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Differential Diagnosis of Neonatal and Infantile Erythroderma

Lena Kotrulja[1], Slobodna Murat-Sušić[2], Karmela Husar[2]

[1]University Department of Dermatology and Venereology, Sestre milosrdnice University Hospital; [2]University Department of Dermatology and Venereology, Zagreb University Hospital Center and School of Medicine, Zagreb, Croatia

Corresponding author:
Lena Kotrulja, MD, MS
University Department of Dermatology and Venereology
Sestre milosrdnice University Hospital
Vinogradska 29
HR-10000 Zagreb
Croatia
lena.kotrulja@zg.t-com.hr

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SUMMARY Neonatal and infantile erythroderma is a diagnostic and therapeutic challenge. Numerous underlying causes have been reported. Etiologic diagnosis of erythroderma is frequently difficult to establish, and is usually delayed, due to the poor specificity of clinical and histopathologic signs. Differential diagnosis of erythroderma is a multi-step procedure that involves clinical assessment, knowledge of any relevant family history and certain laboratory investigations. Immunodeficiency must be inspected in cases of severe erythroderma with alopecia, failure to thrive, infectious complications, or evocative histologic findings. The prognosis is poor with a high mortality rate in immunodeficiency disorders and severe chronic diseases such as Netherton's syndrome.

KEY WORDS: erythroderma, neonatal, infantile, generalized exfoliative dermatitis

INTRODUCTION

Erythroderma is defined as an inflammatory skin disorder affecting total or near total body surface with erythema and/or moderate to extensive scaling (1). It is a reaction pattern of the skin that can complicate many underlying skin conditions at any age. In neonatal period it can be the primary manifestation of numerous conditions (2). However, some disorders in infants may initially be localized and then eventually develop into extensive erythroderma (1). Differential diagnosis includes benign transient, inflammatory, infectious, metabolic and immune diseases, many of which have a hereditary basis. Some of these diseases are potentially life threatening, and erythroderma itself can cause serious medical complications such as electrolyte imbalance, hypoproteinemia, dehydration, sepsis, and temperature instability (3).

Neonatal and infantile erythroderma is a diagnostic and therapeutic challenge. Erythrodermic neonates and infants are frequently misdiagnosed with eczema and inappropriate topical steroid treatment can lead to Cushing syndrome. Delay in the establishment of the correct diagnosis can be fatal. Differential diagnosis of erythroderma is a multi-step procedure that involves clinical assessment, knowledge of any relevant family history, and certain laboratory investigations (2).

Laboratory investigations

Differential diagnosis of erythroderma can be facilitated by some laboratory tests (Table 1). Serum IgE levels are profoundly increased in Netherton's and Omenn's syndromes, and mild-

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Table 1. Laboratory investigations in neonatal and infantile erythroderma

1. Potassium hydroxide (KOH) stain for demonstration of mycelia/spores and fungal culture
2. Gram's stain for bacteria and bacterial culture
3. Tzanck test
4. Demonstration of *Sarcoptes scabiei*
5. Microscopic analysis of hair shaft abnormalities
6. Complete hemogram
7. Skin biopsy for microscopic pathology
8. Serum zinc and alkaline phosphatase levels
9. Sweat chloride levels
10. Lipid profile including essential fatty acid levels
11. Evaluation of humoral and cellular immunity; IgA, IgG, IgM, IgE, complement component, T and B lymphocytes
12. Biotinidase/holocarboxylase synthetase levels
13. Plasma amino acid levels and urine organic acids

ly increased in early atopic eczema. Appropriate smears for potassium hydroxide (KOH) stain, Gram stain, Tzanck test as well as cultures for fungal, bacterial, or viral diseases should be performed if infection is suspected. Chest radiograph may be useful to evaluate thymic shadow, which may be absent in neonates with severe combined immunodeficiency (SCID) (3). Serum electrolyte and albumin concentrations should be measured because children with erythroderma are at a risk of hypernatremic dehydration as well as enteral and transcutaneous protein losses. Complete blood count should be supplemented by more detailed immunologic studies if Omenn's syndrome or graft-versus-host disease is suspected (2). Serum amino and urine organic acids should be determined if primary metabolic diseases such as aminoaciduria or biotin deficiency are suspected. Biotinidase level can be obtained if biotin deficiency is suspected (3).

HISTOLOGY

As it is very important to establish the diagnosis rapidly, it is advisable to take two or three simultaneous skin biopsies from different sites. Histology and immunohistochemistry can differentiate Omenn's from Netherton's syndrome and other ichthyoses. Fibroblast culture from biopsy can help reach definitive diagnosis of several metabolic diseases (3). Non-bullous and bullous ichthyosiform erythroderma are distinguishable on histology (4). In the graft-versus-host reaction, histology is valuable in severe cases, but in milder cases only some of the findings may be present and the diagnosis can easily be missed. In blistering diseases, it is helpful to take biopsy from the border of the blister, including its roof, to facilitate assessment of the level of cleavage (2).

It is helpful to divide the subject of neonatal erythroderma into several categories, roughly according to pathogenesis (Table 2).

Table 2. Causes of neonatal and infantile erythroderma

Transient neonatal dermatoses
Erythema toxicum neonatorum
Miliaria
Cutaneous disorders
Atopic dermatitis
Infantile seborrheic dermatitis
Psoriasis
Diffuse cutaneous mastocytosis
Ichthyosis
Netherton's syndrome
Infections
Staphylococcal scalded skin syndrome (SSSS)
Congenital and neonatal candidiasis
Congenital herpes simplex infection
Syphilis
Toxic and drug reactions
Toxic epidermal necrolysis
Drug reactions
Metabolic disorders
Acrodermatitis enteropathica
Cystic fibrosis
Essential fatty acid deficiency
Amino acid disorders
Disorders of biotin metabolism
Immune disorders
Graft versus host disease (GVHD)
Severe combined immunodeficiency (SCID)
Omenn's syndrome
Hypogammaglobulinemia

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TRANSIENT NEONATAL DERMATOSES

Erythema toxicum neonatorum (ETN) is the most common transient benign rash in healthy neonates. The incidence is controversial, and ranges from 30% to 70% in various surveys. The cause of ETN has not yet been established (5). The presence of ETN correlates well with birth weight and gestational age. It is virtually never seen in premature infants or those weighing less than 2500 g (6).

Congenital lesions may occur, but the majority of cases have the onset between 24 and 48 hours of life. Lesions wax and wane, usually lasting for a week or less, but cases lasting beyond 2 weeks of life have been reported. It is characterized by small erythematous macules with or without central papule or pustule, measuring 1 to 3 mm in diameter, which may appear first on the face and spread to the trunk and proximal extremities, but may appear anywhere on the body except for the palms and soles (Fig. 1a) (5,6). Although the characteristic lesions of ETN are usually discrete and scattered, extensive cases with confluent papules,

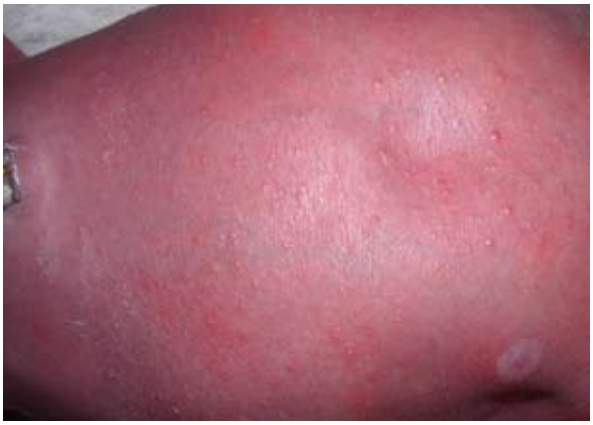
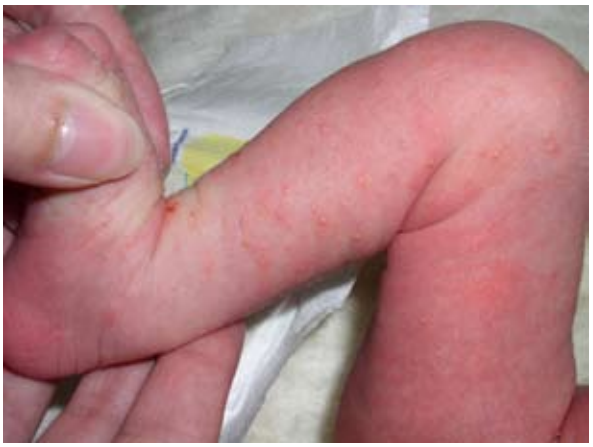


Figure 1. (a) Erythema and pustules in erythema toxicum neonatorum; (b) erythema toxicum neonatorum with numerous pustules.



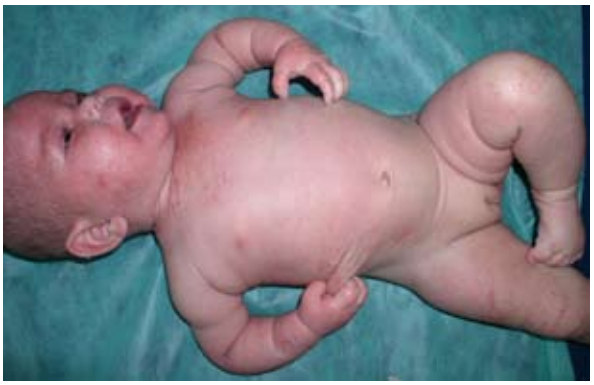


Figure 2. Atopic dermatitis, a more extensive distribution with pronounced pruritus.

or pustules with surrounding erythema forming erythematous plaques can occur and be more difficult to diagnose (Fig. 1b). Peripheral eosinophilia has also been associated in about 15% of cases (6). Skin biopsy is rarely needed. The diagnosis of ETN can usually be made by clinical appearance alone, but scraping of the pustule will reveal eosinophils with a few scattered neutrophils. No therapy is needed, for ETN resolves spontaneously (5,6).

MILIARIA

The term miliaria is used to describe a group of transient eccrine disorders. Miliaria is common in summer months and is also noted in infants housed in incubators (5). There are three forms of miliaria due to occlusion of sweat ducts at various levels, resulting in leakage of sweat in the epidermis or papillary dermis. Only miliaria rubra can progress to erythroderma, mostly in hot and humid conditions (5,6). Miliaria rubra occurs between the 11^{th} and 15^{th} day of life and it usually affects sites of friction or occlusion such as the neck and face, but also occurs on the trunk. Lesions are erythematous, non-follicular papules or papulovesicles of 1-3 mm in size (6).

CUTANEOUS DISORDERS

Atopic dermatitis

Atopic dermatitis (AD) presents within the first 6 months of life in 60% of children. Severe generalized AD is unusual in neonates, but because AD is such a common problem, it is the most common cause of acquired or non-congenital erythroderma in infants (Fig. 2) (3). From the clinical point of view, in the first months of life AD is characterized by exudative lesions. There is considerable overlap between the manifestation of infantile seborrheic dermatitis and AD, and some authors believe that infantile seborrheic dermatitis is a variant of AD (2,7). About 30% of cases of AD starting in the

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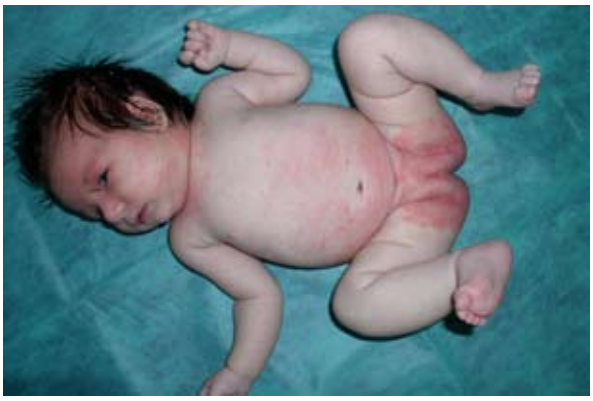

Figure 3. Infantile seborrheic dermatitis with involvement of the head, face, body folds and napkin area.

first months of life involve primarily the scalp with lesions resembling seborrheic dermatitis (2).

Classic infantile AD involves the scalp, cheeks and extensor surfaces of the extremities, and does not appear until the infant is 2 to 3 months of age. Itching in children with AD is usually not apparent until 2 to 3 months of age (2,7). Typically, the diaper region is spared even in cases of widespread AD, as a result of the moist, occlusive environment caused by the diaper. AD may occasionally be complicated by a rare form of food hypersensitivity known as eosinophilic gastroenteritis, mostly to cow's milk protein, with excessive loss of protein through the gastrointestinal tract (8).

When the distribution is generalized and the onset early, the diagnosis can be more difficult. In contrast to infants with severe metabolic or immune disease, infants with AD usually grow and thrive normally, assuming the disease is recognized and treated promptly (3).

Seborrheic dermatitis

Infantile seborrheic dermatitis typically presents during the first month of life. The characteristic feature of infantile seborrheic dermatitis is inflammation, yellowish scaling on the scalp (cradle cap) with frequent involvement of the skinfolds of the neck, axillae, and groin (Fig. 3). The lesions are sometimes more infiltrated and resemble psoriasis. Progression to erythroderma is rare (9).

A syndrome characterized by erythema, infiltration and desquamation in the seborrheic localization with rapid progression to erythroderma, accompanied by recurrent local and systemic infections, severe diarrhea and failure to thrive was called Leiner's disease. It was considered to be caused by complement C5 deficiency or dysfunction (8). The term is no longer appropriate because it probably refers to a heterogeneous group of disorders (10). It has become clear, over the past decade, that Leiner's disease is an "umbrella phenotype" rather than a specific entity, and often applied to babies in whom the known causes of erythroderma have been excluded (2).

Infants with erythroderma, failure to thrive and chronic diarrhea need thorough investigations, searching for the underlying cause of their disorder. In Leiner phenotype, many of the diseases need to be considered, especially immunodeficiencies, Netherton's syndrome and Omenn's syndrome (3).

Psoriasis

Congenital psoriasis, meaning psoriasis present at birth or appearing during the neonatal period, is exceptional. Only 15 cases of congenital erythrodermic psoriasis have been reported (11,12). Positive family history for psoriasis and human leukocyte antigen (HLA) B17 is found in more than half of the patients and their relatives (12). Congenital and neonatal erythrodermic psoriasis are among the most serious and difficult forms of psoriasis to treat. Clinical diagnosis is usually difficult, and many differential diagnoses should be considered, mainly congenital non-bullous ichthyosiform erythroderma (11). Most cases later develop classic erythematosquamous lesions (13).

Less than 1% of all cases of psoriasis occur in infants under 1 year of age (3). Infantile psoriasis may have similar clinical presentation as both seborrheic and atopic dermatitis. Facial involvement may be more common in the infant, and the scalp, palms and soles may have diffuse erythema and scales. Psoriasis in infants often involves the diaper area because it develops in areas of injured skin (Koebner phenomenon), e.g., after prior irritant or candida diaper dermatitis (Fig. 4) (14). Cases of

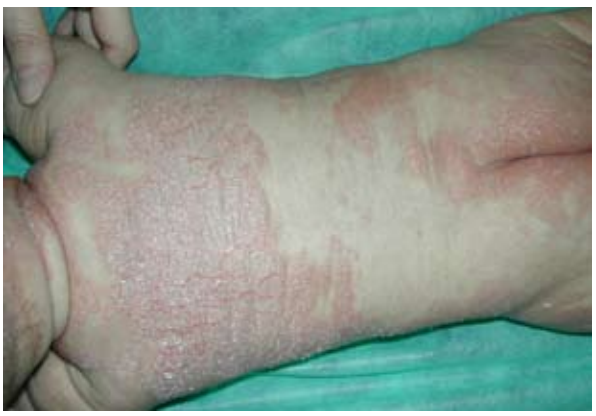

Figure 4. Napkin psoriasis: psoriasiform confluent generalized lesions started in the napkin area.

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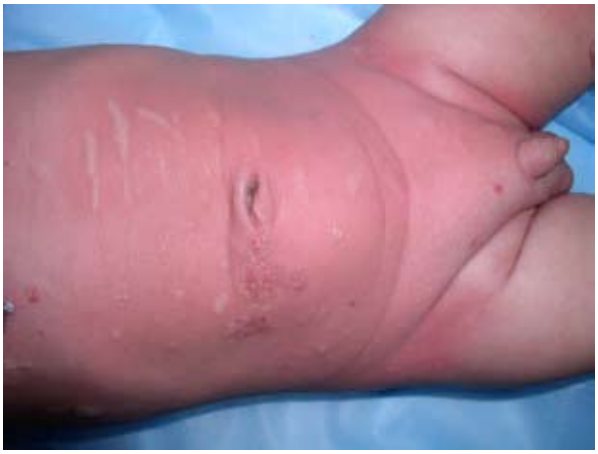

Figure 5. Diffuse cutaneous mastocytosis. The entire skin is erythematous, heavily infiltrated and thickened, Darier's sign is positive with urtication and bullae formation.

infantile psoriasis may prove to be mild and occasionally even clear completely as the child gets older. The prognosis of generalized erythrodermic or pustular psoriasis in infancy is more guarded, and treatment usually requires systemic retinoid therapy as well as supportive care (3).

Diffuse cutaneous mastocytosis

It is a rare variant of mastocytosis that generally presents in the neonatal period. The entire skin is heavily infiltrated with mast cells; the skin is thickened, lichenified and erythematous, and may have leathery appearance (8). Mild pressure or trauma to the skin induces mast cell release with urtication (Darier's sign) that can progress to bulla formation (Fig. 5). In the first months of life, the condition can be dangerous and life threatening due to electrolyte and fluid loss (15). Bullous manifestations in mastocytosis occur only in the first two or three years of life. Blister formation may mimic staphylococcal scalded skin syndrome (16). To distinguish mastocytosis from vesicular and bullous neonatal disorders, Darier's sign and Tzanck smear should be performed. Systemic symptoms such as flushing attacks, respiratory difficulty and diarrhea are common. Rarely, infants may have extracutaneous mast cell infiltration (gastrointestinal tract, bones, liver, spleen and lymph nodes). Systemic mastocytosis and mast cell leukemia are extremely rare in childhood. Mastocytosis tends to remit spontaneously, especially when it occurs in infancy or early childhood. Skin biopsy is diagnostic with a dense, band-like infiltrate of mast cells in the upper dermis, which can be confirmed with Giemsa stain (3).

Treatment is directed at alleviation of symptoms; H1- and H2-receptor antagonists, disodium cromoglycate and ketotifen (a stabilizer of mast cell membranes) are helpful. Particular foods and medicines can liberate histamine and should be restricted. Children with a history of anaphylaxis should be equipped with injectable adrenaline in the form of an Epi-Pen. Special care should be taken when these patients are to undergo anesthesia (8).

Ichthyosis

Hereditary ichthyoses are a large and heterogeneous group of disorders, which have in common rough, dry and scaly skin. Of the different types of ichthyosis, congenital non-bullous ichthyosiform erythroderma (CIE)/lamellar ichthyosis (LI) and bullous ichthyosiform erythroderma (bullous CIE) manifest at birth with variable degrees of erythroderma. CIE is characterized by fine white-grayish scales and erythroderma, and LI manifests as generalized ichthyosis with large, dark, plate-like scales and an underlying mild or minimal erythema. At present, LI and CIE may be considered two polar ends of the clinical spectrum, caused by several different genes and including many intermediate phenotypes (17,18). About 90% of patients present at birth as "collodion babies" with a glistening membrane which envelopes the neonate and produces ectropion, eclabium and nasal obstruction (Fig. 6).

Bullous CIE, also referred to as epidermolytic hyperkeratosis (EH), presents with generalized erythema and superficial blisters that are frequently mistaken for staphylococcal scalded skin syndrome (SSSS) or epidermolysis bullosa.

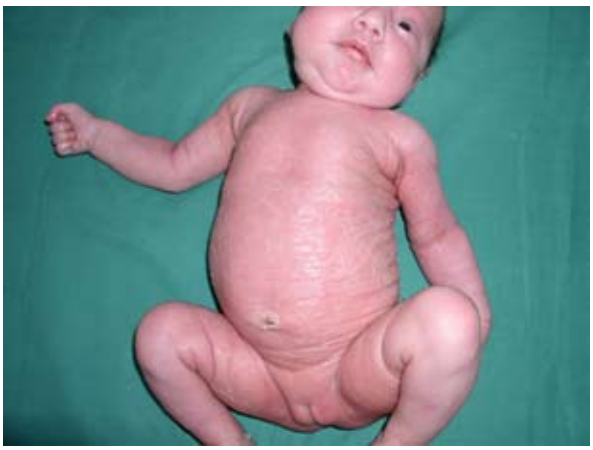

Figure 6. Collodion baby with a generalized glistening, taut membrane stretched over the entire skin, constricting band encircling the digit on the right hand.

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These children later develop typical ichthyosiform hyperkeratosis. It is transmitted as an autosomal dominant trait with mutations in the genes encoding keratin 1 and 10, however, spontaneous mutations may account for approximately one-half of cases (2,18).

Interestingly, some parents to the children with bullous CIE have had limited disease expression in the form of linear epidermal nevi with similar histology to EH. It has been proven that mosaic keratin 10 mutations give rise to an epidermolytic epidermal nevus, whereas the presence of the mutation in all cells gives rise to bullous CIE. The mutation can involve other organs including gonads. In patients with linear epidermolytic epidermal nevus, gonadal mosaicism may be responsible for transmission of the abnormality to the offspring, leading to diffuse skin involvement in the child. Therefore, it is important to do histologic examination in all cases of linear epidermal nevus to look for EH. Patients with epidermolytic epidermal nevus should be informed on the possible risk of transmission of bullous CIE to the next generation (18-20).

Netherton's syndrome

Netherton's syndrome (NS) is a rare autosomal recessive genodermatosis that is classified as an ichthyosiform syndrome. Infants affected with this disorder show a triad of generalized exfoliative dermatitis, sparse hair with trichorrhexis invaginata ("bamboo hair"), and atopic features (Fig. 7). The main differential diagnosis is Omenn's syndrome, but in practice a frequent misdiagnosis is generalized atopic dermatitis (2,10). Ichthyosiform erythroderma in NS is worst in infancy and tends to improve in later childhood. Ichthyosis linearis circumflexa, with its migrating, erythematous patches and fringe of double-edged scales, develop after the age of 2 years (21). During the first year of life, patients with NS undergo a period of life threatening infections, hypernatremic dehydration, diarrhea and failure to thrive, with mortality of 30%-40% during this period (2). Apart from raised total IgE and multiple positive specific IgE reactions, there are no consistent immunologic abnormalities in NS (19,21).

Figure 7. Netherton's syndrome: generalized desquamative erythroderma and alopecia in an infant with failure to thrive complicated by sepsis.

Genetic linkage has been established to the mutation of SPINK-5 gene locus on chromosome 5q31-32 encoding the serum protease inhibitor LEKTI (lymphoepithelial Kazal type inhibitor). It is absent or abnormally expressed on immunohistochemistry staining in the stratum granulosum of patients with NS in comparison with normal skin (1,22). NS can be distinguished from neonatal graft-versus-host disease and Omenn's syndrome by psoriasiform acanthosis, thickening of the basement membrane, prominent dermal blood vessels, and dermal infiltrate in which lymphocytes and macrophages are represented equally (22).

INFECTIONS

Many perinatal or early neonatal infectious diseases are associated with skin eruption present at birth or in the early neonatal period.

Staphylococcal scalded skin syndrome (SSSS)

SSSS is a potentially life-threatening toxin-mediated manifestation of localized infection with certain toxigenic strains of *Staphylococcus aureus* (mostly group II phage, types 71 and 55). Exfoliative toxins (ET-A and ET-B) that have been characterized as serine proteases cause the symptoms. SSSS is predominantly a disease of infancy and early childhood, with most cases seen before the age of 5 years due to renal immaturity and decreased toxin clearance, and the lack of immunity to toxins in these age groups. Congenital and neonatal cases of SSSS following chorioamnionitis have been described (2,13,24). In generalized forms of SSSS, toxin diffuses from an infected focus (conjunctiva, umbilicus, nose, urine) and, in the absence of specific antitoxin antibody, spreads by hematogenous route to produce its widespread effects by cleaving a specific amino acid of desmoglein 1 (8). SSSS is an acantholytic intraepidermal blistering process in which cleft appears in the granular layer just beneath the stratum corne-

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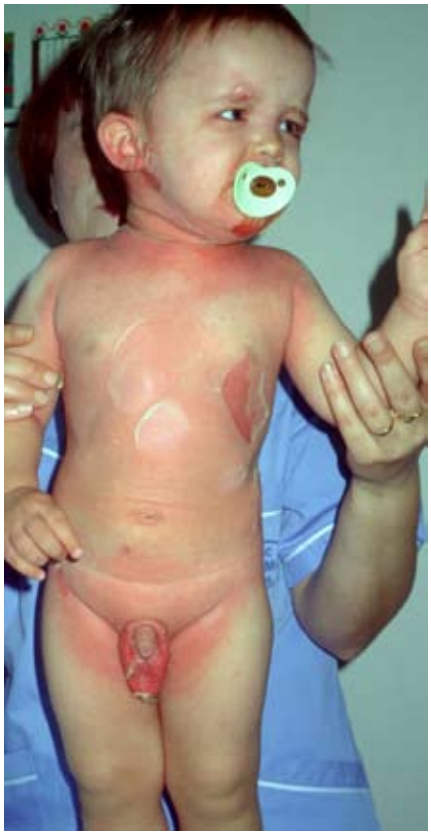

Figure 8. Staphylococcal scaled skin syndrome (SSSS): accentuated erythema in the circumoral, neck and scrotal region with positive Nikolsky's sign (flaccid blisters and erosions) in a high febrile child.

um (2,8). Unlike other erythrodermas, in children with SSSS the onset is acute, accompanied by fever, systemic toxicity, and positive Nikolsky sign. The erythema generalizes rapidly and progresses to sloughing and erosions (Fig. 8). Although there is often periorificial accentuation, the staphylococcal toxin requires keratinizing epithelium and therefore spares mucous membrane surfaces (3). Histopathology of the lesion distinguishes it from toxic epidermal necrolysis.

Staphyloderma pustulosa

Rarely a widespread form of staphylococcal pustulosis can acutely and rapidly develop in an otherwise healthy infant, resembling generalized candidiasis. Hundreds of 1-mm superficial pustules within erythematous patches desquamate, leaving widespread areas of erythema and scales. Cultures grow *Staphylococcus aureus* and the disease clears rapidly with appropriate antibiotics (1,8).

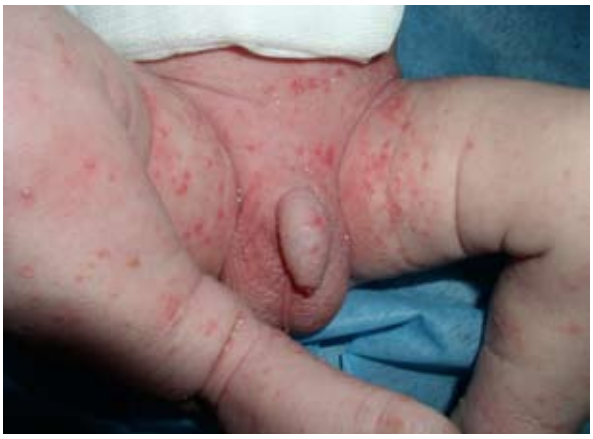

Figure 9. Neonatal candidiasis: generalized erythema with scattered pustules and erythematous papules.

Congenital and neonatal candidiasis

It is assumed that in congenital candidiasis the fetus has been infected *in utero* during the last days of pregnancy. Congenital candidiasis typically presents either at birth or within 48 hours of life with generalized erythema, vesicles, pustules, papules, and scaling (3,25). It spreads rapidly and often involves the umbilicus, palms and soles (Fig. 9) (1). *Candida albicans* can also cause a diffuse burn-like erythema within the first 2 weeks of life in premature infants. The risk of extracutaneous disease and the prognosis depend on the gestational age and weight of the infant. In infants less than 1500 g with either congenital or acquired generalized cutaneous candidiasis, there is a significant risk of disseminated disease, including involvement of the lung, meninges, and urinary tract. An infant with a possible systemic candidiasis must be thoroughly evaluated as systemic infection presents a life threatening condition. After the blood, spinal fluid, and urine have been cultured, it is recommended to introduce systemic antifungal agents (3,8,26). Differential diagnosis includes intrauterine herpes simplex virus infection, erythema toxicum neonatorum, pustular miliaria rubra, and neonatal pustular melanosis (3).

In the neonatal form of cutaneous candidiasis, the lesions usually start in the oral cavity or the napkin area and develop three to seven days after birth. Topical therapy with an antifungal cream is usually sufficient because dissemination does not develop in an immunocompetent infant (3,25).

Congenital herpes simplex infection

Intrauterine variant of herpes simplex infection can present at birth with either isolated or diffuse

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erythema, and scaling or crusted erosions on an erythematous base. It may be difficult to recognize clinically because vesicles may not be present. This type of widespread involvement is generally associated with very severe neurologic disease. Multinucleated giant cells should be demonstrable on Tzanck smears of vesicular lesions (3).

Syphilis

Congenital syphilis may cause diffuse erythema and scaling. This presentation is most typically seen in infants at 6 to 8 weeks of age, in whom exposure to *Treponema pallidum* occurred either very late in pregnancy or at the time of delivery. Superficial erosions or bullae over the hands or feet of the newborn, together with a diffuse scaling dermatitis should alert to the possibility of syphilis. Infiltrated mucosal papules and plaques (condylomata lata) are most often seen in the perianal region. Periosteal changes of long bones as well as hepatosplenomegaly, lymphadenopathy, anemia and thrombocytopenia are additional features (3,27).

DRUG REACTIONS

Drug induced erythrodermas in children are commonly observed with sulphonamides, isoniazid, streptomycin, NSAIDs, and antiepileptic drugs. If the incriminating drug(s) are withdrawn and symptomatic treatment instituted, these cases have an excellent prognosis (1).

Toxic epidermal necrolysis

Toxic epidermal necrolysis (TEN) is an acute severe bullous cutaneous disease characterized by extensive areas of skin necrosis accompanied by a systemic toxic condition. TEN is usually a disease of adults and is less common in childhood. The vast majority (80%-95%) of children with TEN have a drug reaction implicated as the cause. Sulphonamides, anticonvulsants, non-steroidal anti-inflammatory drugs (NSAIDs) and penicillins are most frequently implicated. Several cases of TEN in infants have been described in association with *Klebsiella pneumoniae* (28*)* and *Staphylococcus aureus* sepsis (8). In most children, TEN develops in the form of blistered erythematous patches and plaques that evolve within hours to extensive areas of skin necrosis, with loss of sheets of epidermis. About 90% of patients will have involvement of the mucosa with painful erosions and hemorrhagic crusts. TEN is a severe disease with a high mortality rate of 30% to 70% (29).

Differentiation from SSSS is necessary. High fever and occurrence in older children favor the diagnosis of TEN, whereas evidence of preceding rhinitis and localization to intertriginous and periorificial areas, acutely tender skin and occurrence in newborns or infants suggest the diagnosis of SSSS. Definitive diagnosis depends on the histologic location of the blister; in TEN the separation is subepidermal, and full-thickness epidermal necrosis is noted (8).

METABOLIC/NUTRITIONAL DISORDERS

The diseases in this category need to be considered in an infant who is ill or not thriving, and the dermatitis begins in the periorificial area before it generalizes. Although the etiologies of these disorders differ, the clinical manifestations are strikingly similar, possibly because there is a common link in the pathogenesis at the level of protein or keratin biosynthesis. Epidermal turnover is more rapid on mucous membranes, which could explain the periorificial predilection of many of these disorders as well as profound diarrhea seen in some of them (8).

Acrodermatitis enteropathica

Zinc deficiency is a classic example of a nutritional or metabolic cause of neonatal erythroderma. Acrodermatitis enteropathica is an autosomal recessive disorder thought to be due to impaired intestinal absorption of zinc. The initial lesions are vesiculobullous, crusted or psoriasiform and develop usually in the perioral and perianal areas. Skin lesions are accompanied by diarrhea, failure to thrive, alopecia, recurrent infection, photophobia and irritability. Secondary infection of the skin with *Candida* is not uncommon (8). In addition to low serum zinc levels, serum alkaline phosphatase levels are also reduced, as this enzyme is zinc dependent (30). The signs and symptoms of acrodermatitis enteropathica can also appear in other disorders associated with secondary zinc deficiency, including malabsorption syndromes and long-term use of zinc-deficient parenteral nutrition (31). The response to zinc therapy is rapid and dramatic.

An acrodermatitis-like symptom complex with perioral dermatitis, failure to thrive, diarrhea and low zinc concentrations has been reported in children with acquired immune deficiency syndrome (AIDS) (32).

Essential fatty acid deficiency

Essential fatty acids (EFA), such as linoleic and linolenic acids, must be supplied by the diet as the body cannot synthesize them. EFA deficiency can

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be seen in individuals with severe fat malabsorption. EFA deficiency leads to increased susceptibility to infection, growth impairment, and a characteristic generalized and periorificial cutaneous eruption consisting of dry, thickened, erythematous, desquamating plaques (8,31).

Cystic fibrosis dermatitis

A well-known complication of cystic fibrosis (CF) is protein-energy malnutrition, characterized by hypoproteinemia, edema and anemia. Sweat chloride level is usually elevated. However, confirmation of the diagnosis is complicated by the fact that the sweat test can be falsely negative in edematous infants (33).

Cutaneous manifestations of malnutrition are rare in patients with CF and have been attributed to deficiencies of protein, zinc and EFA, particularly linoleic acid. Zinc and EFA have reciprocal metabolic interactions that alter both the production of prostaglandins from linoleic acid and their subsequent metabolism (31).

Failure to thrive, hypoproteinemia, edema, and cutaneous eruption can be present before the onset of pulmonary and gastrointestinal symptoms and before the diagnosis of CF is confirmed (8,34). The clinical and histologic appearance of the rash in infants with CF most closely resembles acrodermatitis enteropathica. Infants with CF can develop widespread, scaly erythematous lesions as a manifestation of global malnutrition during the first 3 or 4 months of life (3).

Amino acid disorders

In different amino acid disorders, dermatitis similar to acrodermatitis enteropathica can appear due to dietary over-restriction of branched-chain amino acids. Patients with maple syrup urine disease are unable to metabolize three branched-chain amino acids: leucine, isoleucine and valine (3). A diet low in branched-chain amino acids is indicated. Overly strict adherence to this diet may result in deficiency of these amino acids and exfoliative erythroderma (8). Erythematous scaling eruption that becomes erosive begins primarily in the periorificial distribution within days after initiating dietary therapy (35). Treatment requires diligent attention to dietary restriction so that sufficient branched-chain amino acids are delivered (8). Presumably, adequate concentrations of amino acids are needed for normal keratinization (36).

Similar eruptions have also been noted in neonatal citrullinemia and carbamoyl phosphate synthetase deficiency, methylmalonic and propionic acidemia (3,36,37).

Methylmalonic and propionic acidemia may be associated with a variety of cutaneous manifestations such as superficial scalded skin, psoriasiform desquamation after metabolic decompensation, and chronic periorificial acrodermatitis enteropathica-like dermatitis (36).

Multiple carboxylase deficiency

Biotin-responsive multiple carboxylase deficiency (MCD) is a potentially lethal disorder which may manifest in early infancy with metabolic acidosis, central nervous system dysfunction, and recurrent infections. MCD is an autosomal recessive disorder of metabolism in which the function of mitochondrial biotin-dependent carboxylase enzymes are impaired (propionyl CoA carboxylase, β-methylcrotonyl CoA carboxylase, and pyruvate carboxylase) with non-functional branched-chain amino acid and carbohydrate metabolism (38).

The neonatal form of MCD presents in the first weeks of life, due to deficient holocarboxylase synthetase enzyme, with sharply margined dermatitis on the scalp, eyebrows and eyelashes that spreads to the perioral, perianal and other flexural areas. Secondary candidiasis is common. The hair thins and there can be associated blepharitis and keratoconjunctivitis with photophobia. If untreated, profound lactic acidosis, ketosis, and death result. Early recognition and therapy with oral biotin may completely reverse all of the manifestations of the disorder (6,38).

The juvenile form is milder than the neonatal form and presents between the ages of 3 weeks and 2 years. It is caused by total or partial deficiency of the enzyme biotinidase. Dermatologic symptoms are the same as in the neonatal form of MCD. These children also develop hearing loss, seizures, ataxia and coma (6,38,39). Immediate treatment and lifelong management using pharmacological doses of biotin supplements may prevent many of these complications.

IMMUNE DISORDERS

Because of the protective effect of maternal immunity, congenital immunodeficiency syndromes are rarely symptomatic at birth. Graft-*versus*-host reaction from maternal lymphocyte engraftment may, however, occur even during intrauterine development.

Graft-versus-host disease (GVHD)

GVHD is seen mainly in children with T cell immunodeficiency, but can occur in immunocom-

petent newborns as the result of transplacental passage of maternal lymphocytes or in the postnatal period (exchange transfusions) (2). Clinical manifestations include fever, morbilliform rash that gradually progresses to erythroderma, eosinophilia, lymphocytosis, hepatosplenomegaly, and lymphadenopathy (4,8,40). The diagnosis should be suspected in any young infant with erythroderma and frequent infections, chronic diarrhea, and failure to thrive. Clinical presentation may resemble Omenn's syndrome, but the skin eruption is usually less eczematous in GVHD. Infiltration of activated cytotoxic T cells into the skin is the common pathogenic mechanism for both skin lesions (41). In contrast, in the immunocompetent newborn with a small number of transferred cells, clinical symptoms are minimal and may involve only transient macular rash (2).

Histologic examination usually reveals significant lymphocytic infiltration and keratinocytic necrosis with satellite lymphocytes. These findings, however, are not specific for GVHD since similar changes are found in Omenn's syndrome (18). Karyotyping and histocompatibility typing can help detect maternal engraftment in an immunodeficient infant, which will suggest the diagnosis of GVHD (41). Histology findings can rule out Netherton's syndrome and CIE as other possible causes of neonatal and infantile erythroderma.

Severe combined immunodeficiency

Severe combined immunodeficiency (SCID) represents a heterogeneous group of genetic disorders characterized by a profound defect in T cell differentiation or function, accompanied by secondary B cell depletion or dysfunction (42). It is inherited as an autosomal dominant or X-linked recessive trait. The impaired cellular and humoral immunity predispose these infants to a variety of serious infections and sometimes to the development of GVHD due to engraftment of transplacentally acquired maternal T cells (1). The main clinical manifestations of SCID include predisposition to infections, growth retardation, and chronic diarrhea. Cutaneous manifestations include mucocutaneous infections, viral exanthemas and, most importantly, acute GVHD which usually occurs within the first months of life (Fig. 10) (43,44).

Omenn's syndrome/familial reticuloendotheliosis with eosinophilia

Omenn's syndrome is a rare autosomal recessive combined immunodeficiency. Although the condition is primarily due to T-cell dysregulation,

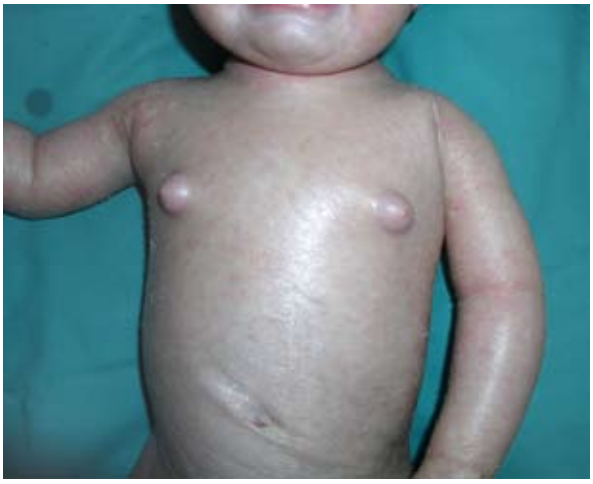

Figure 10. Graft-*versus*-host disease that developed in an 11-month-old infant with severe combined immunodeficiency (SCID) after allogeneic bone marrow transplantation.

both humoral and cellular immune defects are seen. A gene defect has been identified that maps to chromosome 11 (3, 41).

The etiology of Omenn's syndrome is unknown, however, unlike other forms of SCID, patients with Omenn's syndrome have activated T lymphocytes in their circulation capable of non-MHC restricted cytotoxic function (41). It is characterized by exfoliative erythroderma with the onset at birth or in the early neonatal period. It is associated with diffuse alopecia, pronounced lymphadenopathy, hepatosplenomegaly, recurrent infections, and failure to thrive (2). Marked leukocytosis, eosinophilia, anemia, elevated serum IgE levels, hypogammaglobulinemia and depressed T-cell immunity are other characteristics. Skin biopsy may confirm the diagnosis and help in differentiating it from Netherton's syndrome. Keratinocyte necrosis with satellite lymphocytes and significant lymphocytic or eosinophilic infiltration of the skin are highly suggestive of an immnodeficiency syndrome (10). Although it is mostly fatal, cyclosporine and bone marrow transplantation can be effective therapies (1,3,8).

Hypogammaglobulinemia

Patients with hypogammaglobulinemia can present with neonatal erythroderma. An infant who is apparently normal at birth subsequently develops fever, diarrhea and rapidly progressive generalized exfoliative dermatitis (erythroderma). Monthly replenishment by intravenous infusion of gammaglobulins alleviates fever and erythema (1,8,40).

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MANAGEMENT OF CHILDREN WITH NEONATAL AND INFANTILE ERYTHRODERMA

Irrespective of its cause, neonatal and infantile erythroderma is a potentially life threatening condition. Erythrodermic neonates and infants are at a risk of hypernatremic dehydration and hyper- or hypopyrexia. These infants need a warm, humid environment to minimize their metabolic demands (3). Maintaining adequate oral or parenteral fluid intake and monitoring serum electrolytes are therefore mandatory. Topical application of emollients, such as white paraffin, hydrates the skin and prevents fissuring. Blisters and erosions, seen in bullous ichthyosiform erythroderma, SSSS, and cutaneous mastocytosis, should be treated with a topical astringent, such as 0.01% potassium permanganate soaks, and systemic antibiotics should be given if necessary. As transcutaneous absorption is profoundly increased, additives such as salicylic acid or lactic acid should be strictly avoided in the young infant, and topical steroids are to be used cautiously and only after the establishment of a diagnosis warranting their use (2).

CONCLUSION

In neonates and infants numerous diseases can present with erythroderma. These can be transient, benign dermatoses, primary cutaneous diseases, however, more serious infectious, metabolic and immune diseases should also be considered. Recognition of these diseases, i.e. early and precise diagnosis is important for it can spare a healthy child with transient, benign dermatosis from unnecessary or invasive evaluation, antibiotic treatment and hospitalization. On the other hand, recognition of potentially serious diseases that demand early treatment is mandatory. Delay in the establishment of the correct diagnosis can be fatal. Differential diagnosis of erythroderma is a multi-step procedure that involves clinical assessment, knowledge of any relevant family history, and certain laboratory investigations.

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By rain, wind and snow use Nivea cream; year 1935.
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