Review Article

Benign vesicopustular eruptions in the neonate*
*Erupções vesicopustulosas benignas no neonato**

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Abstract: Neonatal vesicopustular eruption comprise a group of disorders with onset in the first four weeks of life. These conditions present multiple differential diagnoses and can be usually identified by clinical examination or simple laboratory procedures. Dermatologists should be able to recognize these eruptions, and most importantly, to differenciate them from serious and life-threatening dermatoses.
Keywords: Acne; Candidiasis; Herpes simplex; Impetigo; Literature review; Melanosis; Newborns; Scabies

Resumo: *As erupções vesicopustulosas neonatais compreendem um grupo de desordens que surgem nas primeiras quatro semanas de vida. Apresentam extensa relação de diagnósticos diferenciais e, na maioria das vezes, podem ser identificadas clinicamente ou mediante recursos laboratoriais simples. Os dermatologistas devem reconhecer esses quadros cutâneos e, sobretudo, saber diferenciá-los de outras dermatoses graves e potencialmente fatais.*
Palavras-chave: Acne; Candidíase; Escabiose; Herpes simples; Impetigo; Literatura de revisão; Melanose; Recém-nascido

INTRODUCTION

Vesicopustular eruptions are common in the neonatal period, defined as the first 4 weeks of life. While the differential diagnosis is extensive (Chart 1), simple diagnostic methods can aid in differentiating between them, and most importantly, in separating transient, benign pustular eruptions from serious and life-threatening conditions.

The initial evaluation of a neonate presenting with a pustular eruption should include a careful history, focusing on complications during pregnancy, family history of skin disorders, delivery method of the neonate and gestational age and presence or absence of systemic symptoms or abnormalities. Several syndromes can present as a vesicopustular eruption in the neonatal period, such as acrodermatitis enteropathica, Langerhans cell histiocytosis, incontinentia pigmenti, hyperimmunoglobulin E syndrome, and focal dermal hypoplasia. Therefore multisystem involvement should prompt the clinician to investigate the characteristic features of such syndromes for accurate diagnosis, treatment, and parent education and counseling.

A complete description of such syndromes and of primary vesicobullous diseases in the neonate which can be potentially serious, such as epidermolysis bullosa, pemphigus vulgaris, herpes gestationis, acrodermatitis enteropathica and urticaria pigmentosa can be found in comprehensive sources such as Schachner and Hansen.[1]

Once a careful history is obtained and comprehensive physical examination performed, routine diagnostic tests used commonly in daily dermatology practice can be performed, such as a Tzanck smear, gram stain, KOH and skin biopsy when relevant for establis-

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CHART 1: Differential diagnosis

Non-infectious: benign
- Acropustulosis of infancy
- Eosinophilic pustular folliculitis
- Erythema toxicum
- Milliaria
- Transient neonatal pustular melanosis

Non-infectious: potentially serious
- Acrodermatitis enteropathica
- Epidermolysis bullosa
- Epidermolitic hyperkeratosis
- Incontinentia pigmenti
- Langerhans cell histiocytosis
- Urticaria pigmentosa
- Herpes gestationis-neonatal
- Pemphigus vulgaris- neonatal

Infectious: usually mild
- Candidiasis-neonatal
- Impetigo neonatorum
- Scabies

Infectious: serious
- Bacterial infections (*Chlamydia, Escherichia coli, Hemophilus influenza, Klebsiella pneumoniae, Listeria Monocytogenes, Pseudomonas aeruginosa, Staphilococcus aureus, Streptococcus* group A Beta hemolytic)
- Syphilis
- Candidiasis-congenital
- Staphylococcal scalded skin syndrome
- Viral infections (Cytomegalic, Herpes, Varicella)

hing the diagnosis. The discussion below will provide information on history, physical and laboratory findings to help distinguish between transient, benign disorders, mild infections, and serious infectious conditions that can occur during the neonatal period.

I. NONINFECTIOUS NEONATAL PUSTULAR ERUPTIONS

1. Erythema Toxicum Neonatorum

Erythema toxicum was originally described by Bartholomaeus Melinger in 1472 and named erythema toxicum neonatorum (ETN) by Leiner in 1912.[2] ETN is a benign, self-limited condition of the neonatal period which is very common in term infants, but rare in preterm infants and infants with less than 2500g birth weight. It is seen in approximately one-third of all full term newborns.[3] There is no racial predilection and males and females are affected equally. In a recently published study, several predisposing factors for ETN where identified such as female sex, term birth, first-pregnancy birth, birth season (summer and autumn), and vaginal delivery.[4]

The skin lesions of erythema toxicum (Figure 1) are asymptomatic red macules, papules, pustules or wheals that can affect any area of the body and most commonly present after 24 to 72 hours of life, but may begin from birth to 2 weeks of age.[5] Since ETN is a short lasting dermatosis, prevalence reports differ according to the time of life the neonate is examined.[6-10] The sites of predilection are the face, trunk, proximal arms and buttocks whereas palm and sole involvement is unusual. The lesions can last several days and rarely persist for several weeks. Red macular areas and wheals range from a few millimeters to several centimeters with superimposed 1 to 2mm papules and pustules. The lesions may be few in number but more often are present in large numbers and often evolve with crops of waxing and waning, with spontaneous resolution of individual lesions within hours to days. Cases of recurrent ETN have been reported as well as cases with only focal lesions.[5,11,12] The etiology of erythema toxicum neonatorum is unknown. Unproven causes include atopic diathesis, immediate sensitivity to allergens or response to thermal, mechanical or chemical stimuli.[13,14] Some authors suggest ETN is a graft versus host-like acute cutaneous reaction triggered by maternal lymphocytes transferred immediately after delivery.[5,15]

Diagnosis is clinical and a Tzanck smear (Giemsa or Wright stain) of lesional content will reveal numerous eosinophils and confirm the clinical suspicion. Laboratory findings may include eosinophilia up to 18% in as many as 15% of the cases.[11] KOH and bacterial culture are negative. A skin biopsy is usually unnecessary but if performed it reveals intrafollicular, subcorneal pustules with a dense accumulation of eosinophils, hence lack of palmo-plantar

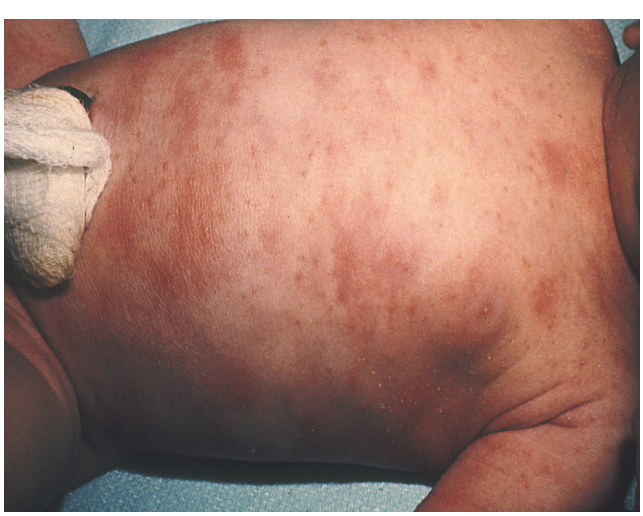

FIGURE 1: Erythema toxicum neonatorum

lesions. Macular lesions show a perivascular eosinophilic infiltrate in the upper dermis.

The differential diagnosis should include transient neonatal pustular melanosis, congenital candidiasis, miliaria, bacterial infections, herpes simplex infection, scabies, eosinophilic pustular folliculitis and acropustulosis of infancy. Erythema and onset at 1 to 3 days of age may distinguish erythema toxicum from transient neonatal pustular melanosis, though both are common and can occur simultaneously. Bacterial infections are usually due to *Staphylococcus aureus*, but occasional neonatal infections with group B *Streptococcus*, *Pseudomonas aeruginosa*, *Listeria monocytogenes*, *Hemophylus influenzae* and *Klebsiella pnemoniae* have occurred with pustules. The Gram stain will reveal organisms and the Tzanck smear of all conditions above will reveal predominant neutrophils. Transient neonatal pustular melanosis will show neutrophil predominance as well. Candidiasis may be differentiated on the basis of a positive potassium hydroxide preparation. Miliaria may be excluded on the basis of its extrafollicular location and the presence of lymphocytes on Wright stain.

Erythema toxicum is self limiting and no treatment is necessary other than reassurance to the parents.

2. Transient Neonatal Pustular Melanosis

Transient neonatal pustular melanosis (TNPM) was first described by Ramamurthy in 1976. The incidence varies from 0.16 to 15% and the disorder is more common in black infants.[16,17] In Brazil TNPM has been estimated to occur in 9.57% of the newborns.10 It is a benign condition of term neonates, characterized by the presence at birth of pustules or vesicles without surrounding erythema (Figure 2). These vesicopustules rupture easily, with subsequent formation of pigmented macules that are characteristically surrounded by a collarette of scale. These macules may persist for months but usually fade spontaneously within 3 to 4 weeks. Most commonly affected areas include the forehead, posterior ears, chin, neck, upper chest, back, buttocks, abdomen, and thighs, but all areas may be affected, including the palms and soles. Purely macular forms may indicate an intrauterine vesico-pustular eruption whereas the vesicle-pustular component has resolved in utero.[1] The cause of TNPM is unknown. Genetic influence seems unlike since the condition has been reported in only one of identical twins.[18]

Wright or Giemsa staining of the pustular contents show neutrophils and occasional eosinophils. No organisms are observed and bacterial and viral cultures are negative.[19] Skin biopsy shows intracorneal or subcorneal pustules. The differential diagnosis is the same as for erythema toxicum neonatorum. No treatment is necessary.

3. Acropustulosis of infancy

Acropustulosis of infancy, or infantile acropustulosis is a chronic or recurrent benign condition of very pruritic vesicles and pustules occurring on the hands and feet (Figure 3). It was first described in 1979 by Kahn and Rywlin and by Jarret and Ramsdell, and its etiology is unknown and it affects primarily black boys.[20] The condition may begin during the neonatal period and continue throughout infancy and early childhood. Infants and children often present with severe prutitus, sleep disturbance, fretfulness and appetite loss. Clinical manifestations are limited to the skin, and affected neonates are healthy other-

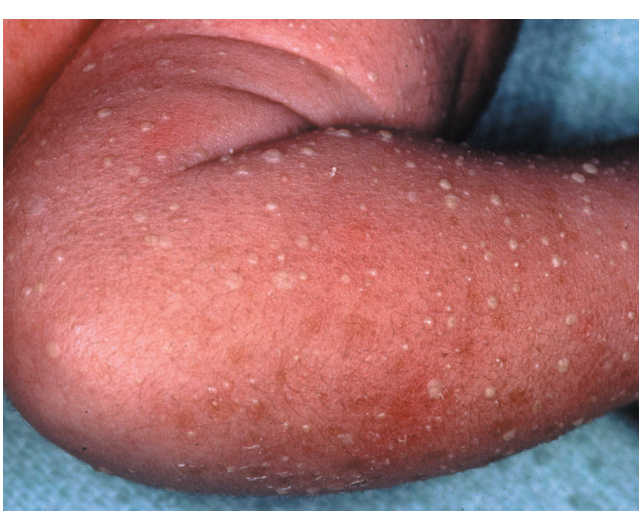

Figure 2: Transient neonatal pustular dermatosis

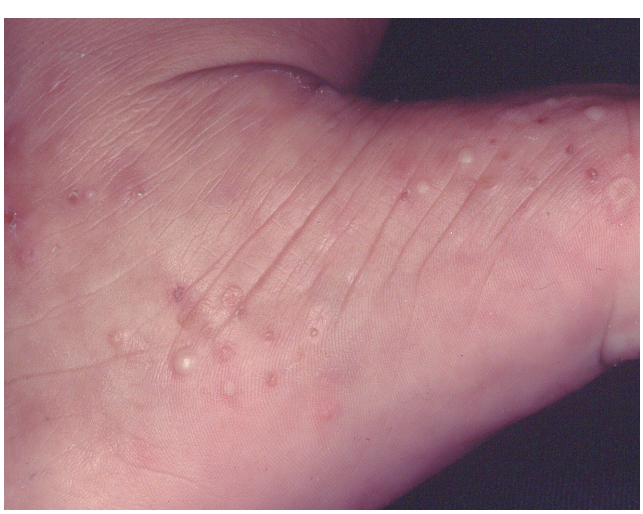

Figure 3: Acropustulosis of infancy

wise. Cutaneous lesions consist of vesicopustules without surrounding erythema characteristically involving palms, soles, dorsal hands and feet, and sides of fingers and toes. Crops of lesions may appear in cycles of two to four weeks, with individual lesions lasting three to seven days. The number of lesions is greatest in the early episodes, becoming less with subsequent episodes until permanent resolution occurs at 2 to 3 years of age.

The etiology remains unknown. Theories suggest a reaction pattern in predisposed individuals to infection or infestation. A history of scabies preceding the diagnosis of infantile acropustulosis is frequently obtained but rarely documented.

Laboratories studies are usually normal, but peripheral eosinophilia has been reported.[1,20]

A Tzanck smear or Gram's stain of pustular contents reveals numerous neutrophils, occasional eosinophils and no bacteria. Skin biopsy shows intraepidermal or subcorneal pustules filled with neutrophils or eosinophils. Focal vesiculation and degeneration of keratinocytes with cell necrosis may also be seen.

The main differential diagnosis is scabies and multiple skin scrapings are necessary to rule out active infestation. Careful examination of patients with a history of "scabies" have overwhelmingly failed to actually confirm infestation.[21] Smears for Gram and Wright stains, and a potassium hydroxide (KOH) preparations should help eliminate candidiasis, impetigo, varicella, and herpes simplex infection. Erythema toxicum and transient neonatal pustular melanosis may be confused, but both are asymptomatic and transient conditions making the differentiation easier.

Acropustulosis of infancy will remit spontaneously over one or two years. Treatment with potent topical corticosteroids is usually succesfull for control of outbreaks. Oral antihistamines may provide relief of itching in older infants but are contraindicated in neonates because of the undesirable side effect of sedation. In severe cases dapsone at a dose of 1 to 2mg/kg/day may be effective, however this therapy should be reserved for severe cases unresponsive to potent topical steroids. Baseline glucose-6-phosphate dehydrogenase (G6PD) levels and close monitoring of complete blood cell counts and platelets are appropriate as well as clinical assessment for methemoglobinemia, fever, jaundice, pallor or purpura.

4. Neonatal Acne

Neonatal acne, or neonatal cephalic pustulosis, has been described as usually beginning at a few weeks of life and manifested by multiple, inflammatory, erythematous papules, comedones and pustules on the nose forehead and cheeks.[22] Although the etiology is not clearly defined, neonatal acne appears to result from stimulation of sebaceous glands by maternal and infant androgens. The involvement of *Malassezia* spp in the etiopathogenesis has been suggested in recent reports.[23-25] Lesions spontaneously resolve within 1 to 3 months as the sebaceous glands involute, and scarring is absent. Acne initiating at 18 months of age versus 18 days is much more worrisome regarding adrenal-genital-pituitary pathology. Most cases of neonatal acne do not require treatment. Benzoyl peroxide 2.5% lotion or erythromycin 2% solution are safe alternatives.

5. Miliaria

Miliaria is a term used to describe obstructions of the eccrine duct resulting in rupture of the ducts and blockage of normal sweating into the skin. The level of obstruction determines the clinical manifestations. It can be seen in up to 15% of neonates, occurring more commonly in warm climates, in nurseries without air-conditioning and in febrile infants.

Miliaria crystalina (sudamina) is the most common type of miliaria and is manifested by minute, non-inflammatory vesicles without surrounding erythema. These lesions are asymptomatic, superficial and may appear like dewdrops on the skin. Commonly affected sites include the forehead and upper trunk. Miliaria crystalina represents rupture of the eccrine duct at the level of the stratum corneum.

Miliaria rubra (prickly heat) is due to intraepidermal obstruction of the sweat duct with sweat leakage into the duct and a secondary local inflammatory response. Lesions are 1-3mm erythematous, non-follicular papules, vesicles or pustules. Common sites include the face, neck and trunk. Miliaria rubra occurs later than miliaria crystalina, usually beyond the second week of life. Occasionally it can progress to pustular lesions (miliaria profunda), most prominent on the trunk and extremities, and reflects eccrine ductal occlusion at the dermo-epidermal junction. Miliaria profunda is rare in neonates.

The diagnosis of miliaria is made by clinical observation. The precise cause is unknown. There is some support for an extracellular polysaccharide substance produced by some strains of *Staphylococcus epidermidis* being involved in sweat duct obstruction and poral occlusion by epidermal cellular edema may be an initial event.

The use of very thick emollients can result in a miliaria profunda picture in infants, especially those with atopic dermatitis.

6. Eosinophilic pustular folliculitis

Eosinophilic pustular folliculitis (or eosinophilic pustulosis) was first described in adults by Ofugi et al and in infants by Lucky et al in 1984.[26] It may present at birth or in the first few days of life with yellowish pustules predominantly on the scalp and face, but also trunk and extremities. The pustules generally crust within two or three days of onset and may recur in crops.[27] The waxing and waning course of the disease may last for several years. Pruritus and irritability in younger infants is common.

A Tzanck smear or Gram's stain of the pustular contents demonstrates numerous eosinophils. Some patients have eosinophilia as well as leukocytosis on blood counts obtained during outbreaks. Biopsy specimens of the pustules show eosinophils and eosinophilic spongiosis in the epidermis, with a dense dermal perifollicular infiltrate of eosinophils, histiocytes, and lymphocytes. Cultures for bacteria, fungus, and viruses are all negative.[28]

The etiology is unknown. It has been suggested that it may represent a more persistent form of erythema toxicum neonatorum, based on histopathologic similarities. Differential diagnosis includes scalp pyoderma, erythema toxicum, transient neonatal pustular melanosis, acropustulosis of infancy, bacterial or fungal folliculitis, scabies, candidiasis, and Langerhans cell histiocytosis. The clinical presentation, location, and histology of these lesions allow differentiation from all these entities.

A persistent generalized, non-remitting EPF has been seen in infants with severe AIDS and is considered a marker of worse prognosis.

Treatment is moderately successful with low or mid-potency topical corticosteroids and/or antibiotic therapy. Antihistamines may be helpful in controlling pruritus. Other therapies that may be useful include dapsone, oral cimetidine and systemic prednisone.

II. INFECTIOUS NEONATAL PUSTULAR ERUPTIONS

II.a. Bacterial Infections

1. Impetigo Bullosa

Impetigo bullosa is characterized by flaccid vesicles, pustules or bullae on erythematous bases that rupture easily leaving a narrow rim of scale at the edge of a moist erosion. It may appear as early as the second or third day of life. These lesions re-epithelialize rapidly and do not result in scars. The diaper area and folds of the skin are commonly involved.

Certain strains of *Staphylococcus aureus* (Phage group II, lysotypes 3A, 3C, 55 or 71) have the ability to produce an exfoliative exotoxin which causes bullous impetigo. When the toxins enter the systemic circulation, there is potential for generalized involvement of the skin, also called staphylococcal scalded skin syndrome.[29] Staphylococcal scalded skin syndrome lesions have a negative Gram stain but often bacterial cultures are positive.

Diagnosis of impetigo is easily made by Gram's stain of a pustule, which reveals neutrophils and Gram- positive cocci in clusters. Bacterial cultures confirm the diagnosis.

Localized infections can be treated with a topical antibiotic such as mupirocin or fucidic acid. More widespread lesions require systemic therapy.

2. Other bacterial infections

Bacterial infections can be acquired prenatally, during delivery, or after birth. Group B beta-hemolytic streptococcus, *Listeria monocytogenes, Hemophilus influenza* and *Pseudomonas aeruginosa* are bacterial pathogens that may produce pustules and sepsis in the neonate.

IIb. Viral infections

1. Herpes simplex infection (HSV)

Approximately 5% of neonatal HSV is a truly intrauterine infection, resulting in a baby infected at birth.[1] Since the primary period of viral inoculation is intrapartum, and given the variable incubation time, neonatal HSV may be present any time in the first 4 to 6 weeks of life. Up to one quarter of infected neonates will have signs of infection on the first day of life.[30]

Most (70%) neonatal herpes simplex virus are due to HSV type 2. HSV-2 may be acquired by the neonate transplacentally, by viremia during gestation, intranatally by passage through an infected birth canal, or postnatally by direct contact with infected humans. About 16% to 30% of women in the United States are seropositive for HSV-2, and 0.3% to 2% of women shed HSV from the vagina at the time of delivery.

The initial symptoms of disseminated HSV infection are lethargy, hypo- or hyperthermia, irritability and poor feeding. Cutaneous findings are the first visible sign in about two-thirds of neonates infected with HSV. Grouped or single vesicles or pustules on erythematous bases appear in crops on the skin and mucous membranes. The eyes may also be affected. Neonatal herpes may spread quickly to involve the central nervous system and/or multiple internal organs. The neonate's condition may deteriorate rapidly, therefore prompt and accurate diagnosis is more than desirable.

A Tzanck smear of vesicles bases reveal multinucleated giant epithelial cells, indicating a herpetic infection. Viral culture and direct immunofluorescence testing may be used to confirm the diagnosis. Biopsy specimens reveal an intraepidermal vesicle produced by ballooning and reticular degeneration of epidermal cells. Marked acantholysis is present.

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6. Eosinophilic pustular folliculitis

Multinicleated cells and eosinophilic inclusion bodies can be seen.

If left untreated, disseminated HSV infection is fatal in many cases. Although it has been demonstrated that vidarabine is as effective as acyclovir in the HSV-infected neonate, most experts utilize acyclovir in these patients because of relative ease of administration.

If active genital herpetic lesions are present in a pregnant woman at the time of labor, a cesarean section is recommend if the fetal membranes have been ruptured for less than 6 hours. Prevention is the best treatment, and newborns should be protected from exposure to HSV whenever possible.

IIc. Fungal Infections

1. Candidiasis

Candida infection can be divided in two forms, congenital and neonatal. Congenital candidiasis is an intrauterine infection, while neonatal candidiasis is acquired as the infant passes through a contaminated birth canal. In both forms the causative organism is *Candida albicans*, a pathogen found in the vaginal canal of 20 to 25% of pregnant women. A possible way in which intrauterine infection may occur is by *Candida* organisms ascending via the vagina and crossing ruptured or intact fetal membranes.

In congenital candidiasis lesions are present at birth or usually within 12 hours following delivery (Figure 4). The rash is usually diffusely scattered over the whole body, including the face, chest, back and extremities. Oral and diaper area involvement is generally absent. The congenital form usually starts as erythematous macules and vesicles, which quickly evolve into pustules. A pronounced desquamation follows the acute phase with exfoliated crusted lesions. Signs of systemic disease and hematologic abnormalities are generally absent.[30]

Neonatal candidiasis is usually seen after the seventh day of life, occurring as oral trush and pustules and vesicles with satellite lesions confined to the diaper area. The intergluteal and cervical folds (Figure 5), perineum, genitalia, suprapubic area, buttocks, and inner thighs are frequently involved. In these areas candidiasis evolves into scaling, bright red plaques, with distinct pustular and vesicular satellite lesions at the periphery. Constitutional symptoms are absent. In neonatal candidiasis, *C. albicans* can often be isolated from the feces.

Diagnosis of candidiasis is made by finding pseudohyphae and spores with a potassium hydroxide preparation of a pustule or scale and confirmed by a fungal culture.

Candidiasis is treated topically with imidazole derivatives, such as miconazole, clotrimazole, or ketoconazole cream. Lesions last approximately 2 weeks, desquamate and resolve without residua. Trush is treated by oral nystatin.

Disseminated systemic candidiasis may occur rarely and is primarily an infection of preterm, low birth weight infants, immunologically compromised patients, and neonates requiring intensive care with invasive procedures. It may affect the lungs, meninges, kidneys, bladder, joints, and less commonly the liver, heart and eyes. Disseminated candidiasis is associated with significant morbidity and mortality. The spreading of a candidal diaper rash to the trunk and extremities should alert the clinician to the possibility of dissemination of infection. Intermittent fever that is resitant to anti pyretics, with cutaneous candidal lesions or cellulitis at the site of an intravenous catheter, and persistent candidemia or candiduria, even in

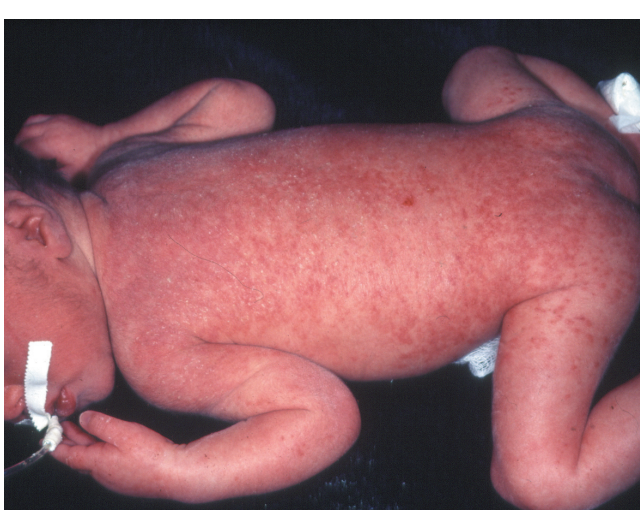

Figure 4: Congenital candidiasis

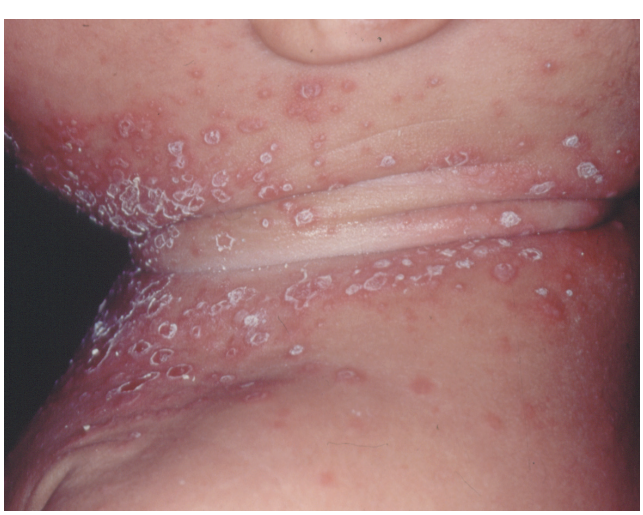

Figure 5: Neonatal candidiasis

the absenceof skin findings or systemic symptoms, indicate the presence of disseminated disease.

Confirming the diagnosis of suspected disseminated candidiasis is difficult. Widespread infection despite negative cultures is common. The diagnosis is confirmed by isolating *Candida albicans* from blood, abscesses, urine, or other body fluids, or by demonstration of the organism in a cutaneous biopsy. The early institution of treatment is the critical prognostic factor. Amphotericin B or 5-flucytosine intravenously are the drugs of choice. The use of these medications requires careful monitoring of side effects. The preterm infant may suffer a devastatingly lethal candidal scalded skin syndrome.

2. Ptyrosporum folliculitis

Pityrosporum yeasts (*Malassezia furfur*) are the cause of pityriasis versicolor, which is usually seen as a disorder of adolescents and young adults, but may be a very rare cause of folliculitis in neonates. Cutaneous lesions consist of follicular papules and sparse pustules on the face and scalp. The diagnosis is based on a positive KOH and culture of pustular contents. Treatment is achieved with topical imidazole derivatives such as miconazole, clotrimazole, or ketoconazole cream.

II.c Parasitic Infections

1. Scabies

Scabies is a contagious disorder caused by *Sarcoptes scabiei*, a parasitic mite, which invades the stratum corneum. After an incubation period of 2 to 6 weeks, an extremely pruritic rash develops. If the infestation occurs soon after the delivery, the disorder may be seen in the neonate.

Scabies is a distinct clinical eruption characterized by pruritic papules, vesicles, and linear burrows mixed with excoriations, eczematization, crusting, or secondary infection. The clinical pattern of scabies in newborns differs from that seen in older infants, children, and adults. In older children and adults most of the lesions are concentrated on the finger webs, wrist, axillae, arm flexure, beltline, perineum and genitals. In infants and young children the infestation rapidly becomes more generalized, usually involving the palms, soles, head, neck and face. Vesicles are common in neonates, and there is a tendency for pustule formation early in the course of the infestation. Irritability, poor feeding, and failure to gain weight are also quite characteristic. A careful history and examination of the baby's caretakers will frequently disclose a history or pruritus and/or typical scabies lesions. Frequent maternal sites are periareolar regions of the breasts, as well as the wrists and fingers.

Definitive diagnosis is made by microscopic examination of scrapings from unexcoriated lesions in a mineral oil preparation. The presence of adult mite, ova, larva or stool confirms the diagnosis.

The treatment of choice is permethrin 5% cream applied from head to toes for 6 hours. When permethrin cream is not available, neonates can also be treated with 5% sulfur in petrolatum. Sulfur-containing preparations are messy, staining, and malodorous, and must be applied for three nights. It's crucial to treat all family members and other caretakers at the same time and launder clothing and bedding in high temperature water. It's important to differentiate nodular neonatal scabies from hystiocytosis X, which it can simulate clinically.

CONCLUSIONS

Pustular eruptions in the neonate can have many clinical presentations and significance. Simple diagnostic methods can aid in differentiating between them, and most importantly, in separating transient, benign pustular eruptions from serious and life-threatening conditions. ❑

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