Table 4-23. Primary Immunodeficiencies Most Commonly Associated With Cutaneous Findings—cont'd

Class	Mutation	Characteristic Infections	Distinct Cutaneous Features	Extracutaneous Features
EDV	*EVER1* *EVER2*	**HPV 5**, **8**, 10, 14, 20, 21, 25 and 47 (extensive verruca plana, along with thicker verrous warts)		Malignant transformation of warts to **SCC**
Monomac	*GATA2*	HPV, atypical mycobacteria, and deep fungal infections		Pulmonary alveolar proteinosis ↑ risk for hematologic malignancies
Immune dysregulation				
Immunodeficiency, polyendrocrinopathy, and X-linked (IPEX)	***FOXP3***		Eczematous dermatitis	Severe diarrhea (enteropathy) Type 1 diabetes mellitus Hypothyroidism Autoimmune hemolytic anemia

SCID, severe combined immunodeficiency; CVID, common variable immunodeficiency; WHIM, warts, hypogammaglobinemia, infections, myelokathexis; EDV, epidermodysplasia verruciformis; IPEX, immunodysregulation, polyendocrinopathy, enteropathy, X-linked

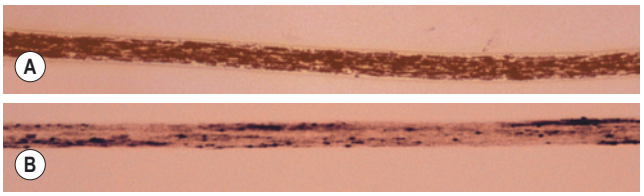

Figure 4-34. Silvery hair syndromes. The giant melanosomes are easily seen in the hair shaft of individuals with Chediak–Higashi syndrome **(A)** and Griscelli syndrome **(B)**. Note the more regular spacing of the melanosomes in the hair from a patient with Chediak-Higashi syndrome. (From Paller S, Mancini AJ. Hurwitz Clinical Pediatric Dermatology, 4th Ed. Elsevier. 2011)

4.14 DISORDERS OF CORNIFICATION

- Inherited ichthyoses generally present at birth or in infancy/early childhood
  - Heterogeneous group of genetic disorders linked by a common finding of abnormal epidermal differentiation or metabolism → hyperkeratosis and/or epidermal hyperplasia
  - Dysfunction of cornified cell envelope disrupts skin barrier function → ↑transepidermal water loss
  - Inherited ichthyoses characterized by localized or generalized hyperkeratosis, scaling, or both, along with variable additional cutaneous and/or systemic manifestations; +/− erythema
  - Collodion membrane at birth seen with some forms of congenital ichthyosis (lamellar ichthyosis and **non-bullous congenital erythroderma most commonly**; also Sjögren-Larsson syndrome, Gaucher disease type 2, Hay-Well syndrome, trichothyodystrophy, Netherton syndrome, ectodermal dysplasia, and neutral lipid storage disease); phenotype reveals itself once the collodion resolves, after several weeks (Fig. 4-35)
  - Routine histology is generally non-diagnostic, but may demonstrate epidermal hyperplasia and variable orthohyperkeratosis; **ichthyosis vulgaris shows a diminished or absent granular layer** and epidermolytic ichthyosis shows epidermolytic hyperkeratosis

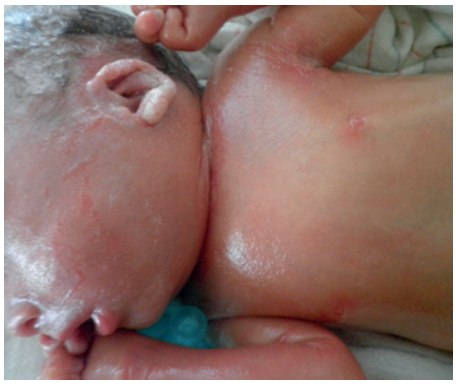

Figure 4-35. Collodion baby: collodion membrane in a 1-day-old newborn. (From Renata Prado MD, Lixia Z. Ellis MD, PhD, Ryan Gamble MD, Tracy Funk MD, Harvey Alan Arbuckle MD and Anna L. Bruckner MD. Journal of the American Academy of Dermatology, Volume 67, Issue 6, Pages 1362-1374. Elsevier. 2012.)

  - Treatments for inherited ichthyosis: **emollients and keratolytics**; topical and systemic **retinoids** can help reduce hyperkeratosis and are useful for some disorders; neonatal care includes humidified incubators, emollients and close observation for infection, dehydration, and electrolyte abnormalities
- Palmoplantar keratodermas (PPK) are a heterogeneous group of inherited and acquired disorders marked by hyperkeratosis of the palms and soles
  - Three types of PPK: focal (localized areas of hyperkeratosis, usually over pressure points), diffuse (hyperkeratosis involves entire palmoplantar surface), and punctate (1- to 2-mm keratotic papules)
  - PPK can be an isolated finding or associated with other abnormalities
  - Treatment: topical keratolytics (salicylic acid 2%–5%, lactic acid 5%–12%, and urea 10%–40%), topical retinoids, and topical corticosteroids when inflammation is present; use of oral retinoids may be helpful in some disorders; CO_2 laser ablation and surgical paring or excision helpful for more severe PPK
- See Table 4-24, and Table 4-25

Text continued on p. 273

Table 4-24. Features of Selected Ichthyoses and Erythrokeratodermas

Diagnosis	Gene	Inheritance	Onset	Primary Cutaneous Features	Associated Clinical Features	Histology and Ultrastructural Features	Ancillary Diagnostic Studies
Ichthyosis vulgaris	*FLG*	Autosomal semidominant	Infancy/ childhood	Fine, adherent scales on **extremities** and trunk with sparing of flexures; larger scale on lower legs; **hyperlinear palms/soles**, and furrowed heels	**Keratosis pilaris; atopic diathesis**	Diminished/**absent stratum granulosum** w/overlying **orthohyperkeratosis**; absent/reduced filaggrin immunostaining	Genetic testing
Steroid sulfatase deficiency (X-linked recessive ichthyosis)	*STS*	XLR Contiguous gene deletion may → Kallmann syndrome	Infancy	Fine to large, **dark/brown**, **adherent scales** on extremities, trunk, neck, and lateral face **spares flexures**, palms, soles, and face	**Corneal** (**comma-shaped**) **opacities**; **cryptorchidism**; ↑risk of **testicular cancer**, and hypogonadism *Female carriers:* corneal opacities; **prolonged labor** with affected child (placental sulfatase deficiency)	Retained corneodesmosomes within stratum corneum	Lipoprotein electrophoresis (increased mobility of β-fraction); plasma cholesterol sulfate increased; decreased steroid sulfatase activity in leukocytes; FISH, array CGH, genetic testing Maternal carriers may have abnormal triple/ quad screen during affected pregnancy with decreased serum estriol
Lamellar ichthyosis (Fig. 4-36)	***TGM1*** *ABCA12** *CYP4F22** *CERS3*	AR	Birth	Frequently collodion membrane at birth with ectropion and eclabium; after collodion resolves, presence of large, **thick**, **plate-like brown scales** in generalized distribution w/**significant flexural involvement**; absent or mild erythroderma; variable palm/ sole involvement (PPK)	**Heat intolerance** (hypernatremic dehydration); frequent **scarring alopecia**; dystrophic nails Hypohidrosis	TGM1: thin cornified envelope and disorganized lamellar bilayers ABCA12: absence of lamellar body content NIPAL4: defective lamellar bodies and perinuclear membranes within stratum granulosum	*In situ* transglutaminase-1 expression and activity assay; genetic testing
Congenital ichthyosiform erythroderma (CIE)	*TGM1* ***ALOXE3***† ***ALOX12B***† *NIPAL4 (ICHTHYIN)*† *PNPLA1*†	AR	Birth	Frequently **collodion membrane** (#1 cause) at birth; after collodion resolves, fine, **white scale** in generalized distribution (**flexures involved**); erythroderma; variable palm/sole involvement	Heat intolerance/hypohidrosis; variable scarring alopecia and ectropion	Same as for lamellar ichthyosis	Genetic testing
Congenital self-healing collodion baby	*TGM1* *ALOXE3,* *ALOX12B*	AR	Birth	**Collodion membrane** at birth; after resolution, skin appears normal without features of ichthyosis	None	Nondiagnostic	Genetic testing

Harlequin ichthyosis	*ABCA12*	AR	Birth	Very thick, yellow-brown plates of scale with large, deep and bright red fissures that tightly encase the neonate; **extreme ectropion**, **eclabium**, **and ear deformities**; survivors develop severe CIE-like phenotype; **early initiation of systemic retinoids** and specialized neonatal intensive care reduce mortality	Premature delivery; risk of neonatal hypothermia, and hypernatremic dehydration; **often neonatal death from sepsis or respiratory insufficiency**	Vesicular lamellar body ghosts, paucity of secreted lamellar structures in stratum corneum	Genetic testing
Epidermolytic ichthyosis (bullous CIE)	*KRT1* *KRT10*	AD May have somatic mosaicism → extensive epidermal nevi (ichthyosis hystrix); if it is gonadal mosaicism, then may have offspring with full blown disease	Birth	*At birth:* erythroderma, **blistering**, and erosions *Later:* **hyperkeratosis** with cobblestone pattern (most prominent over joints), ridging of the flexures; generalized or localized; variable degree of erythroderma, palmoplantar involvement, and blistering/bullae; **retinoids can exacerbate** skin fragility	Frequent skin infections; **malodor**; gait and posture abnormalities	Hyperkeratosis, keratinocyte vacuolization, and a prominent granular layer with **clumped keratin in suprabasal cells**; lamellar body accumulation	Genetic testing
Superficial epidermolytic ichthyosis (ichthyosis bullosa of Siemens)	*KRT2*	AD	Birth	Erythroderma and **superficial blistering** at birth; later, hyperkeratosis with accentuation over joints, flexures, and dorsal hands/feet; "**molting**" of the skin; palms and soles spared		Cytolysis of granular cells	Genetic testing
Ichthyosis hystrix Curth-Macklin	*KRT1*	AD	Birth	Mild to severe, mutilating palmoplantar keratoderma; hyperkeratosis with verrucous, cobblestone, or hystrix-like pattern on extremities and trunk	Pseudoainhum; digital contractures	Binuclear cells; particular concentric perinuclear "shells" of aberrant putatively keratin material	Genetic testing
Ichthyosis en confetti	*KRT10*	AD		At birth, erythroderma and scaling; later, confetti-like areas of scaling (result from revertant mosaicism); palmoplantar keratoderma	Joint contractures	Affected skin: loss of epidermal differentiation above the basal layer with nucleolar vacuolization, loss of granular layer, and acanthosis, Revertant skin: normal	

Continued

Table 4-24. Features of Selected Ichthyoses and Erythrokeratodermas—cont'd

Diagnosis	Gene	Inheritance	Onset	Primary Cutaneous Features	Associated Clinical Features	Histology and Ultrastructural Features	Ancillary Diagnostic Studies
Netherton syndrome (Fig. 4-37)	*SPINK5* (encodes LEKT1, serine protease inhibitor)	AR	Birth/infancy	**Congenital erythroderma** and scaling; two principal phenotypes: **ichthyosis linearis circumflexa** (annular or serpiginous plaques w/**double-edged scale**) and CIE-like; pruritus and eczematous plaques are common **Don't use tacrolimus ointment** (↑absorption → toxic) or keratolytics (irritating)	**Trichorrhexis invaginata**, trichorrhexis nodosa, and pili torti (short/sparse hair and brows; **↑IgE**; neonatal temperature instability, electrolyte imbalance (hyponatremia), and failure to thrive; recurrent infections; **food and other allergies/ anaphylaxis**; nonspecific aminoaciduria	Psoriasiform histopathology; light microscopy of hair shafts may reveal trichorrhexis invaginata ("**bamboo hair**")	Genetic testing
Sjögren-Larsson syndrome	*ALDH3A2/* ***FALDH***	AR	Birth	At birth, erythema and hyperkeratosis; later, fine to plate-like/dark scaling or nonscaling hyperkeratosis; favors abdomen, neck, flexures; lichenification; palmoplantar keratoderma; pruritus can be severe	**Progressive spastic di- and tetraplegia**; developmental delay; intellectual disability; seizures; **perifoveal glistening white dots**; white matter disease of the brain; **photophobia**	Nonspecific; hyperkeratosis, acanthosis, and preservation of granular layer	Fatty aldehyde hydrogenase activity assay in cultured fibroblasts; genetic testing (preferred method)
Neutral lipid storage disease with ichthyosis/ Chanarin-Dorfman syndrome	*ABHD5 (CGI-58)*	AR	Birth	Generalized, fine, white scales with variable erythema	**Developmental delay**; **hepatomegaly** with liver fibrosis, elevated liver enzymes, and creatine kinase; myopathy; hearing impairment; cataracts	**Globular electron-lucent inclusions in epidermis**	**Peripheral blood smear to detect lipid vacuoles in granulocytes**, **eosinophils**, and **monocytes**; oil stains of frozen tissue; genetic testing
Refsum disease	*PHYH* *PEX7*	AR	childhood to adulthood	Fine, white scales on extremities and trunk, resembling ichthyosis vulgaris (50%)	Peripheral motor and sensory neuropathy; cranial nerve dysfunction (deafness, anosmia); **cerebellar ataxia**; atypical retinitis pigmentosa ("**salt and pepper** pigment"); cardiomyopathy, arrhythmias w/ heart block; muscle wasting	Orthokeratotic hyperkeratosis and lipid-containing vacuoles in basal keratinocytes	**Increased plasma phytanic acid**; phytanoyl-CoA hydroxylase activity assay in cultured fibroblasts; genetic testing **Diet is essential: ↓green vegetables, dairy products, and ruminant fats**

Keratitis-ichthyosis-deafness (KID) syndrome	*GJB2* (encodes connexin 26)	AD (nearly all reported cases are sporadic)	Birth/infancy	Transient neonatal erythroderma; erythematous, **hyperkeratotic plaques w/ well-demarcated**, **borders on face and extremities**; follicular keratoses; thickening of the skin with an appearance of "coarse-grained leather;" stippled palmoplantar keratoderma	Congenital **sensorineural hearing impairment**; progressive keratitis with corneal neovascularization that may lead to **blindness**, conjunctivitis; recurrent mucocutaneous infections, especially with *Candida albicans;* increased susceptibility to oral and cutaneous **squamous cell carcinoma**; nail, hair, and dental anomalies; cheilitis	Nonspecific; acanthosis, papillomatosis, and follicular plugging	
Erythrokeratodermia variabilis	*GJB3* *GJB4* (encode connexin 31 GJA1 and 30.3)	AD	Birth/infancy	**Transient**, **variable**, **erythematous patches**; more **stable**, **geographic**, **hyperkeratotic plaques** over knees, elbows, Achilles tendons, extremities, buttocks, and lateral trunk; face and scalp often spared; less common generalized hyperkeratosis; palmoplantar keratoderma in ~50% of patients	Burning or stinging sensation preceding or accompanying erythema	Nonspecific; may reveal reduced lamellar bodies in stratum granulosum and reduced keratinization	Genetic testing
Progressive symmetric erythrokeratoderma	(*LOR*) (*GJB4*) other unknown gene(s)	AD or AR	Infancy/ childhood	Fixed, slowly progressive, erythematous, hyperkeratotic plaques with sharp, figurate borders; on cheeks, over knees, elbows, extremities, and rarely trunk; palmoplantar keratoderma common		Nondiagnostic; acanthosis, hyperkeratosis, and prominent granular layer	
Acral peeling skin syndrome	*TGM5*	AR		Recurrent spontaneous painless superficial peeling on dorsal hands and feet, followed by the development of mild erythema; resolves without scarring; exacerbated by heat and humidity		Separation occurs between the junction of the stratum granulosum and the stratum corneum	

Continued

Table 4-24. Features of Selected Ichthyoses and Erythrokeratodermas—cont'd

Diagnosis	Gene	Inheritance	Onset	Primary Cutaneous Features	Associated Clinical Features	Histology and Ultrastructural Features	Ancillary Diagnostic Studies
Congenital hemidysplasia with ichthyosisiform erythroderma and limb defects (**CHILD**) **syndrome** (Fig. 4-38)	*NSDHL* (3β-hydroxysteroid-dehydrogenase)	**XLD**	Birth	At birth, unilateral (right > left-sided) erythema and waxy, yellowish adherent scale on **1/2 of the body** (trunk/extremities); later, verrucous hyperkeratosis of variable extent, with affinity for skin folds	**Ipsilateral skeletal hemidysplasia** (hypoplastic limbs); **ipsilateral organ hypoplasia**; ipsilateral alopecia; may also see stippled epiphyses/chondrodysplasia punctata (similar to Conradi-Hunermann-Happle)	Nonspecific; acanthosis, papillomatosis, and superficial perivascular infiltrate	Genetic testing
Conradi-Hünermann-Happle syndrome (X-linked dominant chrondrodysplasia punctata) (Fig. 4-39)	*EBP* (emopamil-binding protein)	**XLD**	Birth	At birth, ichthyosiform erythroderma (**generalized**, vs unilateral in CHILD syndrome) with feathery, adherent scale along Blaschko's lines; **erythema resolves** in first few months of life (unlike CHILD syndrome) and is replaced by follicular **atrophoderma** along Blaschko's lines, most prominently on the forearms and dorsal hands	Unilateral cataracts; **stippled epiphyses/chondrodysplasia punctata** seen only during infancy; asymmetric skeletal abnormalities, including scoliosis and rhizomelic limb shortening, but less severe than CHILD syndrome; frontal bossing w/ macrocephaly; patchy scarring alopecia	Nonspecific; hyperkeratosis and focal parakeratosis; may see dystrophic calcification in keratotic plugs	**Epiphyseal stippling on X-ray** only visible during infancy; accumulation of plasma cholesterol; genetic testing
Ichthyosis follicularis-atrichia-photophobia (IFAP) syndrome	*MBTPS2*	XLR	Birth	Erythroderma, scaling, and follicular hyperkeratosis; generalized alopecia, including eyebrows and eyelashes	Growth retardation and microcephly; corneal opacities and ulcerations; photophobia; vascularizing keratitis; variable hearing loss; nail dystrophy; variable intellectual impairment, developmental delay, seizures, and structural CNS anomalies; genitourinary anomalies and skeletal anomalies	Follicular plugging and hypoplastic pilosebaceous structures	

CGH, comparative genomic hybridization; FISH, fluorescence in situ hybridization

**Also occasionally associated with CIE or intermediate LI/CIE phenotypes; a CIE-like phenotype is also seen in harlequin ichthyosis survivors.*

†Also occasionally associated with mild LI or intermediate LI/CIE phenotypes.

(Adapted from Bolognia JL, Jorizzo JL, Rapini RP. Dermatology, 3rd Ed. Elsevier. 2012)

Table 4-25. Selected Hereditary Palmoplantar Keratodermas (PPKs) With Known Genetic Basis

Type	Gene	Gene Product	Synonyms	Inheritance	Onset	Transgrediens	Comments
Diffuse							
Unna-Thost (Fig. 4-40)	***KRT1*** *KRT6c*	**Keratin 1** Keratin 6c	Nonepidermolytic PPK (NEPPK)	AD	2–5 years, sometimes later	No	Second most common type of diffuse PPK (after EPPK) Diffuse, well-demarcated PPK w/ yellow hue; hyperhidrosis Histology w/ prominent orthokeratosis
Vörner	*KRT1* *KRT9*	Keratin 1 Keratin 9	Epidermolytic PPK (EPPK)	AD	0–3 years	No	**Clinically identical to diffuse NEPPK**, **but histology shows epidermolytic hyperkeratosis**
Mal de Meleda	*SLURP-1*	Secreted Ly6/Plaur domain-containing protein-1	Mal de Meleda	AR	0–3 years	Yes	Atopic dermatitis; **transgradiens** PPK erythematous w/ fissures/hyperhidrosis/maceration/ **horrible odor**/often infected; **dystrophic nails**
Greither	*KRT1* (in some families)	Keratin 1	Transgrediens and progrediens PPK	AD	Infancy	Yes	
Mutilating (Vohwinkel) (Fig. 4-41)	*LOR* (+ ichthyosis) *GJB2* (+ deafness)	Loricrin Connexin 26	Vohwinkel syndrome; keratoderma hereditaria mutilans	AD	Infancy	Yes	**Honeycombed palmar PPK**, **pseudoainhum** (esp. fifth finger – constriction bands → autoamputation), **starfish keratoses** on the knuckles/ feet/elbows/knees, linear keratoses on elbows/knees, **sensorineural deafness** (**Cx26**), and generalized **ichthyosis** (**loricrin**)
Papillon-Lefèvre syndrome	*CTSC*	Cathepsin C	PPK with periodontitis	AR	Birth to early infancy	Yes, diffuse	**Transgradiens** PPK w/ erythema/hyperhidrosis/terrible odor (soles > palms); pyogenic infections; **periodontitis/gingivitis → premature loss of teeth**, psoriasiform lesions on elbows/ knees, and pyogenic infections; **dural calcification**
Naxos disease	*JUP*	Plakoglobin	Diffuse NEPPK with woolly hair and cardiomyopathy	AR	Infancy	No	Woolly hair; arrhythmias and **right ventricular cardiomyopathy** develop during adolescence
Focal							
Striate type Areata type	*DSG1* *DSP* *KRT1* *KRT16* *KRT6c*	Desmoglein 1 Desmoplakin Keratin 1 Keratin 16 Keratin 6c	Wachters type, Brünauer-Fuhs-Siemens type	AD	4–10 years	No	Striate on palms and islands on feet; variable phenotype
Richner-Hanhart syndrome	*TAT*	**Tyrosine amino-transferase**	**Tyrosinemia type II**, oculocutaneous tyrosinemia	AR	Infancy (ocular) Early childhood to adolescence (skin)	No	**Focal painful PPK on weight-bearing areas**; **dendritic keratitis**, **corneal ulcers**, **and blindness** (ocular findings prior to skin findings); hyperkeratosis of elbows/knees; mental retardation
Pachyonychia congenita	*KRT16* *KRT6a* *KRT17* *KRT6b*	Keratin 16 Keratin 6α Keratin 17 Keratin 6b	PC1, Jadassohn-Lewandowsky type PC2, Jackson-Lawler type	AD	Infancy to early childhood	No	PC1: more severe NEPPK PC2: steatocystoma multiplex and eruptive vellus hair cysts more common; natal teeth
Carvajal syndrome	*DSP*	Desmoplakin	Striate PPK with woolly hair and cardiomyopathy	AR > AD	Infancy	No	Woolly hair; **dilated left ventricular cardiomyopathy** (variable onset); occasionally skin fragility, nail dystrophy, hypodontia
Howel-Evans syndrome	*RHBDF2/IRHOM2*	Rhomboid 5, drosophila, homolog of 2/inactive rhomboid protein 2	**Tylosis with esophageal cancer**	AD	Childhood	No	**Thick yellow PPK on weight-bearing areas** (heels and balls of feet) starting in second decade **Significant risk for development of esophageal cancer in third to fifth decade**

AD, autosomal dominant; AR, autosomal recessive; SCC, squamous cell carcinoma
(Adapted from Bolognia JL, Jorizzo JL, Rapini RP. Dermatology, 3rd Ed. Elsevier. 2012)

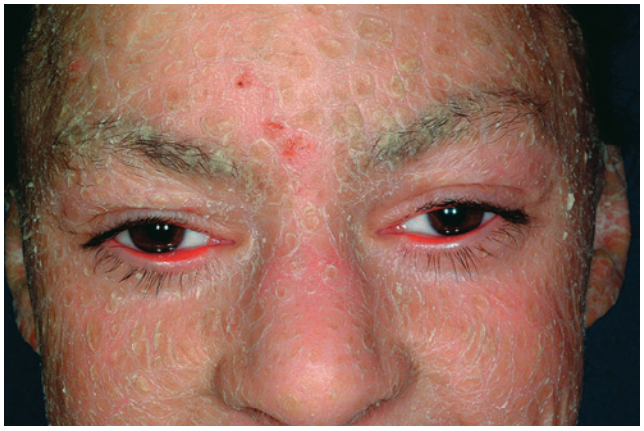

Figure 4-36. Lamellar ichthyosis phenotype of ARCI. Large plate-like scaling on the forehead and cheeks. This patient shows moderate ectropion. (From Paller S, Mancini AJ. Hurwitz Clinical Pediatric Dermatology, 4th Ed. Elsevier. 2011)

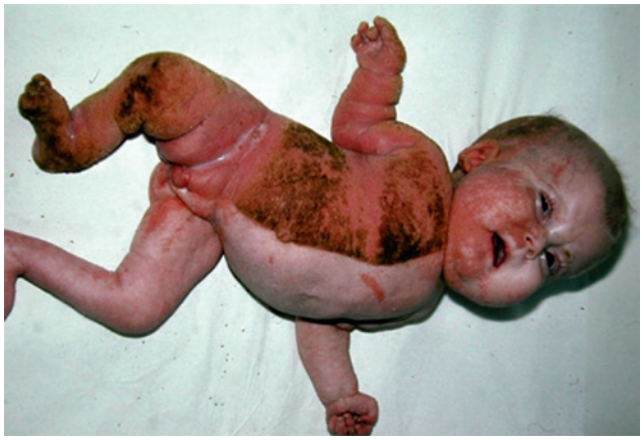

Figure 4-38. CHILD Syndrome. Unilateral erythema and scale with ipsilateral limb defects. (Rimoin D, Michael Connor J, Pyeritz R, Korf B. Emery and Rimoin's Principles and Practice of Medical Genetics e-dition, 5th Ed. Elsevier. 2007.)

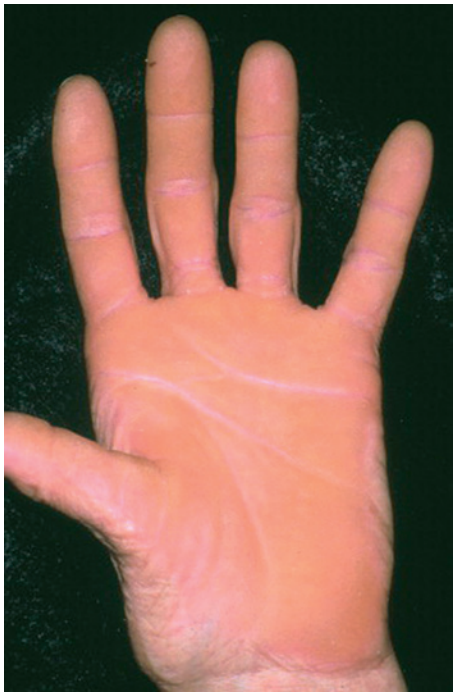

Figure 4-40. Unna–Thost syndrome. (From Gehris, Robin P., Ferris, Laura K. General Dermatology. January 1, 2009. Pages 277-296)

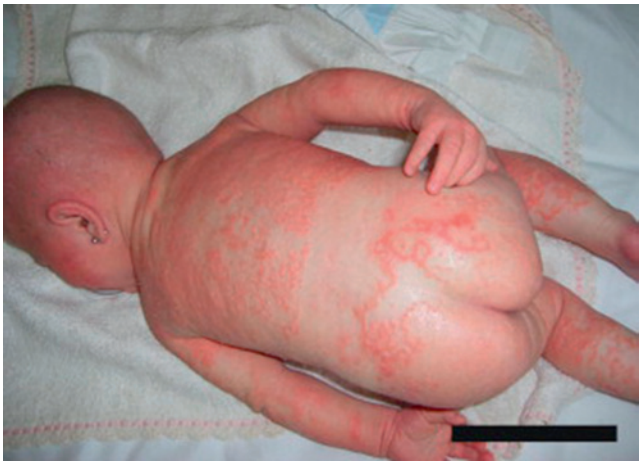

Figure 4-37. Erythroderma, hypotrichosis, and areas with ichthyosis linearis circumflexa. (From Allergology and Immunopathology [Allergologia et Immunopathologia]. Serena Pastore, Gaia Gorlato, Irene Berti, Egidio Barbi, Alessandro Ventura Volume 40, Issue 5. Pages 316-317. Elsevier. 2012)

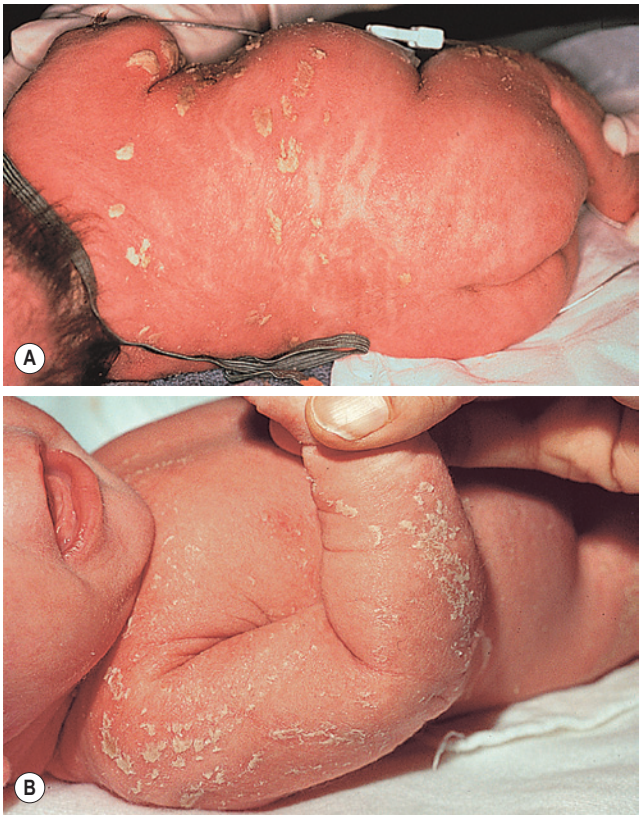

Figure 4-39 Conradi–Hünermann syndrome. **(A)** Thick, psoriasiform scaling overlying erythema in a 1-month-old girl with the syndrome and chondrodysplasia punctata. As the scaling desquamated, the underlying erythema along Blaschko's lines became more apparent. (Eichenfield L.F. et al. Neonatal and Infant Dermatology 3rd ed. Elsevier. 2015) **(B)** The pattern of scale along Blaschko's lines is more evident in this neonate with Conradi-Hünermann syndrome. (From Paller AS. Ichthyosis in the neonate. In: Dyall-Smith D, Marks R, eds. Dermatology at the millennium: Overview of past achievements, current knowledge and future trends. London: Parthenon Publishing Group; 1998, with permission.)