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REVIEW ARTICLE

Cutaneous id reactions: A comprehensive review of clinical manifestations, epidemiology, etiology, and management

Macit Ilkit[1], Murat Durdu[2], and Mehmet Karakaş[3]

[1]Çukurova University, Faculty of Medicine, Department of Microbiology, Adana, Turkey, [2]Başkent University, Department of Dermatology, Adana Hospital, Adana, Turkey, and [3]Çukurova University, Faculty of Medicine, Department of Dermatology, Adana, Turkey

Abstract

Id reactions are a type of secondary inflammatory reaction that develops from a remote localized immunological insult. To date, id reactions caused by various fungal, bacterial, viral, and parasitic infections have been reported. Superficial fungal infections, especially tinea pedis, are the most common cause of id reactions. Id reactions exhibit multiple clinical presentations, including localized or widespread vesicular lesions, maculopapular or scarlatiniform eruptions, erythema nodosum, erythema multiforme, erythema annulare centrifugum, Sweet's syndrome, guttate psoriasis, and autoimmune bullous disease. The mechanisms underlying id reactions vary depending on the type of clinical presentation. The most important aspect of therapy involves the identification and adequate treatment of the underlying infection or dermatitis. This review comprehensively discusses the current state of the field concerning cutaneous id reactions, including diagnostic criteria, clinical presentations, underlying infectious conditions, etiologic agents, immunologic characteristics, histopathologic findings, and management strategies.

Keywords: Bacterid, dermatophytid, herpes simplex virus, leishmanid, tinea pedis

Introduction

"Id" reactions describe a secondary immunologic reaction to circulating antibodies or activated T lymphocytes that are directed against microbial antigens derived from nonliving organisms (Grappel et al., 1974; Gianni et al., 1996). The term "-id" is a suffix originating from the Greek that denotes a "father-son" relationship (Brenner et al., 1993). Briefly, an id response results from a variety of stimuli, including infectious entities and inflammatory skin conditions. In 1918, German dermatologist Josef Jadassohn (1863–1936) was the first to recognize that a generalized cutaneous eruption, such as kerion, was an allergic reaction of the skin sensitized by dermatophytosis. He chose the term id reaction in analogy to Darier's tuberculid after he had originally called this allergic manifestation "lichen trichophyticus." A decade later, Bloch (1928) noted that the dermatophytid reaction appeared at the height of infection or shortly thereafter due to a large-scale release of antigens. In his experience, dermatophytids often occurred after X-ray treatment, trichophytin skin tests, or localized irritations (Bloch, 1928).

This review provides information regarding multiple clinical manifestations of cutaneous id responses, underlying infections, etiologic agents, and management strategies for clinical microbiologists, dermatologists, infectious disease clinicians, and public health workers. Most commonly, id reactions occur due to fungal infections, especially tinea pedis. Other superficial (e.g. tinea corporis, tinea cruris, and candidiasis), subcutaneous (e.g. sporotrichosis), and deep (e.g. coccidioidomycosis) fungal infections can cause id reactions. To date, id reactions have been associated with a variety of bacterial (bacterid, leprid, and tuberculid), viral (caused by herpes simplex virus [HSV] and poxvirus), fungal (dermatophytid, trichophytid, and sporotrichid), and parasitic (leishmanid, pediculid, and scabid) skin infections (Jadassohn, 1918; Scholtz, 1932; e Silvia & de Oliveira,

Address for Correspondence: Macit Ilkit, Department of Microbiology, Faculty of Medicine, University of Çukurova, Adana, 01330 Turkey. E-mail: milkit@cu.edu.tr

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1973; Tan, 1974; Brenner et al., 1984; Brenner et al., 1993; Choudhri et al., 1994; Diven, 2001; Gutierrez-Galhardo et al., 2002; Weston, 2005).

References for this review were identified using PubMed (Medline) searches for articles published from January 1960 to September 2011, using the terms "id reaction," "bacterid," "tuberculid," "leprid," "leishmanid," "scabid," "pediculid," "dermatophytid," and "viral id reactions." Relevant articles published between 1918 and 1954 were identified through searches in the personal files of the authors and Google Scholar. Articles resulting from these searches and relevant references cited in those articles were reviewed. Only articles published in English and German were included.

Clinical manifestations

The dermatological manifestations of id reactions vary depending on the etiological agent and host response (Brasch, 2009). Overlaps may occur, and examples of each id reaction phenotype can occur with almost any infection. The literature review revealed that id reactions most commonly present as the following: (i) localized vesicular lesions in tinea pedis; (ii) erythema nodosum in bacterial, subcutaneous, and deep fungal infections; and (iii) erythema multiforme in herpetic infections.

Id reactions caused by fungal infections

Skin and nail dermatophytic infections have become widespread; however, the incidence of scalp ringworm has decreased markedly in areas that have had access to medication since the 1970′s. Moreover, the distribution of dermatophytes recovered from the skin, nails, and scalp changed significantly in the 20th century (Seebacher et al., 2008). Therefore, several complicating manifestations associated with these dermatomycoses, including id reactions, Majocchi's granulomas, and tinea incognito, require attention from clinicians and laboratory investigators (Degreef, 2008).

Dostrovsky et al. (1955) observed 6390 cases of tinea capitis between 1926 to 1953 and reported that only 0.2% of the patients exhibited an id response. Id reactions usually occurred following X-ray treatment. Recently, Cheng et al. (2011) reported a series of cases that involved five children with tinea capitis who developed dermatophytids before or during (1–2 weeks) griseofulvin therapy. The eruptions resolved in all of the children despite continuing oral therapy. The authors suggested that dermatophytid development secondary to tinea capitis is much more common than reported (Cheng et al., 2011).

Grappel et al. (1974) noted that in a group of patients with dermatophytosis, 4.2% of children and 4.6% of adults had dermatophytids. Additionally, the incidences of dermatophytids with tinea corporis and tinea pedis were reported as 5% and 17%, respectively (Veien et al., 1994; Gianni et al., 1996). In another study, 37 of 213 patients (17%) diagnosed with tinea pedis developed dermatophytids on their hands (Veien et al., 1994). The authors recovered *Trichophyton mentagrophytes* (78), *T. rubrum* (128), and *Epidermophyton floccosum* (6) from foot lesions and described id reactions in 27 (34.6%), 7 (5.5%), and 1 (16.7%) cases of these fungal infections, respectively. Similarly, Kaaman & Torssander (1983) analyzed 10 cases of dermatophytids associated with tinea pedis; the diagnosis of id was verified with a positive delayed skin reaction. Although the authors encountered mostly *T. rubrum* infections in their clinic, *T. mentagrophytes* was recovered from 9 of 10 patients; *E. floccosum* was recovered from the tenth patient. The authors estimated an incidence of 0.7% for proven id reactions among dermatophytic infections (Kaaman & Torssander, 1983). In a retrospective study, Romano et al. (2006a) reviewed 200 tinea incognito patients, and 3% presented with dermatophytids.

Dermatophytid reactions share the following characteristics: (i) the host harbors a proven focus of dermatophytic infection elsewhere; (ii) a positive skin test response to *Trichophytin*, *Oidiomycetes* (*Candida*), or *Epidermophyton* (TOE); (iii) fungal forms are neither recoverable from the site of the cutaneous eruption nor microscopically visible in direct smears or histopathologic preparations; and (iv) the lesions spontaneously resolve after an acute course, provided that the primary infection is identified and eliminated (Jadassohn & Peck, 1929; Peck, 1930; Peck, 1950; Kaaman & Torssander, 1983).

An id reaction that is accompanied a dermatophytic infection, which can be complicated by secondary, distant, aseptic skin lesions, is called "dermatophytid" or "trichophytid" (Kaaman & Torssander, 1983). First, two types of id lesions have been described: (i) generalized lichen-scrofulosorum-like eruptions of grouped or scattered follicular papules on the chest, trunk, and back due to scalp ringworm; and (ii) eczematous eruptions on the hands that are dermatophytids secondary to dermatophytic infections of the skin and nails (Williams, 1926; Jadassohn & Peck, 1929). Several authors established the clinical entities of palmar and digital epidermophytids, microsporids, and trichophytids, and the term "dermatophytids" was used to describe all cases (Williams, 1926, 1930, 1931; Jadassohn & Peck, 1929).

Until today, several clinical types of id reactions have been described. Id reactions may be localized (Kaaman & Torssander, 1983; Veien et al., 1994) or generalized (Iglesias et al., 1994; Cheng et al., 2011). Although id reactions may be widespread and intensely pruritic, in many cases, the astute clinician will observe subtle localized lesions (Cheng et al., 2011). Furthermore, widespread symmetrical vesicles on the trunk and extremities and morbilliform, scarlatiniform, lichenoid, urticaria, erythema multiforme, erythema nodosum, and erythema annulare centrifugum rashes can also occur (Jillson, 1954; Méndez et al., 2002; Atzori et al., 2003). Atzori et al. (2003) observed an erythema multiforme reaction in a patient with a dermatophyte infection on the left ala nasi with marked involvement of the intranasal hairs (rhinothrix infection). Additionally, periorbital papules due to

an id reaction were also noted (Al Aboud et al., 2003). The failure of the clinician to recognize dermatophytids could result in an unwarranted withdrawal of the antifungal treatment to eradicate the underlying infection (Sorey, 2009). Rarely, the general health of the patients can also be affected. High fever, anorexia, generalized lymphadenopathy, splenomegaly, hematologic alterations (leukocytosis and lymphocytosis), and involvement of the joints can accompany the acute onset of the dermatophytids. Cases of anaphylaxis have also been reported (Götz, 1962).

Disseminated or primary cutaneous deep fungal infections can trigger id reactions, such as erythema nodosum, erythema multiforme, Sweet's syndrome, urticaria, and maculopapular rash. Erythema nodosum is the most common reactive cutaneous finding in patients with coccidioidomycosis (Chang et al., 2003; DiCaudo, 2006). Id reactions caused by sporotrichosis have been reported to present as erythema multiforme (Gutierrez-Galhardo et al., 2005) and erythema nodosum (Gutierrez-Galhardo et al., 2002). Additionally, in infants, erythema multiforme (Korting & Vieluf, 1991) and psoriasiform-type (Alex et al., 1999) id reactions could develop due to a *Candida* spp. infection in the diaper area.

Lesions associated with scalp ringworm

Jadassohn (1918) described lichen-like lesions (dermatophytids) predominantly in children with trichophytic kerion and less frequently in adults with tinea barbae. Since this initial report, many published articles about dermatophytids have appeared in the literature. Briefly, dermatophytids that accompany scalp ringworm are characterized by diffuse pruritic papules located mainly on the trunk; in rare cases, these dermatophytids can appear on the extremities, neck, and face (Jadassohn, 1918; Fuller et al., 2003; Cheng et al., 2011; Liu et al., 2011). Although dermatophytid reactions due to inflammatory tinea capitis can occasionally present as a widespread eruption, these reactions are usually follicular, lichenoid, or papulosquamous in nature (Liu et al., 2011). Dermatophytid reactions at times presented as small, pale red, pointed, follicular nodules that were disseminated or arranged in groups. Very fine, spiny projections or pustules sometimes appear on the nodules. Additionally, plaques resembling seborrheic dermatitis were also observed. Rarely, the eruption can be morbilliform or scarlatinoid in appearance (Jadassohn, 1918; Peck, 1930). Interestingly, within 24 h of starting griseofulvin, a patient developed acutely tender, erythematous nodules over the shins and thighs that were consistent with erythema nodosum (Bassi & Kersey, 2009). Recently, a case of severe kerion with dermatophytid reactions that presented as diffuse erythema and pustules was reported (Liu et al., 2011). Generally, id reactions tends to occur at the height of the dermatophytic infection, slightly thereafter, or before or just after the initiation of systemic antifungal therapy, which can last from 5 to 20 days (Jadassohn, 1918; Bloch, 1928; Grappel et al., 1974; Fuller et al., 2003; Cheng et al., 2011). Therefore, antifungal treatment should be continued to treat the underlying infection (Fuller et al., 2003). Although dermatophytids are commonly refractory to topical corticosteroids, they typically clear rapidly after treating the fungal infection (Honig et al., 1994).

Lesions associated with tinea pedis

The probable allergic nature of erythema-squamous and vesicular lesions of the hands or "phytids" in association with dermatophytic infections of the feet has introduced new approaches to the treatment of many obscure and intractable eruptions (Jadassohn & Peck, 1929; Peck, 1930; Wise & Wolf, 1936). However, according to Peck (1930), Dr. Sabouraud attributed the negative observations of the lesions on the hands to technical difficulties. Dr. Sabouraud suggested that fungi were also present on the hands but were more difficult to culture for an unknown reason (Peck, 1930). However, his explanation is highly improbable when one considers a large series of cases ($n = 47$; Jadassohn & Peck, 1929; Peck, 1930).

There are two main types of clinical manifestations of hand dermatophytids: (i) a dyshidrotic-eczematous or vesicular form and (ii) a scaling form that is commonly an end stage of the vesicular form (Figure 1). However, the scaling form can occur primarily. Additionally, the scaling form sometimes resembles postscarlatiniform desquamation (Jadassohn & Peck, 1929; Peck, 1930). In adults with tinea pedis, which is usually caused by *T. mentagrophytes*, the most common type of id reaction is seen on the hands and sides of the fingers (Hall, 1956; Kaaman & Torssander, 1983; Veien et al., 1994). Some patients with tinea pedis develop acute, symmetrical, vesicular eruptions at a secondary site, usually on the fingers or palmar surfaces and the interdigital spaces. Lesions initially include vesicles and bullae; later papules or pustules can form (Kaaman & Torssander, 1983; Veien et al., 1994; Gianni et al., 1996). Generalized follicular papules were rarely observed, and some bacteria, such as beta-hemolytic *Streptococcus*, may have been copathogens (Iglesias et al., 1994). Additionally, a case of vesiculo-bullous tinea pedis with a dermatophytid reaction caused by anthropophilic *T. violaceum* was reported (Romano et al., 2006b).

Peck (1930) was the first to experimentally induce an id reaction. By infecting the toes of previously unaffected persons and producing trauma by friction between the toes, he caused vesicular eruptions on the hands that were typical of id reactions. The hands appear to be a *locus minoris resistentiae* for the development of the secondary lesions. Additionally, Peck (1930) demonstrated that primary localized dermatophytosis of the hands could produce dermatophytids on the feet, which reverses the usual course of events in sensitized patients. Moreover, *Epidermophyton* Kaufmann-Wolf (likely *T. interdigitale*) has been cultured not only from lesions on the feet but also from the circulating blood of a patient with a tinea pedis-associated dermatophytid.

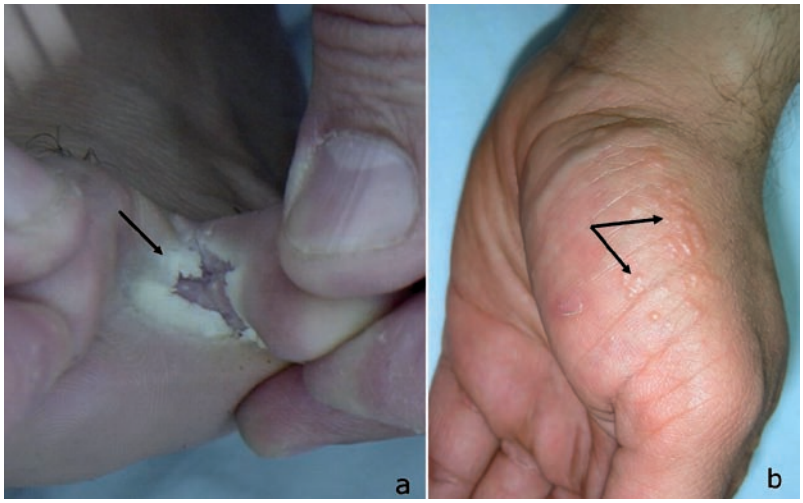

Figure 1. A vesicular id reaction associated with tinea pedis. Maceration (arrow) between the toes (A) and multiple small vesicles (arrows) on the lateral margin of the palm (B) are shown. A potassium hydroxide examination of the specimens obtained from between the toes revealed hyphae. The hand and foot lesions were completely resolved using topical antifungal treatment to the foot.

Taken together, these results demonstrate that epidermophytids of a dyshidrotic and squamous character can arise on the hands by the hematogenous transport of living fungal elements from primary mycoses of the feet (Peck, 1930).

Id reactions caused by bacterial infections

The most common example of a bacterid is panniculitis, which occurs in lobular and septal forms. Erythema nodosum is the most common clinico-pathological variant of septal panniculitis. The most common causes, especially in children, are streptococcal infections (*Streptococcus pyogenes*, Group A), which account for 28%–44% of cases (Gilchrist & Patterson, 2010). Streptococcal upper respiratory system infections and cutaneous bacterial infections, such as cellulitis, can also cause erythema nodosum. Clinically, erythema nodosum presents as erythematous nodules and plaques on the anterior aspects of the legs. Magro et al. (2008) reported 10 cases of acute neutrophilic lobular panniculitis associated with bacterial infections. Lesions resolved following antibiotic treatment and/or abscess drainage. A serologic investigation of these cases revealed polyclonal hypergammaglobulinemia, cold agglutinins, and cryofibrinogens. The authors noted that this particular form of panniculitis could be confused with Sweet's syndrome or rheumatoid arthritis (Magro et al., 2008). Cutaneous bacterial infections can also cause Sweet's syndrome, which is characterized by painful erythematous nodules and plaques. Many bacterial, fungal, and viral pathogens can also trigger Sweet's syndrome. The most common Sweet's-associated infection is streptococcal pneumonia. Cellulitis can also trigger Sweet's syndrome, and in immunocompetent hosts, cellulitis is most commonly caused by *S. pyogenes* or *Staphylococcus aureus* (Dinh et al., 2007).

Pustular bacterid was first described by Andrews and Machacek (1935). It is an acute monomorphic eruption of sterile pustules on the hands and feet. Whether it is a distinct entity or merely an acute variant of palmoplantar pustulosis is unclear. The term "bacterid" implies that the eruption is provoked by a remote bacterial infection (Griffihtis & Barker, 2010). Infections with diphtheroid bacteria can result in pitted keratolysis, erythrasma, and trichobacteriosis. Dyshidrosiform vesicular lesions have been reported in 5.6% of patients with pitted keratolysis that was clinically characterized by isolated or multiple pitted lesions in whitish hyperkeratotic areas and/or coalescent erythematous ringed lesions on the plantar aspects of the feet (Blaise et al., 2008; Figure 2). Additionally, Kaya et al. (2003) reported a case of severe erythema nodosum caused by Behçet's disease. These nodular lesions did not respond to classical treatments; however, the lesions disappeared after erythromycin treatment, which was prescribed for the treatment of erythrasma (Kaya et al., 2003).

Id reactions caused by *Mycobacterium* species have been well-documented and are characterized by distinctive eruptive lesions, which are collectively called tuberculids in response to active *M. tuberculosis* infection. The different types of tuberculids include the following: (i) papulonecrotic tuberculids (Wilson-Jones & Winkelmann, 1986), (ii) erythema induratum (Rademaker et al., 1989), (iii) lichen scrofulosorum (Smith et al., 1976), and (iv) lichenoid tuberculids (Oakley & Montgomery, 1950). Similar tuberculid-like id reactions have been reported after bacillus Calmette-Guérin immunization (Figueiredo et al., 1987) and with *M. bovis* infections (Iden et al., 1978). Vasculitis is present in papulonecrotic tuberculids (Wilson-Jones & Winkelmann, 1986) and erythema induratum (Rademaker et al., 1989). Papulonecrotic tuberculids are characterized by a symmetrical, papular, pustular eruption that involves the hands, feet, and exterior surfaces of the extremities (Wilson-Jones & Winkelmann, 1986). However, id

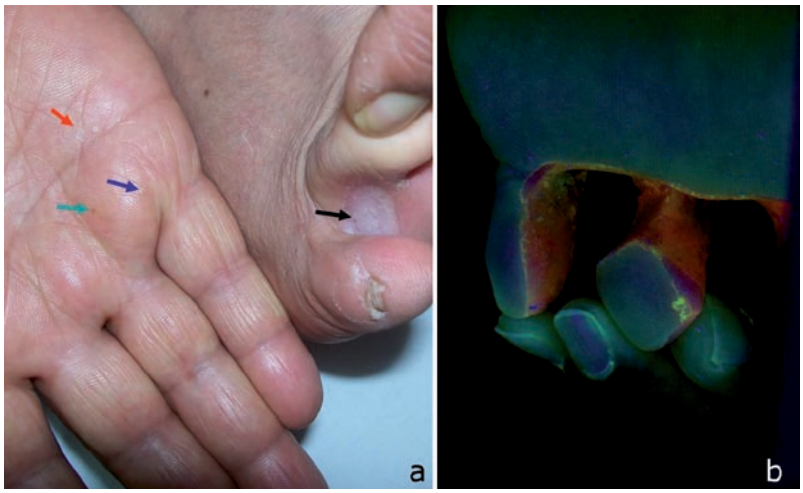

Figure 2. A vesicular id reaction associated with erythrasma. Maceration (black arrow) between the toes and a vesicle (blue arrow), a tiny crust (green arrow) and tiny collarette scales (red arrow) on the palm (A) are shown. A Wood light examination revealed a coral-red appearance, denoting erythrasma between the toes (B). All lesions completely resolved with treatment of the erythrasma.

reactions caused by *M. leprae* presented as a generalized skin rash; histopathologically, the lesion appearance was distinctive, exhibiting elongated granulomas and foci of incipient perineural granuloma formations, similar to the histomorphologic appearance of tuberculoid leprosy (Choudhri et al., 1994).

Id reactions caused by viral infections

The most common cutaneous viral disease is warts. However, viral id reactions most commonly occur in herpetic infections. In adults and children, the most common cause of recurrent erythema multiforme is herpes labialis and herpes genitalis (Weston, 2005). HSV type I-associated erythema multiforme is characterized by a symmetrically distributed macules, papules, bullae, and targetoid lesions with a central vesicle or bulla. These lesions tend to present on the distant extremities and oral mucosa (Aurelian et al., 2003). Although less commonly involved, other mucosal surfaces (genital and ocular) can be affected in recurrent erythema multiforme (Pope & Krafchik, 2005). Cases of nevocentric erythema multiforme have been reported. It is hypothesized that nevocentric localization occurs because of the abnormal vasculature in the nevus (McKenna, 1999). Rarely, herpetic infections can trigger chronic urticaria; thus, a detailed history and dermatologic examination is important for the diagnosis of chronic urticaria. Antiviral treatment provides long-term remission of urticaria without antihistamine therapy (Zawar et al., 2010). Several cases of pemphigus vulgaris (PV) that were caused or exacerbated by HSV have been described in the literature (Sagi et al., 2008). Ruocco et al. (1996) examined 10 patients with PV-associated HSV infections that activated or exacerbated the disease; of these patients, seven had positive viral cultures and five had positive serologies.

In poxvirus infections, id reactions are most frequently associated with orf. Although orf and milker's nodules are clinically similar to each other, id reactions are more rare in patients with milker's nodules. The infectious source of these conditions also differs; sheep and goats are associated with orf, while cows are associated with milker's nodules. Erythema multiforme, morbilliform, and vesicular eruptions have been reported after an orf infection (Figures 3 and 4). Erythema multiforme reactions have been reported in 4%–13% of orf cases (Diven, 2001). Mucous membrane pemphigoid (one case) and bullous pemphigoid (BP)-like eruptions (five cases) have also been reported following orf infection (Murphy & Ralfs, 1996; van Lingen et al., 2006). Additionally, White et al. (2008) reported two cases of an autoimmune bullous disease that were immunologically distinct from bullous pemphigoid, epidermolysis bullosa acquisita, and other known autoimmune immunobullous diseases. In these cases, a histologic examination revealed subepidermal separation and mixed inflammatory cell infiltrates containing neutrophils and eosinophils. A direct immunofluorescence investigation revealed IgG and C3 deposits at the dermoepidermal junctions; indirect immunofluorescence studies revealed antibasement membrane IgG at the dermal side of salt-split skin. The autoantigen could not be identified by extensive immunoblot and immunoprecipitation studies (White et al., 2008). However, erythema multiforme has been reported in one case of milker's nodules, which was triggered by graft-versus-host disease after an allogeneic hematopoietic stem cell transplantation for multiple myeloma (Slattery et al., 2005). Another poxvirus infection is molluscum contagiosum, which is clinically characterized by small, firm, umbilicated papules. This viral infection particularly affects children and sexually active adults; on rare occasions, it can trigger erythema multiforme and erythema annulare centrifugum (Furue et al., 1993; Lee et al., 2009). The eruption of erythema annulare centrifugum begins as small raised erythematous macules or papules that slowly

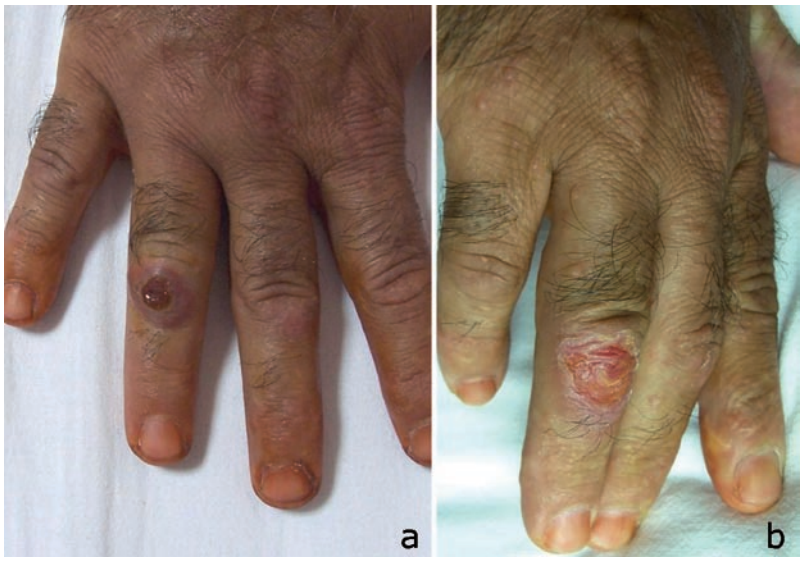

Figure 3. A vesicular id reaction associated with orf. A painless noduloulcerated lesion on the right index finger of a 30-year-old man (A) is shown. The lesion developed 10 days after contact with sheep, and a Tzanck smear revealed a Guarnieri body. The clinical and cytologic findings confirmed orf. Small vesicular lesions were seen on the fingers of the patient 2 weeks after the first admission (B). Lesions resolved within 2 weeks.

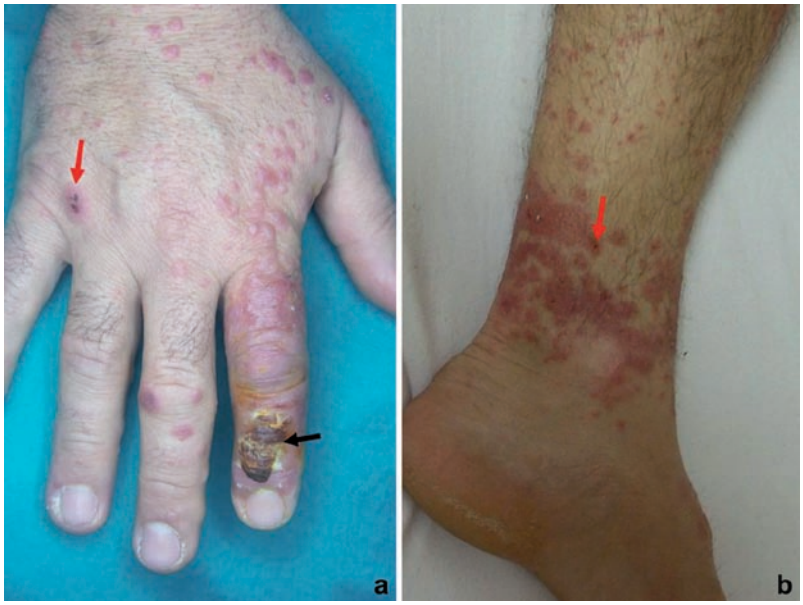

Figure 4. Erythema multiforme due to orf. A painless ulcerated lesion covered with a brown–black crust on the right index finger (black arrow) and partially confluent erythematous papules and plaques with a target formation (red arrow) on the hand (A), the leg, and the ankle (B). The ulcerated lesion occurred 3-weeks prior to admission. The patient had contact with sheep 1-month prior to admission. Tzanck smear examination of ulcerated lesion revealed a Guarnieri body. Clinic and cytologic findings of ulcerated lesion were compatible with orf. Histopathological examination of targetoid lesions indicated compatibility with erythema multiforme. Erythema multiforme lesions resolved within 2 weeks.

enlarge (by about 2–5 mm/day) and form a ring shape while the central area flattens and clears.

Id reactions caused by parasitic infections

Allergic skin diseases caused by cutaneous leishmaniasis were first reported by Chaim Berlin in 1940. Berlin (1940) detected asymptomatic papular eruptions on the faces and extremities of patients with leishmania recidiva cutis. A histopathologic examination of these lesions revealed a "tuberculoid" structure. The leishmanin test was positive, and the eruptions faded completely with antileishmanial therapy. This reaction was termed "leishmanid" (Berlin, 1940). After 13 years, the same author reported a similar case of papular leishmanid associated with leishmania recidiva cutis (Berlin, 1953). Papular lesions with infiltrated bases were spread over the face, neck, trunk, and upper limbs of the patient (Figure 5). Some lesions had undergone pustulation or were ulcerous-crusted

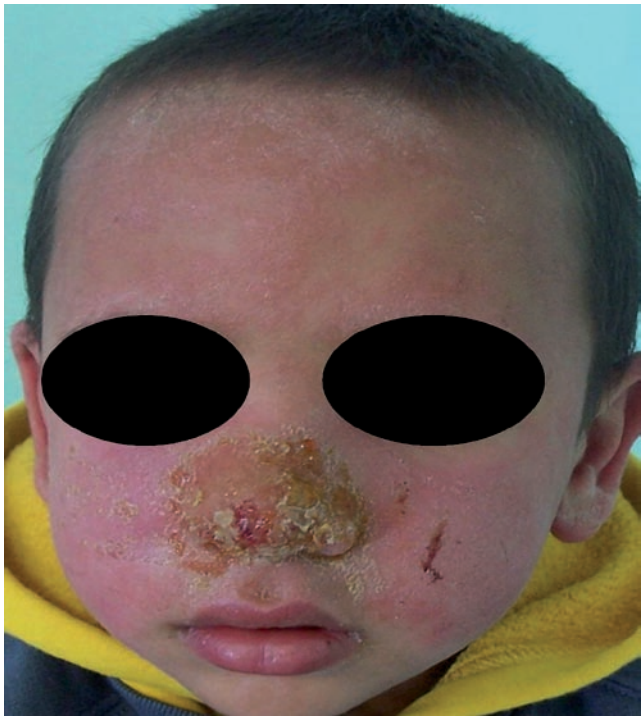

Figure 5. Leishmanid. Pictured is a six-year-old boy with noduloulcerated lesions covered with a yellow crust on the tip of his nose and erythematous and squamous lupoid papules and plaques on his face. The noduloulcerated lesions on the nose had appeared 8 months before admission. Erythematous papules and plaques had developed 2 weeks before admission. A Tzanck smear examination of the noduloulcerated lesions revealed *Leishmania* parasites, but no parasites were found in other papules and plaques. The patient was treated with systemic meglumine antimoniate (Glucantime) at a dose of 20 mg/kg/day (b.i.d, intramuscularly) for 14 days. All lesions completely resolved within 3 weeks.

craters (e Silvia and de Oliveira, 1973). Rarely, cutaneous leishmaniasis can trigger erythema nodosum (Youssef et al., 2009).

Other parasitic infections, such as scabies and pediculosis, can cause id reactions. Id reactions due to scabies, which are known as scabid reactions, can be seen as urticarial lesions. For this reason, scabies should be investigated in patients with urticaria and excoriation (Brenner et al., 1993). Rarely, pediculosis can cause erythema annulare centrifugum, nummular eczema, or pityriasis rosea-like id reactions (Brenner et al., 1984; Bessis et al., 2003).

Differential diagnosis

The differential diagnosis must exclude of the causes of clinical phenotypes that present as localized or widespread vesicular lesions, maculopapular or scarlatiniform eruptions, erythema nodosum, erythema multiforme, erythema annulare centrifugum, Sweet's syndrome, guttate psoriasis, and autoimmune bullous diseases. A differential diagnosis of id reactions depends on the clinical form of the reaction (Table 1). Additionally, erythema nodosum, erythema multiforme, erythema annulare centrifugum, and Sweet's syndrome do not only develop due to id reactions from cutaneous infections; these reactions can also occur in association with systemic or other tissue infections, malignancy, connective tissue diseases, and drug reactions. For example, erythema nodosum is a diagnostic criterion for Behçet's disease. However, this reaction can occur due to infections in patients with Behçet's disease and can disappear after the treatment of the infection. Therefore, patients should be thoroughly questioned, and a detailed dermatologic examination should be performed (Kaya et al., 2003). Clinicians must be able to distinguish dermatophytids from drug-induced allergic reactions, and continuation of systemic treatment is essential to clear the underlying infection and dermatophytid (Fuller et al., 2003; Cheng et al., 2011). Drug-induced allergic reactions most commonly present with diffuse, symmetric, monomorphous, morbilliform eruptions. These reactions remit only after discontinuing the offending medication and recur with re-exposure (Friedmann et al., 2010).

Dermatophytid reactions might occasionally manifest as migratory thrombophlebitis or erysipelas-like dermatitis of the lower extremities (Waisman, 1946; Lazar, 1953). The erysipelas-like dermatophytid is most commonly seen on the skin, where it appears as an elevated, sharply defined, erysipelas-like plaque approximately the size of the hand, usually with tinea pedis on the same side of the body. This id reaction responds to systemic steroids and tinea treatment (Lazar, 1953).

Histopathology

The histopathologic features of id reactions vary depending on the lesion type, but these features are not specific for id reactions. Furthermore, the histopathology can not distinguish between id reactions and other causes of the clinical reaction. For example, the histopathologic features of idiopathic bullous pemphigoid and bullous pemphigoid due to id reactions are similar. Histopathology distinguishes the type of id reaction. For example, Sweet's syndrome and erythema nodosum are clinically characterized by erythematous nodules, but the histopathologic features are different. Erythema nodosum typically presents as septal panniculitis without vasculitis. The inflammatory infiltrate is predominantly neutrophilic during the early stages. A histopathologic examination of Sweet's syndrome lesions reveals dense perivascular neutrophilic infiltration, prominent edema of the upper dermis, vasodilation, endothelium swelling, and leukocytoclasia (Dinh et al., 2007). Both histopathologic and immunofluorescence examinations are required to diagnose pemphigus and other autoimmune bullous diseases (Murphy & Ralfs, 1996; Ruocco et al., 1996).

Etiological agents

A literature review revealed that id reactions secondary to cutaneous infections have been reported most commonly in superficial fungal infections, especially in cases of tinea

Table 1. Differential diagnosis for various clinical presentations of id reactions.

Id reactions	Differential diagnosis	Id reactions	Differential diagnosis
Localized vesicular lesions on the hand	Irritant contact dermatitis	Widespread vesicular eruption	Irritant contact dermatitis
	Allergic contact dermatitis		Allergic contact dermatitis
	Tinea manuum		Dermatitis herpetiformis
	Dyshidrosiform pemphigoid		Pemphigus herpetiformis
	Dyshidrosiform pemphigus		Varicella
	Palmoplantar pustulosis		Insect-bite reactions
			Drug reaction
Maculopapular eruption	Drug reaction	Erythema annulare centrifugum	Tinea corporis
	Serum sickness		Erythema gyratum repens
	Viral exanthem		Erythema migrans
	Scarlet fever		Annular urticaria
	Drug-related hypersensitivity syndrome		Bullous pemphigoid (urticarial phase) Erythema multiforme
	Cholinergic urticaria		Annular psoriasis
	Miliaria rubra		Annular lupus erythematosus
			Erythema marginatum
			Necrolytic migratory erythema
Erythema multiforme	Polymorphic light eruption	Psoriasiform id reactions	Tinea corporis
	Maculopapular drug eruption		Secondary syphilis
	Urticaria		Nummular dermatitis
	Lupus erythematosus		Pityriasis rosea
	Sweet's syndrome		Pityriasis lichenoides chronica
	Paraneoplastic pemphigus		
Sweet's syndrome	Cellulitis and erysipelas	Bullous pemphigoid	Pemphigus
	Erythema nodosum and other panniculitis		Epidermolysis bullosa acquisita Mucous membrane pemphigoid
	Leukemia cutis		Dermatitis herpetiformis
	Pyoderma gangrenosum		Erythema multiforme
	Erythema elevatum diutinum		Pemphigoid gestasyones
	Erythema multiforme		Cicatricial pemphigoid
	Familial Mediterranean fever		Linear immunoglobulin A disease
	Urticaria		Bullous lupus erythematosus
Urticaria	Erythema multiforme	Nummular dermatitis	Tinea corporis
	Viral exanthema		Psoriasis
	Sweet's syndrome		Stasis dermatitis
	Insect bite		Atopic dermatitis
	Erythema annulare centrifugum		Allergic contact dermatitis Mycosis fungoides
	Erythema marginatum		Fixed drug eruption
	Bullous pemphigoid (urticarial phase)		
	Serum sickness		
Generalized follicular papules	Lichen nitidus		
	Lichen planopilaris		
	Lichen spinulosis		
	Lichen scrofulosorum		
	Secondary syphilis		
	Keratosis pilaris		

pedis. The fungi isolated from the primary lesion are often zoophilic and geophilic species; anthropophilic dermatophytes are rarely isolated (Atzori et al., 2003). It appears that an inflammatory dermatophyte species, such as zoophilic *T. mentagrophytes*, is a prerequisite for the induction of a dermatophytid (Hall, 1956; Kaaman & Torssander, 1983). Briefly, *T. mentagrophytes* is one of the two most common pathogens in fungal foot infections and is likely the most common cause of acute foot infections; chronic foot infections are more commonly associated with *T. rubrum*. The association of *T. mentagrophytes* with a dermatophytid formation is likely because *T. mentagrophytes* induces a greater immune response and is, therefore, more likely to produce a reaction, such as erythema multiforme (Salim & Young, 2002). Indeed, the etiologic agents underlying dermatophyte infections are most commonly caused by *T. mentagrophytes* (Hall, 1956; Kaaman & Torssander, 1983; Salim & Young, 2002; Atzori et al., 2003; Bassi & Kersey, 2009;

Liu et al., 2011), followed by *T. rubrum* (Hall, 1956; Veien et al., 1994; Romano, 1999), *E. floccosum* (Veien et al., 1994; Romano, 1999), *T. mentagrophytes* var. *quinckeanum* (Peck, 1930), *T. violaceum* (Romano et al., 2006b), *Arthroderma benhamiae* (Shiraki et al., 2006), *Microsporum canis* (Gianni et al., 2006), and *M. gypseum* (Peck, 1930). Notably, *E. floccosum* can also generate more inflammation than *T. rubrum* (Kaaman, 1981). Additionally, *Coccidioides immitis* (Chang et al., 2003), *C. albicans* (Fergusson et al., 1966), *Corynebacterium* spp. (Blaise et al., 2008), *S. pyogenes*, *S. aureus* (Dinh et al., 2007), *Phthirus pubis* (Brenner & Yust, 1988), and *Sarcoptes scabiei* (Brenner et al., 1993) have also been isolated as the etiologic agents of the related underlying infections. Sometimes bacterial and fungal pathogens in combination can cause id reactions (Iglesias et al., 1994). Id reactions are known to occur following infections caused by *M. tuberculosis* (Oakley & Montgomery, 1950), *M. bovis* (Iden et al., 1978), and *M. leprae* (Choudhri et al., 1994). In cutaneous viral infections, id reactions most commonly develop due to HSV. Other viral infections associated with id reactions are molluscum contagiosum, orf, and milker's nodules.

Immunology

An id reaction is an allergic reaction that is characterized by an increased sensitivity to a microbial antigen. Host T lymphocytes mediate immediate, cytotoxic, immune complex or delayed-type hypersensitivity (Woodfolk et al., 2000; Table 2). The cutaneous findings caused by these cytokines are known as id reactions.

Treatment

The goal of treatment is to adequately treat the underlying infection or dermatitis, which should lead to a prompt resolution of the id reaction. Recurrences is common if the primary source is not treated adequately. Eruption and any associated pruritus are treated by systemic or topical corticosteroids, systemic or topical antihistamines, lubricants, and wet compresses (Cheng et al., 2011; Greenberg, 2011). However, these therapies only treat the symptoms, not the underlying infection (Cheng et al., 2011). Furthermore, corticosteroids hasten the resolution of the id reaction and aid in hyposensitization (Grappel et al., 1974). Additionally, antifungal therapy should be continued through the course of a dermatophytid to clear the infection and consequently resolve the id reaction (Fuller et al., 2003; Cheng et al., 2011). Unfortunately, practical experience has demonstrated that the id eruption can, and often does, persist long after all traces of the primary infection have vanished. In an earlier report, Williams (1927) stressed the necessity of including the nails as a potential depot of fungal persistence. In kerion, systemic corticosteroid therapy is warranted along with antifungal therapy if the dermatophytid reaction is extremely widespread or if inflammation is present (Honig et al., 1994). After the dermatophytid clears, post-inflammatory hyperpigmentation is common and usually resolves without treatment in a month (Cheng et al., 2011).

Id reactions following therapy with griseofulvin (Romano, 1999; Bassi & Kersey, 2009; Cheng et al., 2011), itraconazole (Romano et al., 2006b; Shiraki et al., 2006), and terbinafine have also been reported (Atzori et al., 2003). Treatment with antiviral agents is required in erythema multiforme associated with an HSV infection. A 5-day course of 200 mg of acyclovir five times daily at the first sign of lesions can treat the infection. Additionally, 400 mg of acyclovir four times daily for 6 months or continuous treatment using 500 mg of valacyclovir twice daily is useful for prophylaxis (Scully & Bagan, 2008).

Conclusion

An id reaction is a secondary vesicular dermatitis caused by autosensitization to a remote antigen. A dermatophytid,

Table 2. The mechanisms of id reactions.

Type of hypersensitivity		Immune effector mechanisms	Clinical manifestations
Type I (immediate-type reaction)		IgE binds to the surfaces of mast cells or basophils, and these cells release histamine and other mediators.	Urticaria, angioedema, or anaphylaxis
Type II (cytotoxic reaction)		Antibodies activate the classic complement system or bind to cells through Fcg receptors to activate cytotoxic cells.	Pemphigus and other autoimmune bullous diseases
Type III (immune complex reaction)		Circulating immune complexes are deposited in vascular beds or on tissue surfaces. Complement is activated, neutrophils are attracted, and their products damage tissues.	Vasculitis, erythema nodosum, pemphigus, and other autoimmune bullous diseases
Type IV (delayed-type hypersensitivity reaction)	IV a	T-helper type 1 (Th1) T cells activate macrophages by secreting large amounts of interferon-gamma (IFN-γ) and TNF-α.	Contact dermatitis-like vesicular lesions
	IV b	T-helper type 2 (Th2) T cells secrete the cytokines IL-4, IL-5, and IL-13. These cytokines promote IgE- and IgG_4-type antibody production from B cells in addition to mast-cell and eosinophil responses.	Maculopapular eruption
	IV c	CD8+ cells move to the infected tissues and kill the infected cells in a perforin/granzyme B- and/or FasL-dependent manner.	Erythema multiforme
	IV d	T cells express CXCL-8 and GM-CSF.	Pustular id reactions

an id reaction variant, occurs away from the primary lesion and is usually caused by an immunological reaction to the antigens derived from the fungal pathogen (e.g. dermatophytic fungi). An acute onset of extremely pruritic, erythematous, maculopapular, or papulovesicular eruptions occurs 1–2 weeks after the primary infection or dermatitis. The trichophytin test is always positive in patients who develop dermatophytids. The clinical manifestations of id lesions are polymorphic and include eczema, erysipelas, and erythema multiforme. An id reaction can be diagnosed clinically based on the lesion morphology and chronologic association with the antifungal therapy initiation. Unlike the underlying condition, these lesions are pathogen-negative upon a direct microscopic examination and fungal culture. It is thought that secondary id eruptions clear when the primary focus of the infection is eliminated. The goals of pharmacotherapy are to reduce morbidity and to prevent complications.

Much progress from both clinical and laboratory standpoints has been made in the study of superficial fungal diseases in the last century to enhance our understanding of dermatophytosis and dermatophytids. Today, both clinicians and microbiologists should record and report lesional features, taking into account the underlying clinical picture and etiologic agents. Consequently, more epidemiological data will be required to further advance our understanding of the id response. Additionally, future studies should highlight the pathogenic and immunologic processes relevant to id reactions.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

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