Another Great Imitator: Allergic Contact Dermatitis Differential Diagnosis, Clues to Diagnosis, Histopathology, and Treatment

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Opinion statement

Allergic contact dermatitis (ACD) is a type IV (delayed) hypersensitivity reaction that has a wide spectrum of presentations that often imitate or overlap with other cutaneous eruptions. Differential diagnoses to consider include infections, skin lymphoma-malignancies, inflammatory dermatoses, nutritional deficiencies, and mechanical causes of tissue damage. We discuss clues to the diagnosis of ACD, such as pruritus, localization to the area of skin contact with the allergen, recurrence with repeat exposures, and supportive skin biopsy histology. Epicutaneous patch testing remains the gold standard for diagnosing ACD. Definitive treatment is contact allergen avoidance and, when indicated, dietary restriction. With these measures, most patients will improve clinically. In cases

where avoidance measures and interim topical therapies fail, ultraviolet light therapy or systemic immunosuppression may be considered.

Key points

1. Allergic contact dermatitis (ACD) is a type IV (delayed) hypersensitivity reaction with a range of clinical presentations.
2. Mimickers of ACD include infections, skin lymphoma-malignancies, inflammatory dermatoses, nutritional deficiencies, and mechanical causes of tissue damage.
3. Allergen avoidance, which might include dietary restriction, is the definitive treatment for ACD.

Introduction

Allergic contact dermatitis (ACD) is a cutaneous manifestation of delayed-type hypersensitivity (type IV) reactions, usually manifesting as pruritic eczematoid changes of the skin. Barrier defects further enable allergen entry, subsequent processing, and presentation of the allergen to naïve T cells by dendritic cells. This process is defined as “sensitization” and results in the clonal expansion of memory T cells. After repeated exposure to a particular allergen, the second “re-activation” phase of ACD, named “elicitation,” occurs. Depending on the level of sensitization and frequency of repeat elicitations, some patients develop intermittent dermatitis while

others develop a persistent dermatitis. The persistent dermatitis may expand from a localized presentation to a generalized dermatitis. In addition, a localized reaction may be diffuse or patchy within the exposed area, making identification challenging.

For diagnosis and definitive treatment ACD must be considered within a broad differential diagnosis, but the differential can be narrowed with careful history taking and clues found on physical examination. Herein, we discuss a differential diagnosis of ACD, clues to making the diagnosis, and finally a treatment algorithm for patients with disease refractory to avoidance measures.

Epidemiology

While ACD is known to affect a large percentage of the population, the exact prevalence in the general population is unknown. Estimations of contact sensitization prevalence have been calculated based on patch-tested populations with and without chronic dermatitis. In 2007, the estimated median prevalence of contact allergy in the general population was calculated at 21.2 %, with a weighted average prevalence of 19.5 % [1]. One group of patients that may not be included in these estimates includes those with acute dermatitis, such as with toxicodendron (poison ivy). These patients less commonly present for dermatologic diagnostic evaluation and are more likely to either self-treat or present to the primary care practitioner. The pediatric population is likely under-diagnosed, as the Food and Drug Administration (FDA) has not yet approved patch testing in kids. Also, in patients with concomitant diagnoses, such as atopic dermatitis, the secondary diagnosis of ACD may remain undiagnosed.

Although differences in presentation and allergens follow exposure patterns, ACD affects a large percentage of the population, young and old, all races, and both genders. Populations at higher risk for ACD include those with occupational exposure, such as hairdressers, veterinarians, and athletes. This risk is heightened

in individuals with underlying atopy or other chronic skin barrier defects.

Presentation

The eruption presentation is found on a spectrum of acute, subacute, or chronic. Poison oak is a prototypical example of acute cases, which displays microvesiculation, edema, and erythema. While chronic cases, such as those caused by personal hygiene products, tend to be more eczematous and less exudative in morphology, ACD can imitate a wide spectrum of cutaneous eruptions, from bullae formation mimicking bullous tinea to eczematous eruptions resembling irritant contact dermatitis, atopic dermatitis, asteatotic eczema, stasis dermatitis, and seborrheic dermatitis.

Diagnosis

The epicutaneous patch test remains the gold standard for diagnosing ACD. When positive patch test reactions are elicited, the potential relevance of the identified allergens to the dermatitis must be assessed. Exposure history to allergens, as well as correlation of relapses with exposures and distribution, should be noted.

When the diagnosis is in doubt and patch testing does not identify the relevant allergens or allergen avoidance fails to clear the eruption, skin biopsy for histopathologic examination may be helpful in distinguishing ACD from other conditions. Typically, in the very early stages of ACD, histology of lesional skin is characterized by spongiosis, usually most pronounced in the lower epidermis. Later, spongiotic vesicles may form at various levels in the epidermis. Infiltration of lymphocytes, Langerhans cells, and macrophages is seen in the upper dermis around superficial vessels. Eosinophils are frequently seen but their absence does not exclude ACD. Eosinophilic exocytosis is common in ACD. Chronic lesions reveal less spongiosis with more prominent epidermal hyperplasia, scale crust, and mild papillary dermal fibrosis. Hypergranulosis is often a feature in lesions that are rubbed. Spongiosis and vesiculation are much less common in chronic lesions [2]. A Periodic Acid-Schiff (PAS) stain can help rule out a dermatophyte infection.

Differential diagnosis

The differential diagnosis of ACD includes many dermatitides, such as atopic dermatitis, asteatotic eczema (eczema craquele), dyshidrotic eczema, erythrodermas, lichen planus, perioral dermatitis, psoriasis, rosacea, stasis dermatitis, seborrheic dermatitis and others.

The ACD reaction is usually localized to the area of skin contact with the allergen but may be diffuse or patchy within the exposed area. In either case, meticulous inspection of the distribution of an eruption is critical to diagnosis. For example, localization of the eruption to intertriginous areas should bring consideration of Hailey-Hailey, erythrasma, and candida. Groin ACD must be distinguished from extramammary Paget's disease, inverse psoriasis, and inverse lichen planus. ACD of the face, particularly around the mouth, may mimic nutritional deficiencies, periorificial dermatitis, or rosacea.

Photodistribution of an eruption can also be a valuable clue to the diagnosis as it often suggests an element of photosensitivity. This can be seen in polymorphous light eruption or an underlying autoimmune connective tissue disease, such as cutaneous lupus erythematosus. The cutaneous manifestations of dermatomyositis often involve skin overlying the extensor surface of joints, the shoulders, face, and anterior chest. There is often a component of poikiloderma. These patients may present with or without associated muscle symptoms.

However, the distinction between photodistributed and exposed area dermatitis (airborne dermatitis) can be a very difficult one to make [3]. Exposed area dermatitis involves the same areas usually spared in photodistributed dermatitis, such as behind the ears (Wilkinson's triangle), nasolabial folds, and under the chin. ACD to personal hygiene products (cosmetics, fragrances, and lotions) often mimic photosensitivity as they also affect the face, neck, and arms.

Papular eruptions may resemble folliculitis or Grover's disease. Common skin infections, including dermatophytes (tinea), scabies, and bacterial or pityrosporum folliculitis, should also be considered and treated. Widespread contact with an allergen or autosensitization may be confused for other causes of erythroderma, such as Sézary syndrome or pustular psoriasis. Importantly, a high suspicion must be maintained for malignant neoplasms such as mycosis fungoides (cutaneous T cell lymphoma) or extramammary Paget's disease, as well as paraneoplastic disorders including acquired ichthyosis.

Any history involving possible mechanical trauma to the skin may offer a clue to an irritant contact dermatitis (ICD) or intertrigo. A common example of ICD is chronic hand dermatitis. It is typically symmetrically accentuated on the dorsal hands from just proximal to the metacarpophalangeal joint down to the fingertips (apron sign). This is related to hand washing technique. A history of frequent hand washing and this cutaneous finding would suggest a primarily ICD-induced dermatitis. Protein contact dermatitis is also often on the hand but classically occurs within minutes of exposure. Additionally, recent medication changes (including supplements and other over the counter agents) should raise consideration of a drug eruption.

Underlying medical conditions such as bowel disorders or psychiatric conditions may predispose to nutritional deficiencies, which can cause ACD mimickers. A salient example would be pellagra (niacin deficiency), which can induce a photosensitive dermatitis (Casal's necklace). Biotin, zinc, and essential fatty acid deficiencies present differently and can be in the differential for diaper dermatitis in infants. They present with periorificial pustules and bullae that evolve into scaly and crusted erosions. ACD of the diaper area is often secondary to preservatives in topical preparations. Diaper dermatitis is often multifactorial with ICD frequently playing a role.

Prognosis

Definitive remission of ACD requires the correct diagnosis and avoidance of causative allergens. In addition, barrier maintenance and repair should be addressed for complete clearance. With these measures, the prognosis is excellent. However, patients may have different "thresholds" for reactivity, whereby

a minute amount of allergen may initiate a significant clinical response in more sensitive patients. These patients must observe strict adherence to avoidance measures to remit the dermatitis and symptoms.

Treatment

An algorithmic approach to the management of dermatitis in patients with clinically relevant positive patch tests can be found in Fig. 1, and a comparative review on treatment indications for the differential diagnosis is developed in Table 1.

Unfortunately, not all patients with positive patch test results will clear with avoidance recommendations. There are several possible reasons for recalcitrant dermatitis: the positive results may not have been relevant to the current dermatitis, the clinically relevant allergen was not captured on the patch test due to false negativity or due to not being a tested allergen, patient education/counseling and comprehension for complete allergen avoidance may have been incomplete, and other routes of allergen exposure may have not been identified; in some cases, complete avoidance is not possible. When avoidance fails,

Fig. 1. **a** Allergic contact dermatitis at 10×. **b** Cutaneous T cell lymphoma at 20×. **c** Dermatomyositis at 20×. **d** Grover's disease at 10×. **e** Hailey-Haley disease at 4×. **f** Intertrigo at 10×. **g** Irritant contact dermatitis at 10×. **h** Perioral dermatitis at 10×. **i** Tinea corporis at 20×.

Table 1. The differential diagnosis of allergic contact dermatitis

Differential diagnosis	Clinical setting/ characteristics	Distribution/ morphology of lesions	Mechanism	Histology	Treatment
Allergic contact dermatitis	Chronic/relapsing, potential correlation with exposure to offending allergen	Pruritic, erythematous papules/plaques with or without vesicles in region that came in contact with offending allergen, possible scales, and lichenification	Delayed-type hypersensitivity reaction	Acute: spongiosis, acanthosis, variable parakeratosis, superficial perivascular lymphohistiocytic infiltrate, eosinophils usually present, Langerhans cells microabscesses Chronic: acanthosis, hyperkeratosis, and often hypergranulosis. Eosinophils may be present	Avoidance. See discussion for treatment of recalcitrant cases.
Asteatotic eczema	Chronic, more predominant in older individuals, especially males, more common in the winter	Scaly, xerotic, erythematous, fissured skin, most commonly in the pretibial region	Dehydration of the stratum corneum leading to decreased cell volumes, decreased skin elasticity, increased epidermal water loss, and loss of barrier function	Slight spongiosis, superficial lymphohistiocytic infiltrate. Less likely to have hypergranulosis and eosinophils	Lipid-based emollient creams routinely; topical anti-inflammatory creams as needed.
Atopic dermatitis	Chronic/relapsing, possible atopic triad characteristics, possible family history, most often beginning in childhood or infancy	Pruritic, scaly, erythematous patches; distribution is variable and depends of type of atopic dermatitis and age of patient	Impaired epidermal barrier function, altered immune and inflammatory response to environmental factors	Acute: early lesions may be similar to subacute contact dermatitis with spongiosis, acanthosis, parakeratosis, superficial perivascular lymphohistiocytic infiltrate. Chronic: older lesions are often lichenified and	Lipid-based emollient creams routinely; topical anti-inflammatory creams as needed.

Table 1. (Continued)

Differential diagnosis	Clinical setting/ characteristics	Distribution/ morphology of lesions	Mechanism	Histology	Treatment
Cutaneous T cell lymphoma/ mycosis fungoides	Chronic, often progressive	Nonspecific erythematous or hypopigmented slightly pruritic to very pruritic patches often described as “cigarette paper” in texture and appearance, favoring the trunk and abdomen, possible lymphadenopathy	Malignant expansion of CD4+ T cells, cytokine-induced upregulation of dermal and epidermal adhesion molecules facilitating T cell migration into the skin	resemble chronic ACD with acanthosis, hyperkeratosis, and hyperkeratosis. Eosinophils may be seen, although, regardless of stage, would suggest a secondary etiology, like ACD Epidermotropism is more characteristic than exocytosis, as spongiosis is typically absent. Variable features include Pautrier’s microabscesses, disproportionate intraepidermal basilar or haloed lymphocytes with cerebriform nuclei and papillary dermal fibrosis	Topical anti-inflammatory creams; ultraviolet light therapy; topical nitrogen mustard derivatives; radiotherapy; oral retinoids
Dermatomyositis	Chronic, associated with muscle weakness and a myriad of extra-muscular manifestations, when presenting in adulthood may represent an intra-abdominal or other malignancy	Violaceous to erythematous heliotrope rash, violaceous papules and plaques over bony prominences, particularly the metacarpophalangeal joints, the proximal interphalangeal joints, and the distal	Genetic predisposition combined with environmental insults resulting in a humoral attack against the muscle capillaries and small arterioles	Interface dermatitis, with (sometimes subtle) vacuolar changes at the dermoepidermal junction, variable lymphocytic infiltrate, dermal mucin deposits	Internal malignancy screening; oral corticosteroids and immunosuppressive agents; topical sunscreens; topical anti-inflammatory creams

Table 1. (Continued)

Differential diagnosis	Clinical setting/ characteristics	Distribution/ morphology of lesions	Mechanism	Histology	Treatment
Dyshidrotic eczema	Chronic, recurrent, outbreaks potentially related to increased stress, seasonal changes, or certain allergens, may be associated with personal or family history of atopic dermatitis	interphalangeal joints, poikiloderma in a photosensitive distribution Tense, deep-seated, fragile, pruritic vesicles and bullae on the palms or soles	Exact mechanism unclear	Acral skin, prominent spongiosis with intraepidermal microvesicles, acanthosis, parakeratosis, superficial perivascular lymphohistiocytic infiltrate; can be very difficult to distinguish histologically from ACD or pustular psoriasis	Avoidance of frequent hand washing and restoration of skin barrier with lipid-based emollient creams routinely; topical anti-inflammatory creams as needed.
Enteropathic acrodermatitis	Presents in infancy with dermatitis, refractory diarrhea, irritability, and alopecia, family history is common	Erythematous, scaly patches in periorificial and acral distribution, often complicated by secondary infection	Autosomal recessive disorder affecting the ability for zinc uptake leading to zinc deficiency and dysfunctional epidermal development and maintenance	Confluent parakeratosis, hypogranulosis, pallor of the upper spinous layer, keratinocytic necrosis may lead to intraepidermal vesiculation, papillary dermis edema	Zinc sulfate or gluconate supplementation
Extramammary Paget's disease	Chronic, progressive	Pruritic erythema in the genitalia, perineum, axillae, or external auditory canal often leading to maceration, erosions, and excoriations	Primary cutaneous adenocarcinoma of apocrine glands	Acanthosis, hyperkeratosis, parakeratosis, often ulceration, pagetoid cells in nests in the lower epidermis extending up in pagetoid spread	Mohs micrographic surgery or wide local excision; topical imiquimod

Table 1. (Continued)

Differential diagnosis	Clinical setting/ characteristics	Distribution/ morphology of lesions	Mechanism	Histology	Treatment
Factitious dermatitis	Female predominance, more common in adolescents	Variable presentation; most commonly involved areas are face, distal upper extremities, and lower extremities; possible excoriations, erosions, ulcerations, and scaling erythema	Self-induced to fulfill unconscious emotional or psychological need	Spongiosis, acanthosis, parakeratosis, superficial perivascular lymphohistiocytic infiltrate; may see evidence of excoriation and ulceration; birefractile foreign material may be appreciated with a polarized light	Wound care; antidepressant, anxiolytic, or antipsychotic medications
Fixed drug eruption	Acute, following exposure to offending drug	Variable, round, ovoid erythematous or violaceous patches, sometimes with overlying blistering or desquamation with post-inflammatory hypopigmentation or hyperpigmentation after resolution, often favoring the lips and genitalia	Exact mechanism unclear, likely antibody-dependent or cell-mediated cytotoxic response	Normal basket weave stratum corneum without hyperkeratosis, interface changes with pigment incontinence. Acute lesions may have a lichenoid infiltrate of lymphocytes and eosinophils	Avoidance of offending medication.
Grover's disease	Acute, self-limited, predominantly affecting Caucasian men in the sixth decade or older	Erythematous macules predominantly on the chest, back, or abdomen, generally non-pruritic	Exact mechanism unclear, potential dysfunction or clogging of sweat ducts	Spongiosis, acanthosis, focal acantholytic dyskeratosis	Avoidance of exacerbating factors; topical anti-inflammatory creams, pramoxine, vitamin D analogue creams, oral antihistamines.

Table 1. (Continued)

Differential diagnosis	Clinical setting/ characteristics	Distribution/ morphology of lesions	Mechanism	Histology	Treatment
Hailey-Hailey disease	Chronic, often worse in the summer	Painful erosions and bullae in the intertriginous areas exacerbated by friction, heat, and moisture	Inherited ATP2C1 gene mutation causing desmosome dysfunction	Acanthosis, acantholysis involving most of the epidermis, minimal dyskeratosis	Loose clothing; topical anti-inflammatory creams with topical antimicrobial cleansers; monthly oral antifungal agents; may consider surgery for recalcitrant cases.
Intertrigo	Sub-chronic, effects primarily the very old and very young	Erythema with maceration affecting areas of skin folds, e.g., neck, axilla, inframammary region, and groin. Diaper rash in infants is prototypical	Secondary to friction, heat, irritation from sweat, urine, or stool	Laminated orthokeratosis, superficial perivascular lymphohistiocytic infiltrate	Protective barrier creams and powders; topical anti-fungal and/or anti-bacterial creams when needed.
Irritant contact dermatitis	Chronic, intermittent, temporally related to exposure to cutaneous irritants, often occupational	Macular erythema with scaling, possible fissuring. Effects the area that comes in contact with offending irritant, often dorsal hands with web-space involvement	Direct tissue damage	Spongiosis, neutrophilic infiltrate; may have necrotic keratinocytes	Avoidance, if possible, and protective barrier creams and lipid-based emollient creams routinely.
Lichen planus	Presents predominantly in the fourth to seventh decades of life, often associated with	Pruritic, classically polygonal, violaceous papules on the distal extremities, especially the	Exact mechanism unclear, immunologically mediated, known associations with	Orthokeratosis, hypergranulosis, lichenoid infiltrate with saw-tooth rete ridges, melanin incontinence, and an	Topical anti-inflammatory creams as needed. Screening for hepatitis C.

Table 1. (Continued)

Differential diagnosis	Clinical setting/ characteristics	Distribution/ morphology of lesions	Mechanism	Histology	Treatment
Periorificial dermatitis	chronic hepatitis C infection Increased prevalence in young females	wrists; may have oral involvement Non-pruritic papules, vesicles, and pustules on an erythematous base; may coalesce, predominantly in a perioral distribution	hepatitis C and HLA mutations Exact mechanism unclear; use of topical steroids and certain cosmetics may play a role	absence of parakeratosis and eosinophils Minimal epidermal changes, with mild acanthosis, spongiosis, and hyperkeratosis. Perivascular and perifollicular lymphocytic infiltrate, possible perifollicular abscesses	Discontinuation of topical corticosteroids. Oral tetracycline antibiotic.
Pityrosporum folliculitis	Chronic, affecting predominantly young to middle-aged individuals	Follicular-based erythematous monomorphic papules, predominantly on back, chest, shoulders, and scalp	Invasion of <i>Malassezia furfur</i> , part of the normal skin flora, into the ostium and deeper segments of the hair follicle causing cell-mediated inflammatory response	Dilated ostia of hair follicles with inflammatory infiltrate and keratin plugging; yeast spores but not hyphae are often seen on PAS staining	Topical anti-fungal creams or shampoo; systemic anti-fungal agents for extensive or recalcitrant cases.
Protein contact dermatitis	Chronic, intermittent, associated with contact with offending protein-containing plant	Erythematous, pruritic papules, and vesicles favoring the lower arms, dorsal hands, and fingertips, possible transient urticaria	Not completely understood, likely a combination of type I and IV hypersensitivity reactions and IgE-mediated hypersensitivity	Spongiosis, acanthosis, parakeratosis, superficial perivascular lymphohistiocytic infiltrate	Avoidance; topical anti-inflammatory creams as needed.
Psoriasis	Chronic, relapsing course	Scaly, thick, erythematous patches, plaques, and papules favoring the scalp,	Genetic factors causing abnormal excessive growth of epidermis	Hyperkeratosis, neutrophils in stratum corneum (Munro's microabscesses) and	Topical anti-inflammatory creams; vitamin D analogue creams;

Table 1. (Continued)

Differential diagnosis	Clinical setting/ characteristics	Distribution/ morphology of lesions	Mechanism	Histology	Treatment
		lower back, and extensor surfaces, nail dystrophy, Koebner phenomenon changes; specific forms of psoriasis have additional characteristic distributions		spinous layer (spongiform pustules of Kogoj), hypogranulosis, regular acanthosis, often with clubbed rete ridges, thinning of the suprapapillary plates with tortuous capillary loops in the dermal papillae	ultraviolet light therapy.
Rosacea	Chronic, increased prevalence in fair-skinned individuals with Northern European ancestry	Erythema with papules, flushing, and telangiectasias typically on the central face	Exact mechanism unclear, increased vasculature, dermal matrix degenerations, and Demodex mite infestation may all play a role	Perivascular and perifollicular lymphohistiocytic infiltrate, possible neutrophilic follicular infiltrate or granulomatous response	Topical metronidazole, azelaic acid, or sulfacetamide creams; oral tetracycline antibiotics.
Scabies infection	Acute, following exposure to mite	Superficial erythematous, pruritic linear or S-shape burrows favoring the web spaces of the hands, the wrists, genitalia accompanied by erythematous papules	Cutaneous infection by the mite, <i>Sarcoptes scabiei</i>	Eosinophilic spongiosis, hyperkeratosis, superficial and deep lymphocytic infiltrate; possible mites, eggs, larvae, or feces seen in the cornified layer	Topical permethrin 5 % cream, topical 10 % sulfur ointment, 25 % benzyl benzoate lotion, 10 % crothamiton cream or 1 % lindane lotion.
Seborrheic dermatitis	Chronic, intermittent, worse in winter and early spring	Scattered pruritic, erythematous, scaly patches, and plaques, sometimes with adherent crust, predominantly	<i>Malassezia</i> infection combined with immune dysregulation and increased sebum production	Mild spongiosis, acanthosis, follicular shoulder parakeratosis, superficial perivascular lymphohistiocytic	Ketoconazole 2 % shampoo and/or cream; topical anti-inflammatory creams as needed.

Table 1. (Continued)

Differential diagnosis	Clinical setting/ characteristics	Distribution/ morphology of lesions	Mechanism	Histology	Treatment
Stasis dermatitis	Chronic, progressive, slight female predominance; occurs almost universally in individuals over 50	Erythema, reddish-brown discolored patches on the lower extremity, predominantly on the medial ankles, edema, pruritus	Lower-extremity venous valve incompetency leading to venous insufficiency and stasis	infiltrate, possible neutrophilic crust, spongiosis of ostia or upper infundibula of hair follicles Spongiosis, acanthosis, superficial perivascular lymphohistiocytic infiltrate, increased number of upper dermal blood vessels with thickened walls, hemosiderin deposition, and fibrosis in the dermis	Compression stockings; topical anti-inflammatory creams as needed.
Tinea infection	Acute; may result from contact with infected animals or individuals	Mildly pruritic annular plaque or plaques with an advancing border	Cutaneous infection by various dermatophytes	Parakeratosis, acanthosis, spongiosis, and collections of neutrophils in the upper layers of the epidermis, fungi in the stratum corneum, highlighted by PAS staining	Topical anti-fungal cream.

Source: [2]

adjuvant management with topical and/or systemic treatment may be warranted to control disease activity [4•]. Of note, much of the working knowledge of the use of systemic immunosuppressants in severe refractory ACD is derived from the atopic dermatitis literature as well as the treatment of parthenium dermatitis, which is characteristically refractory in nature. In addition, allergen avoidance in patients with multifactorial dermatitis is unlikely to clear the other dermatitides without additional therapy.

Antihistamines

Antihistamines are generally safe and can be useful for relief of pruritus.

Topical and systemic corticosteroids

Evidence supports the continued use of topical corticosteroids as the mainstay of treatment of inflammatory, eczematous dermatitides, including ACD [5]. Long-term systemic corticosteroids use should be limited due to adverse effects. When possible, lower or taper the patient off of corticosteroids for patch testing, as they may suppress allergic patch test reactions [6].

Topical and systemic calcineurin inhibitors

Topical calcineurin inhibitors are effective options for topical steroid-sparing treatment of ACD. Pimecrolimus 1 % cream and tacrolimus 0.03 and 0.1 % ointments have been shown to inhibit T lymphocyte and dendritic cell activation and thus work to inhibit both ICD and ACD [7]. Furthermore, pimecrolimus 1 % cream, tacrolimus 0.1 % ointment, clobetasol propionate 0.05 % ointment, and triamcinolone acetonide 0.1 % ointment were found to be equal in their ability to suppress experimentally induced nickel contact dermatitis in one study [8]. Pimecrolimus 1 % cream and tacrolimus 0.1 % ointment have excellent utility in treating ACD of the eyelids and genital skin. These topical calcineurin inhibitors also inhibit inflammatory cytokines; this is thought to explain the anti-pruritic effects as well as the burning sensation or pruritus reported by some patients when treatment is initiated [9]. Mixing the medicine with a bland refrigerated emollient can mitigate the burning sensation with initial application and can be then titrated up as tolerated.

Cyclosporine is a systemic calcineurin inhibitor that has been shown to be rapidly effective for the management of moderate to severe atopic dermatitis as well as severe generalized dermatitis needing to undergo evaluation with patch testing [10, 11•]. It blocks activation of the c-Jun N-terminal kinases and p38 signaling pathways that are involved in T cell activation following antigen recognition [12].

Phototherapy (UVB, UVA)

Narrowband UVB and UVA light therapies are effective in several inflammatory dermatologic conditions, including atopic dermatitis, psoriasis, and hand dermatitis. Contraindications to treatment include photosensitivity, photo-contact dermatitis, photosensitive autoimmune disorders, the use of photosensitizing medications, and a history of non-melanoma skin cancer or melanoma.

Azathioprine

Azathioprine is a systemic immunosuppressive and anti-inflammatory agent useful for the treatment of dermatologic conditions with T and B cell over reactivity. It is considered a second-line option for moderate to severe atopic dermatitis [11•]. Thiopurine methyltransferase enzyme activity should be tested prior to initiation of treatment to determine correct dosing and identify individuals with susceptibility for side effects, notably pancytopenia.

Methotrexate

Methotrexate is a dihydrofolate reductase antagonist that provides immunosuppressive activity through inhibition of lymphocyte proliferation. Several trials demonstrate efficacy of methotrexate similar to azathioprine in the treatment of atopic dermatitis, with a significant improvement in several disease severity measures [13]. One small study of patients with parthenium dermatitis treated with methotrexate showed a decrease in disease severity after 1 month [14].

Mycophenolate mofetil and mycophenolic acid

Mycophenolate mofetil is a well-tolerated prodrug of the antimetabolite mycophenolic acid. Small studies have shown improvement in a majority of patients with refractory atopic dermatitis treated with mycophenolate mofetil [15].

Diet and lifestyle

Restrictive diets in sensitized patients' intake of nickel, balsam of Peru, and propylene glycol, have shown improved clinical outcome. The utility of diet modification in other cases of ACD remains controversial.

Pediatric considerations

ACD is as likely to occur in pediatric patients as it is in adults. The mainstay of treatment across all the ages is allergen avoidance. Notably, in the setting of atopic dermatitis, ACD is more likely to occur in children than adults.

Compliance with Ethics Guidelines

Conflict of Interest

Antoanella Calame declares that she has no conflict of interest.

Ashley Hamstra declares that she has no conflict of interest.

Jessica So declares that she has no conflict of interest.

Sharon E. Jacob served as an independent investigator on the safety and efficacy of T.R.U.E. Test™ (Smart Practice; Phoenix, AZ) panels 1.1, 2.1, and 3.1 in children and adolescents, Pediatric Research Equity Act (PREA-1) trial, and now serves as an investigator on PREA-2. She has served as a consultant for Johnson & Johnson. She has no conflicts of interest associated with the specific subject matter in this manuscript.

Carsten R Hamann is a first degree relative of Curt Hamann, owner of SmartPractice, a company that produces and sells diagnostic contact allergy products.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by the author.

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