICD; however, prolonged use of gloves may also exacerbate hand dermatitis, in which case, the use of a cotton liner glove is recommended.⁵⁶

Patients who fail treatment with the aforementioned interventions may benefit from topical corticosteroids, oral corticosteroids, oral retinoids, immunosuppressive agents, such as cyclosporine, phototherapy and even radiotherapy; however,, the strength of evidence regarding these approaches is variable as there is a dearth of good quality RCTs.

Topical corticosteroids

Topical corticosteroids are recommended as first line treatment for acral dermatitis (Grade A recommendation), because multiple studies have shown significant improvement in patients with hand dermatitis(Evidence level 1). Even short-term application of potent corticosteroids such as clobetasol can have a deteriorative effect on the skin barrier and can delay recovery. Fortunately, replacement of epidermal lipids through moisturizers helps to reverse this effect.⁵⁷ Once daily

application may be as effective as twice daily application and may reduce the incidence of side effects.⁴⁸ In an open label randomized trial, nearly 50% of patients had control of their hand dermatitis with daily mometasone furoate within 6 weeks. Twenty seven percent required a total of 6 weeks and another 25% required a total of 9 weeks. Those patients who cleared were split into three arms and treated with either intermittent thrice-weekly dosing, weekend dosing, or asked to use emollients only. Intermittent dosing was effective in reducing relapse rates (17% vs. 32%) when compared to patients who had been using emollients only (74%).⁵⁸

Topical calcineurin inhibitors

Topical calcineurin inhibitors (TCI) include topical tacrolimus and pimecrolimus. There is a paucity of RCTs looking at the utility of TCI in acral dermatitis. The efficacy of tacrolimus in ICD is equivocal, with some studies even supporting increased irritancy (Evidence level 2).⁵⁹

In a randomized comparative study, 30 adults with chronic hand dermatitis and positive patch testing to relevant allergens were treated with either topical tacrolimus 0.1% ointment or mometasone furoate 0.1% ointment. Both arms showed improvement and there was no statistical difference between the groups.⁶⁰ Therefore, tacrolimus may be a useful option in chronic contact dermatitis of the hands and allow the physician to circumvent the side effects associated with topical corticosteroids.

In a RCT looking at patients with moderate to severe hand dermatitis, patients were started on a 3-week course of oral prednisone and either asked to use topical tacrolimus or a vehicle. There was a statistically significant improvement in clinical symptoms (induration and scaling) and a non-statistically significant trend of prolonging the time to recurrence in the tacrolimus treatment arm; however, 69% of the patients had relapses. This study was limited by the small sample size of patients.⁶¹

Similarly, a double blind RCT evaluated pimecrolimus in achieving remission in patients with atopic hand dermatitis initially treated with a 3-week course of mometasone furoate 0.1% and then maintained either on pimecrolimus or vehicle control. Pimecrolimus treatment was not found to be superior when compared to vehicle controls.⁶²

Retinoids

Systemic retinoids are an effective option for patients with clinical manifestations recalcitrant to topical corticosteroids and particularly in the hyperkeratotic subtype of hand dermatitis.²⁶ (Evidence level 1)

Their use is limited primarily due to the untoward side effects in addition to the need for contraception and pregnancy monitoring in women. In a European multicenter, double blind RCT, alitretinoin (9-cis-retinoic acid) was administered daily to a total of 319 patients at a dose of 10 mg, 20 mg or 40 mg per day. After 3 months of treatment, dose related near or complete clearance was appreciated in

53% of patients treated with 40 mg per day; 41% in the 20 mg group and 39% in the 10 mg group. The response rate for placebo was 27%. Adverse effects were similarly seen more frequently in the 40 mg group, with headaches, dry lips, flushing, dry mouth, hyperlipidemia, decreased hemoglobin and decreased free thyroxine being the most frequently reported side effects.⁶³ Similarly, in a large multicenter placebo controlled RCT, 1032 patients were divided in 1:2:2 ratios for treatment with a placebo, 10 mg or 30 mg of alitretinoin daily for 24 weeks. Complete or near complete clearance was seen in 48% of patients on 30 mg, and in 27% of patients on 10 mg, compared with 17% for placebo.⁶⁴ Alitretinoin use is currently reserved for severe hand dermatitis not responsive to traditional therapies (Grade A recommendation). It is not approved for this indication in the U.S.A.

In a single blind RCT evaluating the use of acitretin in hyperkeratotic dermatitis of the palms, 30 mg of acitretin daily was administered to 14 patients, whereas 15 patients received a placebo. After 4 weeks of treatment, a statistically significant reduction of symptoms was documented in the patients treated with acitretin as opposed to placebo. Acitretin was well tolerated at this dose and no changes in blood work were reported.⁶⁵

Cyclosporine

The efficacy of oral cyclosporine versus topical betamethasone cream was evaluated in a double-blind RCT (n=41) in which one arm was treated with oral cyclosporine (3mg/kg) twice a day and the other was treated with placebo capsules and topical betamethasone dipropionate cream for a total of six weeks. Both arms showed improvement, with disease activity scores reducing to 57% of baseline in the cyclosporine arm and 58% of baseline in the bethamethasone dipropionate arm. The difference between the arms was not significant. Oral cyclosporine may be effective in patients who are non-responsive to topical corticosteroids (Evidence level 2), though they must be monitored closely for the development of hypertension and renal dysfunction.⁶⁶

Steroid sparing agents

When cyclosporine is not a viable option, other steroid-sparing agents such as azathioprine, mycophenolate mofetil or methotrexate can be considered, though the safety and efficacy of these agents in acral dermatitis has yet to proven in RCTs (Level of evidence 3).

A recent retrospective study demonstrated that low dose methotrexate (5-10 mg increased to 20 mg maximum per week) was effective in controlling hand dermatitis in 36.7% of patients by 8-12 weeks. The most effective response was seen in the hyperkeratotic hand dermatitis group (47.6%). Side effects and lack of response were the most common causes of discontinuation of therapy. The median time reported for the use of methotrexate without interruptions was 5.2 months.⁶⁷

Phototherapy

Both ultraviolet B (UVB) and psoralen with ultraviolet A (PUVA) phototherapy is used in patients refractory to topical treatments (Evidence level 2). In a 9-week comparative trial, both local narrow-band UVB and paint based PUVA thrice-weekly treatments were equally effective in controlling hand dermatitis, though the difference between the two modalities was not statistically significant. It is reasonable to start with NB-UVB treatments first and then progress to PUVA if there is no response (Grade B recommendation).⁶⁸

Home based tanning units that utilize ultraviolet A light may be used to circumvent the need for patients to follow up for office based light treatments. An open labeled RCT (n=158) reported that the efficacy of home based phototherapy sessions, utilizing portable facial commercial tanning units with oral methoxsalen capsules, was similar to hospital based PUVA sessions utilizing trioxsalen baths for the treatment of severe hand dermatitis. After 10 weeks, thrice-weekly sessions of home-based phototherapy resulted in 41% improvement, whereas twice-weekly hospital based phototherapy resulted in a 31% improvement.⁶⁹ This may be a viable option for patients who are unable to travel to an office based setting for their phototherapy treatments. It is reasonable to initiate therapy in the office setting for several weeks or months and document a beneficial effect prior to burdening the patient's insurance or personal finances with the purchase of a home phototherapy unit.

Ultraviolet A treatments are used with systemic oral photosensitizers, such as 8-methoxypsoralen (8-MOP), or topical 8-MOP baths, if the dermatitis is limited to the acral surfaces. Gels containing 8-MOP have also been used with good response in palmoplantar dermatitis. This is an attractive option because of the lower incidence of side effects, reduced costs and fewer organization requirements when compared to bath or systemic treatments.⁷⁰

Grenz ray treatment

Grenz ray treatments have been utilized for chronic severe hand dermatitis. In a retrospective study from Oregon, 73% of patients achieved moderate improvement with this treatment (mean 5.5 treatments; 21 Grays) with minimal side effects. More than half of these patients had psoriasis or palmoplantar pustulosis and the patients were not followed adequately to address the main concern for the development of skin cancer.⁷¹ At the present time most guidelines do not recommend the use of this modality.⁴⁸

Conclusions

Acral dermatitis presents a unique challenge in diagnosis and management. A meticulous and detailed history is essential to identify possible irritants and/or allergens. A skin scraping should always be performed to rule out tinea infections. If applicable, patch testing should be initiated to identify common allergens. Negative testing and high clinical suspicion may demand expanded patch testing. Patients should be counseled to avoid irritants and/or allergens. In addition, they should

receive extensive education on gentle skin care recommendations and the use of emollients and humectants. Topical corticosteroids are the logical starting point for therapy. If there is no response, phototherapy, systemic retinoids and steroid sparing agents are useful alternatives to consider depending on the clinical presentation and the patient's comorbidities.

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