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Contact dermatitis: a great imitator

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Abstract Contact dermatitis (CD) refers to a group of cutaneous diseases caused by contact with allergens or irritants. It is characterized by different stages of an eczematous eruption and has the ability to mimic a wide variety of dermatologic conditions, including inflammatory dermatitis, infectious conditions, cutaneous lymphoma, drug eruptions, and nutritional deficiencies. Irritant CD and allergic CD are the two main presentations of the disease. The diagnosis is based on a detailed history, physical examination, and patch testing, if necessary. Knowing the conditions mimicked by CD should improve the accuracy of the diagnosis. Avoiding the causative substances and taking preventive measures are necessary for the treatment.

Introduction

Contact dermatitis (CD) describes a group of skin diseases caused by contact allergens or irritant substances. CD is characterized by an eczematous eruption and can imitate many dermatologic conditions.[1,2] Irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD) are considered as the two subgroups of the entity. ICD is a nonspecific cutaneous reaction to the direct tissue damage after a single or repetitive exposure to an irritant substance, whereas ACD is an immunologic response to exogenous contact antigens and is considered as a delayed (type 4) hypersensitivity reaction.[2] This review focuses on the diagnostic clues and the differential diagnosis of CD as one of the great imitators in dermatology.

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Epidemiology

CD can be seen at any age, and its estimated prevalence ranges from 1.7% to 6.3% in various published studies.[3] It is more common in urban areas, with the incidence being higher in women and the elderly.[3] Many studies, however, suggest that sex and age cannot be considered as independent risk factors for CD. Varying professional and household activities in women and the elderly may explain the higher incidence.[3] Occupation is the strongest risk factor for developing CD, and 80% of the occupational dermatitides are ICD.[2] Individuals with an atopic diathesis seem to be more susceptible to CD.[2]

Etiology

Almost any substance may cause irritant dermatitis; however, concentration and duration of the contact agent determine the likelihood of ICD. Environmental factors,

including dry air and high temperature, can increase the irritant effect of a contact agent. Solvents such as alcohol and xylene, metal working fluids, rubber gloves, sodium lauryl sulfate, hydrofluoric acid, alkalies, and plants are well-known causes of ICD. Continual or repetitive exposure to mild irritants, that is, water and cleansing gels, is also a common culprit for ICD and is known as cumulative ICD.[2,4–6]

Nickel, neomycin, cobalt, fragrance mix, balsam of Peru, thiomersal, and formaldehyde rank high as the common allergens causing ACD.[2,7]

Pathogenesis

ICD is the result of activated innate immunity to direct damage of the skin without prior sensitization. Skin barrier impairment, epidermal cellular changes, and release of such proinflammatory mediators as IL-1α, IL-1β, TNF-α, IL-6, and IL-8 from keratinocytes in response to chemical stimuli are main pathogenic factors for ICD.[8] Previous sensitization to the contactant is unnecessary for the development of ICD.

Skin contact with the allergen is the first step in the pathogenesis of ACD. The allergen then penetrates the horny layer of the skin, where the Langerhans cells migrate toward the regional lymph nodes, and the antigens are presented to the T lymphocytes (the sensitization phase). Activated T lymphocytes produce various chemical mediators, including interferon-γ, creating antigen-specific inflammation (the elicitation phase).[9] Only previously sensitized patients who have produced allergen-specific T lymphocytes can develop ACD.[10]

Clinical manifestations

Burning and pain are the main clinical manifestations of ICD, although itching can also occur, which is more common and prominent in ACD.[10] CD usually presents with an eczematous eruption; however, noneczematous CD can also be infrequently seen. The morphologic spectrum of both eczematous ICD (Figure 1) and ACD (Figure 2) includes acute, subacute, and chronic presentations. The acute stage should show erythema, edema, and vesiculation. Crusts and scales are the main findings of the subacute phase, whereas lichenification is limited to the chronic phase.[2,10]

No clinical findings ostensibly exist for the differential diagnosis between ICD and ACD; however, ICD is usually limited to the contact site, whereas ACD can occur elsewhere. The time interval between contact of the agent and the onset of eruption is another clue in the differential diagnosis. Acute ICD usually develops within minutes to hours after exposure to the irritant, whereas ACD generally becomes evident 24 to 96 hours after contact with the allergen.[10] The main differences between ACD and ICD are summarized in Table 1.

CD can be seen anywhere on the body, but hands are the most common sites for both ACD and ICD.[2]

Noneczematous contact dermatitis

Noneczematous CD is rare, but the diagnosis can be very challenging, as it has the ability to imitate many dermatologic diseases. Noneczematous patterns of CD include erythema-multiforme-like, lichenoid, urticarial, papular, pustular, pigmented, purpuric, granulomatous, and lymphomatoid eruptions (Table 2). Both ACD and ICD may show these noneczematous patterns; however, most of the reported noneczematous CD cases may be considered as forms of ACD.[11]

Erythema-multiforme-like allergic contact dermatitis (urticarial allergic contact dermatitis)

Erythema-multiforme-like ACD, is the most common form of noneczematous CD.[12] It is characterized by targetoid, urticarial, and vesicular lesions. Medications, exotic woods, and ethylenediamine are the common causative agents. Early lesions show the classic eczematous morphology at the contact site. The erythema-multiforme-like eruption occurs 1 to 15 days after the initial eczematous lesions.[11] Classic urticaria, contact urticaria, and erythema multiforme are the main differential diagnoses. Lack of typical histologic findings of erythema multiforme, such as epidermal dyskeratotic cells or interface dermatitis, is an important clue for erythema-multiforme-like ACD. The diagnosis is mainly based on positive patch testing with the suspected allergen. The patch test reaction is usually of the eczematous type; rarely, it can be urticarial.[12,13]

Lichenoid allergic contact dermatitis

Lichenoid ACD is characterized by itchy lichen-planus-like papular lesions at or away from the contact area. Mucosal lichenoid CD resembling oral lichen planus may also be seen. P-phenylenediamine, which is used in henna tattoo and photographic film processing, is the most common cause of cutaneous lichenoid CD. Amalgam, gold, and copper, used in dentistry, are the main causes of mucosal lichenoid CD. Pigmented photocontact lichenoid dermatitis caused by photosensitization by fragrances is also known. Histologically, there are epidermal spongiosis and eosinophilia, despite the dermal lichenoid band infiltration. Paucity of inflammatory infiltration, may differentiate lichenoid ACD from lichen planus.. The diagnosis is mainly based on the positive patch or photo-patch testing with the suspected allergen. The patch test usually shows an eczematous reaction; it rarely can be lichenoid.[11,12]

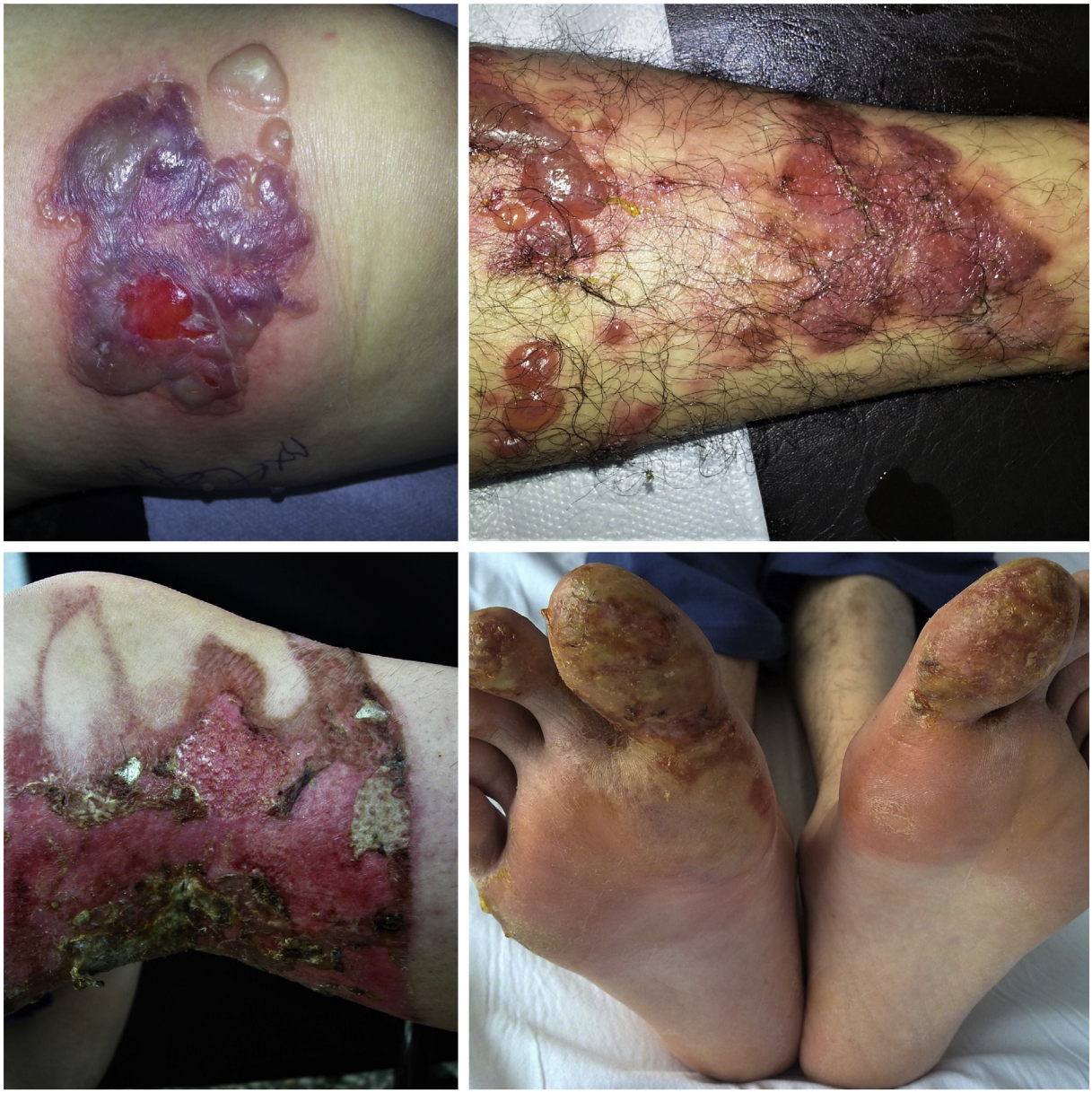

Fig. 1 Irritant contact dermatitis on different sites.

Bullous allergic contact dermatitis

Bullous ACD (Figure 3) is characterized by blistering at the contact site, possibly suggesting bullous pemphigoid, bullous impetigo, or bullous arthropod reactions. Histopathologic examinations and direct immunofluorescence testing may be needed to exclude autoimmune bullous disorders. The more common contactants include cinnamic aldehyde, cinnamyl alcohol, bufexamac, and thimerosal. The diagnosis is confirmed by positive patch testing, which may create a vesicular eruption.[11,14]

Pigmented allergic contact dermatitis

Pigmented ACD includes ill-defined spotted or reticulated hyperpigmentation. It is often observed in patients with Fitzpatrick II or higher. Pigmented cosmetic dermatitis is a well-known presentation of pigmented ACD and usually associated with cinnamic alcohol derivatives, dyes, and carbanilide- and bactericide-containing soaps. Riehl's melanosis is considered as a form of pigmented CD caused by cosmetic sensitizing fragrances and chemicals. Poikiloderma of Civatte (Figure 4), which is often associated with photocontact sensitivity to perfume ingredients, may also be considered as a pigmented CD.[15] The entity is characterized by mottled hyperpigmentation and dilation of the fine blood vessels on the sides of the neck. It typically spares the sun-protected area under the chin.[16] Although PCD and RM are often considered as the same disease, recently it has been suggested that PCD may be accepted as a separate entity as it has distinct histological features such as marked dermal dilated vessels.[17]

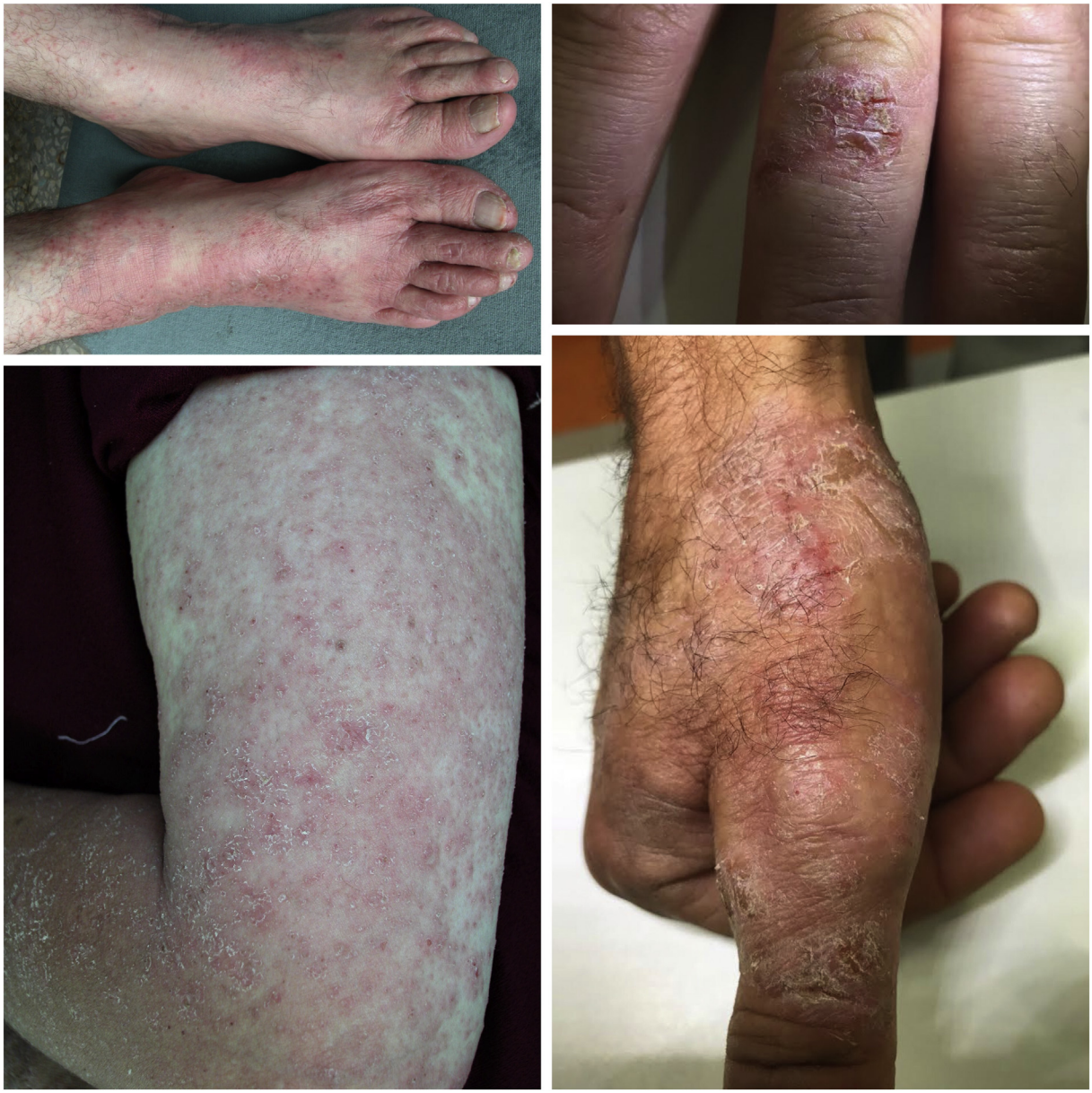

Fig. 2 Allergic contact dermatitis on different sites.

Optical whiteners used in washing powders can also cause pigmented ACD. Frictional melanosis, primary cutaneous amyloidosis, fixed drug reaction, and pigmented lichen planus may have similar presentations. Atrophic epidermis, basal vacuolar degeneration, and pigment incontinence are the main histologic findings in PCD. The diagnosis is based on the positive patch testing with the suspected allergen. The test usually shows an eczematous reaction, but pigmentation on the test area can also occur. A photo-ACD may also be developed due to photo-contact sensitization to fragrances, which may be confirmed by photo-patch testing besides patch testing.[11,12,18,19]

Purpuric allergic contact dermatitis

Purpuric ACD (Figure 5) is characterized by macular petechial-purpuric lesions at the contact site with no accompanying bleeding diathesis. Over time, the color of the eruption turns brown and fades away. Isopropyl-*N*-phenyl-p-phenylenediamine, present in clothing with elastic in various forms, boots, and elastic bandages, is the main culprit. Balsam of Peru, proflavine, oxyquinoline, and benzoyl peroxide and optical whiteners may also be considered. Vasculitis, bleeding diathesis, and pigmented purpuric dermatosis are the main differential diagnoses. In addition to spongiotic

Table 1 The main differences between ACD and ICD

Variables	ICD	ACD
Clinical manifestations	Burning sensation, pain	Itching
Site	Limited to the contact area	Limited or not limited to the contact area
Time of occurrence	Within minutes to a few hours after exposure	24-96 hours after exposure
Patch test	Negative	Positive
Histopathology	Epidermal necrosis, spongiotic dermatitis	Spongiotic dermatitis
Key pathogenetic mechanism	Direct irritant-toxic effect of the contact agent	Activated antigen specific T lymphocytes

ACD, allergic contact dermatitis; ICD, irritant contact dermatitis.

dermatitis, erythrocyte extravasation and lack of a leukocytoclastic vasculitic process are the histologic clues for purpuric allergic CD. The diagnosis can be made through a positive patch testing, which usually shows an eczematous reaction although purpuric reaction has also been reported.[11,12]

Granulomatous allergic contact dermatitis

Granulomatous ACD (GACD) is characterized by solitary or grouped reddish-to-brown shiny papular or nodular lesions that develop 4 to 6 weeks after the initial eczematous eruption at the contact site. Zirconium-containing deodorant associated GACD is the best known example of this entity. Aluminum-hydroxide-containing vaccines, mercury, chrome, cobalt, cadmium-containing tattoo dyes, titanium-containing pacemakers, and gold- and palladium-containing jewelry are other recognized causes. Beryllium and extravasated intravenous hirudin have also reported to be causative agents. The main histologic finding of GACD is sarcoidal granulomas, and it may be almost impossible

Table 2 Noneczematous contact dermatitis: main clinical findings, causative agents, and differential diagnoses

Noneczematous allergic contact dermatitis	Main clinical findings	Causative agents	Differential diagnosis
Erythema-multiforme-like allergic contact dermatitis	Targetoid, urticarial and vesicular lesions	Medications, exotic woods, and ethylenediamine	Urticaria, contact urticaria, erythema multiforme
Lichenoid allergic contact dermatitis	Itchy lichen-planus-like papular lesions, mucosal lichen-planus-like lesions	P-phenylenediamine, amalgam, gold, and copper	Lichen planus, lichenoid drug eruption
Bullous allergic contact dermatitis	Localized bullous eruption	Cinnamic aldehyde, cinnamyl alcohol, bufexamac, thimerosal	Bullous pemphigoid, bullous impetigo, bullous arthropod reactions
Pigmented allergic contact dermatitis	Poorly defined spotted or reticulated hyperpigmentation	Cinnamic alcohol derivatives, dyes, and carbanilide- and bactericide-containing soaps	Frictional melanosis, primary cutaneous amyloidosis, fixed drug reaction, pigmented lichen planus
Purpuric allergic contact dermatitis	Macular petechial-purpuric lesions	Isopropyl-*N*-phenyl-p-phenylenediamine, balsam of Peru, proflavine, oxyquinoline and benzoyl peroxide, and optical whiteners	Vasculitis, bleeding diathesis, pigmented purpuric dermatosis
Granulomatous allergic contact dermatitis	Solitary or grouped reddish-to-brown shiny papular or nodular lesions	Zirconium, aluminum hydroxide, mercury, chrome, cobalt, cadmium, titanium, gold, and palladium	Sarcoidosis, cutaneous tuberculosis lymphocytoma cutis
Lymphomatoid allergic contact dermatitis	Itchy erythematous papulonodular eruption	Gold, aluminum hydroxide, nickel, cobalt, diaminodiphenylmethane, and ethylenediamine dihydrochloride	Cutaneous lymphomas, lymphocytoma cutis
Pustular allergic contact dermatitis	Sterile pustular lesions on an erythematous base	Disperse blue, disperse red, nitrofurazone, isoconazole, minoxidil, and merbromin	Acute generalized exanthematous pustulosis, subcorneal pustular dermatosis, palmoplantar pustulosis, pustular psoriasis
Papular/follicular allergic contact dermatitis	Grouped papular or follicular lesions	Nickel, polyoxyethylene lauryl ether, formaldehyde, and vitamin E	Lichen nitidus, papular sarcoidosis, folliculitis, polymorphous light eruption

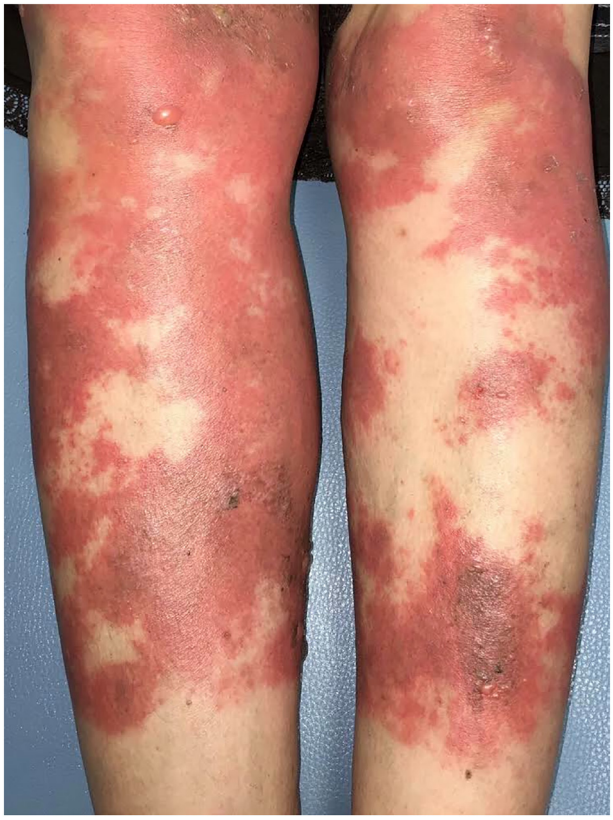

Fig. 3 Bullous allergic contact dermatitis caused by *Plantago* spp.

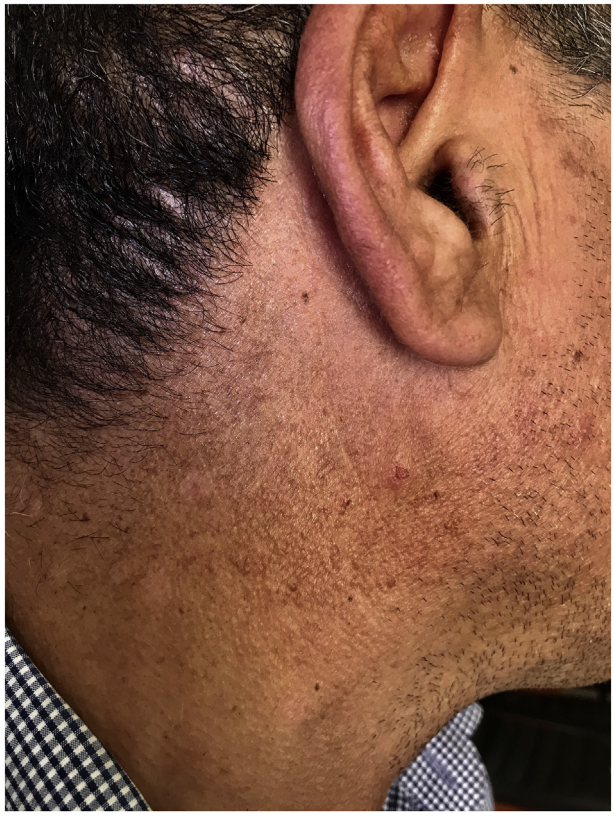

Fig. 4 Poikiloderma of Civatte showing mottled pigmentation on the neck.

to differentiate it histologically from sarcoidosis. The diagnosis is based on the positive scratch patch test with the suspected allergen. The test is considered to be positive if a reddish-to-brown papule occurs at the test site within 4 weeks after the testing.[11,20]

Lymphomatoid allergic contact dermatitis

Lymphomatoid ACD is characterized by an itchy erythematous papulonodular eruption at the contact site. Gold earrings, vaccines containing aluminum hydroxide, and dentistry materials are the known causes. Cases associated with nickel, cobalt, diaminodiphenylmethane, and ethylenediamine dihydrochloride have also been reported. Histologically, there may be spongiotic dermatitis pattern and dense dermal lymphomonocytic infiltration mimicking mycosis fungoides. Absence of atypical lymphocytes may exclude true lymphoma, only after confirmation with a broad panel of immunohistochemical staining. The diagnosis can be made through a positive patch testing, which usually shows an eczematous reaction.[11,21]

Pustular allergic contact dermatitis

Pustular ACD is characterized by sterile pustular lesions on an erythematous base at the contact site. Pustular ACD is one of the common causes of textile dermatitis and is usually associated with such fabric dyes as disperse blue and disperse red. Nitrofurazone, isoconazole, minoxidil, and merbromin are the other recognized contactants. The differential diagnoses include secondary infection, acute generalized exanthematous pustulosis, subcorneal pustular dermatosis, palmoplantar pustulosis, and pustular psoriasis. The diagnosis is based on positive patch testing, which often demonstrates a pustular reaction; rarely is it eczematous.[11]

Papular/follicular allergic contact dermatitis

Nickel-sensitization-associated papular ACD has been reported. Cosmetic products containing polyoxyethylene lauryl ether, textile products containing formaldehyde, and vitamin E may be associated with follicular- and papular-type CD.[22,23]

Noneczematous irritant contact dermatitis

Bullous phytophotodermatitis is a well-known form of non-eczematous ACD and is characterized by erythema, blisters in a linear fashion, and postinflammatory pigmentation. It usually occurs after contact with a furanocoumarin-containing irritant plant and activated by exposure to sunlight.

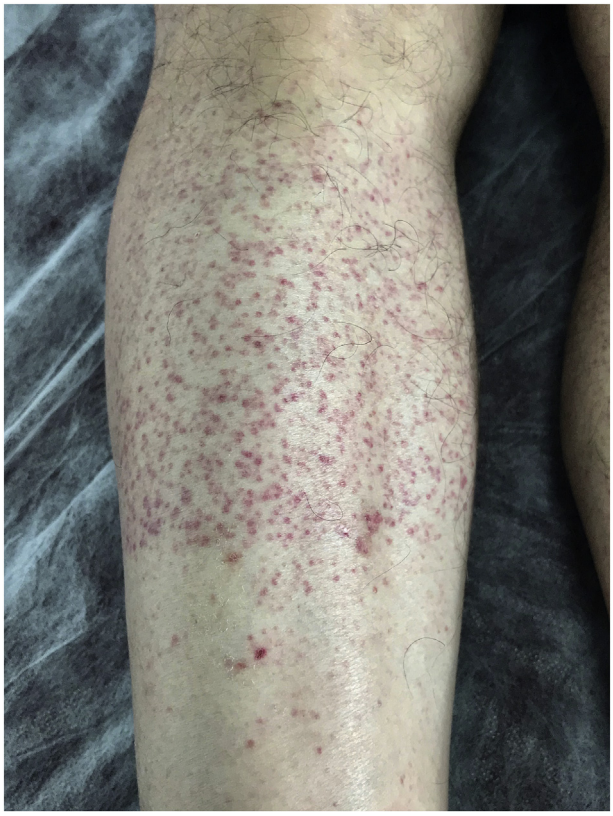

Fig. 5 Purpuric contact dermatitis on the lower extremities. Note the sharp lower margins of the eruption.

Sudden appearance of the bullous lesions on the sun-exposed areas and the concurrent history of outdoor activities may point toward bullous phytophotodermatitis. Pustular ICD is usually associated with croton oil. Paederus dermatitis, caused by contact exposure with the potent toxin of the Paederus beetle, is also a form of pustular ICD. Photo-irritant pigmented CD, also known as berlocque dermatitis, is often caused by exposure to ultraviolet light after contact with the perfumed cosmetic products. Fiberglass particles in clothing may also cause purpuric ICD. Granulomatous ICD cases due to inoculation of talc, zinc, stearate, silicon, and magnesium have also been reported.[11]

Photo-contact dermatitis

Photo-CD refers to a group of cutaneous reactions that develop as a result of concurrent exposure to a contact agent and to ultraviolet light. Photo-allergic and photo-irritant dermatitis are the main subtypes. Plants, oral medications, and psoralen are the common causes of photo-irritant reactions, whereas photo-allergic reactions are usually caused by sun protection creams and topical anti-inflammatory medications. Photo-CD may imitate solar urticaria, actinic prurigo, polymorphic light eruption, cutaneous porphyrias, hydroa vacciniforme, and connective tissue disorders with photosensitivity such as dermatomyositis and lupus.[24]

Systemic contact dermatitis

Systemic contact dermatitis (SCD) is an eczematous reaction that occurs after systemic exposure, that is, ingestion, inhalation, intravenous, and intramuscular administration, to an allergen, which is previously associated with allergic CD in the same person. Nickel and balsam of Peru are well-described culprits of systemic CD. Propylene glycol, chamomile, and formaldehyde are the other known allergens causing SCD. Delayed type hypersensitivity is the main pathogenic mechanism of SCD; however, immediate-type hypersensitivity reaction and complement system may also play a role. Helper T-cells, cytotoxic T-cells, and natural killer cells mediate the inflammatory process by releasing proinflammatory cytokines. Diagnostic methods include patch test, elimination diet, and oral provocation test.[25]

Diagnosis

Diagnosis of CD is usually based on the history and clinical appearance. Occupation, hobbies, and history of topical or systemic medications should be evaluated in detail.[2] The suspicion of CD is the first step of the diagnosis.

Patch testing

Patch testing is used to identify the exact allergens causing delayed-type allergic reaction and considered as the gold standard in the diagnosis of ACD. The most common chemicals used in patch testing are nickel, rubber, formaldehyde, lanoline, fragrance, toiletries, medications, preservative, hair dyes, food, and drinks.[2]

Indications

Patch testing is indicated in any patient with an eczematous or non-eczematous dermatitis if underlying ACD is suspected.[26]

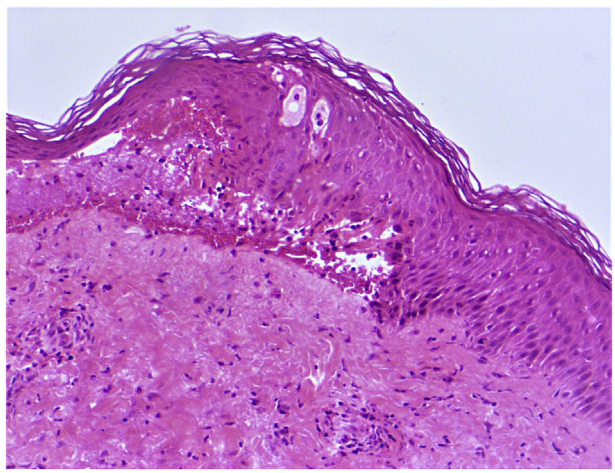

Fig. 6 Histopathology of irritant contact dermatitis demonstrating spongiosis, epidermal blisters, and epidermal necrosis.

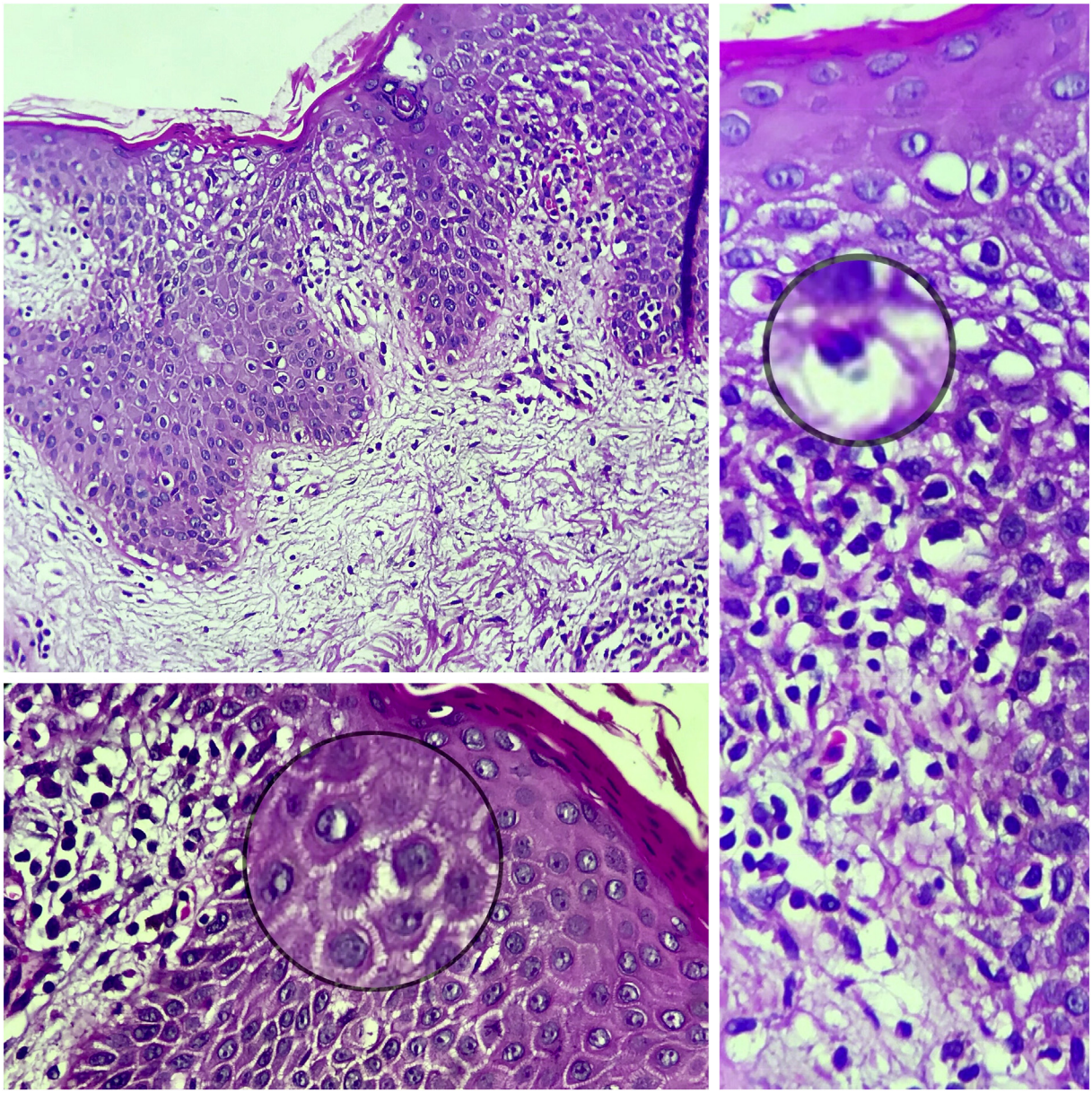

Fig. 7 Histopathology of allergic contact dermatitis showing spongiosis, exocytosis, dermal edema, sparse eosinophils, and perivascular mononuclear inflammatory infiltration.

Contraindications

Patch testing should not be performed in the case of acute generalized dermatitis localized on the back until the condition is controlled. A patient receiving immunosuppressant agents, including systemic corticosteroids, mycophenolate mofetil, azathioprine, and cyclosporine, are also not ideal candidates for patch testing; however, patients taking less than 20 mg/day prednisone or cyclosporine may still show positive reactions. The application of topical steroids and topical calcineurin inhibitors on the test site within 7 days before testing may induce false-negative reactions. Ultraviolet radiation applied to the testing area within 2 weeks before the testing is another cause of false-negative reactions. Systemic antihistamines do not affect the test result.[26,27]

Testing methods and interpretation

Patch testing can be performed through ready-to-use systems or Finn chambers. The thin-layer rapid-use epicutaneous (TRUE) test is a ready-to-use patch test system including preloaded 36 chambers with 35 allergens and a negative control. Nickel, balsam of Peru, cobalt, paraben, formaldehyde, lanolin, rubber, neomycin, and potassium dichromate are the main allergens used in the TRUE test. The TRUE test can determine the responsible chemicals

Table 3 The diagnostic clues to the diseases mimicked by contact dermatitis

Eczematous conditions	
Atopic dermatitis	Beginning in childhood or infancy, personal or familial history of atopic diathesis, and typical distribution of the lesions by the ages[1]
Asteatotic dermatitis	Older male predominance, aggravation in winter, pretibial distribution of the lesions, and marked xerosis[31]
Dyshidrotic eczema	Typical distribution of the small vesicles on the lateral and ventral surfaces of the fingers, seasonal aggravation, family history, and a possible association with emotional stress[32]
Inflammatory dermatoses	
Psoriasis	Well-defined erythematous plaques varying in size and peculiar histopathologic pattern composed of regular acanthosis hypogranulosis, parakeratosis, neutrophils in parakeratotic mounds, tortuous blood vessels, and thinning of suprapapillary plate[51]
Seborrheic dermatitis	Typical distribution on the scalp, face and chest, intermittent course, and seasonal aggravation[1]
Lichen planus	Polygonal violaceous papular lesions distributed over the flexor surface of the extremities, mucosal involvement, and histopathological evidence of interface dermatitis[1]
Transient acantholytic dermatosis	Erythematous papulovesicular eruption usually localized on the upper part of the trunk and histopathologic evidence of dyskeratosis and acantholysis[33]
Lichen aureus	Predilection of lower extremities, ivory red patches, dermatoscopic red dots and globules, and histological evidence of red blood cell extravasation[52]
Acneiform eruptions	
Rosacea	Peculiar distribution on the central face, flushing, and diffuse telengiectasias[34]
Perioral dermatitis	Yellow-brown hue of the papular lesions, perioral and periorbital distribution, and history of using topical corticosteroids[35]
Neoplastic conditions	
Mycosis fungoides	Chronic and progressive course, atrophy, hypopigmentation, and histologic evidence of epidermotropism[36]
Mammary and extramammary Paget diseases	A solitary circumscribed erythematous scaly plaque unresponsive to the topical corticosteroid[37]
Drug eruptions	
Fixed drug eruption	History of medication, genital and lips involvement, presence of round, violaceous, and blistering lesions, and postinflammatory pigmentation[38]
Maculopapular drug eruptions	History of medications and morbilliform distribution of the lesion[39]
Connective tissue diseases	
Discoid lupus erythematosus	Dermatoscopic follicular plugs, irregular linear vessels and patchy distributed brown-to-gray dots, histological evidence of keratotic plugs, thickened basement membrane, and perivascular and periadnexal dense mononuclear inflammatory infiltration[41]
Cutaneous dermatomyositis	Extracutaneous involvement including muscular weakness, accompanying malignancy, characteristic distribution of the lesions (periorbital, metacarpophalangeal and interphalangeal areas), and the histological pattern of interface dermatitis[1]
Infectious conditions	
Scabies	History of contact with infected clothes or person, itching, mainly at night, burrows, and mites on dermatoscopic examination[44]
Erythrasma	Skin discoloration usually limited to body folds and coral red fluorescence under wood's lamp[45]
Tinea	History of contact with infected animals or patients, annular morphology, and active erythematous border of the lesion[45]
Bullous diseases	
Bullous pemphigoid	Elderly patient predominance, large tense fluid filled blisters, and normal skin around the blisters[46]
Hailey–Hailey disease	Erosive nature of the disease, seasonal aggravation, and a special type of acantholysis known as dilapidated brick wall[47]
Vascular conditions	
Stasis dermatitis	Ill-defined erythematous plaques usually located on the medial malleolus, accompanying findings of venous insufficiency[13]
Leukocytoclastic vasculitis	Palpable purpuric lesions and histological evidence of vasculitis[53]
Nutritional deficiencies	
Acrodermatitis enteropathica	Periorificial and acral distribution of erythematous scaly lesions, family history, diarrhea, irritability, and alopecia[48]
Pellagra	Photosensitive and symmetrical distribution of the lesions, diarrhea, and dementia[49]

in approximately half of the affected individuals. Finn chambers system is the other testing method in which the antigens are applied directly into the chambers. Different studies reported high positive concordance rates between the Finn chamber system and the TRUE test.[26,28]

The patches are removed and usually read at 48 hours. The test area is also examined at 72 hours and 1 week after initial application. Reactions to the allergens may be considered as negative, irritant reaction, uncertain, weak positive, strong positive, or extreme reaction.[2,26]

A positive patch test result alone does not identify the exact cause of the dermatitis. The relevance of the detected allergens must be correlated with the clinical history and findings.[1] Before coming to the final diagnosis of CD, all other possible diagnoses should be excluded.

False-positive reactions

False-positive hyperreactive reactions may be observed, particularly in patients having active dermatitis at the time of patch testing. This phenomenon is known as angry back syndrome or excited skin syndrome. The presence of more than 5 reactions in close proximity to each other should direct the clinician the possibility of angry back syndrome. In such cases, retesting the patients with a small series of the allergens may be helpful to exclude false-positive reactions.[29] Bullous, pustular, and purpuric reactions are also usually considered as irritant reactions.[26]

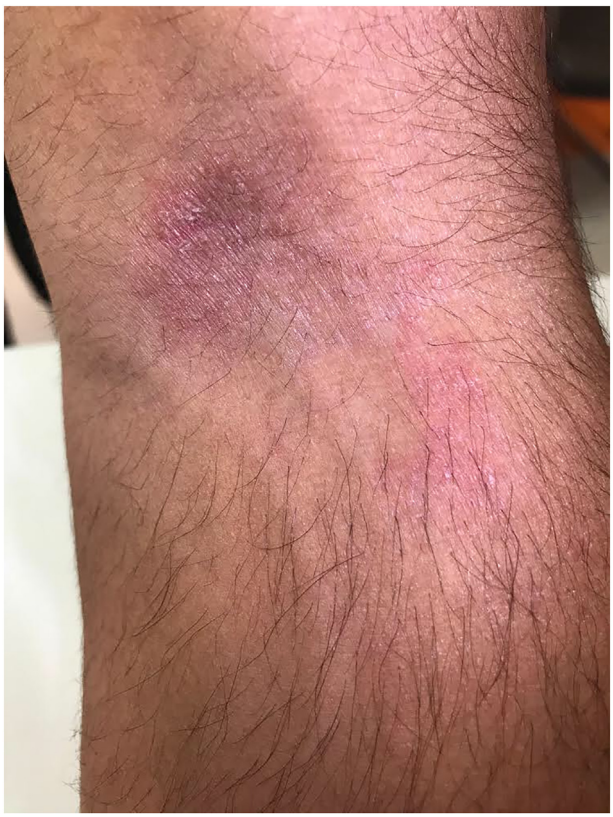

Fig. 8 Atopic dermatitis with flexural eczematization mimicking allergic contact dermatitis.

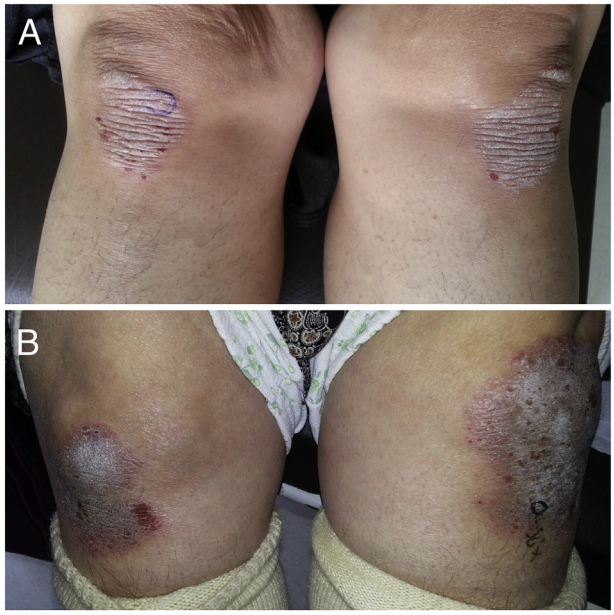

Fig. 9 Psoriasis mimicking contact dermatitis. A, Psoriasis. B, Allergic contact dermatitis.

False-negative reactions

Approximately 30% of the patients tested have been estimated to demonstrate false-negative results. Lack of patient cooperation, insufficient concentrations of the antigens, inappropriate carrier vehicle, prior ultraviolet light exposure, topical corticosteroids or topical immunomodulator application on the testing site, and immunosuppressive therapies are the known causes of false-negative reactions.[26]

Photo-patch testing

Photo-patch testing is used for diagnosing photo-allergic CD. Standard test series include concentration of Para-aminobenzoic acid, oxyl dimethyl Para-aminobenzoic acid, octyl methoxycinnamate, benzophenone 3, and butyl methoxydibenzoylmethane kept in petroleum jelly. Patches containing the same allergens are applied symmetrically onto both sides of the back. One of the patches is removed and evaluated 48 hours later, and then 5 to 15 J/cm^2 UVA is applied and the area is covered with an opaque material such as a black band. Two days later, all materials on the back are removed and the two sides are compared. If there is an equal reaction on both sides, the case is considered to be ACD. The diagnosis of photoallergic CD can be made in the case of the more prominent reaction on the irradiated site. As for the classic patch testing, the relevance of the detected allergens must be correlated with the clinical history and findings.[24,28]

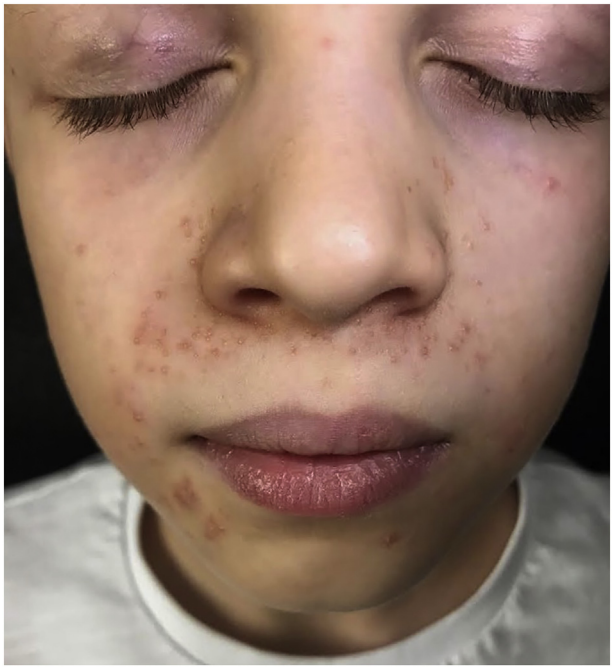

Fig. 10 Perioral dermatitis mimicking papular contact dermatitis.

Histopathology

Spongiosis, epidermal vesicles or bullae, and epidermal necrosis are the main histologic features of acute ICD (Figure 6). Dermal perivascular mixed inflammatory infiltration, vasodilatation, and edema are the other findings. With chronicity, ICD shows the histologic evidence of lichenification with hyperkeratosis, hypergranulosis, and acanthosis.[30]

The histopathology of ACD (Figure 7) reveals spongiosis, exocytosis, dermal edema, and perivascular mononuclear inflammatory infiltration. Acanthosis and hyperkeratosis may also be seen in chronic cases of ACD and ICD.[30]

Both ICD and ACD may demonstrate nonspecific pathologic findings.

Differential diagnosis

CD can imitate a wide variety of dermatologic diseases, including eczematous conditions, inflammatory dermatoses, acneiform eruptions, cutaneous neoplastic conditions, drug eruptions, connective tissue diseases, infectious conditions, bullous diseases, and nutritional deficiencies.[1,2] Table 3 summarizes the diagnostic clues to the entities mimicked by CD.

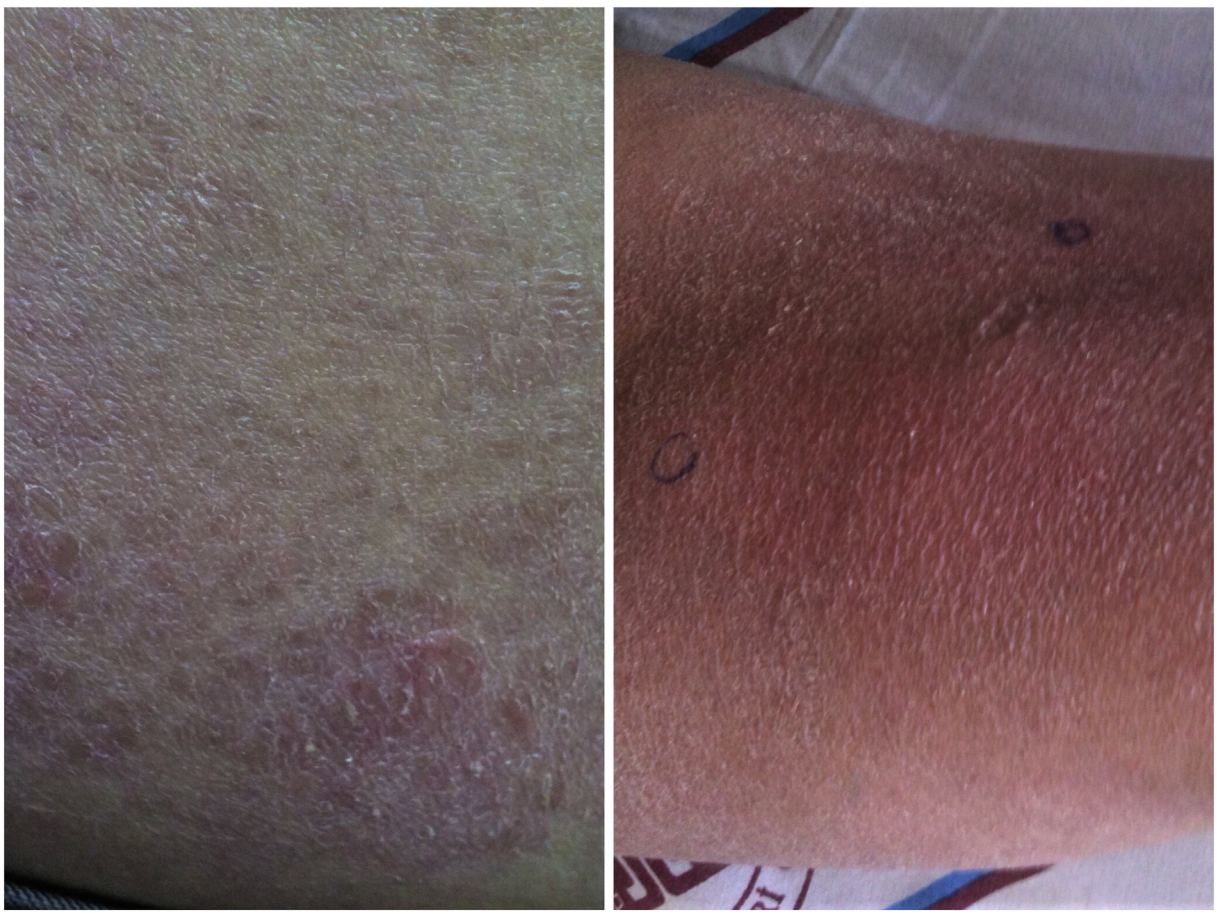

Fig. 11 Mycosis fungoides mimicking contact dermatitis.

Eczematous conditions

CD is a common mimicker of atopic dermatitis (Figure 8). Beginning in childhood or infancy, personal or familial history of atopic diathesis and typical distribution of the lesions are the main clues to differentiate atopic dermatitis from CD.[1] Contact hypersensitivity in patients with atopic dermatitis may cause an overlap between both conditions and lead to confusion in the diagnosis. In this case, patch testing may be useful to exclude or confirm a possible accompanying contact reaction.

Asteatotic dermatitis is another eczematous condition that may have a similar presentation to CD. There is often a predominance in men and aggravation in winter. Pretibial distribution of the lesions is also in favor of asteatotic dermatitis.[31]

Dyshidrosis is an eczematous process demonstrating small vesicular lesions localized on the palmoplantar area, typically distributed on lateral and ventral surfaces of the fingers. The exact mechanism is unknown; however, hyperhidrosis is accused.[32] The typical distribution of the small vesicles, seasonal aggravation and family history, may be helpful clues to diagnosis of dyshidrosis.[1]

Inflammatory dermatitides

Psoriasis is a highly prevalent chronic relapsing skin disorder that may have a similar presentation to ACD (Figure 9). Histopathological examination may provide useful clues for the differential diagnosis.

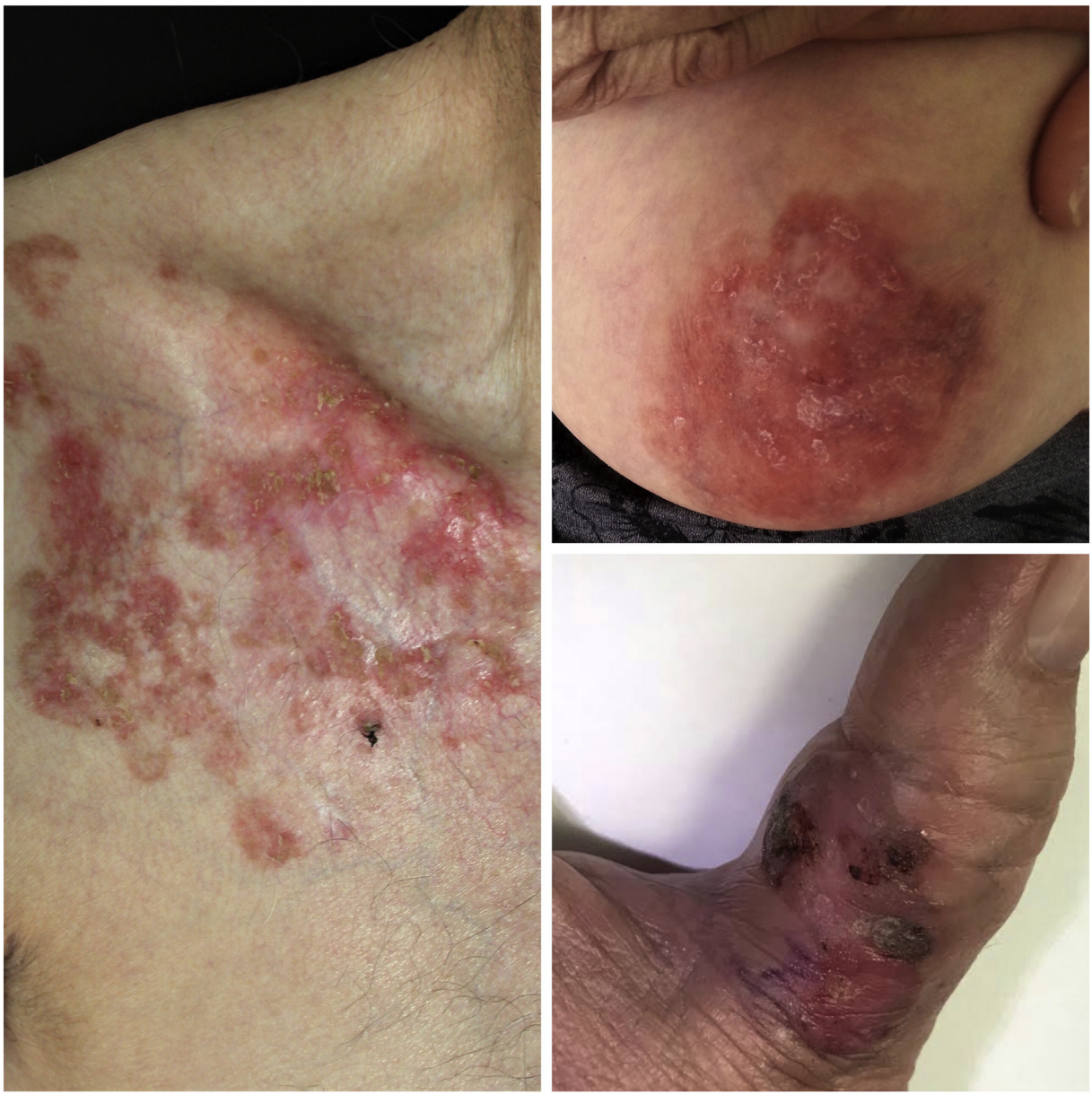

Fig. 12 Bowen's disease on different sites mimicking contact dermatitis.

Seborrheic dermatitis is another common inflammatory dermatosis that may mimic CD. Typical distribution on the scalp, face, and chest, an intermittent course, and seasonal aggravation are clues in differentiating seborrheic dermatitis from CD.[1]

Lichenoid CD can imitate lichen planus. Polygonal violaceous papular lesions distributed over the flexor surface of the extremities, mucosal involvement, and histopathologic evidence of interface dermatitis favor lichen planus.[1]

Transient acantholytic dermatosis, also known as Grover disease, is characterized by erythematous papulovesicular eruption usually localized on the chest and back. The entity can easily be differentiated from CD with its typical histopathologic findings of dyskeratosis and acantholysis.[33]

Acneiform eruptions

Rosacea may have a similar clinical appearance with the CD. A peculiar distribution on the central face, flushing, and diffuse telangiectasias are useful diagnostic clues to rosacea.[34] Perioral dermatitis (Figure 10) is another acneiform eruption that may mimic the CD, and sometimes it can be very challenging to differentiate perioral dermatitis from CD. The yellow-brown hue of the papular lesions, perioral and periorbital distribution, and the history of using topical corticosteroids are in favor of perioral dermatitis.[35]

Neoplastic conditions

Mycosis fungoides (MF) (Figure 11), being the most common form of cutaneous T-cell lymphoma, is characterized by a wide variety of clinical findings. MF is also considered as one of the great imitators in dermatology and dermatopathology.[36] Chronic and progressive course, atrophy, hypopigmentation, and histologic evidence of epidermotropism are helpful clues in differential diagnosis between MF and CD.

Mammary and extramammary cutaneous Paget diseases, and Bowen's disease (Figure 12) are the other neoplastic conditions that may present with a CD-like appearance.[1,37] A solitary circumscribed erythematous scaly plaque unresponsive to the topical corticosteroids should always be a reminder of the possibility of a cutaneous intraepithelial neoplasia.

Drug eruptions

Fixed drug eruption (FDE) is a peculiar type of cutaneous drug reaction with an unknown mechanism of action. The eruption occurs on the same site with subsequent administration of the offending agent.[38] The history of medication, the predilection sites (genital, lips), the presence of round, violaceous, blistering lesions, and postinflammatory pigmentation are useful clues to diagnosis of FDE.[1] Maculopapular drug eruptions may also mimic noneczematous CD. A thorough history of medications, distribution, and course of the lesion can provide diagnostic clues for the diagnosis.[39]

Connective tissue diseases

Discoid lupus erythematosus (DLE) has been confused with chronic lichenified CD, whereas the possible triggering role of ACD in DLE has been shown.[40] Dermatoscopic examination may provide important clues to DLE, with follicular plugs, irregular linear vessels, and patchy distributed brown-to-gray dots, whereas an acute or chronic dermatitis may show dotted vessels in a patchy distribution.[41,42] Histopathologic examination of DLE also demonstrates characteristic findings, including keratotic plugs, thickened basement membrane, and perivascular and periadnexal dense mononuclear inflammatory infiltration.[43]

Cutaneous dermatomyositis is another connective tissue disease imitating CD. Extra cutaneous involvement including muscular weakness, accompanying malignancy, characteristic distribution of the lesions (periorbital, metacarpophalangeal and interphalangeal areas), and a histologic pattern of interface dermatitis are the clues to dermatomyositis.[1]

Infectious conditions

Scabies is a parasitic, itchy dermatosis caused by *Sarcoptes scabiei.* Primary or secondary lesions of the scabies in the finger webs or on the palms may be misdiagnosed as CD. Scrapings of the burrows for the mites and dermatoscopic examination can be highly rewarding.[44]

Erythrasma (Figure 13), as a cutaneous bacterial infection caused by *Corynebacterium minutissimum,* is characterized by skin discoloration usually limited to body folds and may be confused with intertriginous CD. Wood's light examination can serve as a helpful tool to the diagnosis.[45]

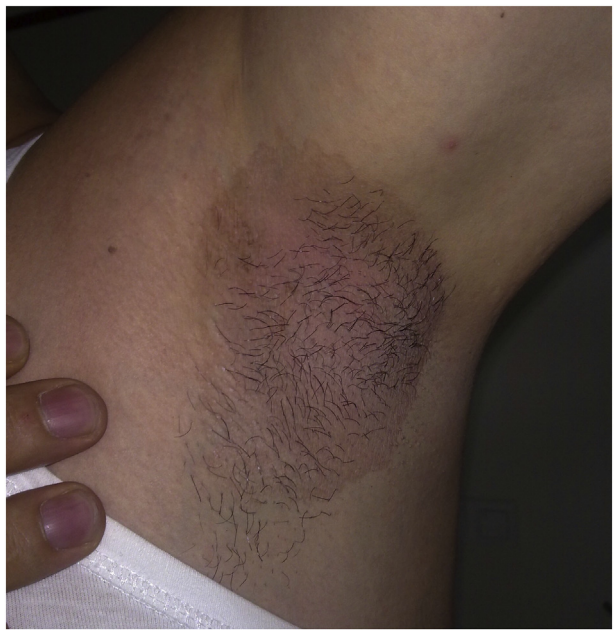

Fig. 13 Erythrasma mimicking contact dermatitis.

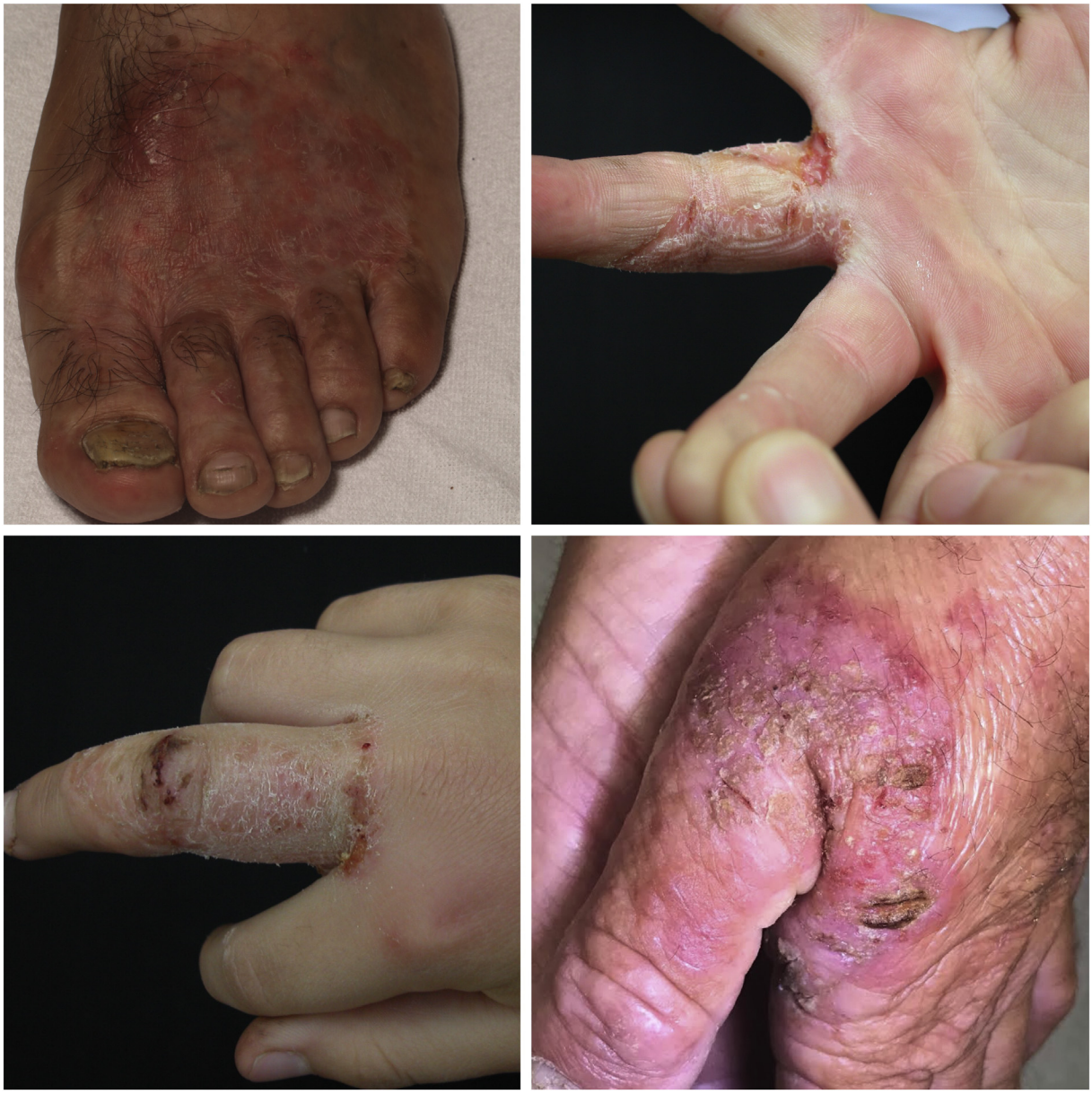

Fig. 14 Dermatophyte infections mimicking contact dermatitis.

Dermatophytosis (Figure 14), especially with a history of contact with infected animals or patients, plus an annular morphology and active erythematous border of the lesion would suggest the diagnosis.[1]

Bullous diseases

Bullous CD, especially bullous ICD, may imitate autoimmune bullous disorders such as bullous pemphigoid and pemphigus. The opposite is also possible.[46] In such cases, the correct diagnosis can be made through a carefully obtained medical history and physical examination. The localized appearance of the lesions and abrupt borders should direct the clinician to the possibility of CD.

Familial benign pemphigus, also known as Hailey–Hailey disease (Figure 15), is an inherited autosomal dominant disorder characterized by erosions and fissured plaques in the body fold. It is often misdiagnosed, but it may mimic CD with its erosive and seasonal aggravation. Histologic findings of acantholysis are the clues to differentiate it from intertriginous CD.[47]

Nutritional deficiencies

Acrodermatitis enteropathica (Figure 16) is a low-incidence disorder caused by acquired or inherited zinc deficiency. The entity may mimic many dermatologic disorders, ranging from superficial fungal infection to CD. Clues pointing toward

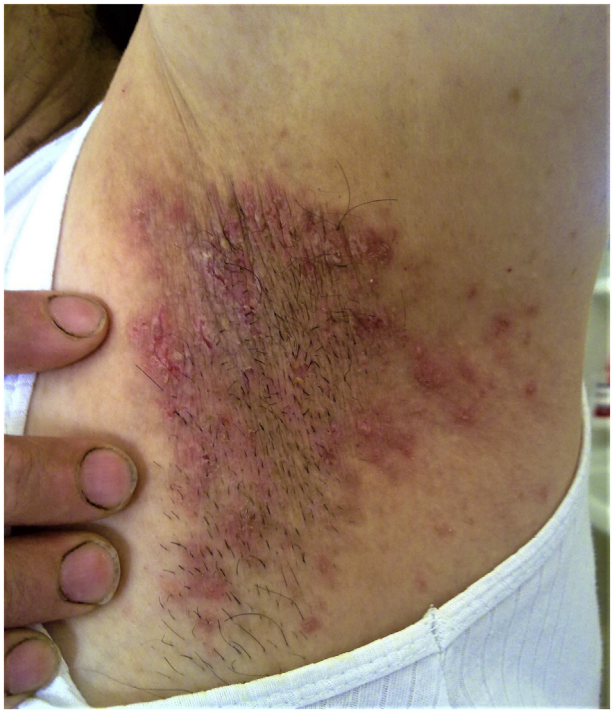

Fig. 15 Hailey–Hailey disease mimicking contact dermatitis.

acrodermatitis enteropathica include a periorificial or acral distribution of erythematous scaly lesions, family history, accompanying diarrhea, irritability, and alopecia.[48]

Dietary niacin deficiency, also known as Pellagra, is another nutritional deficiency mimicking CD. Photosensitive and symmetrical distribution of the lesions and the other accompanying findings such as diarrhea and dementia are the key diagnostic features for pellagra.[49]

Management

The first step in the management of both ICD and ACD is the determination and elimination of the causative agent. Once the irritant or allergic agent has been identified, protective measures should be taken to reduce the risk of possible forthcoming exposure, including using gloves with cotton liners, personal protective equipment in the workplace, and barrier creams. Emollients may improve skin barrier function with petrolatum-based emollients and/or skin-related lipids providing an effective and cheap moisturization.[50]

A short course of mid- to high-potency topical corticosteroid is the treatment of choice for ACD. Systemic corticosteroids can be used in severe cases of ACD.[1] Use of topical

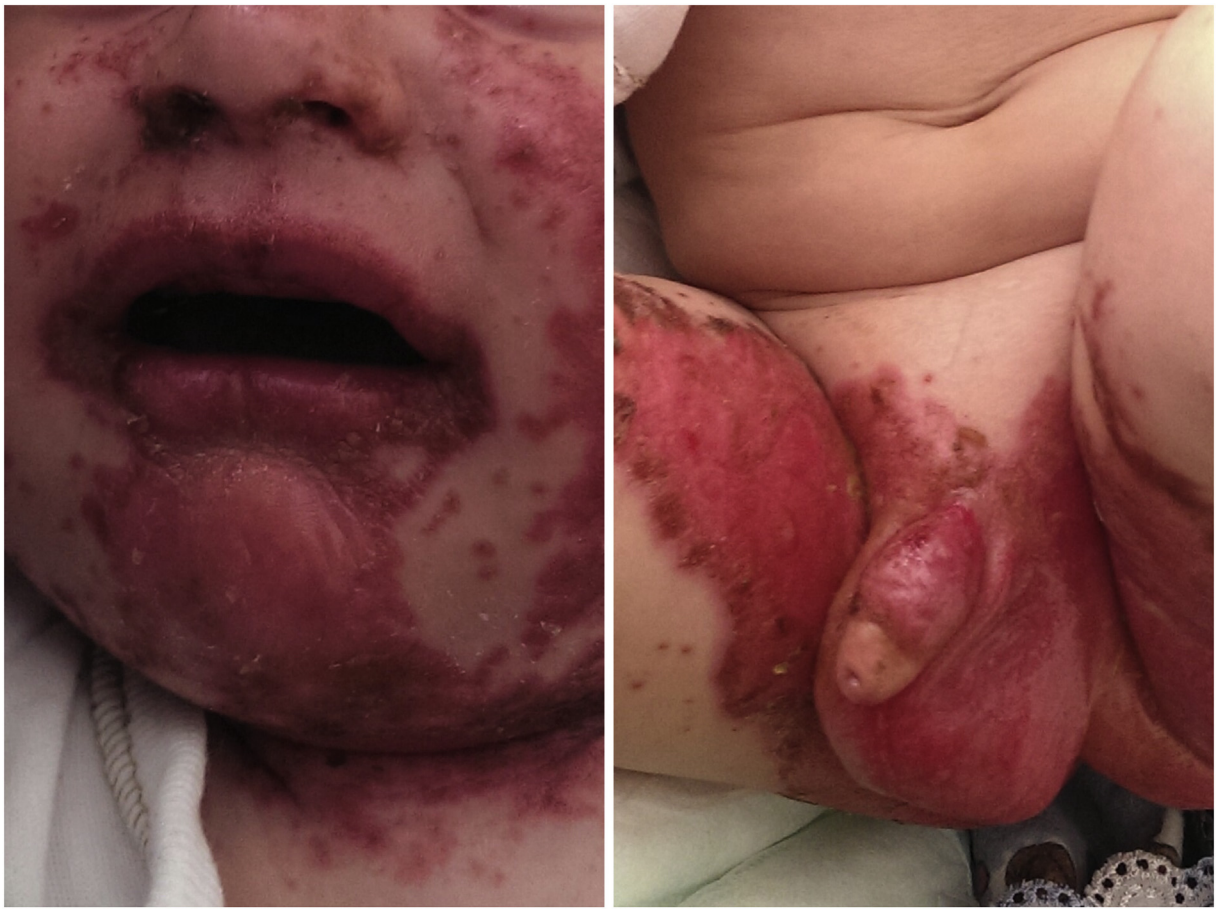

Fig. 16 Acrodermatitis enteropathica mimicking contact dermatitis.

corticosteroids in ICD is controversial but can help to reduce inflammation and itching.[50] Antihistamines can also be helpful to reduce itching in ACD.[1]

Topical immunomodulators, including tacrolimus and pimecrolimus for their steroid-sparing treatment, may also be helpful in ACD. The main advantage of the topical immunomodulators is the avoidance of cutaneous atrophy and telangiectasia, which are usually associated with long-term use of topical corticosteroids. Phototherapy and immunosuppressive agents, including cyclosporine, mycophenolate mofetil, and azathioprine, can be used in recalcitrant or severe chronic cases of ACD. Lastly, dietary restriction of the chemicals and minerals identified allergic in the patch test as the culprits of systemic CD may also provide additional benefits.[1]

Conclusions

CD, especially ACD, has the ability to imitate many dermatologic diseases. In this context, it is not uncommon to misdiagnose the entity. Along with a suspicious approach, a detailed history and physical examination are essential for diagnosis. Patch testing may be helpful in detecting the causative agents, especially in ACD; however, the relevance of the identified agents should be correlated with the clinical history and findings; nevertheless, all possible diagnoses should be excluded before coming to the final diagnosis of CD. Being aware of the conditions imitated by CD may increase the accuracy of diagnosis. Avoiding the causative agent and taking preventive measures are the basis of treatment.

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