SWISS SOCIETY OF NEONATOLOGY

# Neonatal blistering - a butterfly child

August 2010

Kaelin S, Weibel L, Arlettaz Mieth R, Neonatal Intensive Care Unit (KS, AMR), Department of Dermatology (WL), University Hospital Zurich, Switzerland and Division of Dermatology, University Children's Hospital Zurich, Switzerland

This male premature infant was born at 31 5/7 weeks of gestation by vaginal delivery following preterm labor. The pregnancy of the 21-year-old mother had otherwise been uneventful. Maternal serologies were normal: hepatitis B, HIV and toxoplasmosis were negative, and she was rubella and VZV immune. There was no colonization with B streptococcus.

Apgar scores were 7, 8, 8 at 1, 5, and 10 minutes, respectively. Birth weight was 1770 g (P 25-50), and length and head circumference were between the 10-25th percentiles. The baby was transferred to the neonatal intensive care unit because of his gestational age and mild respiratory distress.

The baby was the second child of non-related parents who originated from Kosovo. The parents as well as the one-year-old sister were in good health and the family history was unremarkable.

At the age of 4 hours, a sharply demarcated superficial erosion was detected on the right forearm (Fig. 1A) and, at the age of 10 hours, a similar lesion was noted over the left ankle (Fig. 1B). These areas had been mechanically stressed by the pulse oximetry sensor as well as the ECG electrodes. After removing all electrodes except the pulse oximetry sensor, no further skin lesions were detected until the 3rd day of life when a blister was noted on the left thumb (Fig. 2).

The skin lesions did not appear to be painful. Clinically the infant was always in a very good general condition. Although the histology of the placenta revealed mild chorioamnionitis, the baby never showed any clinical signs of infection. The bacterial and viral cultures of the wound were negative.

This presentation was suspicious for a hereditary bullous skin disorder such as epidermolysis bullosa. Other differential diagnoses were less likely for several reasons: the baby was otherwise healthy, neither he nor his mother had received any drugs, the lesions occurred on mechanically stressed areas, there were no associated inflammatory or disseminated skin changes, and the mother did not have any skin lesions. With the use of topical diluted gentian violet and chlorhexidine acetate tulle dressing (Bactigras®) the skin lesions healed completely with mild residual erythema and hypopigmentation (Fig. 3).

The initial course of the skin lesions was mild and the problem appeared to be self-limited. However, prior to discharge at the age of 4 weeks, the baby developed new superficial blisters on the left index finger and in the folds of his neck. A skin biopsy of unaffected skin was performed on the thigh, after gently rubbing the skin for 30 seconds. Routine histology and immunohistochemic antigen mapping were performed in Freiburg (Kompetenznetz Epidermolysis bullosa, Prof. L. Bruckner-Tudermann). With these analyses, severe

forms of epidermolysis bullosa, such as epidermolysis bullosa junctionalis Herlitz or epidermolysis bullosa dystrophica could be excluded. However, it was impossible to determine the specific subtype of epidermolysis bullosa at this stage.

During the first year of life until current follow-up (age 14 months), the child continued to develop crops of small blisters predominantly in the large skin folds and on exposed areas of the body such as hands and feet. There were no mucosal lesions and nail growth remained normal. Interestingly, the blisters and erosions tended to heal with superficial atrophic scarring leaving hypo- and hyperpigmented macules (Fig. 4-7).

At the age of 7 months, another skin biopsy of a fresh blister was performed. The findings of the immunohistochemic antigen mapping were consistent with epidermolysis bullosa junctionalis non-Herlitz or Kindler syndrome. Mutation analysis for the KIND1/FERMT1 gene was negative, thus excluding Kindler syndrome. To this date, epidermolysis bullosa junctionalis non-Herlitz is the most likely diagnosis and genetic analysis for the most common underlying mutations is ongoing.

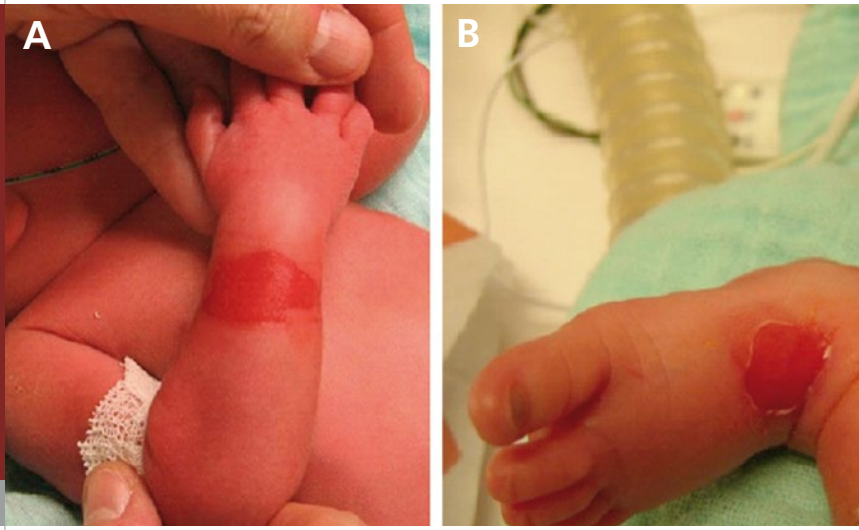


Fig. 1

*Blisters on day of life 1. A) Sharply demarcated superficial erosion on right forearm in the area of earlier ECG electrode placement, B) Eroded superficial blister on left ankle.*

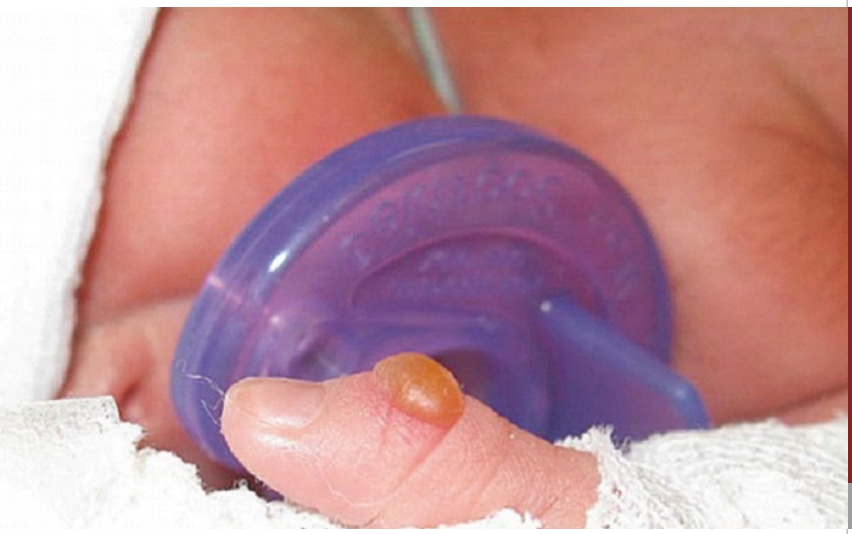

Fig. 2

*Newly developed tense blister on left thumb on day of life 3.*

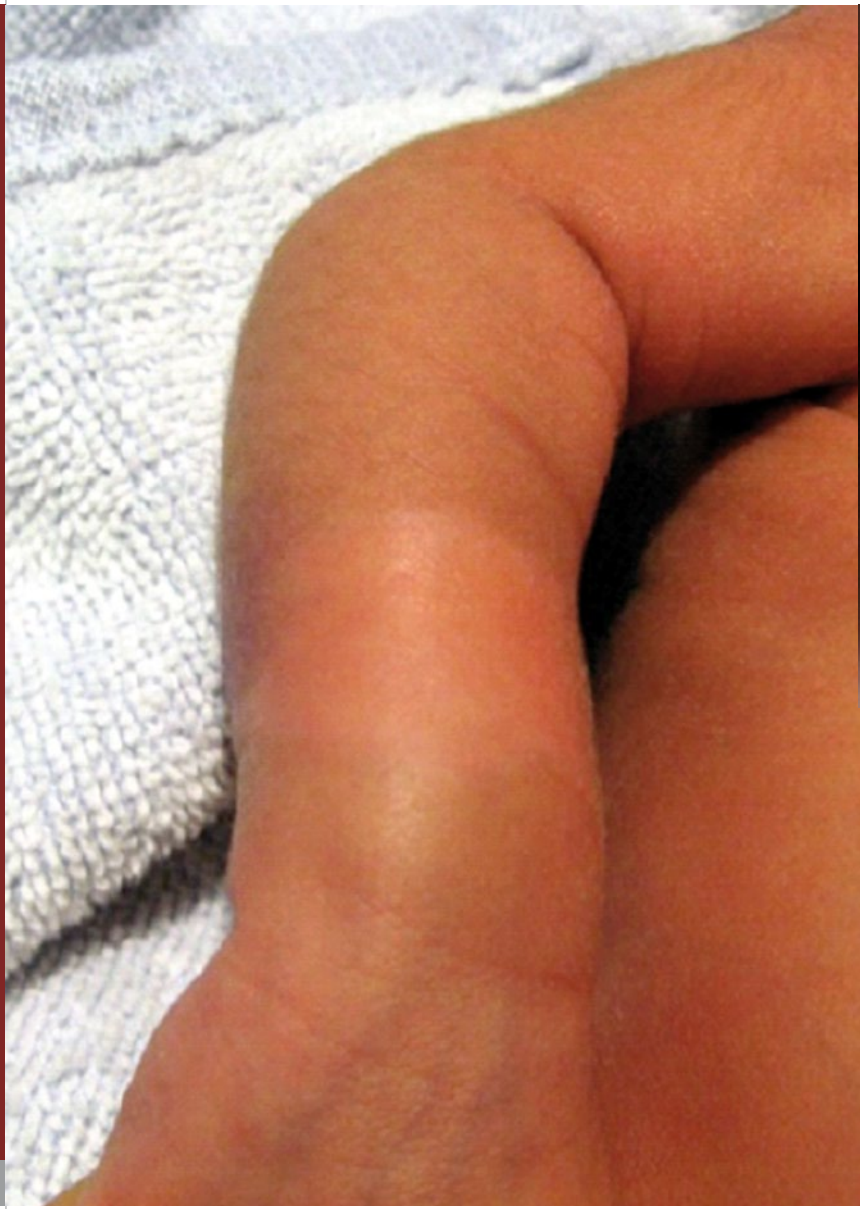

**Fig. 3**

*Healed lesion on right forearm with mild residual erythema and hypopigmentation on day of life 23.*

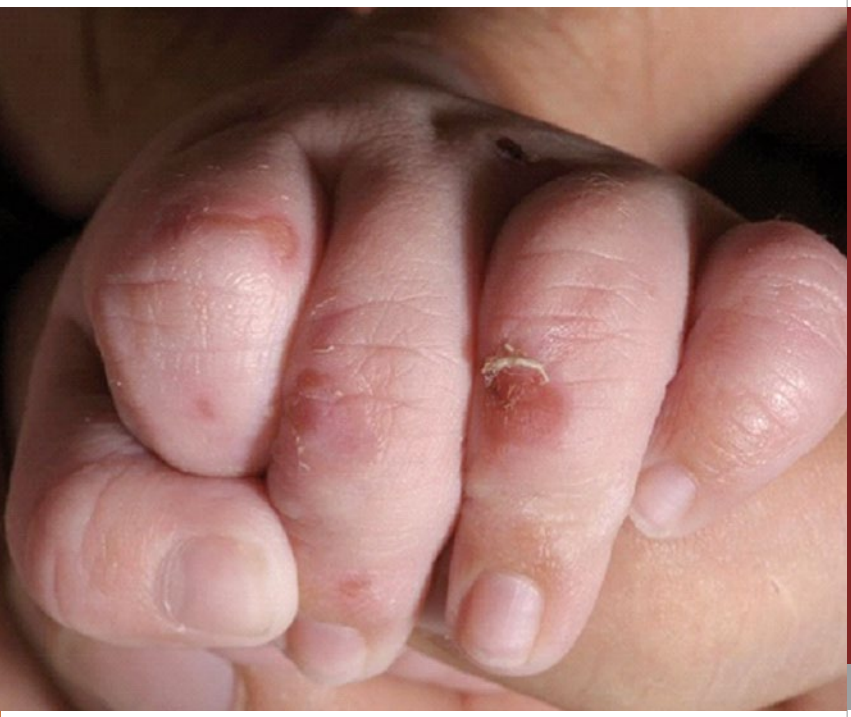

Fig. 4

*Different healing stages of eroded blisters on the dorsum of the fingers of left hand at the age of 4 ½ months.*

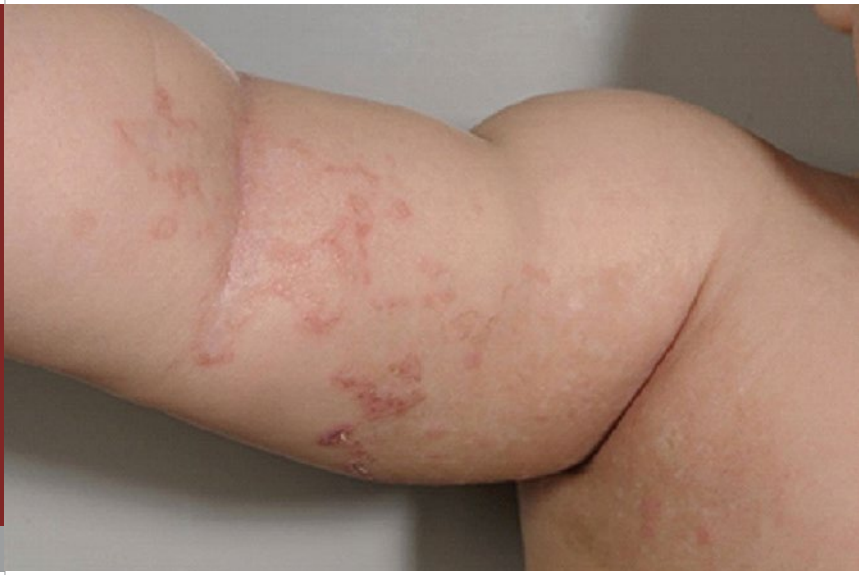

Fig. 5

*Annular erythematous macules, papules, small blisters and crusts as well as hyper- and hypopigmented superficial scarring on right axilla and upper arm at the age of 7 months.*

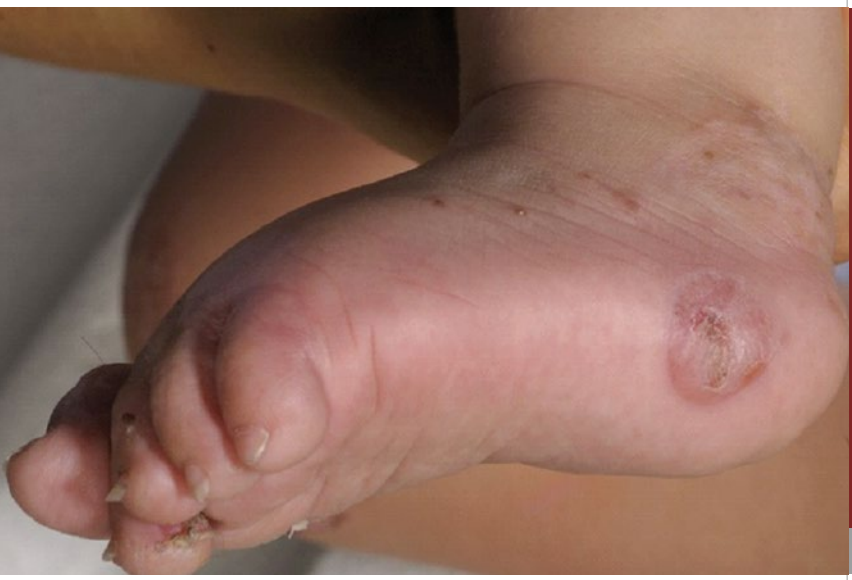

Fig. 6

*Large healing blister on the lateral aspect of the foot. Additionally, there is sharply demarcated hypopigmented superficial atrophic scarring along the lateral aspect of the ankle at the age of 14 months.*

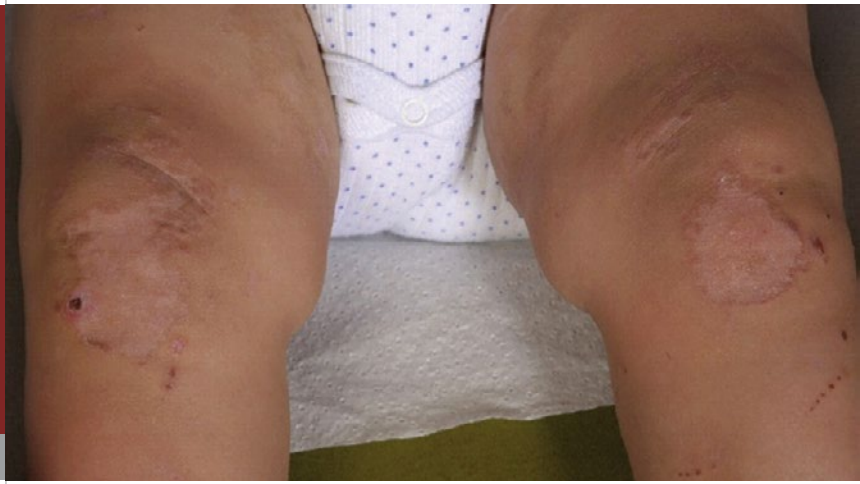

Fig. 7

*Atrophic and hypopigmented annular scars on both knees at the age of 14 months.*

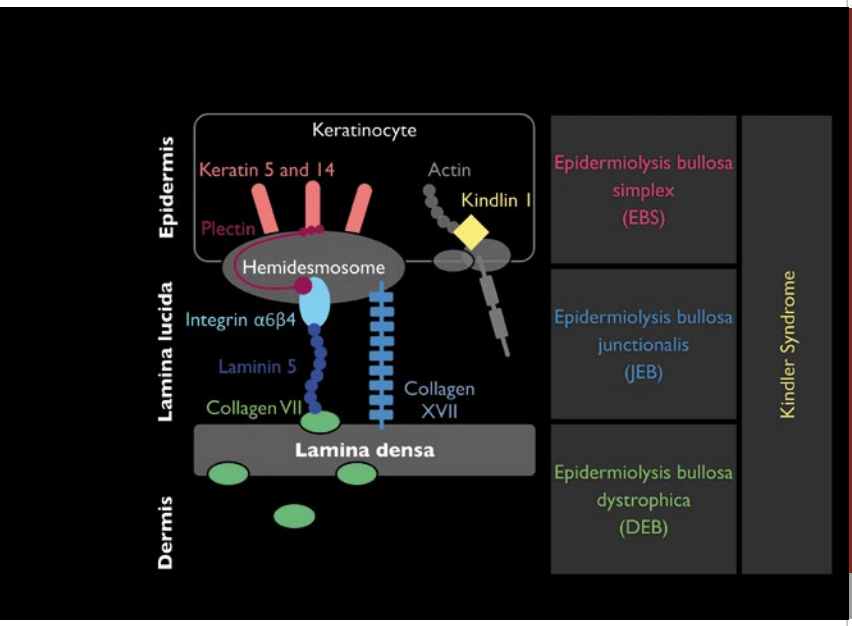


**Fig. 8**

*Schematic representation of the dermal-epidermal basement membrane zone (BMZ) and corresponding subtypes of EB. EBS is characterized by intraepidermal skin cleavage. Known targeted proteins are Keratin 5 and 14 and Plectin. JEB is defined by skin cleavage in the lamina lucida. The corresponding targeted proteins are 6β4 Integrin, Laminin 5 and Collagen XVII. DEB shows skin cleavage below the lamina densa and the mutated protein is Collagen VII. Kindler syndrome is caused by a mutation in the Kindlin-1 protein and is characterized by multiple cleavage planes.*

Fig. 9

| Hereditary/Autoimmune | Drugs | Infections |
|---|---|---|
| Epidermolysis bullosa | Drug eruption | Bullous impetigo |
| Congenital bullous ichthyosiform erythroderma | Stevens Johnson Syndrome | Staphylococcal scaled skin syndrome (SSSS) |
| Aplasia cutis | | Congenital neonatal herpes simplex |
| Incontinentia pigmenti | | |
| Congenital erythropoietic porphyria | | |
| Pemphigus vulagris | | |
| Bullous pemphigoid | | |
| Congenital Histiocytosis | | |

*Differential diagnoses of blistering diseases. The red colored diagnoses are described in the supplement.*

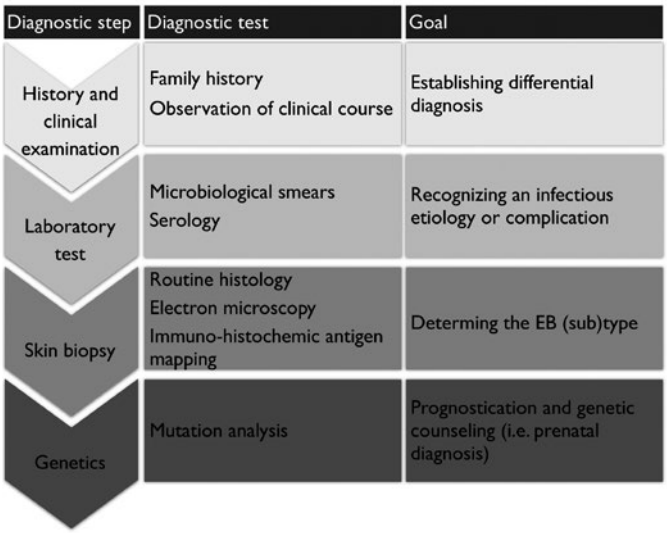


**Fig. 10**

*Evaluation of suspected EB.*

## DISCUSSION

Epidermolysis bullosa (EB) comprises a large heterogeneous group of hereditary dermatoses characterized by fragility of the skin and mucous membranes, leading to blistering and erosions as a result minor trauma. "Butterfly Children" is a term often used to describe younger patients because the skin is said to be as fragile as a butterfly's wings.

The fragility is caused by gene mutations encoding a range of epidermal basement membrane molecules (1). The inheritance can be either autosomal recessive or dominant. Currently, over 1000 mutations in 13 distinct genes are known (2). The clinical picture ranges from mild subtypes with minor skin reactions to severe generalized forms with lethal outcome within the first months of life. The incidence is 19-26 to 1'000'000 live-births (3).

On the basis of the level of the cleavage plane within the dermal-epidermal basement membrane zone, EB can be categorized into 4 major groups: EB simplex, EB junctionalis, EB dystrophica and, according to the latest classification of 2008 (2), the Kindler syndrome (Fig. 8). All together, 33 subtypes can be distinguished, based on the new EB classification system (2) and the molecular background.

Blistering skin diseases are rare but the differential diagnosis, especially in the neonatal period, is wide. As some of these disorders can be life-threatening or

result in long-term impairment one should be aware of the most common ones (Fig. 9). Clinical course and presentation of the skin lesions, family history and gender help in establishing the diagnosis. Essentially, there are no conditions that can mimic EB in every respect. In neonates, the clinical presentation of EB (e.g., involved areas, extension of skin lesions) does not allow to differentiate one form of EB from another and the main challenge usually is to determine the specific subtype of EB (5).

Diagnosis in blistering diseases and EB in particular is sequential (Fig. 10). With routine histology, electron microscopy and immuno-histochemic antigen mapping an initial classification of EB can be made. Allowing a semi-quantitative evaluation of the expression of structure proteins (normal, reduced or missing), immuno-histochemic antigen mapping should precede the far more complex mutation analyses. For the definite diagnosis, prognosis and genetic counselling including prenatal testing, however, the identification of the underlying mutation is essential (6, 7).

Treatment of EB is symptomatic. Attempts at gene therapy (cell therapy, vector therapy and protein therapy) in animal models are in progress (8-10) and there are a few reports on promising approaches to gene therapy in humans (11).

Please, also note the attached picture book of neonatal blistering skin disorders (Supplement). See also: COTM **08/2005**: Epidermolysis bullosa.

## REFERENCES


1. Has C, Bruckner-Tuderman L. Molecular and diagnostic aspects of genetic skin fragility. J Dermatol Sci 2006 Dec;44:129-144

2. Fine JD, Eady RA, Bauer EA et al. The classification of inherited epidermolysis bullosa (EB): Report of the Third International Consensus Meeting on Diagnosis and Classification of EB. J Am Acad Dermatol. 2008;58:931-950

3. Fine JD et al (1999). The epidemiology of inherited epidermolysis bullosa: findings within American, Canadian and European study population. In: Fine JD, Bauer EA, Mc Guire J, Moshell A (eds) Epidermolysis bullosa: clinical, epidemiologic and laboratory advances and findings of the national epidermolysis bullosa registry. Johns Hopkins University Press, Baltimore, 1999, pp 101-113

4. Lai-Cheong JE, Tanaka A, Hawche G et al. Kindler syndrome: a focal adhesion genodermatosis. Br J Dermatol. 2009; 160:223-242

5. Lin AN, Carter DM (1992). Differential Diagnosis in Epidermolysis bullosa. In: Epidermolysis bullosa Basic and Clinical Aspects, Springer Verlag, pp 8-11

6. Laimer M, Landschützer CM, Nischler E et al. Hereditary blistering diseases. Symptoms, diagnosis and treatment of epidermolysis bullosa. Hautarzt 2009;605:378-388

7. Shimizu H. Prenatal diagnosis of epidermolysis bullosa. Prenat Diagn 2006;2613:1260-1261

8. Tamai K, Kaneda Y, Uitto J. Molecular therapies for heritable blistering diseases. Trends Mol Med 2009;157:285-292

9. Remington J, Wang X, Hou Y et al. Injection of recombinant human type VII collagen corrects the disease phenotype in a murine model of dystrophic epidermolysis bullosa. Mol Ther 2009;171:26-33

10. De Luca M, Pellegrini G, Mavilio F. Gene therapy of inherited skin adhesion disorders: a critical overview. Br J Dermatol 2009;1611:19-24

11. Mavilio F, Pellegrini G, Ferrari S et al. Correction of junctional epidermolysis bullosa by transplantation of genetically modified epidermal stem cells. Nat Med 2006;12:1397-1402

# Neonatal blistering diseases

**Supplement**

The authors confirm that they are the copyright owners of these images, or, alternatively, that they have obtained a reprint permission from the copyright owners.

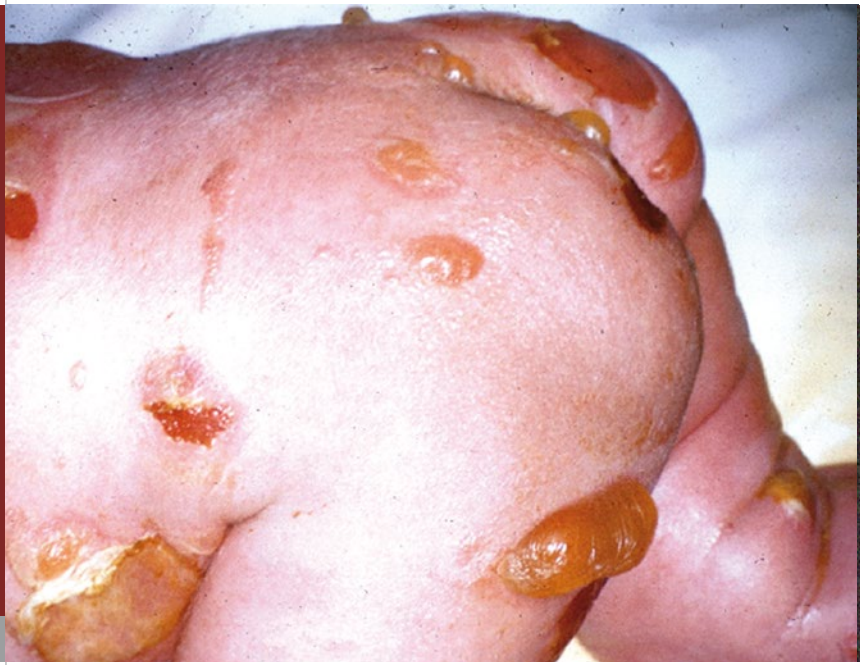

Fig. 1

***Epidermolysis bullosa (EB):*** *a group of inherited bullous disorders characterized by blister formation in response to mechanical trauma.*

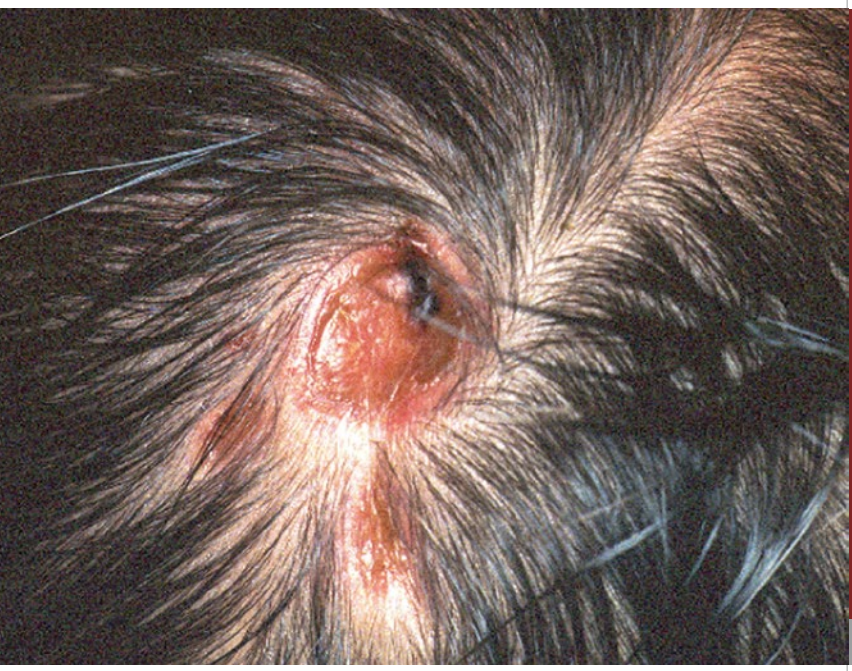

Fig. 2

***Aplasia cutis congenita*** *is characterized by the absence of a portion of skin in a localized or widespread area at birth. Most commonly it is localized on the scalp. Defects in the skin that form early in gestation may heal before delivery and appear as an atrophic, membranous or bullous scar with associated alopecia, whereas less mature defects present as ulcerations. It may be an isolated finding or associated with other congenital malformation syndromes (i.e. Adams-Oliver Syndrome (see also COTM* ***12/2001****) or Trisomy 13). Bart-Syndrome is an overlap of Aplasia cutis congenita and epidermolysis bullosa (see also COTM* ***05/2003****).*

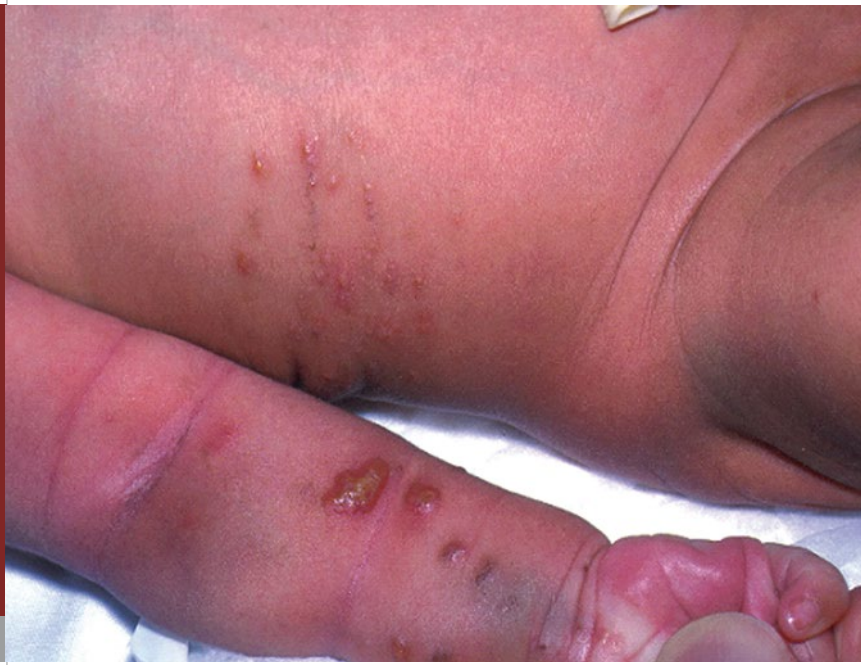

Fig. 3

***Vesicular stage of Incontinentia pigmenti (IP):***
*IP is a multisystemic disorder. It is due to mutation of the NEMO gene on the X chromosome. The condition is lethal in males. Affected females in the same family often exhibit a wide-spread phenotypic severity which has been attributed to the pattern of X-inactivation during development. The skin manifestations follow the Blaschko's lines and are divided into four stages. In the first stage (vesicular), a spongiotic dermatitis is present, histologically the intraepidermal vesicles are filled with eosinophils (see also COTM* ***08/2007****). The second stage (verrucous) shows acanthosis and hyperkeratosis of the involved areas. In stage 3, the skin is hyperpigmented and melanin deposits in melanophages in the dermis are present. In the final stage, the epidermis is atrophic and hypopigmented.*

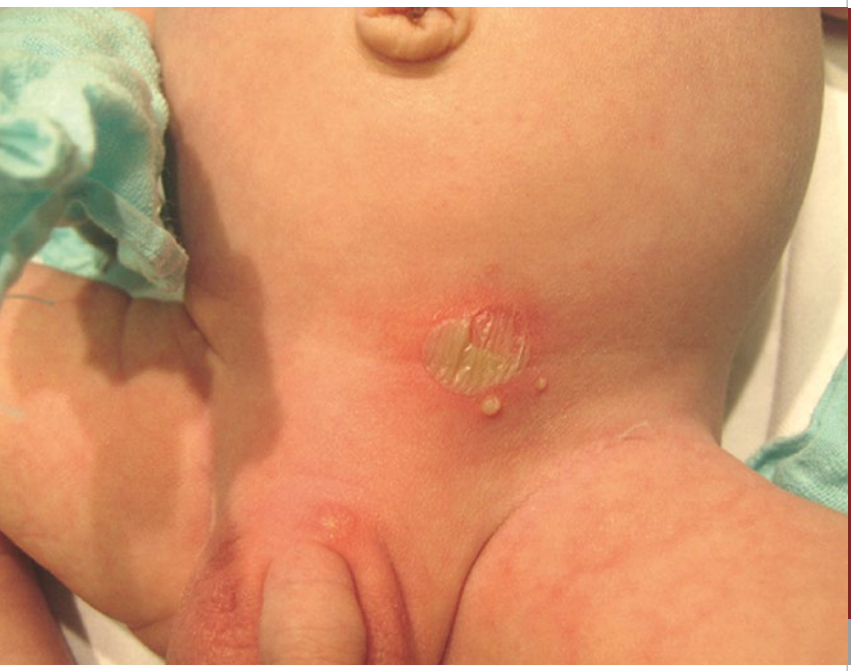

Fig. 4

***Bullous impetigo:*** *Contagious superficial infection of the skin that is associated with staphylococci. It is characterized by small vesicles or pustules that may develop into thin-walled bullae which rupture easily; the resulting erosive lesions may be covered by a yellow crust.*

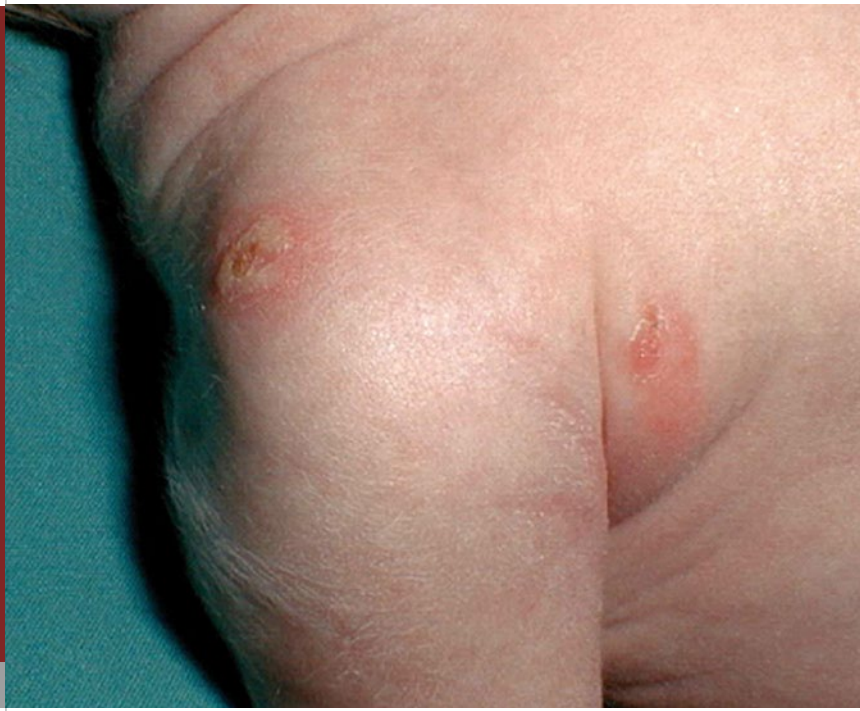

Fig. 5

***Congenital herpes simplex:*** *Characteristic cluster of vesicles on an erythematous base. Neonatal HSV usually manifest within the first 2 weeks of life and clinically ranges from localized skin, mucosal or eye infections to encephalitis, pneumonitis and disseminated infection. Most women who deliver infants with neonatal HSV had no prior history, signs, or symptoms of HSV infections. Risk of transmission is highest in pregnant woman who are seronegative for both HSV-1 and HSV-2 and acquire a new HSV infection in the third trimester of pregnancy (see also COTM* ***12/2000****).*

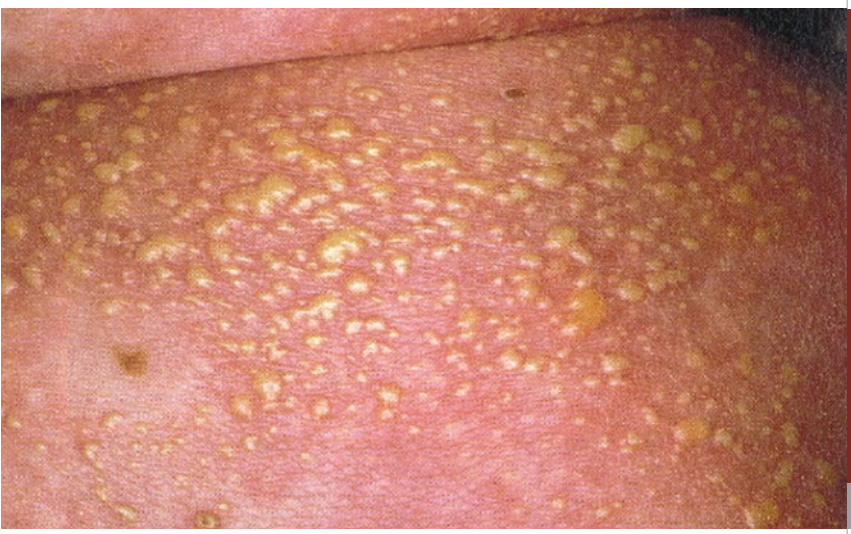

Fig. 6

***Transient neonatal pustular melanosis*** *is a benign idiopathic skin condition mainly seen in newborns with skin of color. It is characterized by superficial pustules. These rupture easily and transform to brown macules which may persist for several months. Histologic findings show intracorneal and subcorneal collections of neutrophils.*

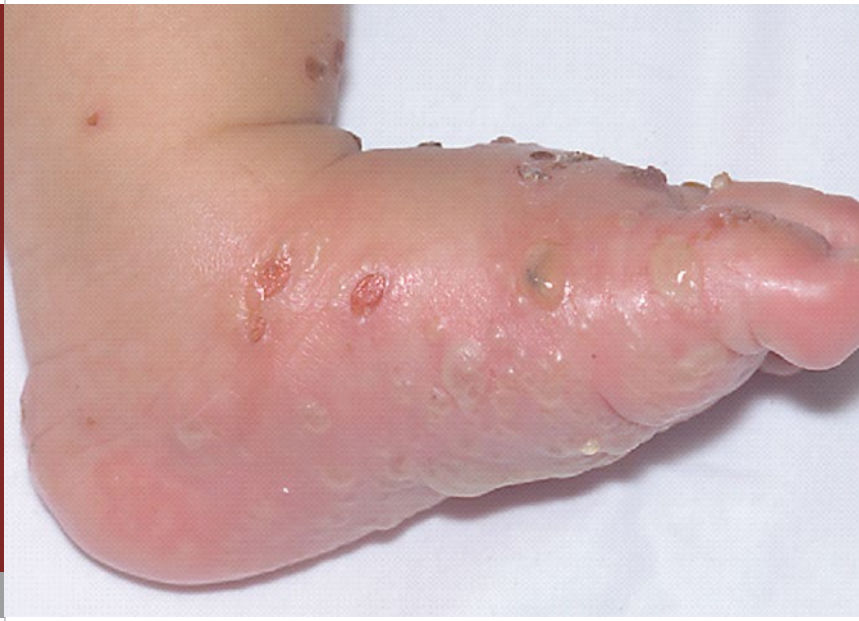

Fig. 7

***Infantile bullous pemphigoid:*** *Bullous pemphigoid (BP) is the most common blistering disease in the adult population but is very rare in children. It is characterized by the presence of IgG auto-antibodies directed against the hemidesmosomal BP antigens. Diagnosis is made by direct immunofluorescence: a linear band of IgG deposits along the dermoepidermal junction is seen.*

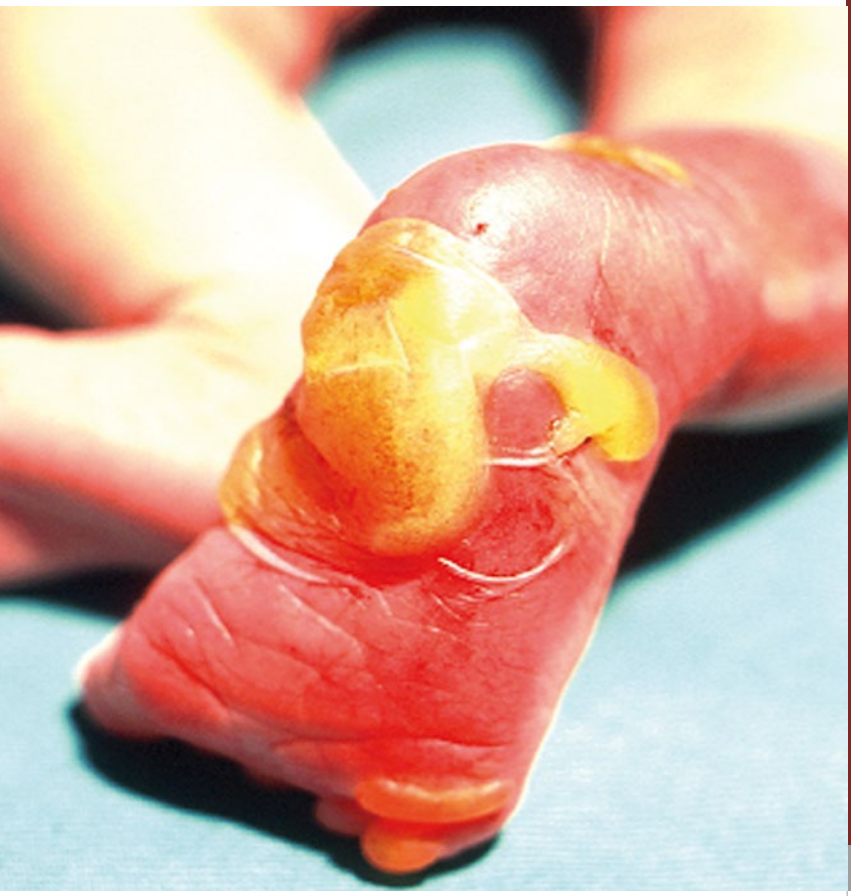

Fig. 8

*Accidental scalding injury after preparation for capillary blood sampling.*

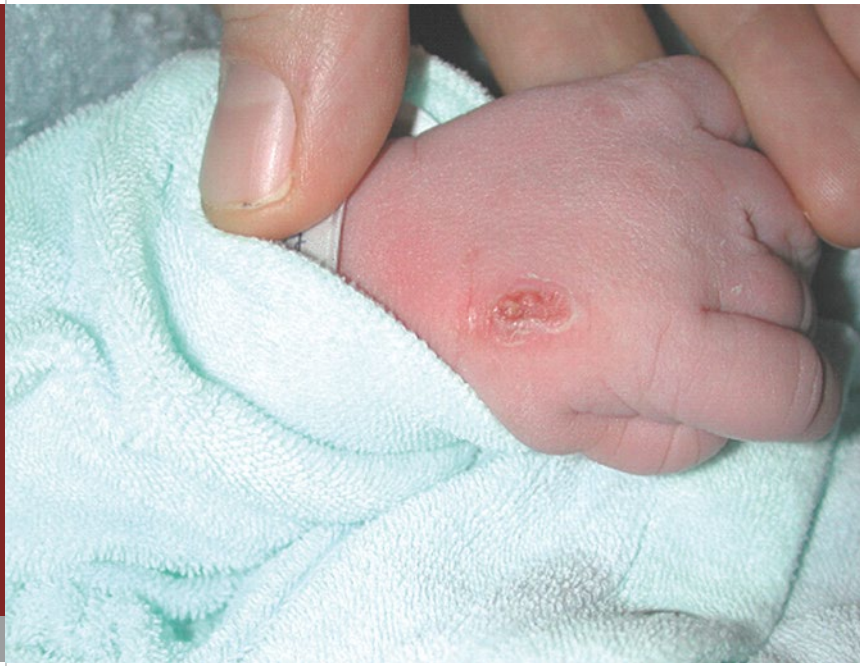

Fig. 9

***Sucking blister:*** *These lesions are present at birth, most often over the dorsal and lateral aspect of the wrist. They are due to sucking of the affected areas in utero. They appear as well demarcated bruises and may be vesicular. Commonly, the infant shows excessive sucking activity.*

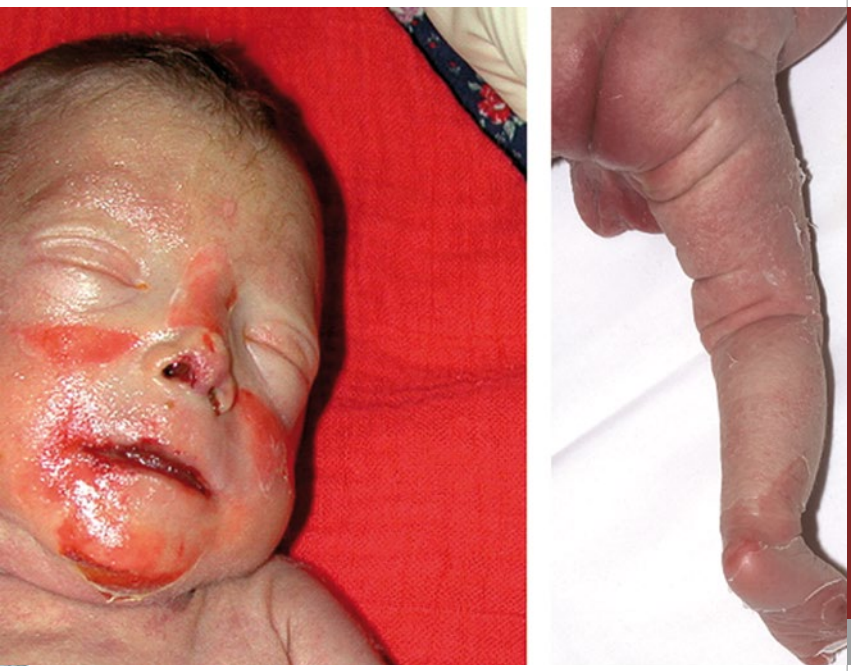

Fig. 10

***Staphylococcal scaled skin syndrome:*** *In newborns this condition is also known as Ritter von Rittershain disease. It is a superficial blistering skin disorder caused by the exfoliative toxin of some strains of Staphylococcus aureus. The toxins likely act as proteases that target the protein desmoglein-1, an important cell-to-cell attachment protein found only in the superficial epidermis. In contrast to bullous impetigo, the exfoliative toxins are not restricted to the area of infection but can spread hematogenously from a localized source.*

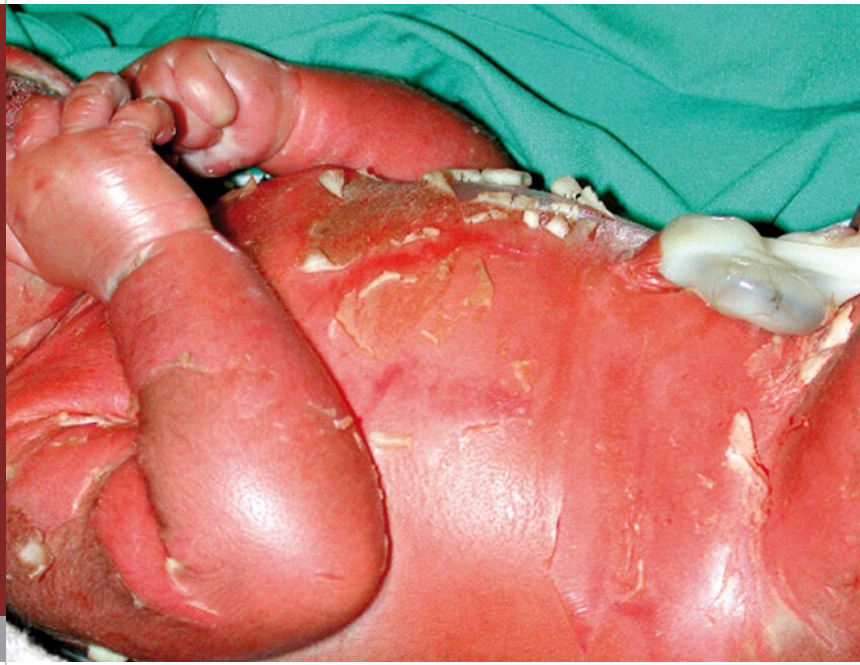

Fig. 11

***Collodion baby:*** *Characteristic clinical entity which may precede the development of one of a variety of ichthyoses or occur as an isolated and self-limiting condition. The infants are born covered with a yellow-brown, glistening, film-like membrane resembling collodion, often resulting in ectropion and eversion of the lips.*

concept & design by mesch.ch

SUPPORTED BY

NYCOMED

CONTACT

Swiss Society of Neonatology
www.neonet.ch
webmaster@neonet.ch