2

Pediatric Dermatology

Contents

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2.1 NEONATAL DERMATOLOGY

Transient Neonatal Pustular Melanosis (Figure 2.1A)

- Onset at birth; common in darkly pigmented infants
- Presents with small pustules or residual hyperpigmented macules with collarette of scale
- Smear of sterile pustule shows numerous neutrophils
- Histology: subcorneal pustules with neutrophils

Erythema Toxicum Neonatorum

- Onset typically 24–48 h after birth; occurs in half of all full-term infants
- Presents with blotchy erythematous macules, papules, pustules, and wheals
- Smear of sterile vesicle/pustule shows eosinophils
- Histology: subcorneal pustules with eosinophils, associated with pilosebaceous unit

Neonatal Cephalic Pustulosis (Neonatal Acne) (Figure 2.1B)

- Onset typically within first 30 days; *Malassezia* spp. implicated in pathogenesis
- Presents with erythematous follicular comedones, papules, and pustules on face
- Histology: follicular pustules with neutrophils

Sclerema Neonatorum

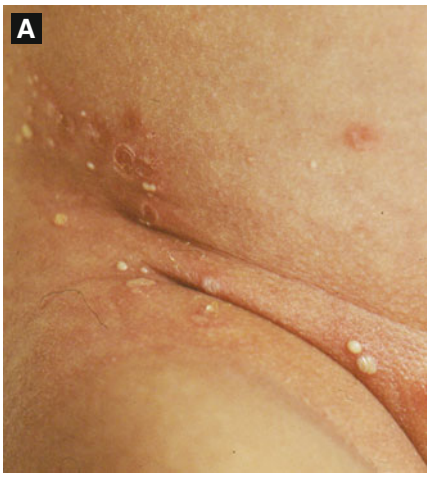
- Onset usually within first week of life; form of panniculitis in severely ill, premature infants; often fatal
- Presents with diffuse woody hardening of skin; spares genitalia, palms, and soles
- Histology: needle-shaped clefts with necrotic adipocytes with little surrounding inflammation

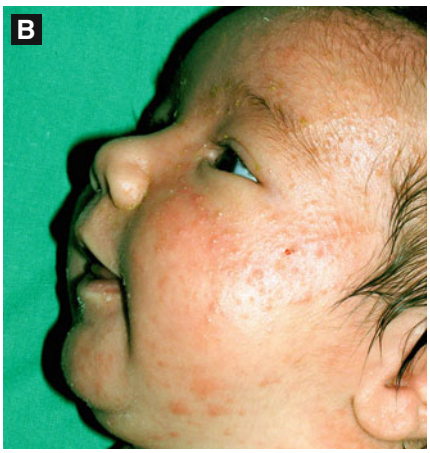
Subcutaneous Fat Necrosis of the Newborn (Figure 2.1C)

- Onset within first weeks of life; localized form of sclerema neonatorum in healthy infants
- Presents with indurated subcutaneous nodules favoring cheeks, shoulders, back, buttocks, and thighs
- Associated with hypothermia, perinatal hypoxemia (from preeclampsia, meconium aspiration, etc.), hypoglycemia
- Calcification may occur; ± profound hypercalcemia with resolution, so prudent to monitor calcium levels until 1 month after full resolution of lesions
- Histology: panniculitis with prominent inflammatory infiltrate, needle-shaped clefts and fat necrosis

Pedal Papules of Infancy

- Soft, non-painful papules involving heels





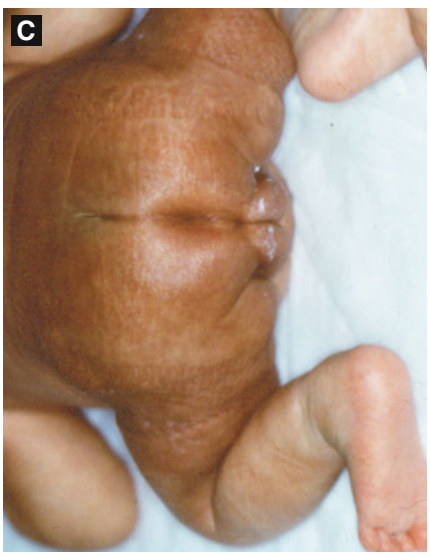


Figure 2.1
A: Neonatal pustular melanosis*
B: Neonatal cephalic pustulosis
(*Reprint from Boekhout T, Gueho-Kellerman E, Mayser P, Velegraki A. Malassezia and the Skin. New York, NY: Springer; 2010*)
C: Subcutaneous fat necrosis*
**Reprint from Laxer RM, ed. The Hospital for Sick Children: Atlas of Pediatrics. Philadelphia, PA: Current Medicine; 2005*

Seborrheic Dermatitis (Figure 2.2A)

- Onset typically 1 week after birth; lasts several months, mostly resolves by 1 year of age
- Presents with ill-defined erythematous patches with waxy scale over scalp ("cradle cap"), ± axillae and groin; lesions may appear psoriasiform

Miliaria Crystallina (MC) or Miliaria Rubra (MR)

- Onset within first few weeks of life; due to obstructed sweat glands and associated with ↑ temperature (i.e., occlusion)
- Presents with clear vesicles favoring head, neck, and upper trunk (MC) or erythematous papules/vesicles grouped in intertriginous areas or occluded areas (MR)

Aplasia Cutis Congenita (ACC) (Figure 2.2B, C)

- Onset before birth; localized defect in epidermis, dermis and/or fat; variable appearance, typically along midline
- Presents with erosion, ulceration, scar, or membranous defect (ovoid lesion covered by an epithelial membrane)
- Hair collar sign: ring of dark long hair encircling lesion; ± marker of underlying neural tube defect
- Typically isolated abnormality, but may be associated with developmental anomalies or following disorders:

Bart Syndrome	ACC of **lower extremities + epidermolysis bullosa** (dominant dystrophic)
Adams–Oliver Syndrome	ACC on scalp (with skull ossification defect) + extensive **CMTC + limb defects** (reductions, syndactyly) + cardiac abnormalities
Seitles Syndrome	**Bilateral temporal** ACC + abnormal eyelashes, "**leonine**" facies, upward-slanting eyebrows

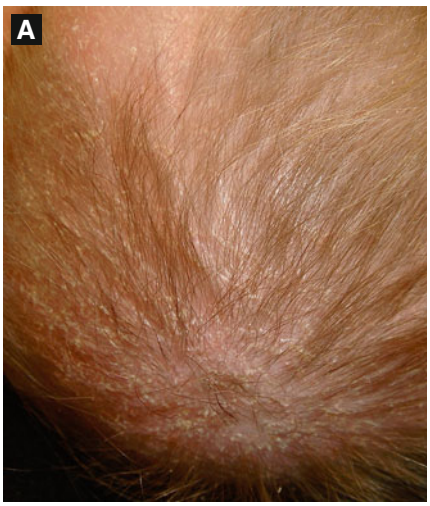
Cutis Marmorata Telangiectatica Congenita (CMTC)

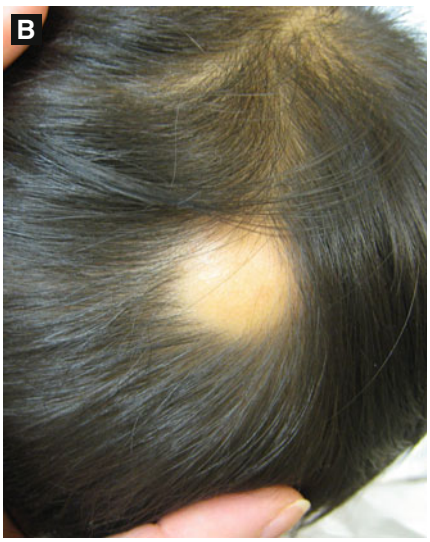
- Onset at birth; typically improves with age
- Presents with blanching reticulated vascular pattern on trunk/extremities with segmental distribution
- Associated anomalies in ½ of patients (varicosities, nevus flammeus, macrocephaly, ulceration, hypoplasia, and/or hypertrophy of soft tissue and bone)

Sucking Blister

- Onset at birth or soon after; due to sucking
- Presents with solitary blister (hand, wrist, or lip)

Congenital Infections of the Newborn (see Table 2-1)
Differential Diagnosis of 'Diaper Dermatitis' (see Table 2-2)





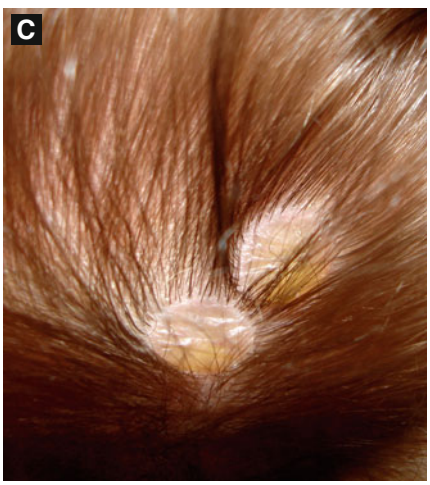


Figure 2.2
A: Seborrheic dermatitis
B: ACC, cicatricial
(*Courtesy of Dr. Michelle B. Bain*)
C: ACC, bullous
(*Courtesy of Dr. Michelle B. Bain*)

Table 2-1 Congenital Infections of the Newborn

Infection	Clinical Findings	Extracutaneous Findings	Important Points
Cytomegalovirus (CMV)	Petechiae, purpura, vesicles, and **"blueberry muffin"** lesions Blueberry muffin lesions: red-blue papules/nodules due to dermal erythropoiesis	Intrauterine growth retardation, chorioretinitis, intracranial calcification	⇒ Leading infectious cause of **deafness** and mental retardation ⇒ Typical findings on histology: **enlarged endothelial cells with intranuclear inclusions**
Herpes Simplex Virus (HSV)	Localized or disseminated skin lesions (vesicles, erosions, scarring)	Encephalitis (predilection for **temporal** lobes), multi-organ failure, ocular infection	⇒ Majority HSV2, 85% acquired perinatally ⇒ **50–75% mortality** if left untreated
Rubella	"**Blueberry muffin**" lesions	Cataracts, deafness, congenital heart disease, CNS findings (microcephaly, hydrocephaly), hepatosplenomegaly (HSM)	⇒ 50% chance of deafness ⇒ Severe birth defects if within **first 16 weeks** of pregnancy ⇒ Non-immune pregnant woman transfer the virus to the fetus
Toxoplasmosis	"**Blueberry muffin**" lesions favoring the trunk	Ocular abnormalities (chorioretinitis, blindness), CNS abnormalities (deafness, mental retardation, seizures), thrombocytopenia, intracranial calcification	
Varicella	**Cicatricial** skin lesions	Ocular abnormalities (chorioretinitis, cataracts), cortical atrophy, psychomotor retardation, hypoplastic limbs	⇒ Greatest risk in **first 20 weeks** ⇒ 2% risk of embryopathy in women with infection within first two trimesters
Syphilis, Early Congenital	Syphilitic pemphigus, **rhagades** (radial furrows/ fissures in perioral area, turn into parrot lines), papulosquamous macules/ papules (like secondary syphilis)	**Snuffles** (rhinitis, secondary to ulcerated mucosa), enlarged lymph nodes and spleen, neurosyphilis Be able to differentiate early and late congenital syphilis findings	⇒ Early congenital syphilis occurs from **birth to 2 years of age** ⇒ Only congenital syphilis may show **bullous lesions** ⇒ Papulosquamous lesions common in the diaper area
Syphilis, Late Congenital	Hutchinson's teeth, Higoumenakis sign, mulberry molars, saddle nose, saber shins, parrot lines and furrows	Interstitial keratitis, gummas along long bones/skull, tabes dorsalis, generalized paresis	⇒ Includes permanent sequelae of early congenital signs ⇒ Higoumenakis sign: congenital thickening of the medial aspect of the clavicle

Table 2-2 Differential Diagnosis for Diaper Dermatitis

Entity	Clinical Findings
Candidal Dermatitis	Bright red patches with pustules and satellite papules, ± intertriginous involvement **(including scrotum)**, ± thrush
Irritant Dermatitis	Poorly demarcated erythematous plaques, **spares inguinal folds**
Seborrheic Dermatitis	Typical salmon-covered scaly patches and plaques involving the scalp, groin, and other intertriginous areas
Psoriasis	Sharply demarcated bright pink to red plaques **involving inguinal creases**, minimal scale; most common psoriatic presentation in infants
Allergic Contact Dermatitis	Rare in infants, ± related to topical preparations or foods
Atopic Dermatitis	Increased incidence of diaper dermatitis in atopic patients
Miliaria	Clear vesicles or erythematous papules/pustules due to blocked eccrine ducts from heat or humidity in diaper area
Granuloma Gluteale Infantum	Red to violaceous granulomatous nodules over the vulva, perianal area, buttocks, ± scrotum; due to irritation, occlusion, candidal infection
Perianal Pseudoverrucous Nodules	Erythematous nodules and papules in children with fecal incontinence
Acrodermatitis Enteropathica	Erythematous crusted patches/plaques with flaccid bullae in perineal, periorificial, and distal extremities; due to ↓ **zinc level** (also ↓ **alkaline phosphatase** as zinc-dependent); may occur in following settings:
	1. **Premature** infants (poor absorption and ↑ requirement of zinc) when **weaned off breast milk** (which has adequate zinc level)
	2. Inherited form (AR) manifests when **weaned off breast milk**
	3. Healthy infants if low zinc level in maternal milk
	4. Acquired form if malabsorption or inadequate nutrition
Cystic Fibrosis	Resembles acrodermatitis enteropathica, also due to zinc deficiency ± pedal edema, failure to thrive, infections and malabsorption
Multiple Carboxylase Deficiency	Both resemble acrodermatitis enteropathica (periorificial dermatitis); treatment for both forms (listed below) is **biotin**
Biotin Deficiency	1. Neonatal form: AR, **holocarboxylase synthetase deficiency**, ± erythroderma with alopecia, fatal if not treated
	2. Juvenile form: **biotinidase deficiency**, ± seizures, alopecia, hearing loss, developmental delay
Langerhans Cell Histiocytosis	Yellow-brown crusted papules with purpura in **seborrheic** distribution; ± systemic involvement; Langerhans cells **(CD1a +, S100+)**
Kawasaki Disease	Tender erythema in perineal area which later desquamates
Perianal Strep	Bright red, well-demarcated perianal erythema and involving creases
Bullous Impetigo	Honey-colored crusts and flaccid bullae
Scabies	Erythematous nodules involving diaper area, ± genitalia
Congenital Syphilis	Reddish-brown papulosquamous eruption, may be **erosive or bullous**

2.2 CHILDHOOD INFECTIOUS DISEASES

Table 2-3 Childhood Infections

Disease	Exanthem	Etiology/Course
Acute Hemorrhagic Edema of Infancy (Finkelstein Disease)	Large circinate painful purpuric plaques involving face, ears, distal extremities → evolve into edematous targetoid lesions	Etiology: likely infectious (viral or bacterial) Age: 6 months–3 years; self-limited **Leukocytoclastic vasculitis** seen on histology May be hypersensitivity reaction to infection (medication/vaccination less likely)
Erythema Infectiosum ('Slapped Cheek' or Fifth Disease)	Bright red macular erythema over cheeks → **lacy eruption** mainly on the extremities	Etiology: parvovirus B19 (ssDNA) also causes hydrops fetalis; peaks in spring and winter Age: school-age children; self-limited Mild prodrome, 10% with arthralgias
Gianotti–Crosti Syndrome	Abrupt onset of skin-colored to pink-red edematous papules to cheeks, buttocks, extremities	Etiology: likely infectious (HBV, EBV) Age: 6 months–2 years; self-limited May have low-grade fever and lymphadenopathy
Hand-Foot-Mouth Disease	Elliptical grayish vesicles, pustules, and erosions on hands, feet, and buttocks Oral: vesicles/erosions red base	Etiology: **coxsackievirus A16** (enterovirus 71 less often) Age: children <10 years (± adults); self-limited Fever, sore mouth, anorexia, abdominal pain; enteroviral infection may also cause myocarditis, pneumonia, meningoencephalitis
Henoch–Schönlein Purpura (HSP)	Purpuric macules and papules favoring **lower extremities and buttocks**	Etiology: possibly infectious (viral, strep) Age: peaks at 4–7 years (± adults); self-limited Presents 1–2 week after upper respiratory infection Arthralgias, GI bleeding, abdominal pain, nephritis with **hematuria → IgA vasculitis**
Herpangina	Exanthem: often absent Oral: painful gray vesicles on tonsillar, palate, buccal mucosa	Etiology: various enteroviruses (often coxsackie group A/B and echovirus) Age: 3–10 years old; self-limited
Kawasaki Disease (Mucocutaneous Lymph Node Syndrome)	Polymorphous eruption (morbilliform, erythema multiforme-like or bullous); ± edema and erythema of distal extremities; can be generalized or localized (groin, LE) Oral: red swollen or dry fissured lips; strawberry tongue; pharyngeal erythema	Etiology: unknown but likely infectious Age: children <5 years of age Arthritis, abdominal pain, GI symptoms Complications: **cardiac aneurysm (in ¼ of untreated patients), myocarditis**, pericarditis Need 5 of 6 criteria for diagnosis: rash • fever >5 days • conjunctivitis • palmoplantar erythema, edema, or desquamation • swollen lips or red tongue • cervical lymphadenopathy
Measles (Rubeola or First Disease)	Erythematous macules/papules over forehead, hairline, and behind the ears → spreads downward Oral: Koplik spots (gray papules on buccal mucosa)	Etiology: measles virus (paramyxovirus) Age: unvaccinated children Prodrome: fever, cough, nasal congestion, rhinorrhea, conjunctivitis; rash appears after Koplik spots Complications: encephalitis, otitis media, pneumonia, myocarditis, ± subacute sclerosing panencephalitis

Table 2-3 Childhood Infections (cont'd)

Disease	Exanthem	Etiology/Course
Infectious Mononucleosis	Polymorphous: morbilliform (common), urticarial, petechial, or erythema multiforme-like lesions Of note, morbilliform eruption may occur after treatment with ampicillin	Etiology: infectious (EBV) Age: children, young adults (15–25 years); self-limited Fever, pharyngitis, fatigue, myalgias, headaches, hepatosplenomegaly, lymphadenopathy Complications: splenic rupture, airway obstruction, hepatitis
Papular Purpuric Gloves and Socks Syndrome	Erythema, edema, petechiae, and purpura on palms/soles (± extension to dorsal aspect), + **burning and pruritus**	Etiology: **parvovirus B19** Age: children and young adults; self-limited Mild prodromal symptoms, occurs mainly in young adults; peaks in spring
Roseola (Exanthem Subitum or Sixth Disease)	Circular to elliptical "rose red" macules or papules involving trunk, occasionally surrounded by white halo	Etiology: human herpesvirus 6 (HHV6) Age: 6 months–3 years **Sudden-onset high fever**; rash begins as fever subsides Complications in healthy patient: mainly **seizures**
Rubella (German Measles or Third Disease)	Erythematous macules and papules on face → spreads acrally, accompanied by **tender lymphadenopathy** (occipital, postauricular, cervical)	Etiology: togavirus (ssRNA) Age: unvaccinated children/adults; self-limited Usually mild prodrome Complications: arthralgia/arthritis, hepatitis, myocarditis, pneumonia
Scarlet Fever (Second Disease)	Erythema of axilla, neck, chest → evolve to pink papules with erythematous background (sandpaper-like) → hand and foot desquamation (7–10 days later); **Pastia's lines** (linear petechial streaks in body folds) Oral: "**red strawberry**" tongue	Etiology: group A β-hemolytic streptococci (erythrogenic toxin A, B, C) Age: children (1–10 years old) Extracutaneous: sore throat, headaches, chills, fever, nausea, abdominal pain, anorexia Treatment: PCN 10–14 days (erythromcyin in PCN- allergic pts)
Unilateral Laterothoracic Exanthem	Morbilliform or eczematous eruption in axilla and lateral trunk with unilateral dominance (± bilateral involvement)	Etiology: likely viral Age: children (6 months–10 years); self-limited
Varicella (Chickenpox)	Pruritic, erythematous macules/papules of scalp, face → spreads to trunk and extremities, evolves into vesicles with narrow red halo ("**dew drops on rose petal**"), central crust or necrosis seen within lesions	Etiology: varicella zoster virus (VZV) Age: children and adults; self-limited in healthy children Complications in children: secondary bacterial infection Adults with more severe presentation (pneumonia, 10–30% mortality if untreated) **All stages of development** seen simultaneously

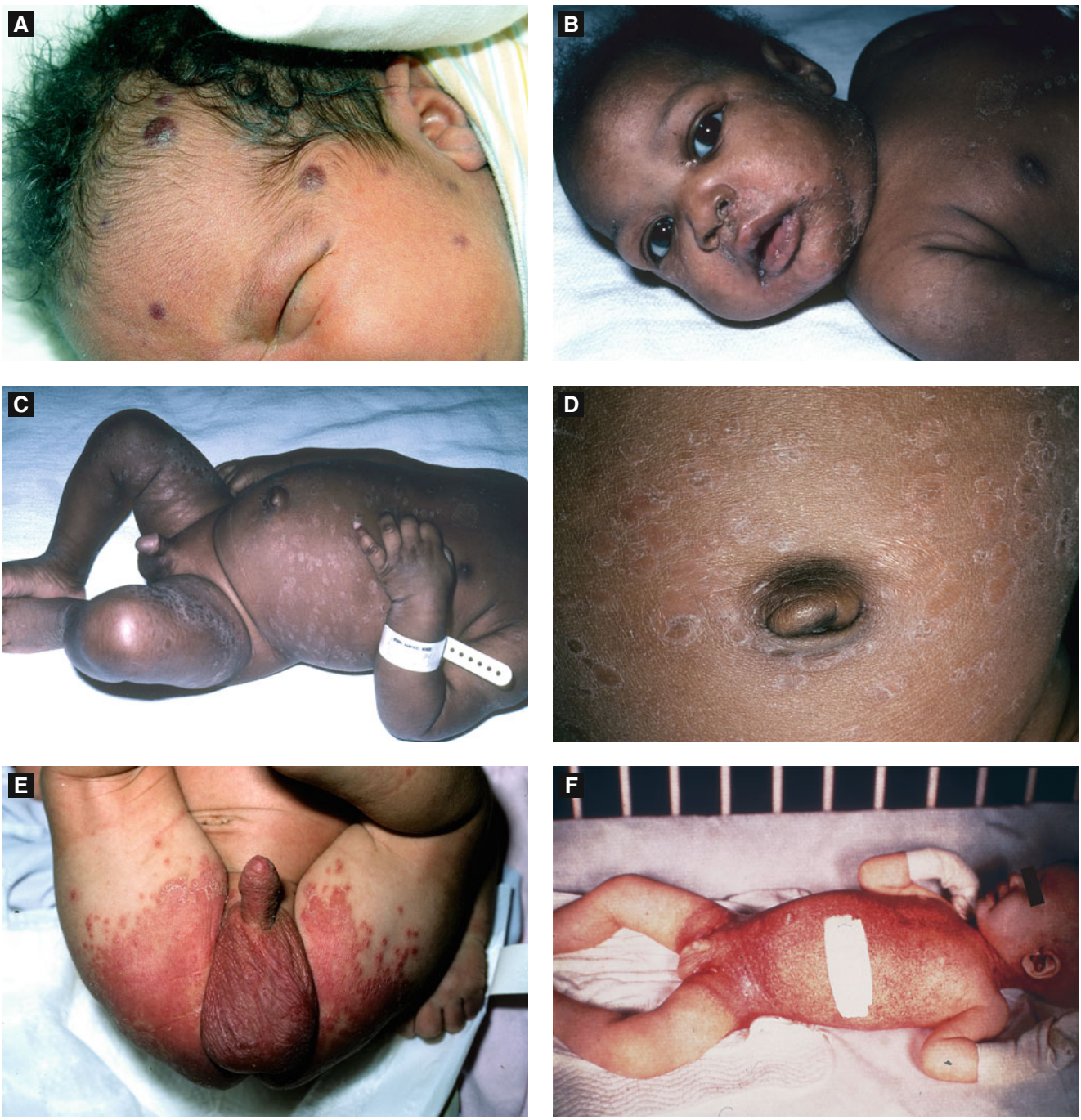


Figure 2.3
A: Dermal hematopoiesis (*Courtesy of Dr. Vandana Mehta*)
B: Congenital syphilis (*Courtesy of Dr. Paul Getz*)
C: Congenital syphilis (*Courtesy of Dr. Paul Getz*)
D: Congenital syphilis (*Courtesy of Dr. Paul Getz*)
E: Candidiasis (*Courtesy of Dr. Paul Getz*)
F: Langerhans cell histiocytosis (*Reprint from Morgan MB, Smoller BR, Somach SC. Deadly Dermatologic Diseases. New York, NY: Springer; 2007*)

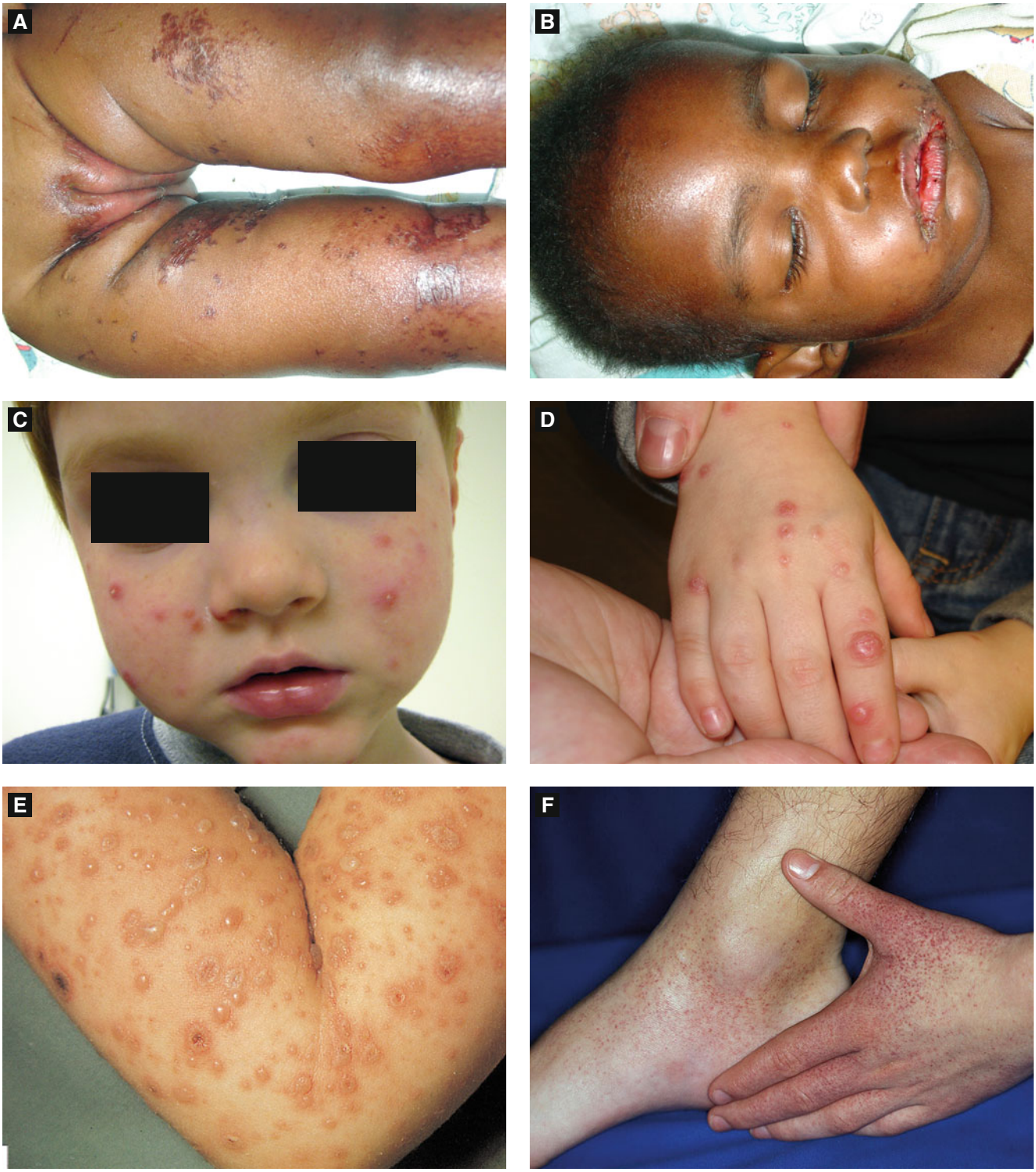


Figure 2.4
A: Acrodermatitis enteropathica
(*Courtesy of Michelle B. Bain*)
B: Acrodermatitis enteropathica
(*Courtesy of Michelle B. Bain*)
C: Gianotti–Crosti syndrome
(*Courtesy of Dr. Michelle B. Bain*)
D: Gianotti–Crosti syndrome
(*Courtesy of Dr. Michelle B. Bain*)
E: Varicella
(*Reprint from Abdel-Halim AW. Passing the USMLE. New York, NY: Springer, 2009*)
F: Papular purpuric gloves and socks syndrome
(*Reprint from Burgdorf WH, Plewig G, Wolff HH, Landthaler M, eds.. Braun-Falco's Dermatology. 3rd ed. Heidelberg: Springer; 2009*)

2.3 PAPULOSQUAMOUS AND ECZEMATOUS DERMATOSES

Psoriasis (Figure 2.5A)

- Approximately 25% patients will have presentation before age 15
- Presents as erythematous well-demarcated plaques with micaceous scale
- Guttate psoriasis more common in children; presents with raindrop-like papules in an eruptive pattern; common triggers include strep infection, viral infection, stress, and trauma

Pityriasis Lichenoides (PL)

- Two diseases forming spectrum of PL: pityriasis lichenoides et varioliformis acuta (PLEVA) and pityriasis lichenoides chronica (PLC)
- PLEVA: abrupt onset of erythematous papules and vesicles with crusted or necrotic centers, often involuting within weeks to months; treat with oral erythromycin, phototherapy, and/or topical corticosteroid
- PLC: reddish-brown papules with adherent scale, heals with dyschromia; more chronic course lasting months to years

Acropustulosis of Infancy (Figure 2.5B)

- Onset from 6 months to 2 years; resolves by age 3
- Presents with recurrent crops of pruritic pustules on palms, soles, distal extremities (may mimic scabies infection so prudent to perform mineral oil scraping)
- Treatment: topical corticosteroid

Pityriasis Rubra Pilaris (PRP) (Figure 2.5C)

- Three juvenile forms in addition to two adult forms (I/II)

Classic Juvenile Form (III)	Resembles classic adult form but with early onset (first 2 years of life); most resolve within 3 years; 10% cases
Circumscribed Juvenile Form (IV)	Lesions on extensor surfaces and present in prepubertal years; 25% cases (50% persist into adulthood)
Atypical Juvenile Form (V)	Similar to type III + scleroderma-like changes of hands/feet, familial basis; presents in early childhood with unrelenting course; 5% cases

Pityriasis Rosea (PR)

- Self-limited papulosquamous eruption; likely viral pathogen (human herpesvirus 7, less likely HHV 6)
- Presents with initial herald patch (precedes eruption by 1–2 weeks) followed by salmon-colored oval patches and plaques with inner scale along long axis of Langer's lines of cleavage ("Christmas tree" pattern on posterior trunk); variants include inverse pattern (flexural accentuation) and papular PR (young children and darker-skinned patients)

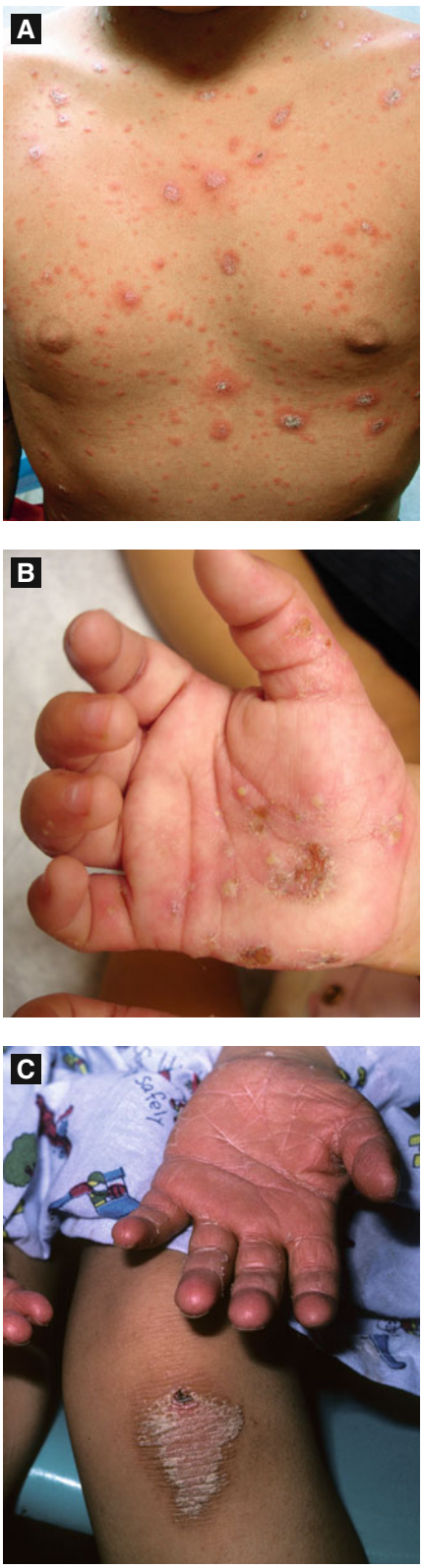


Figure 2.5
A: Guttate psoriasis
B: Acropustulosis of infancy
C: Pityriasis rubra pilaris
(*Courtesy of Dr. Paul Getz*)

Lichen Striatus (Figure 2.6A, B)

- Self-limited, linear inflammatory condition in children
- Presents with small erythematous scaly papules forming linear band → spreads down extremity or trunk and typically follows lines of Blaschko, ± nail involvement
- Hypopigmentation may persist for months to years after lesions resolve and points to diagnosis

Keratosis Pilaris (KP)

- Excessive keratinization causing horny follicular plugs on upper arms, thighs, and cheeks; associated with atopy

KP Atrophicans

- Group of disorders in children with faulty follicular keratinization followed by atrophy and scarring
  - **KP atrophicans faciei:** erythema with follicular spiny papules of eyebrows, cheeks, and scalp; involute and leave pitted atrophic scars; term ulerythema ophyrogenes if limited to lateral 1/3 of eyebrows, associated with Noonan syndrome
  - **Atrophoderma vermiculata:** pit-like atrophic scarring of follicles on face ("honeycomb" atrophy), associated with Rombo syndrome and Down syndrome

Rombo syndrome: milia, atrophoderma vermiculata, acral cyanosis, trichoepitheliomas, multiple BCCs, hypotrichosis, alopecia

Atopic Dermatitis (AD) (Figure 2.6C)

- Occurs in 10–15% children, often presenting at 2–3 months of age; multifactorial pathogenesis but includes ↑ secretion of T_H2 cytokines (IL-4, IL-5)
- Triad of atopy: AD, allergic rhinitis, asthma
- Few may have allergy to specific foods, which may exacerbate AD (eggs, milk, soybeans, fish, wheat, peanuts)
- Presents with eczematous lesions, xerosis, and lichenification
- Distribution varies with age
  - Infants: face, scalp, and extensors
  - Children: antecubital/popliteal fossae, neck, wrists, ankles
  - Adults: typically hands (chronic hand eczema)

Atopic patients with ↓ amount of innate antimicrobial peptides: human β-defensins (HBD) and cathelicidins (LL37)

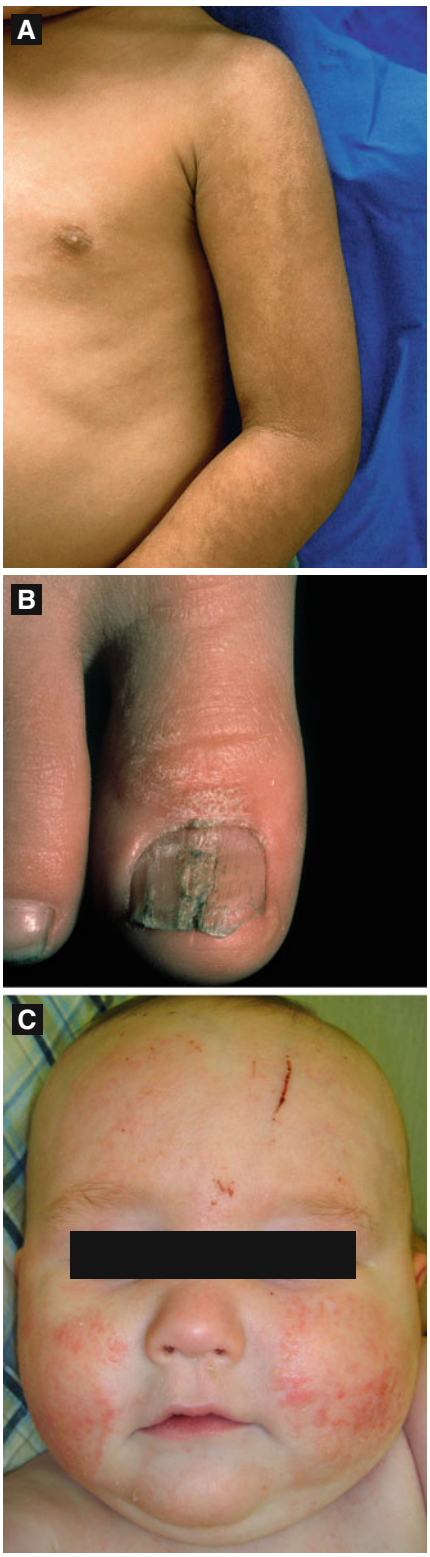


Figure 2.6
A: Lichen striatus
(*Courtesy of Dr. Michelle B. Bain*)
B: Lichen striatus
(*Courtesy of Dr. Paul Getz*)
C: Atopic dermatitis

- **Pityriasis alba**: hypopigmented patches with minimal scale; may be only manifestation of AD (Figure 2.7A)
- Complications: keratoconus (conical deformity of cornea), eyelid dermatitis, ↑ risk of infection (impetigo, eczema herpeticum, molluscum contagiosum) (Figure 2.7B)
- Treatment: topical corticosteroid, topical calcineurin inhibitor, oral corticosteroid (short course), oral antihistamine, phototherapy

Juvenile Plantar Dermatosis

- Typically in children with an atopic diathesis; related to increased humidity from impermeable material in shoes
- Presents with dry, scaly glazed patches with fissures involving forefoot plantar surface
- Chronic but typically self-limited

2.4 PIGMENTED LESIONS

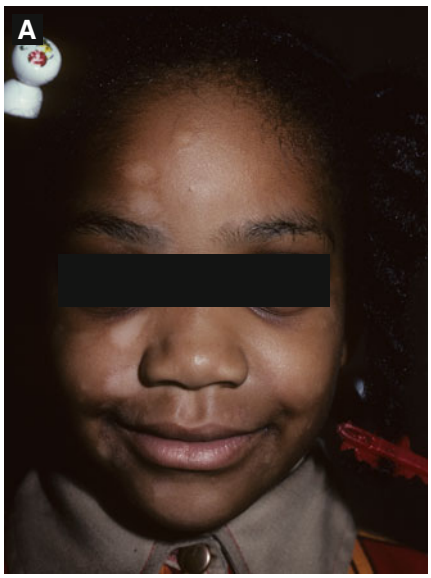
Café Au Lait Macule (CALM)

- Presents as a light to dark brown macule or patch
- Single lesion in 10–20% of normal population; multiple lesions ± associated with different genodermatoses (McCune-Albright syndrome, neurofibromatosis)

Lentigines

- Presents as brown macules with increased number of melanocytes; no relationship to sunlight
- Multiple lentigines may be associated with the following:

LEOPARD Syndrome	AD, PTPN11 gene, café-noir macules, EKG changes, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, growth retardation, deafness
Carney Complex (LAMB or NAME syndrome)	AD, PRKAR1A gene, psammomatous melanotic schwannomas, cardiac/cutaneous myxomas, blue nevi, endocrine overactivity
Peutz–Jeghers Syndrome	AD, STK11 gene (serine threonine kinase), mucocutaneous (oral/acral) lentigines, intestinal polyposis, ± intussusception, various malignancies
Laugier–Hunziker Syndrome	Mucocutaneous lentigines, longitudinal melanonychia, genital melanosis
Bannayan–Riley–Ruvalcaba Syndrome	AD, PTEN gene, penile > vulvar lentigines, lipomas, hemangiomas



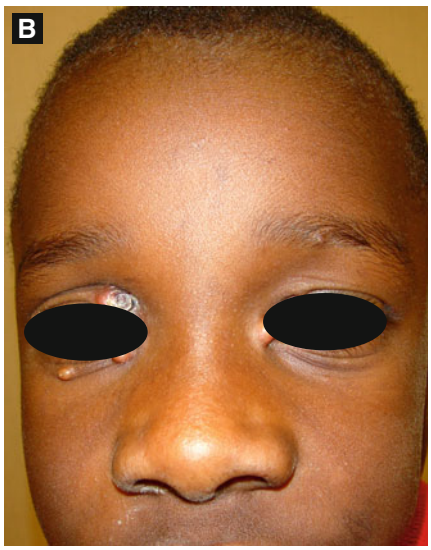


Figure 2.7
A: Pityriasis alba
(*Courtesy of Dr. Paul Getz*)
B: Molluscum contagiosum

Ephelides (Freckles)

- Present as light brown macules in sun-exposed areas; more prominent in children with fair skin and during summer time; onset typically within first 3 years of age
- Can be a marker for UV-induced damage if acquired
- Histology: normal number of melanocytes, increased pigment in keratinocytes

Congenital Nevus (CN) (Figure 2.8A)

- Onset at birth or first year typically; 1–2% of population
- Categorized as small (<1.5 cm), medium (1.5–20 cm), and large (>20 cm or 10% BSA)
- Slight ↑ risk of melanoma (highest in large CNs); 3–12% of giant (large) CNs may develop melanoma (different studies show varying percentages); axial nevi with greatest risk
- If large nevus over scalp, rule out neurocutaneous melanosis with MRI

Neurocutaneous melanosis: ↑ intracranial pressure, leptomeningeal melanoma, spinal cord compression

Spitz Nevus (Epithelioid or Spindle Cell Nevus) (Figure 2.8B)

- Presents as dome-shaped red-brown or tan-pink smooth surfaced papule; typically occurs within first two decades
- Pigmented, congenital, and agminated variants reported
- Histology: Kamino bodies (PAS + globules)
- Characteristic starburst dermoscopic finding in pigmented Spitz nevi

Halo Nevus (Sutton's Nevus)

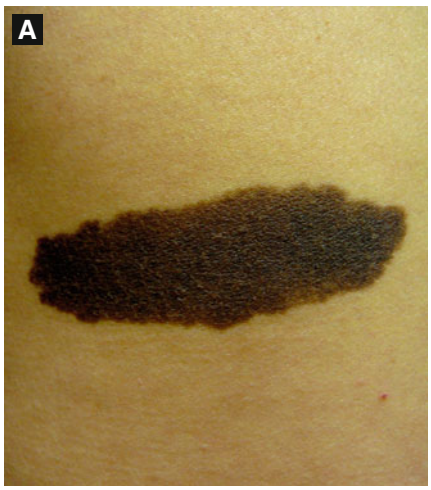
- Melanocytic nevus with surrounding hypopigmented halo in which central nevus either persists or involutes
- Typically appears in adolescence; may appear in setting of vitiligo; prudent to rule out concomitant melanoma (rare) by performing full skin exam

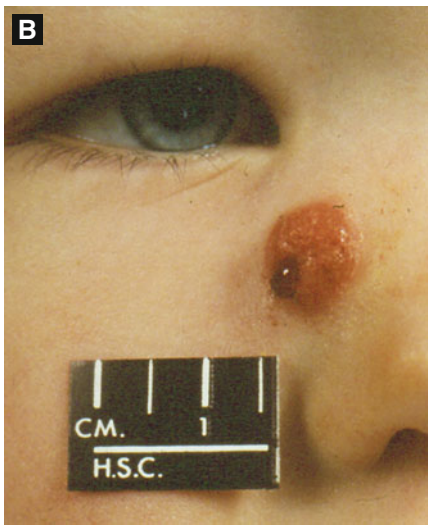
Nevus Spilus (Speckled Lentiginous Nevus) (Figure 2.8C)

- Presents as tan, regularly bordered patch with darker macules within lesion
- Melanoma rarely arises within nevus component
- Associated with phakomatosis pigmentovascularis and pigmentokeratotica (latter with organoid nevus + hemiatrophy + neurologic defects)

Melanoma

- 0.3–0.4% of melanomas in prepubertal children
- ↑ Risk with fair skin, blue eyes, blonde/red hair, CDKN2A or p16 mutation, xeroderma pigmentosum, dysplastic nevus syndrome, large congenital nevus, or neurocutaneous melanosis





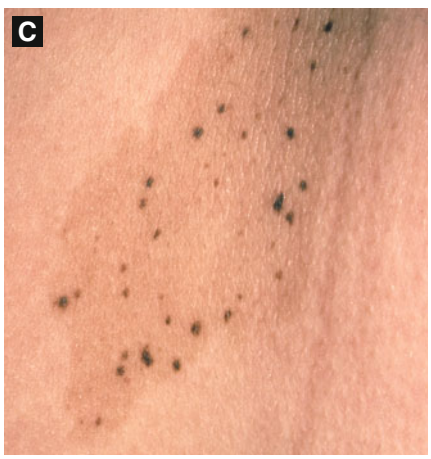


Figure 2.8
A: Congenital nevus
B: Spitz nevus
(*Reprint from Laxer RM, ed. The Hospital for Sick Children: Atlas of Pediatrics. Philadelphia, PA: Current Medicine; 2005*)
C: Nevus spilus
(*Courtesy of Dr. Paul Getz*)

Becker's Nevus (Becker's Melanosis) (Figure 2.9A, B)

- Acquired unilateral lesion found in adolescent males (second or third decade) typically on shoulder, upper chest, or back
- Presents as hyperpigmented hypertrichotic patch or plaque associated with underlying smooth muscle hamartoma (arrector pili)
- Histology: ↑ melanin in epidermis, often smooth muscle hamartoma present in dermis

Blue Nevus (Figure 2.9C)

- Congenital or acquired (typically early childhood)
- Different types: common, cellular, and combined
- Multiple blue nevi associated with Carney complex (LAMB/NAME syndrome)
- Histology: normal epidermis, many elongated dendritic melanocytes within dermis, large amounts of melanin often seen within melanocytes

Nevus of Ota (Nevus Fuscoceruleus Ophthalmomaxillaris, Oculodermal Melanocytosis) (Figure 2.9D)

- Onset either near birth or during puberty
- Most common in Asian population, mainly women
- Presents as unilateral, blue-gray macules typically involving V1 and V2 distribution of trigeminal nerve
- Most common extracutaneous sites: sclera > tympanum > nasal mucosa > pharynx > palate

Nevus of Ito (Nevus Fuscoceruleus Acromiodeltoideus)

- Similar presentation to nevus of Ota but typically occurs in shoulder region (supraclavicular, scapular, and deltoid)

Hori's Nevus (Acquired Nevus of Ota-like Macules)

- Onset in late adolescence, mainly in Asian women
- Bilateral nevus of Ota-like macules of the zygomatic region; may be misdiagnosed as melasma

Congenital Dermal Melanocytosis (Mongolian Spot)

- Common in infants with pigmented skin
- Presents with blue-gray macules or patches typically over lumbosacral skin or buttocks
- If extensive, consider phakomatosis pigmentovascularis
- Histology: dendritic melanocytes situated in lower half of dermis, cells arranged parallel to epidermis

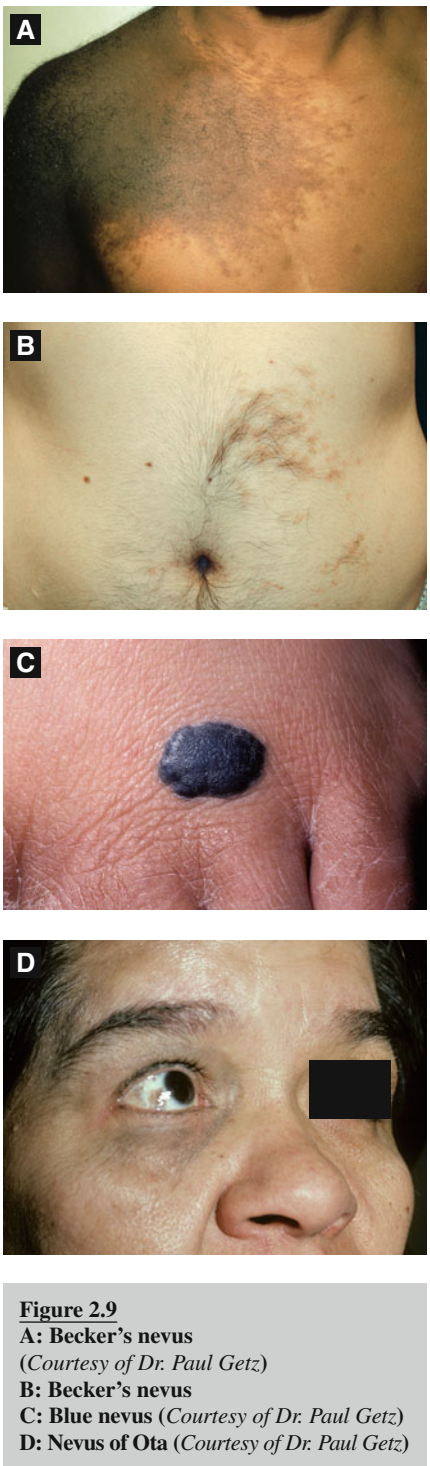


Figure 2.9
A: Becker's nevus (*Courtesy of Dr. Paul Getz*)
B: Becker's nevus
C: Blue nevus (*Courtesy of Dr. Paul Getz*)
D: Nevus of Ota (*Courtesy of Dr. Paul Getz*)

2.5 BULLOUS DISEASES

Table 2-4 Epidermolysis Bullosa

EB Subtype	Inh	Gene	Clinical Features
EB SIMPLEX (EBS) Split: Epidermal Basal Layer			
Dowling-Meara (EBS Herpetiformis)	AD	K5/K14	Onset at birth, grouped or herpetiform blisters (figurate), **significant mucosal membrane and laryngeal/esophageal involvement (± hoarseness)**, nail dystrophy, confluent PPK, scarring, early death
			EM: **clumped tonofilaments** in basal keratinocytes
Weber-Cockayne (Localized)	AD	K5/K14	Onset typically childhood/adolescence, palmoplantar bullae/erosions, heal without scarring
Koebner (Generalized)	AD	K5/K14	Generalized bullae at birth, PPK, nail dystrophy, mucosal erosions, heals **without scarring**
EBS Muscular Dystrophy	**AR**	**Plectin**	Widespread bullae at birth, **muscular dystrophy**, scarring, hair/nail/tooth/oral disease, early death
EBS Mottled Pigmentation			Resembles localized and generalized EBS + **reticulated hyperpigmentation over trunk**
JUNCTIONAL EB (JEB) Split: Basement Membrane (Lamina Lucida)			
Herlitz (EB Lethalis) Premature termination codon	AR	**Laminin 5** (**laminin-332**)	Severe, widespread bullae, nonhealing **exuberant granulation tissue** (perioral, axillae, neck), enamel defects, absent nails, mucosal involvement (respiratory/GI tract with hoarseness), early death
Non-Herlitz (Generalized Atrophic Benign EB or GABEB)	AR	Laminin 5 or BPAG2 (BP180)	Widespread bullae at birth, **heal with atrophic scars**, mild oral involvement, **scarring alopecia**, nail dystrophy, improves with time
JEB with Pyloric Atresia	AR	**α6β4 integrin**	Severe congenital blistering, hydronephrosis, **pyloric atresia**, mucosal erosions
DYSTROPHIC EB (DEB) Split: Dermal (Sublamina Densa)			
Hallopeau-Siemens Recessive DEB (RDEB-HS) Premature termination codon	AR	**Type VII collagen**	Severe widespread bullae at birth, heals with atrophic scarring (on hands/feet → "**mitten deformity**"), milia, nail dystrophy, mucosal strictures, **oral, esophageal, cutaneous SCCs**
Non-Hallopeau-Siemens (RDEB-nHS)	AR	Type VII collagen	Skin changes localized to acral bony prominences, Hallopeau-Siemens symptoms but less severe
Cockayne-Touraine (DDEB-CT)	AD	Type VII collagen	Bullae mainly over extremities, heal with milia/atrophic scars/keloids, nail dystrophy
Pasini Variant (DDEB-P)	AD	Type VII collagen	Similar to Cockayne subtype + albopapuloid lesions (**white perifollicular papules, slowly enlarge**)

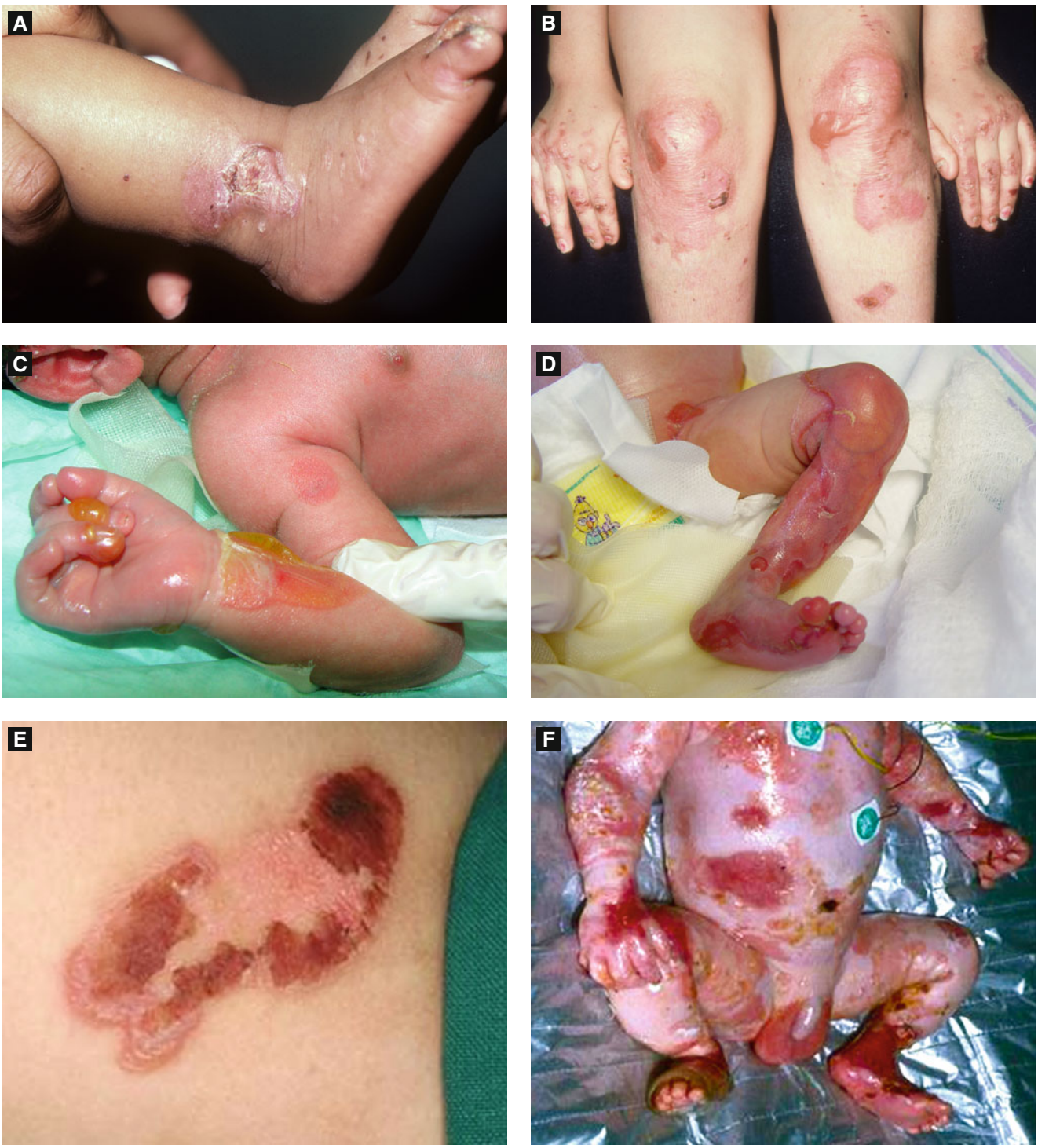


Figure 2.10
A: EB simplex (Weber–Cockayne) (*Courtesy of Dr. Paul Getz*)
B: Dominant dystrophic EB (Cockayne–Touraine) (*Courtesy of Dr. Paul Getz*)
C: Recessive dystrophic EB
D: Recessive dystrophic EB
E: EB simplex (Dowling-Meara) (*Reprint from Laimer M et al. Epidermolysis bullosa hereditaria. Monatsschrift Kinderheilkunde Zeitschrift für Kinder und Jugendmedizin. 2008: 156* (*2*)*;110–21*)
F: EB simplex (Dowling-Meara) (*Reprint from Has C et al. Hereditare Blasen bildende Hauterkrankungen. Der Hautarzt. 2004: 55*(*10*)*;920–30*)

Chronic Bullous Disease of Childhood (Figure 2.11A)

- Blistering disorder with onset typically before age 5
- Target antigen: 97 kDa Ag (LAD-1 or LABD97): cleaved ectodomain of BPAG2
- Presents with annular and herpetiform bullae favoring extensor surfaces/groin ("crown of jewels" configuration)
- Histology: subepidermal bullae with neutrophils in dermal papillae (similar to dermatitis herpetiformis)
- Treat with dapsone or sulfapyridine

Neonatal Pemphigus

- Presents in infants whose mothers have pemphigus vulgaris; due to passive transfer of maternal IgG to fetus
- Self-limited; resolves within few weeks of birth

Hailey–Hailey Disease (Familial Benign Chronic Pemphigus) (Figure 2.11B)

- AD, ATP2C1 gene (encodes Golgi-associated Ca2+ ATPase hSPCA1), results in abnormal intracellular calcium signaling; onset typically second to third decade
- Presents with flaccid vesicles initially on erythematous base over intertriginous areas, ruptures easily, and gives rise to macerated or crusted erosions
- Histology: extensive epidermal acantholysis "dilapidated brick wall"

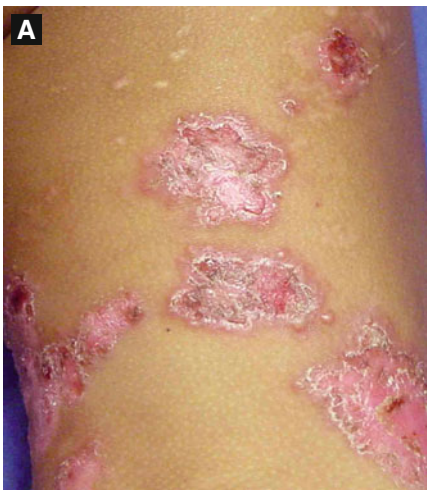
Think of "Hailey's **C**omet" to remember ATP2 **C** 1

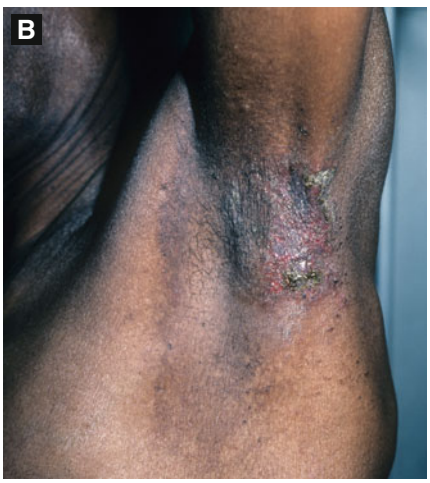
2.6 EPIDERMAL, APPENDAGEAL, AND DERMAL TUMORS

Epidermal Nevus (EN) (Figure 2.11C)

- Hamartoma of epidermis and papillary dermis; onset typically at birth (± adolescence, rare in adulthood)
- Presents as hyperpigmented papillomatous papules and plaques along lines of Blaschko
- Ichthyosis hystrix: extensive bilateral systematized lesions
- **ILVEN** (inflammatory linear verrucous epidermal nevus): erythematous scaly plaque along lines of Blaschko; not associated with any neurologic defects
- **Epidermal nevus syndrome** (Schimmelpenning syndrome): sporadic; epidermal nevus, underlying CNS, ocular, cardiac, and skeletal defects, biopsy to r/o epidermolytic hyperkeratosis (EHK)

Of note, if biopsy of EN shows EHK, the patient may be at risk with offspring with full-blown EHK





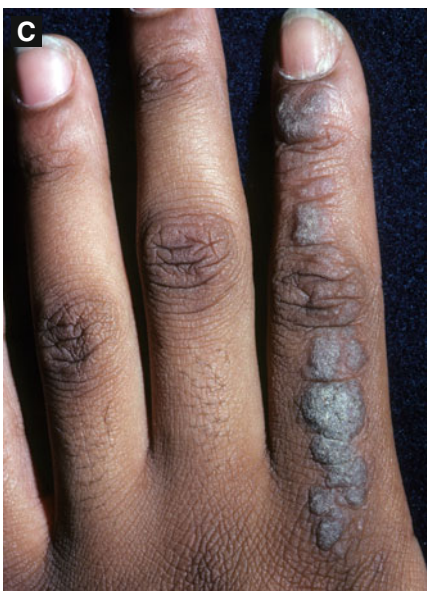


Figure 2.11
A: Chronic bullous disease of childhood (*Courtesy of Dr. Michelle B. Bain*)
B: Hailey–Hailey disease (*Courtesy of Dr. Paul Getz*)
C: ILVEN (*Courtesy of Dr. Paul Getz*)

Nevus Sebaceus (Figure 2.12A, B)

- Presents as solitary yellow-orange slightly raised plaque typically on scalp or face; plaque typically thickens and becomes more verrucous or pebbly during childhood
- Mutation in PTCH gene has been reported (deletion)
- Benign tumors (trichoblastoma, syringocystadenoma papilliferum) and malignant tumors (BCC < 1% cases) can arise within lesion

Basal Cell Carcinoma

- Seen in children with xeroderma pigmentosum (XP) and basal cell nevus syndrome (BCNS)

Squamous Cell Carcinoma

- Seen in children with XP, dystrophic EB, and albinism

Pilomatricoma (Calcifying Epithelioma of Malherbe)

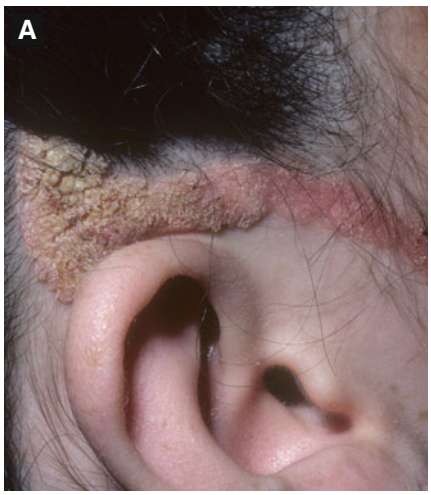
- Onset typically in childhood
- Presents as solitary firm, skin-colored to faint blue papule or cyst on face or upper trunk
- Histology: anucleate cornified cells ("ghost" or "shadow" cells), calcification seen in late lesions
- Multiple pilomatricomas may be associated with myotonic dystrophy (β-catenin defect)

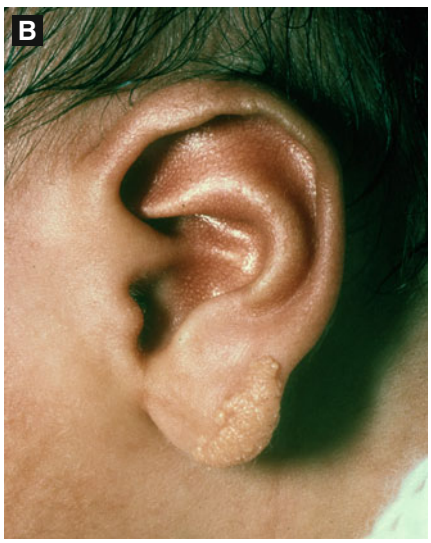
Trichoepithelioma (Figure 2.12C)

- Benign adnexal neoplasm usually appearing in childhood
- Presents as skin-colored translucent papules (usually multiple) along the nasolabial folds or periorbital regions
- Multiple lesions in Brooke–Spiegler syndrome (trichoepitheliomas, cylindromas, spiradenomas)

Angiofibroma (Fibrous Papule)

- Skin-colored firm papule on face
- Multiple lesions associated with tuberous sclerosis (once known as adenoma sebaceum) with onset in early to mid-childhood





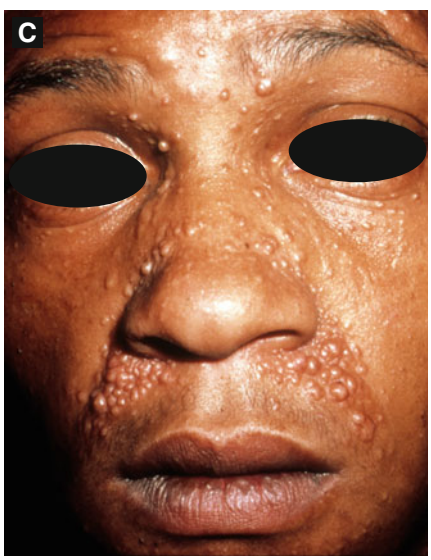


Figure 2.12
A: Nevus sebaceus*
B: Nevus sebaceus*
C: Trichoepitheliomas*
** Courtesy of Dr. Paul Getz*

Neurofibroma (NF) (Figure 2.13A)

- Presents as skin-colored, soft or rubbery papulonodule with positive "buttonhole" sign (easily invaginated)
- Commonly seen as solitary lesion; multiple lesions associated with neurofibromatosis
- Plexiform NF considered pathognomonic for NF1, malignant transformation in 2–13%

Connective Tissue Nevus (Figure 2.13B, C)

- Also known as shagreen patch (tuberous sclerosis) collagenoma, elastoma, or dermatofibrosis leticularis disseminata (latter in Buschke–Ollendorff syndrome)
- Onset at birth or early childhood; likely hamartoma
- Presents as firm, solitary, or multiple skin-colored papules, nodules, or plaques

Infantile Digital Fibroma (Figure 2.13D)

- Onset within 1 year of age
- Presents as multiple firm, smooth dome-shaped nodules on dorsolateral fingers/toes (spares thumb and great toe)
- Benign with spontaneous regression within 2–3 years typically; high local recurrence rate with surgical excision
- Histology: eosinophilic intracytoplasmic perinuclear inclusions within spindle cells

Infantile Myofibromatosis (Congenital Generalized Fibromatosis)

- Rare, onset at birth or within first 2 years
- Presents as one or more firm, rubbery skin-colored to purple papulonodules on head, neck, or trunk
- Two types: localized with no visceral involvement, good prognosis; visceral involvement with high mortality

Fibrous Hamartoma of Infancy

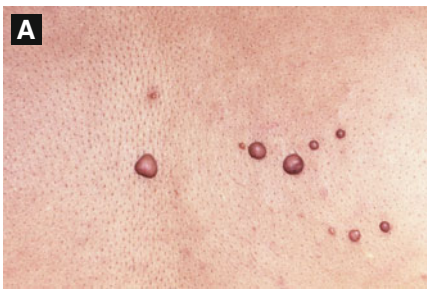
- Onset at birth or within first year of life
- Presents as painless, solitary skin-colored subcutaneous nodule typically involving axilla, shoulder, or upper arm (less likely groin area)
- Treat with local excision

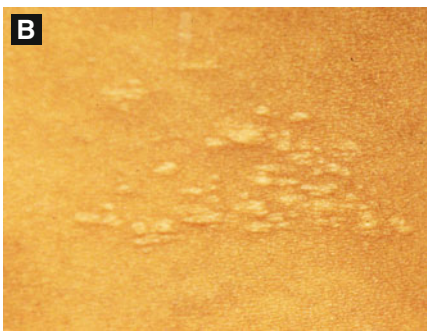
Fibromatosis Colli

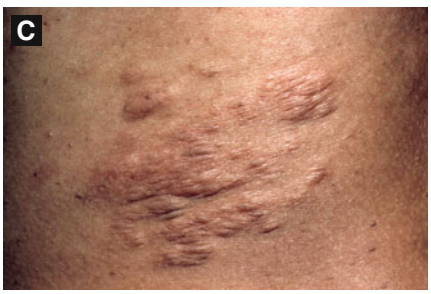
- Infiltration of fibrous tissue involving the lower third of the sternocleidomastoid muscle at birth
- Typically spontaneous remission within few months

Juvenile Hyaline Fibromatosis

- Due to mutation in capillary morphogenesis protein 2
- Multiple firm papules and nodules involving the face, extremities, and scalp; hypertrophic gums and disfigurement with flexion contractions







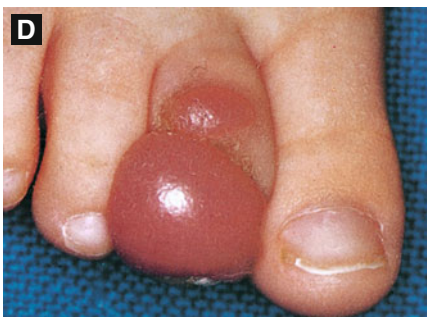


Figure 2.13
A: Neurofibromas
(*Courtesy of Dr. Paul Getz*)
B: Connective tissue nevus
(*Reprint from Laxer RM, ed. The Hospital for Sick Children: Atlas of Pediatrics. Philadelphia, PA: Current Medicine, 2005*)
C: Connective tissue nevus
(*Courtesy of Dr. Paul Getz*)
D: Infantile digital fibroma
(*Reprint from Burgdorf WH, Plewig G, Wolff HH, Landthaler M, eds. Braun-Falco's Dermatology. 3rd ed. Heidelberg: Springer; 2009*)

Juvenile Xanthogranuloma (JXG) (Figure 2.14A, B)

- Non-Langerhans cell histiocytosis with Touton giant cells; onset typically within first year of life
- Two types: micronodular (small, multiple) or macronodular (larger size, few in number)
- Presents as single or multiple firm, pink-red papulonodules with yellow hue on head/neck > trunk/upper extremities
- Regression typically seen in children (not in adults)
- 0.5% with ocular involvement: glaucoma, hyphema (may rarely result in blindness)
- Association with NF1 and juvenile myelomonocytic leukemia (JMML)

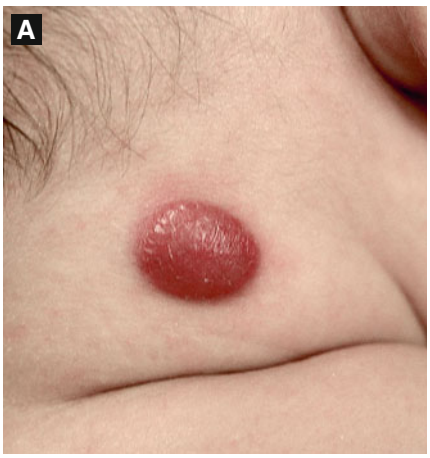
Langerhans Cell Histiocytosis (LCH) (Figure 2.14C)

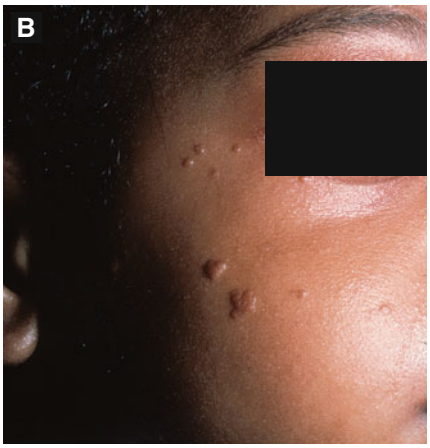
- Clonal proliferative disease of Langerhans cells (comma-shaped nuclei, S100+, CD1a+, intracytoplasmic Birbeck granules seen on EM), four overlapping syndromes
- Current classification by number of organ systems involved (single vs. multisystem), but historically grouped as follows:

Letterer–Siwe Disease	– Multisystem involvement, (acute disseminated form); onset typically before 2 years of age – Small, pink papules, pustules, vesicles with scale/crust/petechiae in seborrheic distribution
Hand–Schuller–Christian Disease	– Onset between 2 and 6 years of age – Typical triad: diabetes insipidus, bone lesions, exophthalmos – Osteolytic bone lesions (cranium)
Eosinophilic Granuloma	– Onset in older children, localized LCH variant – Asymptomatic granulomatous lesions involving bone (cranium), spontaneous fractures
Congenital Self-Healing Reticulohistiocytosis	– Onset at birth or soon after, limited to skin; also known as Hashimoto-Pritzker disease – Widespread, red-brown papulonodules – Self-healing within weeks to months

Benign Cephalic Histiocytosis

- Self-limited histiocytosis (S100 negative non-LCH); onset within first 3 years of life
- Presents with small red-brown macules and papules on face, spreading to neck and ears > trunk and arms; spontaneous resolution after months or years





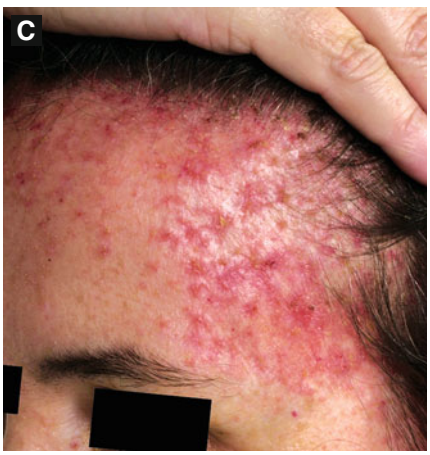


Figure 2.14
A: Juvenile xanthogranuloma
(*Courtesy of Dr. Michelle B. Bain*)
B: Juvenile xanthogranuloma
(*Courtesy of Dr. Paul Getz*)
C: LCH
(*Reprint from Morgan MB, Smoller BR, Somach SC. Deadly Dermatologic Diseases. New York, NY: Springer; 2007*)

Dermoid Cyst (Figure 2.15A)

- Seen typically in infants along embryonic fusion plane
- Presents as discrete, subcutaneous nodule commonly around eyes or nasal root
- Histology: lined by stratified squamous epithelium (with granular layer) containing appendageal elements
- CT/MRI should be performed to rule out connection to CNS before excision

Mastocytosis (Figure 2.15B, C)

- Spectrum of disorders with mast cell hyperplasia in skin and other organs
- Childhood mastocytosis – onset before puberty (50% before age 2), c-kit alteration (proto-oncogene, tyrosine kinase subfamily); several forms in children:

Solitary Mastocytoma	– Tan to brown, minimally infiltrated plaque or nodule; spontaneous resolution over months – Positive Darier sign
Urticaria Pigmentosa (UP)	– Onset early childhood, may occur in adults – Hyperpigmented to pink pruritic macules or papules on trunk; positive Darier sign – Variant: bullous UP
Diffuse Cutaneous Mastocytosis	– Doughy or boggy skin texture with lichenification and yellow hue – Extreme pruritus, friction may cause bullae – Systemic symptoms: bronchospasm, diarrhea
Telangiectasia Macularis Eruptiva Perstans (TMEP)	– Persistent eruption of macules and papules with red-brown hue – Rare in childhood

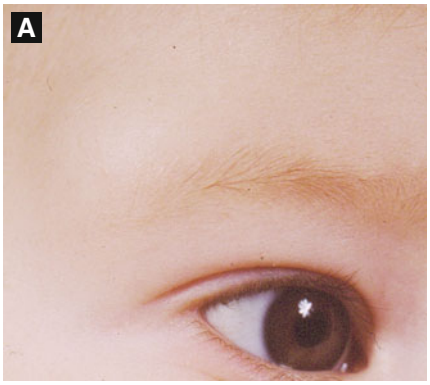
- Avoid mast cell degranulators: aspirin, alcohol, opiates, quinine, polymyxin B sulfate, amphotericin B, tubocuraine, scopolamine

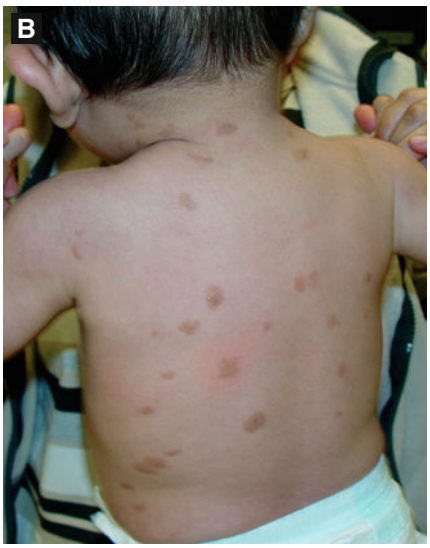
2.7 TUMORS OF FAT, MUSCLE AND BONE

Lipoma

- If located over lumbosacral region at birth, consider underlying spinal dysraphism (incomplete closure of mesenchymal, osseous, and nervous tissue of the spine) → perform MRI

Associated syndromes with lipomas: Bannayan–Riley–Ruvalcaba syndrome, Gardner syndrome, MEN I





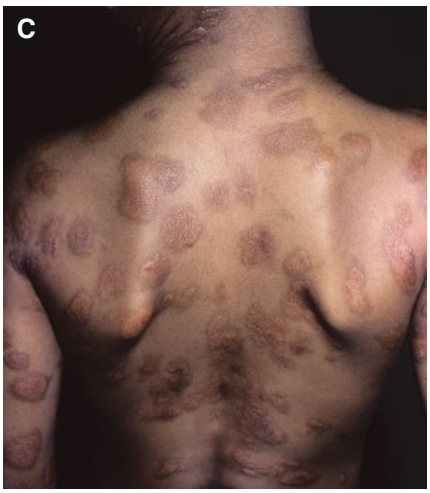


Figure 2.15
A: Dermoid cyst
(*Reprint from Laxer RM, ed. The Hospital for Sick Children: Atlas of Pediatrics. Philadelphia, PA: Current Medicine; 2005*)
B: Urticaria pigmentosa
(*Courtesy of Dr. Michelle B. Bain*)
C: Urticaria pigmentosa
(*Courtesy of Dr. Paul Getz*)

Cutaneous Calcification

- **Solitary nodular calcification**: benign nodule in infants typically from heel sticks
- **Osteoma cutis**: idiopathic or associated with Albright's hereditary osteodystrophy
- **Supepidermal calcified nodule**: solitary firm nodule on scalp or face (ears) of children

2.8 VASCULAR DISORDERS

Hemangiomas and Vascular Malformations

Hemangiomas are vascular tumors arising in infancy with true cellular proliferation, which eventually regress. Vascular malformations represent errors in vascular morphogenesis (dysplastic vessels) without true cellular proliferation and without regression.

Vascular Tumors	Vascular Malformations
Infantile and Congenital Hemangiomas	Capillary Malformation (slow flow): *Port-Wine Stain* (*Nevus Flammeus*)
Kaposiform Hemangioendothelioma	Venous Malformation (slow flow): *Cavernous Hemangioma*, *Phlebectasia*
Pyogenic Granuloma	Lymphatic Malformation (slow flow): *Lymphangioma* (*Lymphangioma Circumscriptum Cystic Hygroma*, *Cavernous Lymphangioma*)
Tufted Angioma	Arteriovenous Malformation (fast flow): *Cirsoid Aneursm*
Congenital Hemangiopericytoma	Combined Malformation (slow or fast flow)

A. VASCULAR TUMORS

Hemangioma of Infancy (Figure 2.16A)

- Benign vascular tumor presenting soon after birth (first few weeks after life)
- More common in premature infants, 15% have multiple lesions with higher risk for visceral involvement, GLUT1 positive (endothelial marker, useful in differentiating from malformation)
- Precursor lesion: pink or bruised macule or patch with surrounding telangiectasias
- **Superficial hemangioma** (strawberry hemangioma) situated in the superficial dermis and bright red in color during the proliferative phase
- **Deep or cavernous hemangioma** (located deep dermis and/or subcutis) presents as blue-purple mass with normal overlying skin, ± bruit
- Involution: 30% by age 3, 50% by age 5, 70% by age 7, 90% by age 9
- Complications: ulceration (most common), anatomic distortion with interference of normal function, high-output congestive heart failure (greater risk with visceral hemangiomas, especially if in liver)
- Regionally significant hemangiomas: periocular (obstruct vision and cause ophthalmologic complications), beard region (clue for laryngeal hemangiomatosis with airway obstruction), segmental hemangioma over lumbosacral area (MRI of spine to r/o GU/GI/spinal/skeletal abnormalities), nasal tip (textural changes and scarring)

PHACES
- **P**osterior fossa malformation, **h**emangioma, **a**rterial anomalies, **c**ardiac defect, **c**oarctation of the aorta, **e**ye abnormalities, **s**ternal defects, and **s**upraumbilical raphe
- Hemangiomas tend to be plaque-like on the face involving more than one dermatome
- Most common posterior fossa malformation: Dandy–Walker malformation

Diffuse Neonatal Hemangiomatosis
- Cutaneous and visceral hemangiomas; liver hemangioma may be complicated by obstructive jaundice
- If multiple cutaneous hemangiomas, perform ultrasound, urinalysis, stool guiaic, CBC to r/o systemic involvement
- If no visceral involvement → benign neonatal hemangiomatosis
- ↑ Mortality with systemic form due to high-output cardiac failure, GI bleeding, and respiratory compromise

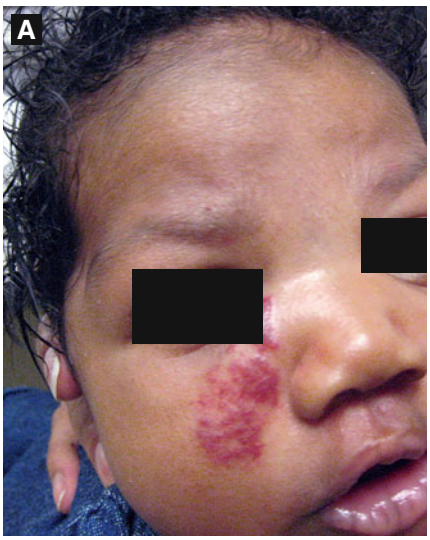
Tufted Angioma (Figure 2.16B)
- Onset during infancy or early childhood
- Presents as ill-defined red-brown plaque or patch over neck or upper trunk; plaque slowly extends with time (typically does not regress)

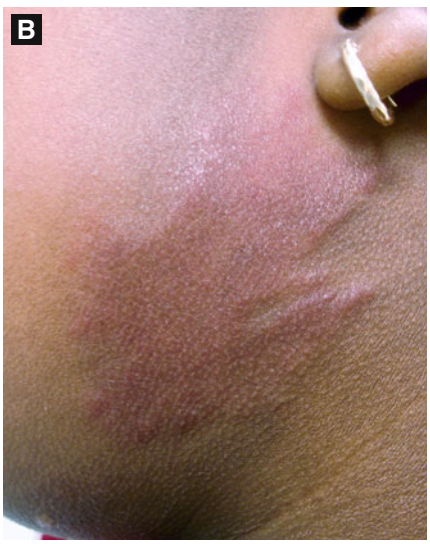
PELVIS Syndrome
- **P**erineal hemangioma, **e**xternal genital malformation, **l**ipomyelomeningocele, **v**esicorenal anomalies, **i**mperforate anus, and **s**kin tag

Pyogenic Granuloma (Figure 2.16C)
- Presents as rapidly growing, friable red papule of skin or mucosa with frequent ulceration
- Common in children and young adults
- Associated with antecedent trauma, pregnancy, oral medications (retinoids, inidinavir, EGFR inhibitors)

Kaposiform Hemangioendothelioma (Figure 2.17A)
- Usually onset before age 2
- Presents as vascular macules, plaques, nodules, or bulging indurated masses
- Associated with Kasabach–Merritt syndrome → consumptive coagulopathy with thrombocytopenia (platelet sequestration) and purpura; deep-seated tumors (i.e., retroperitoneal) likely to cause above syndrome

Glomeruloid Hemangioma
- Distinct vascular proliferation in POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin lesions)
- Presents as firm, red-purple papules over trunk or extremities





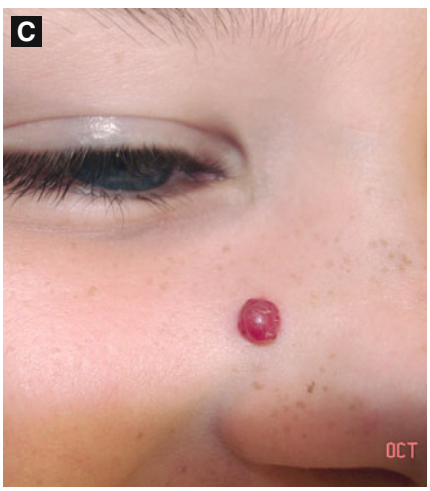


Figure 2.16
A: Hemangioma
(*Courtesy of Dr. Michelle B. Bain*)
B: Tufted angioma
C: Pyogenic granuloma

B. VENOUS MALFORMATIONS

Capillary Malformation (Nevus Flammeus, Port-Wine Stain, PWS) (Figure 2.17B)

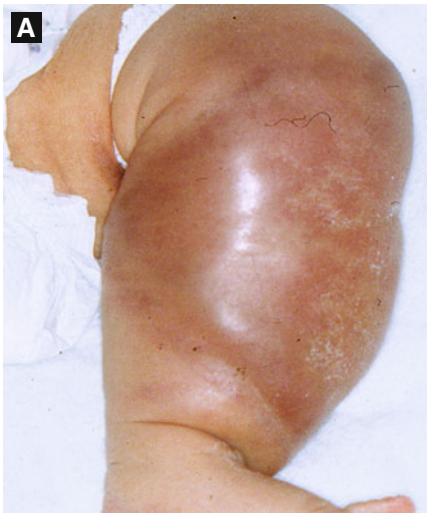
- Presents as a well-demarcated erythematous patch or plaque that grows in proportion to general growth of the body; does not spontaneously recede (unlike "salmon patches" over forehead, glabella, nose/philtrum, nape or eyelid which typically disappear by age 3)
- Facial PWS follows sensory CN V distribution (V1–V3); over time, skin changes from pink to deep purple and thickens with ↑ nodularity and pyogenic granulomas
- GLUT1 negative
- PWS can be seen with combination of epidermal or melanocytic abnormalities: phakomatosis pigmentovascularis (see below)
- Associated syndromes: Sturge–Weber syndrome, Klippel–Trénaunay syndrome, Proteus syndrome

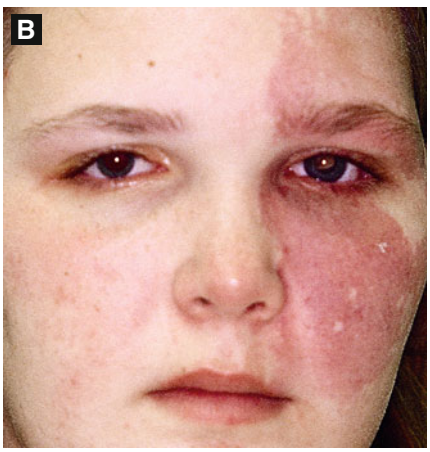
Phakomatosis Pigmentovascularis

- Type 1: PWS + epidermal nevus
- Type 2: PWS + dermal melanocytosis ± nevus anemicus
- Type 3: PWS + nevus spilus ± nevus anemicus
- Type 4: PWS + dermal melanocytosis + nevus spilus ± nevus anemicus

Glomangioma (Glomuvenous Malformation) (Figure 2.17C)

- Arises in children and adolescents; may be sporadic or inherited (autosomal dominant with incomplete penetrance; defect in glomulin gene)
- If solitary lesion (glomus tumor), onset typically in adulthood with subungual location
- Presents as soft pink to deep blue papules or nodules in segmental distribution; tender to palpation, ± attacks of pain with pregnancy or menstruation
- Histology: resembles vascular malformation but vessels lined with one or more rows of cuboidal glomus cells





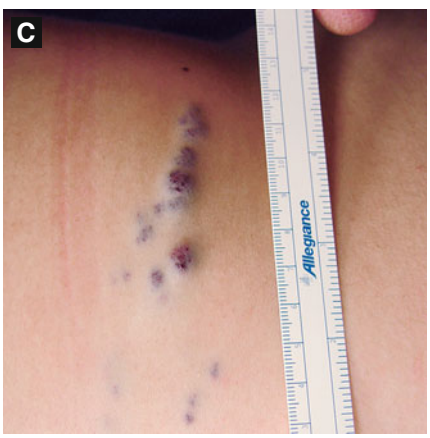


Figure 2.17
A: Kaposiform hemangioendothelioma (in Kasabach-Merritt) (*Reprint from Laxer RM, ed. The Hospital for Sick Children: Atlas of Pediatrics. Philadelphia, PA: Current Medicine; 2005*)
B: Port-wine stain (*Reprint from Abel-Halim AW. Passing the USMLE. New York, NY: Springer; 2009*)
C: Glomangiomas (*Courtesy of Dr. Michelle B. Bain*)

Angiokeratoma (Figure 2.18A)

- Ectasias of dermal capillaries
- Presents as a dark red to purple papule; either solitary or multiple; distribution varies by type

Solitary Angiokeratoma	Single red to dark brown papule usually on the lower extremity
Angiokeratoma Circumscriptum	Large verrucous papules or plaques typically involving the extremity, onset in early childhood/infancy
Angiokeratoma of Mibelli	Rare, presents as several 1–5 mm dark, red-gray papules over acral areas with verrucous surface
Angiokeratoma Corporis Diffusum (Fabry Disease)	Numerous tiny telangiectatic red papules associated with hereditary lysosomal storage disease, XLR, α-galactosidase A deficiency
Angiokeratoma of the Scrotum (Fordyce)	Multiple small red-violaceous papules studding the scrotum, less often the vulva, onset in adulthood

Lymphangioma

- Uncommon congenital malformation of the lymphatic system; either superficial (lymphangioma circumscriptum) or deep-seated (cavernous lymphangioma)
- Lymphangioma circumscriptum: multiple translucent vesicles with clear lymph fluid (resembling frog spawn)
- Cystic hygroma (variant of cavernous lymphangioma): deep-seated large translucent soft mass typically over neck, axilla, or lateral chest

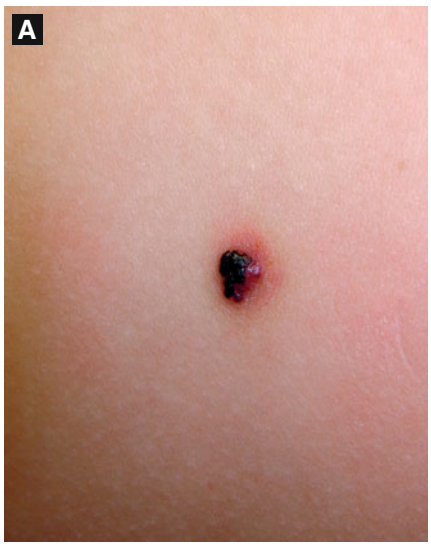
C. TELANGIECTASIAS

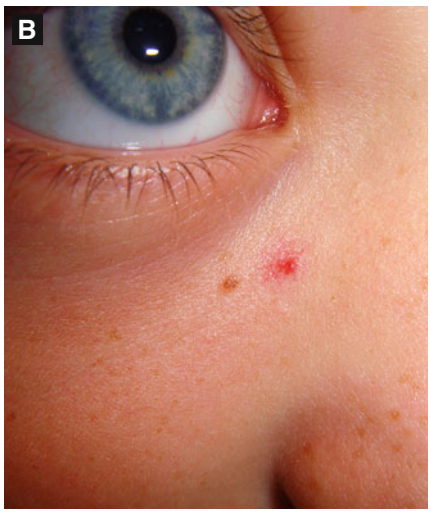
Spider Angioma (Spider Nevus) (Figure 2.18B, C)

- Common acquired lesion seen in children and adults
- Comprised of central arteriole with radiating thin walled vessels; temporary obliteration seen with compression
- Presents as bright red papule with central papule surrounded by distinct radiating vessels
- Multiple lesions associated with liver disease, pregnancy, and estrogen therapy

Angioma Serpiginosum

- Onset typically within first two decades of life
- Presents as small, red punctate asymptomatic macules in serpiginous pattern typically over extremity





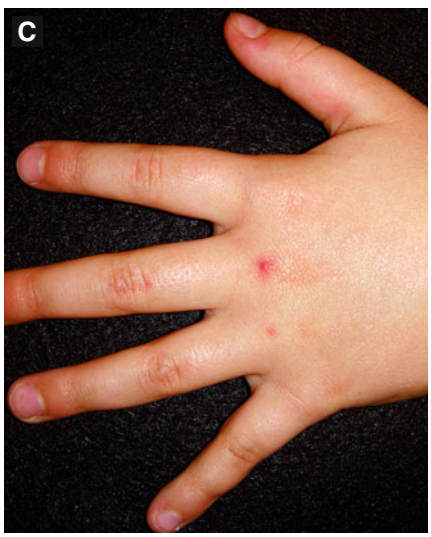


Figure 2.18
A: Angiokeratoma
B: Spider angioma
C: Spider angioma

2.9 GENODERMATOSES

X-Linked Recessive

CHAD'S Kinky WIFE, CHANdra

- **C**: Chronic Granulomatous Disease
- **H**: Hunter Disease
- **A:** Anhidrotic (Hypohidrotic) Ectodermal Dysplasia (Christ-Siemens-Touraine)
- **D:** Dyskeratosis Congenita
- **S:** SCID
- **Kinky**: Kinky Hair Disease (Menkes Disease)
- **W**: Wiskott–Aldrich Syndrome
- **I**: Ichthyosis, X-linked
- **F**: Fabry Disease
- **E**: Ehlers–Danlos Syndrome (type V and IX)
- **C**: Chondrodysplasia Punctata (not Conradi–Hünermann type)
- **H**: Hypohidrotic ED with Immunodeficiency
- **A**: Agammaglobulinemia, Bruton
- **N:** Lesch-Nyhan Syndrome

Of note, type IX EDS (occipital horn syndrome) is NOT part of the revised EDS classification (since it is NOT due to a collagen defect) and type V is classified as "other" in EDS classification

X-Linked Dominant

BIG ChOMP

- **B**: Bazex Syndrome (do not confuse with acrokeratosis paraneoplastica {Bazex syndrome})
- **I**: Incontinentia Pigmenti (Bloch-Sulzberger Syndrome)
- **G**: Goltz Syndrome (Focal Dermal Hypoplasia)
- **C**: CHILD Syndrome
- h: –
- **O:** Oro-Facial-Digital Syndrome
- **M**: MIDAS Syndrome (micrognathia, dermal aplasia, sclerocornea)
- **P**: Chondrodysplasia Punctata (Conradi–Hünermann type)

A. SYNDROMES WITH DEFECTIVE DNA REPAIR

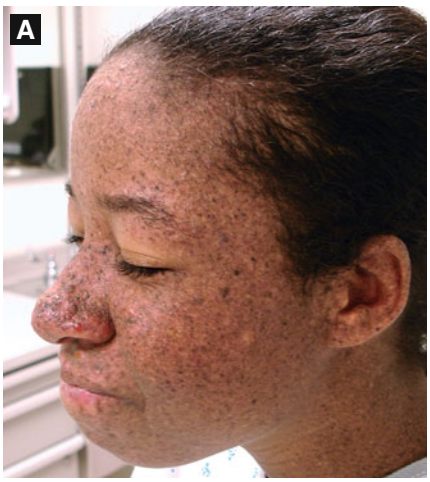
Xeroderma Pigmentosum (XP) (Figure 2.19A, B)

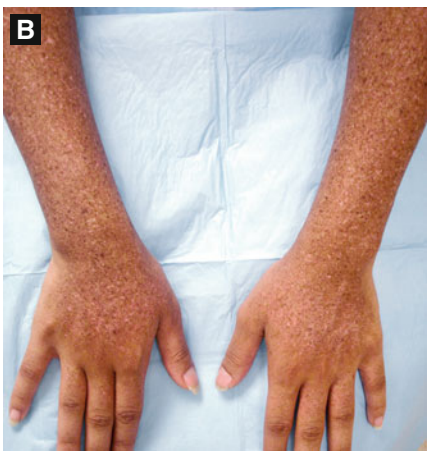
- AR, due to defect in DNA repair
- Seven complementation groups (A–G) and one XP variant described, each encoding different proteins in the nucleotide excision repair (NER) pathway (except XP variant)
- Presents with marked photosensitivity, early onset of all major skin malignancies, exaggerated sunburn following minimal sun exposure, solar lentigines by age of 2, ocular abnormalities (photophobia, keratitis, corneal opacification, vascularization), neurologic abnormalities (progressive deafness)
- XP variant (mutation in DNA polymerase): no neurologic abnormalities
- DeSanctis–Cacchione syndrome (Gr. A): severe neurologic abnormalities (MR, deafness, ataxia)

Cockayne Syndrome

- AR, defective excision repair: unable to repair cyclobutane pyrimidine dimer products after irradiation, ↑ chromosomal breaks
- Two complementation groups: CS-A (ERCC8) and CS-B (ERCC6)
- Presents with photosensitivity, mental retardation, cachectic dwarfism, peripheral neuropathy, sunken eyes, prominent ears, "salt and pepper" retinitis pigmentosa, dental caries, thinning hair, basal ganglia calcification

COCKAYN**E** – **eight** letters (ERCC**8**), **C**achectic dwarfism, **O**cular (salt/pepper RP), **C**ataracts, **A**void sun, **E**ars ("mickey mouse")





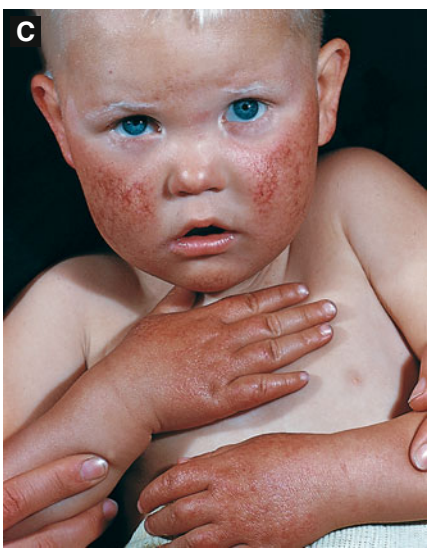


Figure 2.19
A: Xeroderma pigmentosum (*Courtesy of Dr. Michelle B. Bain*)
B: Xeroderma pigmentosum (*Courtesy of Dr. Michelle B. Bain*)
C: Rothmund-Thomson (*Reprint from Burgdorf WH, Plewig G, Wolff HH, Landthaler M, eds. Braun-Falco's Dermatology. 3rd ed. Heidelberg: Springer; 2009*)

Trichothiodystrophy (PIBIDS)

- AR, mutation in gene ERCC2 (XPD protein) and ERCC3 (XPB protein) in NER pathway, sulfur deficiency in hair
- PIBIDS: **P**hotosensitivity (50%), **i**chthyosis (variable severity), **b**rittle hair (alternating bright and dark bands known as "tiger tail," flattened hair shafts like a ribbon), **i**ntellectual impairment, **d**ecreased fertility, **s**hort stature, receding chin, protruding ears

Tricho**T**hiodystrophy – **T**iger **T**ail abnormality

Bloom Syndrome

- AR, BLM gene mutation, RecQ protein-like two (RecQL2, some sources say RecQL3 {Spitz}), DNA helicase family, mutation results in ↑ spontaneous sister chromatid exchanges, breakage, and rearrangements
- Presents with photodistributed erythema/telangiectasias over cheeks within first few weeks of life, short stature, normal intelligence, immune deficiency causing chronic respiratory/GI infections, ↓ fertility, ↓ IgM/IgA, high-pitched voice
- ↑ Risk cancer: leukemia, lymphoma, GI adenocarcinoma

BLoo**M** – **2** O's (RecQL**2**)
Butterfly rash, **L**eukemia, i**M**mune deficiency, ↓ Ig**M**

Rothmund–Thomson Syndrome (Poikiloderma Congenitale)

(Figure 2.19C)

- AR, RECQL4 (DNA helicase)
- Presents with photodistributed erythema and vesicles on face in first few months of life, evolves into poikiloderma and extends to buttocks and extremities, premalignant acral keratoses, alopecia, cataracts, hypoplastic thumbs/ radii/ulnae, ↑ risk osteosarcoma, normal intelligence

Rothmund **T**homson – **R**educed **T**humbs
ROTH (**4** letters) – RecQL**4**

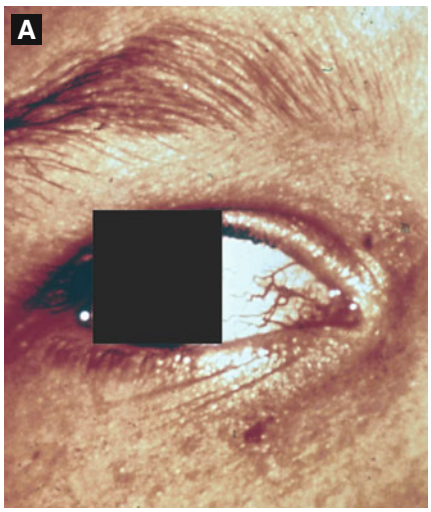
Dyskeratosis Congenita (Zinsser-Engman-Cole Syndrome)

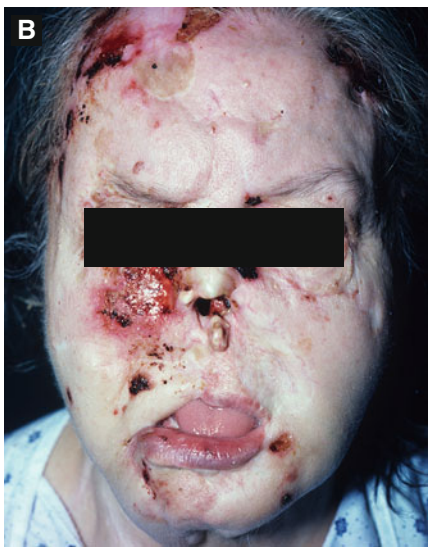
- Two forms: XLR and AD
- XLR, DKC1 gene mutation, encodes protein dyskerin (interacts with telomerase), ↑ sister chromatid exchanges
- AD, hTR (human telomerase RNA component) and hTERT (human telomerase reverse transcriptase) mutations
- Cutaneous poikiloderma (face, trunk, thighs), nail dystrophy (atrophy, pterygium), premalignant leukoplakia (buccal mucosa most common), frictional bullae, palmoplantar hyperhidrosis
- Bone marrow failure with anemia, thrombocytopenia, or pancytopenia → major cause of mortality
- ↑ CA: mucosal SCC, Hodgkin's lymphoma, AML

DYSke**R**a**TOS**is – **DYS**trophy (nails), m**R**, **T**hrombocytopenia, **O**ral premalignant leukoplakia, **S**un avoidance (poikiloderma)

Ataxia-Telangiectasia Syndrome (Figure 2.20A)

- AR, ATM gene mutation, inability to repair chromosomal strand breaks, sensitivity to ionizing radiation





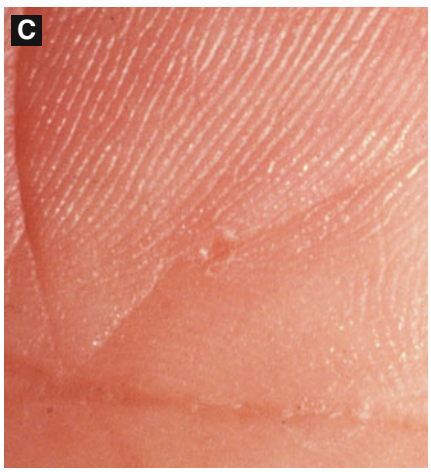


Figure 2.20
A: Ataxia-Telangiectasia
(*Reprint from Morgan MB, Smoller BR, Somach SC. Deadly Dermatologic Diseases. New York, NY: Springer; 2007*)
B: Basal cell nevus syndrome*
C: Palmar pits (BCNS)*
**Courtesy of Dr. Paul Getz*

- Presents first with ataxia (2–3 years old) → telangiectasias on bulbar conjunctivae (spreads to cheeks/ears), premature aging (atrophic/sclerotic face), ↓ Purkinje fibers in cerebellum
- Defects in cellular and humoral immunity (↓ IgA, IgG, IgE), severe and frequent sinopulmonary infections, ↑ lymphoreticular malignancy, ↑ breast CA

Fanconi Syndrome

- AR, ↑ chromosomal breakage
- Presents with diffuse hyperpigmentation, multiple CALMs, pancytopenia, ↑ SCC, ↑ solid organ CA, ↑ leukemia, hypoplasia of radius/thumb

FanCONi – CONe-shaped defect (hypoplasia of distal structures – radius/thumb)

B. SYNDROMES OF TUMOR SUPPRESSION

Basal Cell Nevus Syndrome (Gorlin Syndrome) (Figure 2.20B, C)

- AD, PTCH (PATCHED) gene, inhibits sonic hedgehog signaling (unbound PTCH inhibits Smoothened (SMO) signaling; when inactivating mutation occurs in PTCH → repression of SMO removed → constitutive activation of Gli and downstream targets)
- Presents with numerous BCCs, palmar/plantar pits, odontogenic keratocysts of jaw, characteristic facies (frontal bossing, hypertelorism), cataracts, glaucoma, bifid ribs, calcification of falx cerebrum, agenesis of corpus callosum, ovarian fibromas, medulloblastoma, meningioma

Neurofibromatosis, Type I (Von Recklinghausen Disease) (Figure 2.21A–C)

- AD, NF-1 gene, encodes neurofibromin (tumor suppressor protein)
- Criteria: two or more of the following six:

Six or more CALMs or two or more neurofibromas or one plexiform neurofibroma	Cafe au lait macule (CALM): > 0.5 cm prepubertal, >1.5 cm postpubertal
Axillary or inguinal freckling (Crowe's sign)	
Optic glioma	
Lisch nodules	
Sphenoid wing dysplasia or thinning cortex of long bone	
First degree relative with NF	

- ↑ Risk of tumors: optic glioma, malignant peripheral nerve sheath tumor, neurosarcoma, juvenile myelomonocytic leukemia, rhabdomyosarcoma
- ± Hypertension, mental retardation (MR), seizures, kyphoscoliosis, endocrine disorder (precocious puberty, acromegaly, thyroid/parathyroid abnormalities)

Neurofibromatosis, Type II (Bilateral Acoustic NF)

- AD, NF-2 gene, encodes merlin/schwannomin
- Diagnosis requires bilateral CNVII masses OR first degree relative AND either unilateral CN VIII mass OR two of the following: schwannoma, optic glioma, meningioma, juvenile posterior subcapsular opacity

Carney Syndrome (NAME or LAMB Syndrome)

- AD, PRKAR1A gene

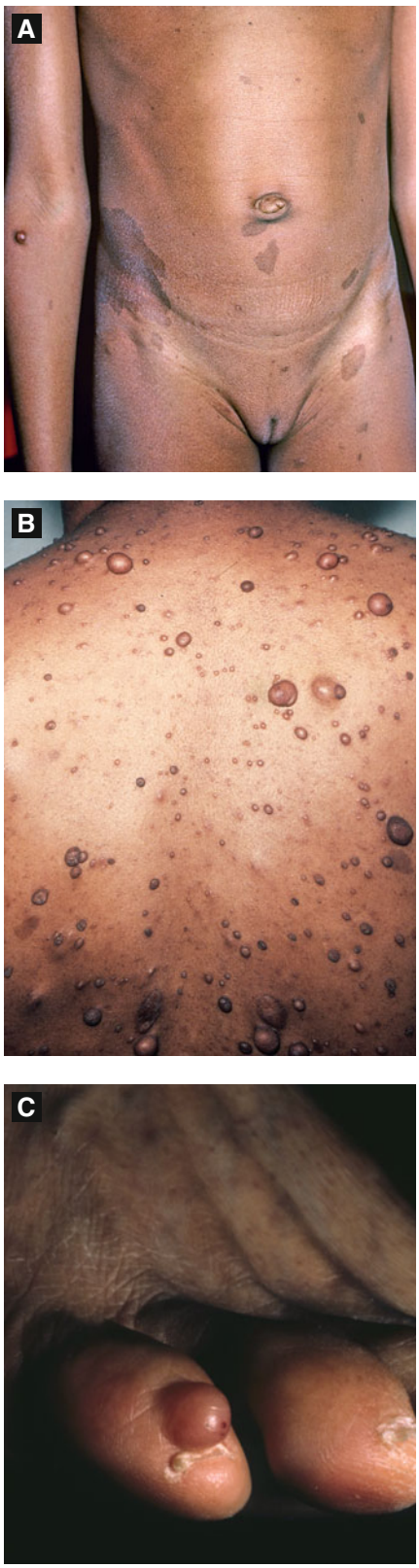


Figure 2.21
A: CALMs*
B: Neurofibromatosis*
C: Neurofibromatosis*
**Courtesy of Dr. Paul Getz*

- Presents with ephelides, blue nevi, lentigines, cutaneous myxomas (flesh-colored papules over ears, eyelids, nipples), primary pigmented nodular adrenocortical disease (results in Cushing syndrome)
- Tumors: testicular tumors, pituitary GH-secreting tumors, psammomatous melanotic schwannomas

NAME: nevi, atrial myxoma, myxoid tumors, ephelides
LAMB: lentigines, atrial myxomas, mucocutaneous myxomas, blue nevi

Muir–Torre Syndrome

- AD, mutation in MLH1 and MSH2 (DNA mismatch repair genes) causing microsatellite instability
- Multiple sebaceous neoplasms and keratoacanthomas
- ↑ Risk of colon adenocarcinoma, less common GU, lung, breast or heme malignancy

Muir–Torre: think of "**more**" and more sebaceous neoplasms

Tuberous Sclerosis (Figure 2.22A, B)

- AD, TSC1 gene mutation (hamartin), and TSC2 (tuberin)
- Ash-leaf macules (earliest finding), facial angiofibromas, connective tissue nevi (shagreen patch), fibromas (gingival and subungual), CALMs, dental enamel pits
- Renal angiomyolipomas, retinal hamartomas, seizures, pulmonary lymphangioleiomyomatosis, cortical tubers, cardiac rhabdomyoma

Cowden Syndrome (Multiple Hamartoma Syndrome) (Figure 2.22C)

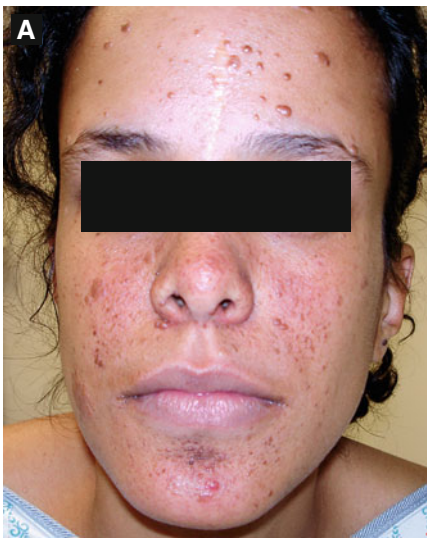
- AD, PTEN gene mutation, encodes tyrosine phosphatase protein, mutation causes cell proliferation
- Trichilemmomas (smooth to verrucous small papules on face), "cobblestone" appearance of the mucosa including tongue (oral papillomas), acral keratotic papules
- ↑ Breast fibroadenoma, ↑ CA: breast, thyroid follicular; GI polyps

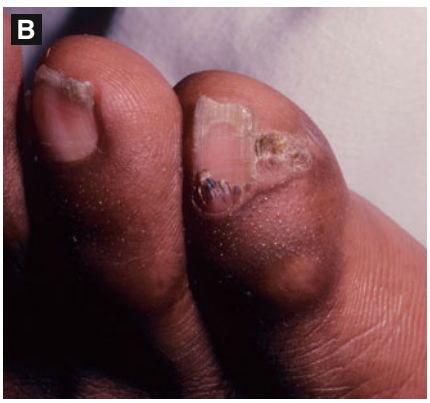
COWden – trichile**MOO**mas; other PTEN syndromes: Lhermitte–Duclos and Bannayan–Zonana syndrome

Multiple Endocrine Neoplasia (MEN)

Type 1 (Wermer Syndrome)	– AD, **MEN1** mutation (menin: tumor suppressor)
	– Angiofibromas, collagenomas, lipomas, CALMs
	– Pituitary, parathyroid, pancreatic tumors
Type 2a (Sipple Syndrome)	– AD, **RET** mutation (tyrosine kinase receptor)
	– **Lichen or macular amyloidosis**, hemangiomas, genital lentigines, hamartomas, lipomas
	– Parathyroid tumor, **thyroid medullary carcinoma**, pheochromocytoma
Type 2B (Multiple Mucosal Neuroma Syndrome)	– AD, **RET** mutation
	– **Multiple mucosal neuromas**, thickened lips
	– **Thyroid medullary carcinoma**, pheochromocytoma, marfanoid habitus, diffuse ganglioneuromatosis (megacolon, diarrhea)

MEN 1: 3 P's (pituitary, pancreas, parathyroid) + CALMs
MEN 2**A**: **A**myloidosis ("sipple" syndrome: think "rippled" macular amyloid)
MEN2**B**: **B**lubbery lips due to mucosal neuromas





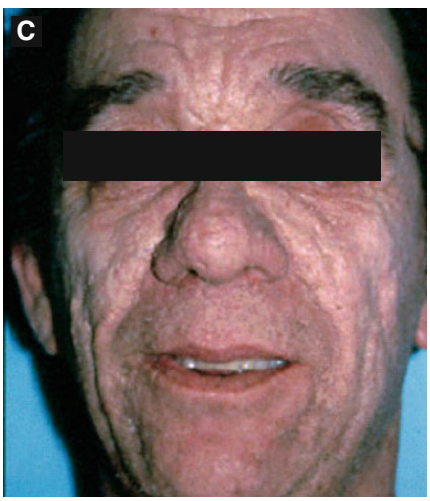


Figure 2.22
A: Angiofibromas in TS (*Courtesy of Dr. Michelle B. Bain*)
B: Koenen tumor in TS (*Courtesy of Dr. Paul Getz*)
C: Cowden syndrome (*Reprint from Morgan MB, Smoller BR, Somach SC. Deadly Dermatologic Diseases. New York, NY: Springer; 2007*)

Bannayan–Riley–Ruvalcaba Syndrome

- AD, PTEN mutation
- Genital lentigines, hamartomas, lipomas, hemangiomas, mental retardation, macrocephaly

Bannayan – think of an old **ban**ana with dark spots on the outside resembling lentigines

LEOPARD Syndrome (Multiple Lentigines Syndrome)

- AD, PTPN11 gene mutation, encodes tyrosine phosphatase Shp2
- **L**entigines, **E**CG abnormalities, **o**cular hypertelorism, **p**ulmonic stenosis, **a**bnormal genitalia, **r**etarded growth and **d**eafness
- Multiple lentigines at birth/early infancy (sun exposed and protected areas, including genitalia, hands, feet)

Peutz–Jeghers Syndrome (Figure 2.23A)

- AD, STK11/LKB1 gene mutation, encodes serine-threonine kinase tumor suppressor
- Hyperpigmented macules on lip/oral mucosa/fingers (starts in infancy/early childhood) and intestinal polyposis (± bleeding, intussusception)
- ↑ GI adenocarcinoma, ↑ other solid organ malignancies

Peu**T**z(**S**) Jeghers – **T**hreonine **S**erine kinase

Gardner Syndrome

- AD, APC gene encoding tumor suppressor gene (ras proto-oncogene)
- Cutaneous epidermoid cysts, osteomas (mandible, maxilla), supernumerary teeth, odontomas, fibromas, congenital hypertrophy of the retinal pigment epithelium (CHRPE)
- Tumors: GI adenocarcinoma (inevitable), osteochondromas, thyroid papillary carcinoma, hepatoblastoma, adrenal adenomas

Gardner – birds **CHiRP** in the **GARD**en

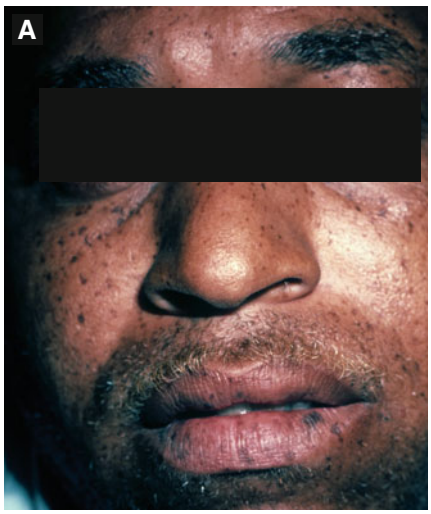
Birt–Hogg–Dubé Syndrome (Figure 2.23B, C)

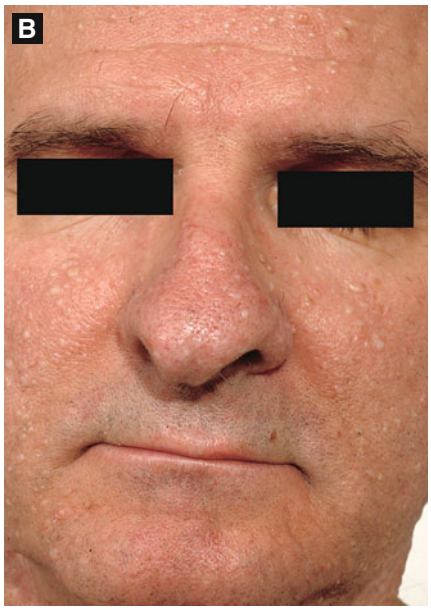
- AD, BHD gene (encodes folliculin)
- Multiple fibrofolliculomas, trichodiscomas, acrochordons on the face, scalp, neck, and upper trunk
- Associated with renal cell carcinoma, medullary carcinoma of thyroid, spontaneous pneumothorax (multiple pulmonary cysts)

Birt **HOGG** Dube – think of a **hog** with rough textured skin (because of fibrofolliculomas and trichodiscomas)

Dysplastic Nevus Syndrome

- AD, CDKN2A (p16 tumor suppressor gene, inhibits cyclin-dependent kinase 4 [CDK4])
- Dysplastic nevi, melanoma, pancreatic CA, astrocytomas





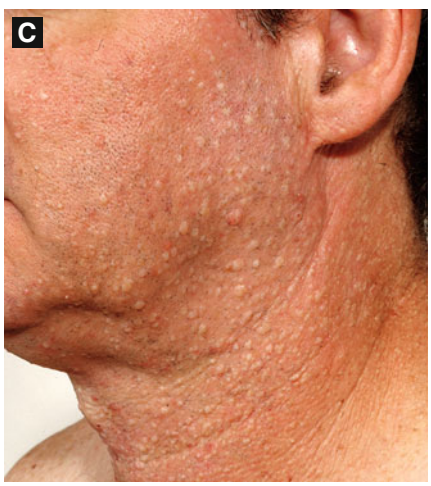


Figure 2.23
A: Peutz–Jeghers syndrome
(*Courtesy of Dr. Paul Getz*)
B: Birt–Hogg–Dube syndrome*
C: Birt–Hogg–Dube syndrome*
(**Reprint from Morgan MB, Smoller BR, Somach SC. Deadly Dermatologic Diseases. New York, NY: Springer; 2007*)

C. SYNDROMES WITH PREMATURE AGING

Werner Syndrome (Adult Progeria) (Figure 2.24A)

- AR, RECQL2 gene mutation (WRN gene), encodes RecQ DNA helicase, genomic instability (↑ aging/cancer)
- Normal growth until second decade, then short stature/thin limbs, graying of hair in adolescence, central obesity, pinched facial expression, beaked nose, micrognathia, high-pitched voice, mottled hyperpigmentation, sclerodermoid changes, cataracts, diabetes mellitus, premature atherosclerosis, chronic leg ulcers
- ↑ Soft tissue sarcomas, osteosarcomas, SCCs

Werner – t**W**o (recql**2**)

Progeria (Hutchinson–Gilford Syndrome) (Figure 2.24B)

- AD, lamin A gene mutation (LMNA), encodes lamin A and lamin C (nuclear envelope protein)
- Markedly premature aging (median lifespan 12 years), large appearing cranium, frontal bossing, prominent scalp veins, beaked nose, micrognathia, "plucked bird" appearance, loss of subcutaneous tissue, scleroderma skin; alopecia, high pitched voice, average intelligence, severe premature coronary atherosclerosis

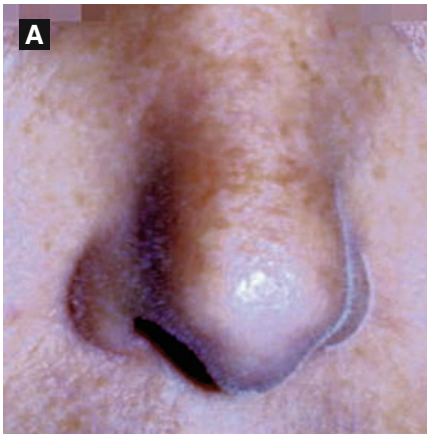
D. DISORDERS WITH IMMUNODEFICIENCY

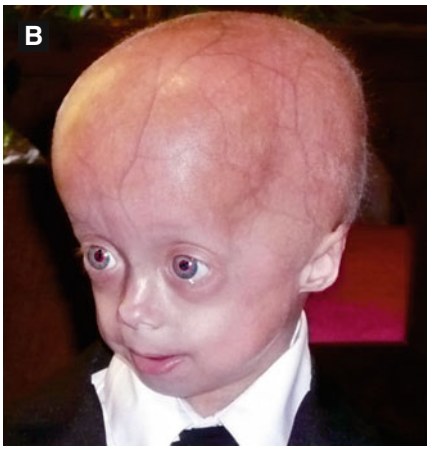
Familial Chronic Mucocutaneous Candidiasis (FCMC)

- Recurrent, progressive candidal infections (skin, nails, and mucosa) presenting with recurrent oral thrush, nail dystrophy, crusted cutaneous plaques

Hyper-IgE Syndrome (Job Syndrome) (Figure 2.24C)

- AD, mutation in gene encoding STAT3 (signal transducer and activator of transcription 3), AR (gene encoding tyrosine kinase 2 TYK2)
- ↑ IgE levels, peripheral eosinophilia, cold abscesses, coarse facies, eczematous dermatitis, lung abscesses, pneumonia, retained primary teeth, pneumatocele, otitis media, osteopenia with recurrent fractures





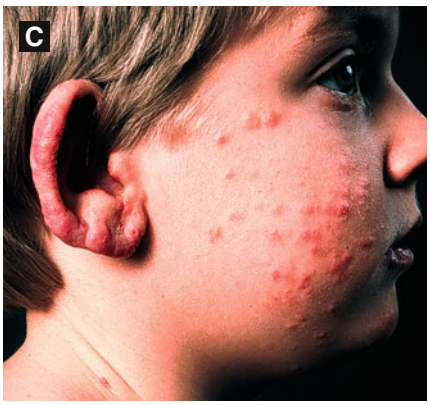


Figure 2.24
A: Werner syndrome
(*Reprint from Baykal C, Yazganoglu KD. Dermatological Diseases of the Nose and Ears. Berlin: Springer; 2010*)
B: Progeria
(*Courtesy of the Howard family*)
C: Hyper-IgE syndrome
(*Reprint from Burgdorf WH, Plewig G, Wolff HH, Landthaler M, eds. Braun-Falco's Dermatology. 3rd ed. Heidelberg: Springer; 2009*)

Wiskott–Aldrich Syndrome (WAS)

- XLR, WASP gene, encodes WAS protein (controls assembly of actin filaments)
- Thrombocytopenia and platelet dysfunction (since birth) → petechiae and ecchymoses of skin, epistaxis, melena, hematemesis, hematuria
- Atopic dermatitis (face, scalp, flexures), excoriated areas with crust/petechiae, recurrent bacterial infections
- Hepatosplenomegaly, lymphadenopathy, ↑ lymphoma (non-Hodgkin's lymphoma)
- Death from infections > hemorrhage > malignancy
- Treatment: bone marrow transplantation

Severe Combined Immunodeficiency (SCID)

- XLR, deficiency of γ chain of IL2 receptor (IL2RG); AR, defect in tyrosine kinase JAK3 or adenosine deaminase (ADA); heterogeneous disorders with severely impaired humoral and cellular immunity
- Deficiency or total absence of circulating lymphocytes

Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED)

- AR, AIRE gene (autoimmune regulator gene) mutation
- Candidal infections, endocrinopathy (thyroid/parathyroid abnormality, diabetes mellitus, hypoadrenocorticism), cutaneous and other autoimmune disorder (alopecia areata, vitiligo, pernicious anemia)
- Varied cutaneous presentations: seborrheic-like dermatitis or morbilliform eruption, recurrent candidiasis and bacterial infections, chronic diarrhea, failure to thrive

E. DISORDERS OF PIGMENTATION

Oculocutaneous Albinism (OCA) (Figure 2.25A)

Type	Inheritance/Defect	Clinical
OCA, Type 1a (Tyrosinase-negative)	AR **TYR** (Tyrosinase enzyme deficiency)	No melanin in skin/hair/eyes, white hair (over time may turn slightly yellow), milky white-pink skin, blue-gray eyes, **amelanotic nevi** (pink), extreme UV sensitivity, ↑ skin CA, nystagmus, strabismus, ↓ visual acuity
OCA, Type 1b (Yellow mutant)	AR **TYR**	↓ Tyrosinase activity, little or no pigment at birth, develop some pigment over time, milder eye findings
OCA, Type 2 (Tyrosinase-positive)	AR **P gene** (↓ Eumelanin synthesis)	**Most common** OCA, broad clinical phenotype (minimal to moderate dilution), pigmented nevi develop over time, light brown hair/skin
OCA, Type 3 (Rufous)	AR **TYRP-1** (Tyrosinase-related protein 1)	Light brown hair/skin, blue or brown irides, nystagmus, ↓ visual acuity

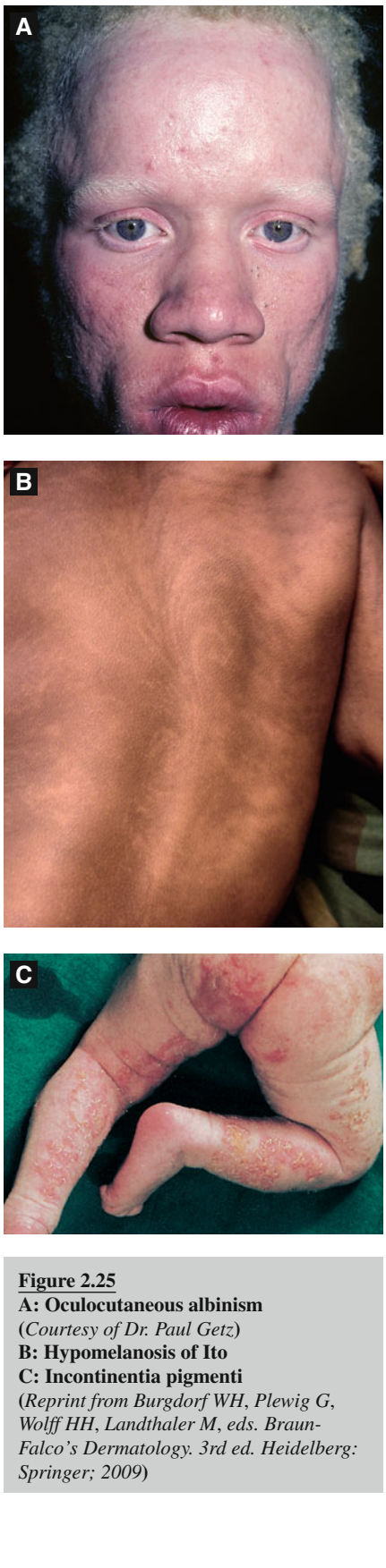


Figure 2.25
A: Oculocutaneous albinism
(*Courtesy of Dr. Paul Getz*)
B: Hypomelanosis of Ito
C: Incontinentia pigmenti
(*Reprint from Burgdorf WH, Plewig G, Wolff HH, Landthaler M, eds. Braun-Falco's Dermatology. 3rd ed. Heidelberg: Springer; 2009*)

Chédiak–Higashi Syndrome

- AR, LYST/CHS1 gene mutation (lysosomal trafficking regulator), defect in vesicle trafficking
- Giant intracytoplasmic granules (involving melanocytes, platelets, leukocytes)
- Onset at infancy: oculocutaneous albinism with immunologic deficiency, silvery metallic hair (clumps of melanin microscopically), recurrent infections, easy bruising, progressive neurologic deterioration, giant lysosomal granules, slate-gray skin color
- "Accelerated phase": pancytopenia, lymphohistiocytic infiltration of reticuloendothelial system
- Treatment: stem cell transplantation

Hermansky–Pudlak Syndrome

- AR, HPS gene mutation (lysosomal transport protein) or AP3B1 (formation of vesicles and protein trafficking)
- Oculocutaneous albinism, hemorrhagic diathesis (absent dense bodies in platelets) with epistaxis, ecchymosis, menorrhagia, pulmonary fibrosis, granulomatous colitis, renal failure, cardiomyopathy

Griscelli Syndrome

- AR, myosin Va or Rab27a gene mutation, encodes GTPase (ras family)
- Variable pigmentary dilution, silvery metallic hair, recurrent pyogenic infections, pancytopenia, neurologic involvement, immunodeficiency
- Uneven clumps of melanin in medulla on microscopy of hair; giant melanosomes NOT seen

Hypomelanosis of Ito (Figure 2.25B)

- Sporadic, due to somatic mosaicism
- Onset at birth/early childhood, whorled/linear/patchy hypopigmentation (unilateral or bilateral) following lines of Blaschko; ± CNS, eye, skeletal, or tooth abnormalities

Incontinentia Pigmenti (Bloch–Sulzberger Syndrome) (Figure 2.25C)

- XLD, NEMO gene mutation (NFκβ essential modulator), lethal in males; cutaneous lesions follow lines of Blaschko
- Four stages:

Vesicular stage: vesicles in linear/whorled streaks
Verrucous stage: hyperkeratotic linear plaques
Hyperpigmented: linear/whorled hyperpigmentation
Hypopigmented: hypopigmented thin streaks

- Associated with patchy scarring alopecia, absent or peg-shaped teeth, CNS abnormalities (seizures, delayed psychomotor development), ocular disease (retinal vascular abnormalities, blindness)

Piebaldism

- AD, c-kit gene mutation (proto-oncogene, tyrosine-kinase receptor family), defective melanocyte migration and development
- White forelock, irregularly shaped leukoderma favoring anterior trunk, extremities, forehead (leukoderma spares hands, feet, hips, shoulders), otherwise healthy

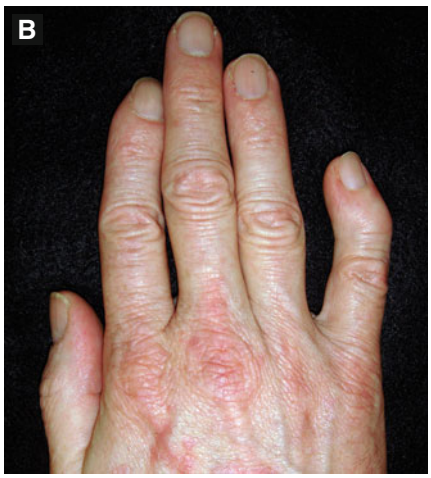


Figure 2.26
A: Waardenburg syndrome
(*Reprint from Levine N, Levine CC. Dermatologic Therapy: A–Z Essentials. New York: Springer; 2009.*)
B: Clinodactyly of 5th finger

Waardenburg Syndrome (Figure 2.26A)

- Four types below:

Type	Inh	Defect	Clinical
WS, Type 1	AD	**PAX3** (transcription factor)	White forelock, leukoderma, **heterochromia iridis, synophrys**, **dystopia canthorum** (characteristic), broad nasal root, **deafness uncommon**
WS, Type 2	AD	**MITF** (transcription factor)	Similar to WS1 but dystopia canthorum absent, **deafness common**
WS, Type 3	AD	**PAX3**	Similar to WS1 + **upper limb abnormalities** (hypoplasia, syndactyly, flexion contractures)
WS, Type 4	AD AR	**SOX10** (TF) EDN3 (endothelin-3) EDNRB (endothelin receptor)	Similar to WS1 + **Hirschsprung disease**, deafness common

F. DISORDERS WITH PIGMENTED LESIONS

McCune–Albright Syndrome (Polyostotic Fibrous Dysplasia)

- Sporadic, GNAS 1 gene mutation, encodes α subunit of Gs adenylate cyclase
- Large café-au-lait macules (geographic border), precocious puberty, pathological fractures, endocrine abnormalities (hyperparathyroidism, hyperthyroidism, acromegaly), sclerosis at base of skull

MCCune –Café au lait macules, preCocious puberty; do **NOT** confuse with Albright hereditary osteodystrophy (pseudohypoparathyroidism)

Russell–Silver Syndrome (Figure 2.26B)

- Presents with triangular facies, hemihypertrophy, clinodactyly of the fifth finger, syndactyly of second/third toes

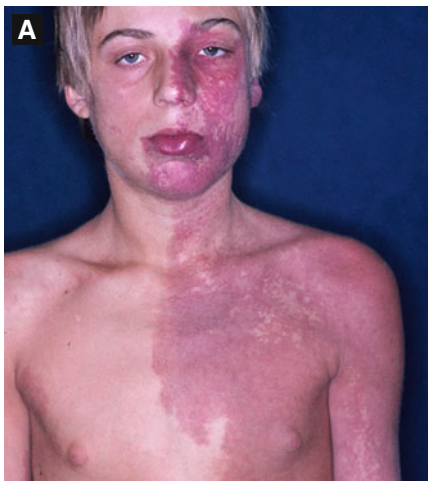
G. VASCULAR DISORDERS

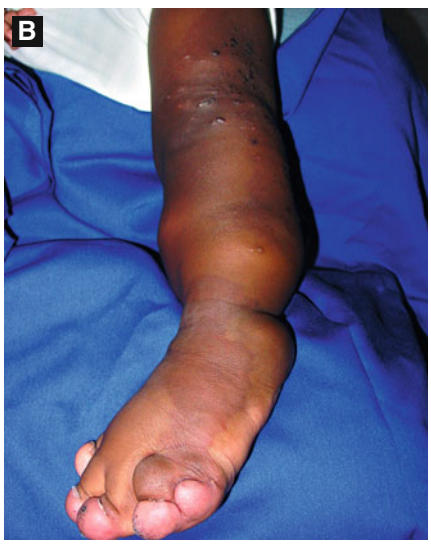
Sturge–Weber Syndrome (SWS) (Figure 2.27A)

- Sporadic neurologic disorder, facial PWS associated with ipsilateral ocular and leptomeningeal anomalies
- Facial PWS typically involves V1 distribution (can be more extensive or bilateral), congenital or acquired ocular abnormalities (glaucoma), neurologic abnormalities (seizures, motor dysfunction, mental retardation), intracranial "tram-track" calcification
- 10–15% patients with PWS of V1 distribution have underlying SWS

Klippel–Trénaunay Syndrome (KTS) (Figure 2.27B, C)

- Sporadic, vascular malformation of a limb associated with bone and soft tissue hypertrophy of the affected extremity with lymphatic and deep venous insufficiency
- Gigantism of the involved limb; may become painful and edematous, even ulcerate, ± recurrent cellulitis





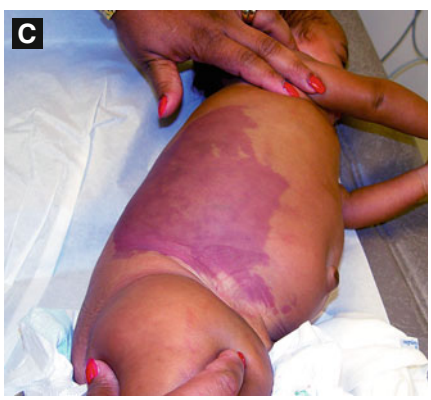


Figure 2.27
A: Sturge–Weber syndrome (*Reprint from Burgdorf WH, Plewig G, Wolff HH, Landthaler M, eds. Braun-Falco's Dermatology. 3rd ed. Heidelberg: Springer; 2009*)
B: Klippel–Trenaunay syndrome (*Courtesy of Dr. Michelle B. Bain*)
C: Klippel–Trenaunay syndrome (*Courtesy of Dr Michelle B. Bain*)

- Can also have urinary/GI vascular lesions, less frequently can have intermittent claudication, venous ulcers, lymphedema, recurrent pulmonary emboli
- If multiple arteriovenous fistulas associated with skeletal and soft tissue hypertrophy → Parkes Weber syndrome

Proteus Syndrome

- Sporadic, mosaic mutation in PTEN
- Named after the Greek god, Proteus, who could change his shape at will (due to dramatic variation in manifestations of syndrome)
- Cutaneous findings: hyperkeratotic epidermal nevi, palmoplantar cerebriform connective tissue nevi, capillary malformation, hemangiomas, lipomas
- Systemic findings: asymmetric growth with partial gigantism of hands/feet, hyperostoses of epiphyses and skull (especially external auditory canal), bilateral ovarian cystadenomas

Cobb Syndrome

- Rare, nonfamilial disorder with capillary malformation on the posterior trunk in association with spinal arteriovenous malformation (most common intramedullary)
- Kyphoscoliosis common, spinal AVM can cause neurologic deficits and can affect vertebral body (pain, weakness, muscular atrophy)

Von Hippel–Lindau Syndrome (VHL)

- AD, VHL gene (tumor suppressor)
- Bilateral retinal/cerebellar hemangioblastomas, PWS rarely of face, ↑ renal and pancreatic CA, pheochromocytoma, progressive and fatal by age 40

Beckwith–Wiedemann Syndrome

- AD, KIP2 gene (inhibitor of G1 cyclin)
- Circular depression over rim of helices, linear earlobe crease, facial vascular malformation, macroglossia, visceromegaly, hemihypertrophy of tissue/viscera with associated Wilms tumor and hepatoblastoma

BECK WITH – think of a baby named BECKy WITH earlobe creases, circular depressions (ears), protruding tongue, and Wilms tumor

Rubinstein–Taybi Syndrome (Figure 2.28A)

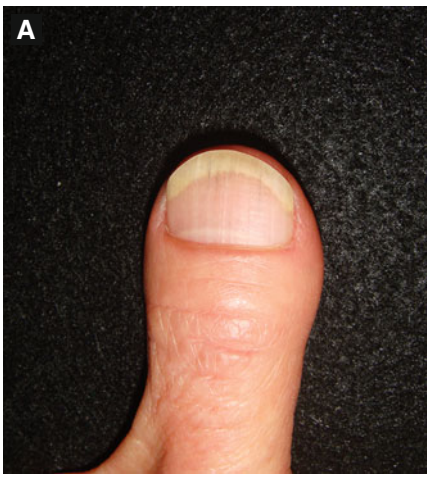
- Sporadic, CREB binding protein
- Vascular malformation, broad thumbs, beaked nose, mental retardation, congenital heart defects, cryptorchidism

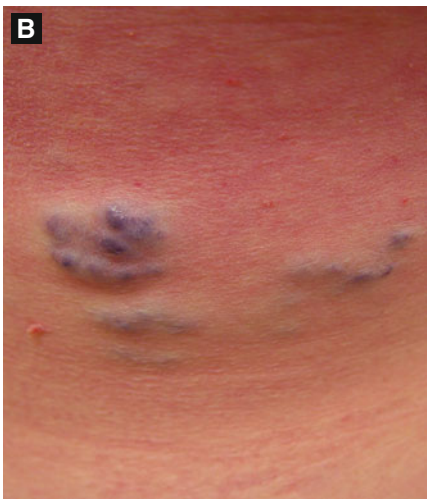
Rubinstein **T**aybi – **R**oomy (broad) **T**humbs

Mafucci Syndrome

- Sporadic, PTH/PTHrP type I receptor
- Venous malformations (superficial/deep) of hands/feet, benign endochondromas (benign cartilaginous tumor), ↑ risk of chondrosarcomas within endochondromas and other less common sarcomas; angiosarcomas usually fatal

Mafu**CC**I – **C**artilaginous tumor (endochrondroma), **C**hondrosarcoma





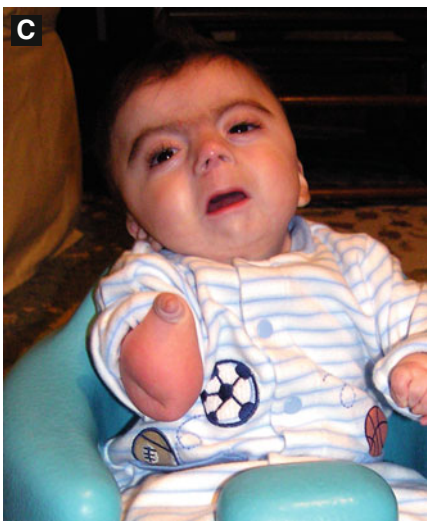


Figure 2.28
A: Rubinstein–Taybi syndrome
B: Blue rubber bleb syndrome (*Courtesy of Dr. Michelle B. Bain*)
C: Cornelia de Lange syndrome (*Courtesy of Dr. Karen Bryson*)

Blue Rubber Bleb Nevus Syndrome (Bean Syndrome) (Figure 2.28B)
- Sporadic (sometimes AD), TIE2 gene mutation (tyrosine kinase activating mutation)
- Multiple tender cutaneous and GI venous malformations
- Presents with compressible, blue papulonodules on trunk/arms, painful with ↑ lesional hyperhidrosis, + nocturnal pain characteristic, GI malformations can cause GI bleeding, intussusception

Cornelia de Lange Syndrome (Figure 2.28C)
- AD, but mainly sporadic, NIPBL (nipped-beta-like gene)
- Cutis marmorata, synophrys, trichomegaly, craniofacial abnormalities, MR, deafness, low-pitched cry, clinodactyly

Hereditary Hemorrhagic Telangiectasia (Osler–Weber–Rendu) (Figure 2.29A, B)
- AD, HHT1 (endoglin), and HHT2 (ALK1) gene mutation
- Multiple mucocutaneous and GI telangiectasias: epistaxis, telangiectasis (skin/mucosa), GI bleeding, pulmonary arteriovenous malformations

Hereditary Lymphedema (Milroy Disease)
- AD, FLT4 gene mutation, encodes VEGF receptor-3 (tyrosine kinase R in lymphatic vessels)
- Congenital lymphedema, chylous ascites, ± cystic hygroma

Lymphedema–Distichiasis Syndrome
- AD, FOXC2 mutation, encodes transcription factor
- Late-onset lymphedema, double row of eyelashes (distichiasis), ± trichiasis

Noonan Syndrome
- AD, PTPN11 gene, encodes protein tyrosine phosphatase SHP2
- Webbed neck (mimics Turner syndrome), characteristic facies (hypertelorism), undescended testicles, low posterior neck hairline, pulmonary stenosis, lymphedema, keloid formation, KP atrophicans (ulerythema of the eyebrows)

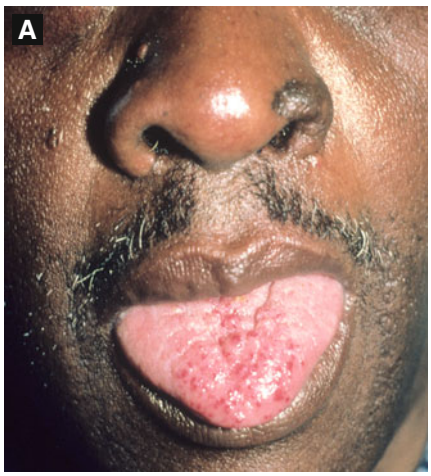
Turner Syndrome
- XO genotype
- Webbed neck, low posterior hairline, congenital lymphedema, abnormal sexual development, primary amenorrhea, aortic coarctation

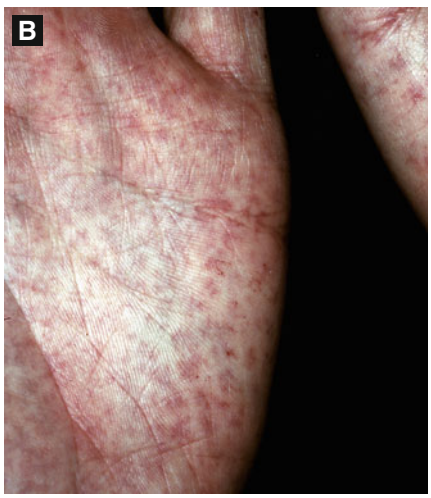
Meige Lymphedema (Hereditary Lymphedema II)
- Late-onset lymphedema (around puberty)

H. DERMAL DISORDERS

Osteogenesis Imperfecta (OI)
- AD/AR, mutation in type I collagen gene (α1 and α2 chains)
- Decreased elasticity, easy bruising, hearing loss secondary to otosclerosis, mitral valve prolapse
- Type I: fractures, bowing, kyphoscoliosis
- Type II (severe): beaded ribs, crumpled humeri, abducted thighs

Ehlers–Danlos Syndrome (Figure 2.29C, Table 2-5)





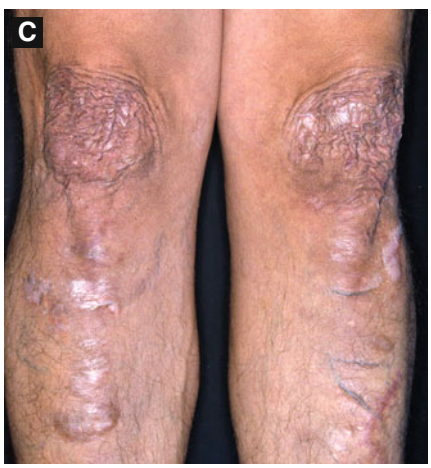


Figure 2.29
A: HHT (*Courtesy of Dr. Paul Getz*)
B: HHT (*Reprint from Morgan MB, Smoller BR, Somach SC. Deadly Dermatological Diseases. New York, NY: Springer; 2007*)
C: Molluscoid tumors in EDS (*Reprint from Burgdorf WH, Plewig G, Wolff HH, Landthaler M, eds. Braun-Falco's Dermatology. 3rd ed. Heidelberg: Springer; 2009*)

Table 2-5 Classification of Ehlers–Danlos Syndrome (EDS)

EDS Type	Traditional Classification	Inh	Gene Defect	Clinical Findings
Classic	I (Gravis)	AD	COL5A1 or COL5A2 (**Type V collagen**)	Hyperextensible skin, joint laxity, skin fragility with fish-mouth scars and cigarette paper texture, + Gorlin sign (touch tip of nose with tongue), **absence of frenulum** (inferior labial or lingual), molluscoid pseudotumors (spongy tumors over scars/pressure points), ± mitral valve prolapse, ± premature rupture of membranes in labor (type I)
	II (Mitis)	(AR)	(Tenascin X deficiency)	
Hypermobility	III (Benign hypermobile)	AD	TNXB (**Tenascin X** in 10%)	Striking joint hyperextensibility (subluxations/dislocations), **minimal skin involvement**, degenerative joint disease
Vascular	IV (Arterial-ecchymotic)	AD	COL3A1 (**Type III collagen**)	Thin translucent skin, **visible veins** under skin, **vascular fragility** (arterial, GI, uterine rupture), extensive **bruising**, hypermobility of small joints (hands/feet)
Kyphoscoliosis	VI	AR	PLOD (**Lysyl hydroxylase**)	Kyphoscoliosis, respiratory problems, muscle weakness, joint laxity, **ocular fragility** (glaucoma, retinal detachment)
Arthrochalasia	VIIA, VIIB	AD	COL1A1 or COL1A2 (**Type I collagen**)	**Marked joint hypermobility** with moderate cutaneous elasticity, **dislocation of large joints (bilateral congenital hip dislocations)**, scoliosis, easy bruising
Dermatosparaxis	VIIC	AR	ADAMTS2 (**Procollagen N-proteinase**)	Extremely **fragile and sagging skin**, easy bruising, hernias
Other	V, VIII, X	Of note, type IX reclassified as occipital horn syndrome, allelic with Menkes disease (ATP7A, lysl oxidase defect)		
		Type XI reclassified as familial joint hypermobility syndrome (new type X)		
	V	XLR		Hyperextensible skin, orthopedic abnormalities, bruising
	VIII	AD	?	**Periodontitis** + EDS I/II findings
	X		Fibronectin deficiency	Bruising, joint hypermobility
	EDS, cardiac valvular	AR	Collagen I (α2 chain)	Heart valve defects + EDS I findings
	EDS, progeroid	AR	B4GALT7 (**Galactosyl transferase 1**)	Progeroid facies, osteopenia, MR, growth retardation, skin hyperextensibility, joint hypermobility

Marfan Syndrome

- AD, fibrillin 1 and 2 defect
- Tall stature, ectopia lentis (upward dislocation), myopia, arachnodactyly, long limbs, aortic dilation with rupture, mitral valve prolapse (MVP), striae, elastosis perforans serpiginosa (EPS); death from cardiac complications

Pseudoxanthoma Elasticum (PXE) (Figure 2.30A)
- AR (most common) or AD, ABCC6 gene mutation (transmembrane transporter gene)
- Fragmented/calcified elastin of skin/eyes/arteries, "plucked chicken" skin on flexures, angioid streaks (rupture in Bruch's membrane) with retinal hemorrhage, gastric artery hemorrhage, MVP, hypertension, myocardial infarction

Cutis Laxa
- AR, FBLN5 gene, fibulin 5, AD (elastin gene and FBLN5), XLR (ATP7A gene)
- Presents with loose, pendulous skin (inelastic), arterial rupture, lung abnormalities, visceral diverticulae/hernia, joint dislocation, pulmonary emphysema (AR inheritance), newborn with hypoplastic lungs
- Acquired form: Marshall syndrome

Congenital Contractural Arachnodactyly
- AD, fibrillin 2, crumpled ears, long limbs, arachnodactyly

Focal Dermal Hypoplasia (Goltz Syndrome) (Figure 2.30B, C)
- XLD, lethal in males
- Presents with linear atrophy following Blaschko's lines following areas of fat herniation, osteopathia striata, colobomas, oral papillomas, lobster claw deformity of hands, syndactyly, alopecia, notched nasal ala

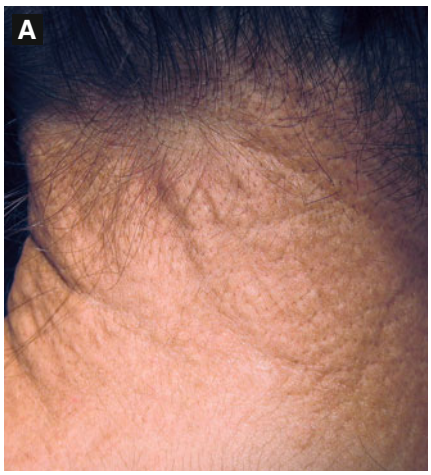
Goltz – think of a lobster using its claw along the sand causing linear striations (osteopathia striata)

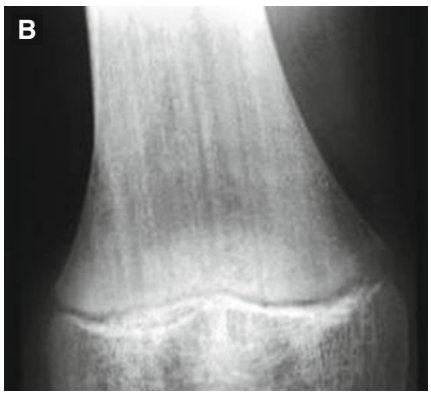
Berardinelli–Seip Congenital Lipodystrophy
- BSCL2 gene mutation (nuclear lamins)
- Generalized lipodystrophy, hyperlipemia, acanthosis nigricans, insulin-resistant DM, hepatomegaly

Familial Partial Lipodystrophy
- AD, LMNA gene mutation (lamin A/C)
- Symmetric lipoatrophy of trunk/limbs, tuberoeruptive xanthomas, acanthosis nigricans, hypertriglyceridemia

Buschke–Ollendorf Syndrome (Figure 2.31A, B)
- AD, LEMD3 (MAN1) gene mutation, encodes inner nuclear membrane protein
- Elastomas (dermatofibrosis lenticularis disseminata) presenting as yellow papules involving trunk, buttocks, arms, and osteopoikilosis (ectopic calcifications in bone), not prone to fracture

BUSHke – think of small **bush**-like opaque areas within the bone (osteopoikilosis)





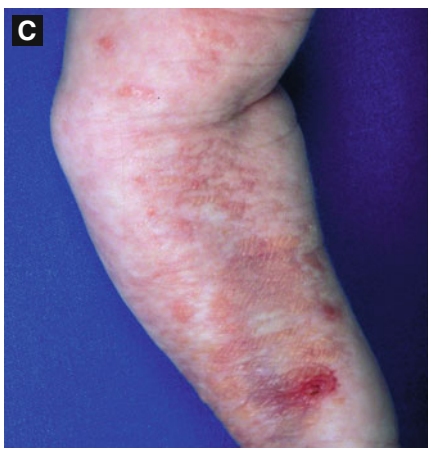


Figure 2.30
A: Pseudoxanthoma elasticum
(*Courtesy of Dr. Sophie M. Worobec*)
B: Osteopathia striata
(*Reprint from Offiah AC, Hall CM. Radiological diagnosis of constitutional disorders of bone. Pediatric Radiology. 2003; 33(3): 153–61*)
C: Focal dermal hypoplasia
(*Reprint from Burgdorf WH, Plewig G, Wolff HH, Landthaler M, eds. Braun-Falco's Dermatology. 3rd ed. Heidelberg: Springer; 2009*)

Lipoid Proteinosis (Urbache–Wiethe Disease)

- AR, ECM1 gene mutation (extracellular matrix protein 1)
- "String of pearls" over eyelids, hoarse voice, bean-shaped temporal/hippocampal calcification (with occasional seizures), large wooden tongue, waxy yellow papules of face/oropharynx

Beare-Stevenson Cutis Gyrata Syndrome (Figure 2.31C)

- FGFR2 gene mutation (fibroblast growth factor receptor 2)
- Cutis gyrata, acanthosis nigricans, anogenital anomalies, craniosynostosis, furrowed palms/soles

I. DISEASES OF THE HAIR AND NAILS

Menkes Disease

- XLR, ATP7A mutation, encodes ATP-dependent copper transporter
- ↓ Serum copper levels, pili torti (most common), trichorrhexis nodosa, short brittle "steel wool" hair, sparse eyelashes/eyebrows, cupid's bow upper lip, progressive CNS deterioration, seizures, tortuous arteries

Monilethrix

- AD, human hair keratin hHb1 and hHb6
- Beaded hair with elliptical nodes along hair shaft, keratosis pilaris

> Moneli**T**h**RIX** – think of **trix** cereal and each piece as an elliptical node causing a beaded appearance

Trichorhinophalangeal Syndrome

- AR/AD, TRPS1 gene
- Sparse hair, pear-shaped nose, cone-shaped epiphyses

> **T**richo**R**hino**P**halangeal (**TRP**) –think of **TRiP**ping so many times that your nose becomes pear-shaped

Uncombable Hair Syndrome (Figure 2.32A)

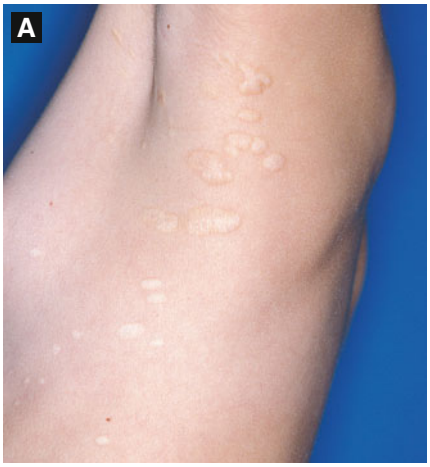
- AD, AR or sporadic
- Pili trianguli et canaliculi (triangular cross-sectional appearance, longitudinal groove), blonde "spun glass" hair
- Possible improvement with biotin

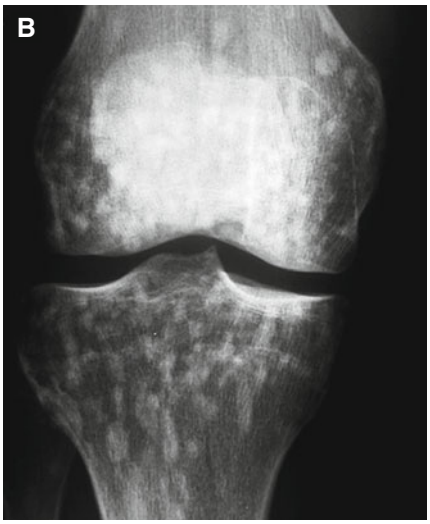
Tricho-dento-osseous Syndrome

- AD, DLX3 homeobox gene, curly/kinky hair at birth (may straighten after puberty), dental pits, ↑ bone density

Björnstad Syndrome

- AR, pili torti, deafness, normal intelligence and lifespan





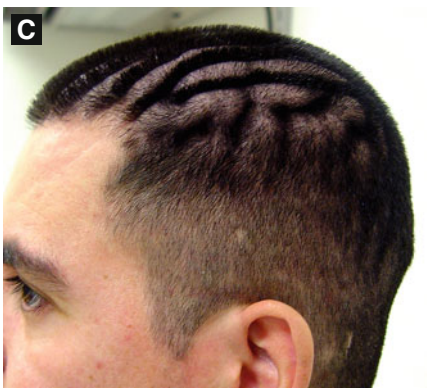


Figure 2.31
A: Elastomas
(*Reprint from Burgdorf WH, Plewig G, Wolff HH, Landthaler M, eds. Braun-Falco's Dermatology. 3rd ed. Heidelberg: Springer; 2009*)
B: Osteopoikilosis
(*Reprint from Dheedene A. The heterozygous Lemd3+/GT mouse is not murine model for osteopoikilosis. Calcified Tissue Int. 2009; 85* (*6*)*: 546–51*)
C: Cutis verticis gyrata
(*Courtesy of Dr. Michelle B. Bain*)

Papular Atrichia
- AR, human homolog of mouse hairless gene mutation
- Loss of natal hair with subsequent generalized atrichia

Nail–Patella Syndrome (Figure 2.32B)
- AD, LMX1B mutation
- Triangular lunulae, absent/hypoplastic patella, posterior iliac horns, thickened scapulae, glomerulonephritis, Lester iris (hyperpigmented papillary margin of iris), radial head subluxation

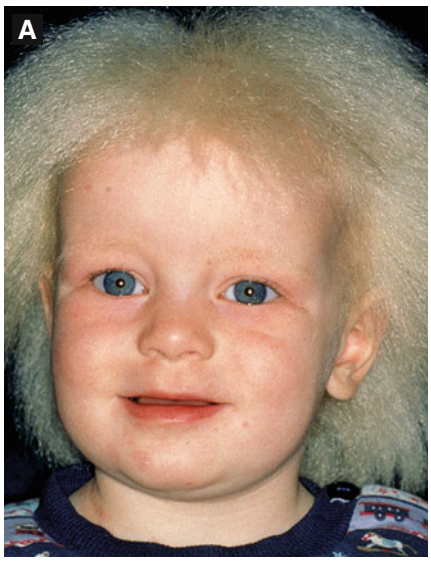
PATELLa – **P**osterior iliac horns, **A**bsent patella, **T**hickened scapula, **E**ye (lester iris), **L**unulae (triangular), g**L**omerulonephritis

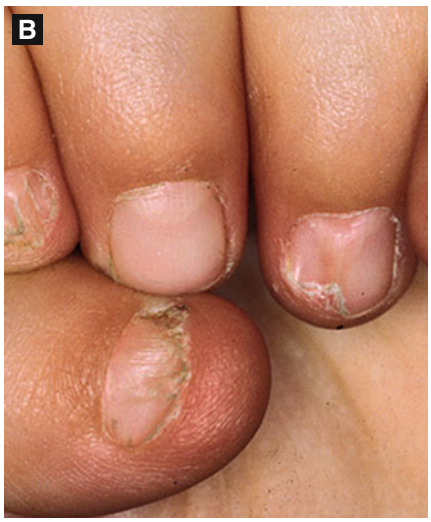
Pachyonychia Congenita
- Mainly AD, K6a/16 mutation (type I), K6b/17 (type II)

Jadassohn–Lewandowsky (Type I)	Dystrophic nails, palmoplantar keratoderma (PPK), oral leukokeratosis (benign)
Jackson–Lawler (Type II)	Dystrophic nails, PPK, steatocystomas, epidermal cysts, natal teeth

J. DISORDERS OF CORNIFICATION

Ichthyosis Vulgaris (IV) (Figure 2.32C)
- AD, decreased/absent profilaggin (keratohyalin granules)
- Presents few months after birth to early childhood with fine, white scales on extensor surfaces; flexures spared, hyperlinear palms/soles, atopic diathesis
- Histology: attenuated/absent granular layer, retention hyperkeratosis
- Acquired form of IV associated with internal disease, malignancies, and some medications





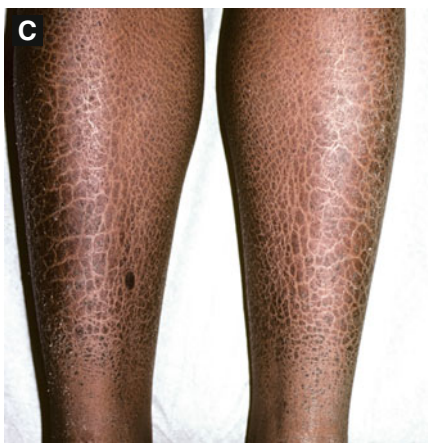


Figure 2.32
A: Uncombable hair syndrome
(*Reprint from Burgdorf WH, Plewig G, Wolff HH, Landthaler M, eds. Braun-Falco's Dermatology. 3rd ed. Heidelberg: Springer; 2009*)
B: Triangular lunulae (NPS)
(*Reprint from Tosti A, Ralph DC, Piraccini BM, Iorizzo M. Color Atlas of Nails. Heidelberg: Springer; 2010*)
C: Ichthyosis vulgaris
(*Courtesy of Dr. Paul Getz*)

X-linked Ichthyosis (XLI)

- XLR, defect in steroid sulfatase (STS, arylsulfatase C)
- Presents around infancy with mild erythroderma and large translucent scales → evolves into adherent brown "dirty" scales over extremities, trunk, neck; variable involvement of flexures, sparing of palms/soles/face
- Mother (with affected fetus): low/absent estrogen in urine/amniotic fluid → labor fails to progress
- Other associations: comma-shaped corneal opacities, cryptorchidism (↑ risk of testicular CA)
- Histology: hyperkeratosis or parakeratosis overlying normal or slightly thickened granular layer
- Tests: serum lipoprotein electrophoresis (detects accumulation of cholesterol sulfate)

Lamellar Ichthyosis (Nonbullous Congenital Ichthyosiform Erythroderma, Nonbullous CIE) (Figure 2.33A–C)

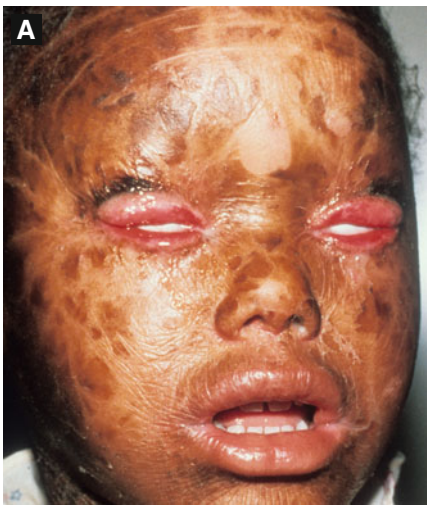
- AR, mutation in TGM1 gene (transglutaminase deficiency) or ABCA12 mutation (ATP binding cassette A12)
- Presents at birth with collodion membrane with underlying erythroderma → evolves to thick, dark scales with prominent flexural involvement; no improvement with age
- Associated ectropion, eclabium, scarring alopecia
- PPK, heat intolerance (heat stroke), hypernatremia
- Histology: massive orthokeratotic hyperkeratosis, acanthosis

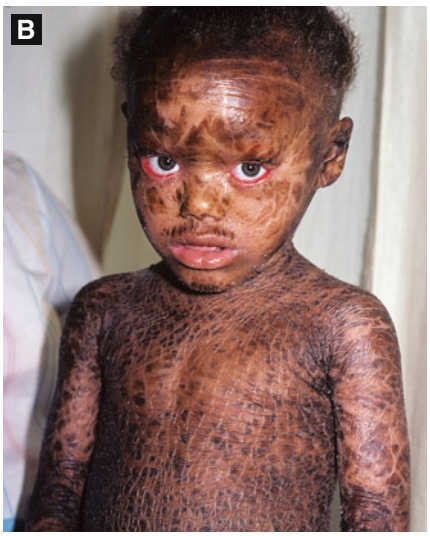
Congenital Ichthyosiform Erythroderma (Nonbullous CIE)

- AR (some AD), TGM1 gene, few ALOXE3 or ALOX12B gene mutation (encode lipoxygenase 3 and 12R-lipoxygenase, respectively)
- Presents at birth with collodion membrane → generalized erythroderma and persistent scaling, flexures involved, PPK; no improvement with age
- Associated scarring alopecia, ectropion, nail dystrophy (similar to LI but milder), heat intolerance

Ichthyosis Bullosa of Siemens

- AD, keratin 2e (K2) gene defect
- Presents at birth with mild erythroderma and mild blistering → evolves into brown hyperkeratotic plaques over joints, flexures, dorsal hands and feet; spares palms/soles





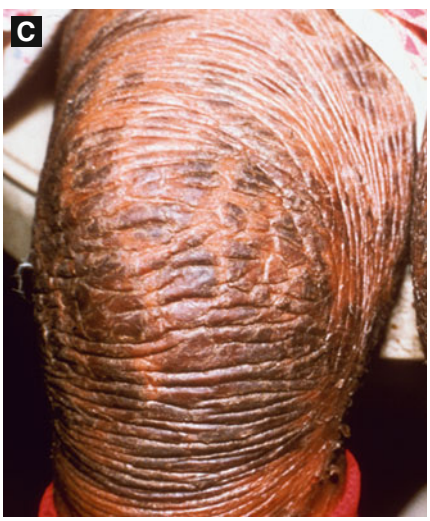


Figure 2.33
A: Lamellar ichthyosis*
B: Lamellar ichthyosis*
C: Lamellar ichthyosis*
** Courtesy of Dr. Paul Getz*

Epidermolytic Hyperkeratosis (EHK or Bullous CIE) (Figure 2.34A–C)

- AD, keratin 1 and keratin 10 gene mutations
- Presents at birth with initial erythroderma, bullae, denuded skin → evolves into verrucous hyperkeratotic plaques, flexural involvement, PPK
- Histology: massive orthokeratotic hyperkeratosis, hypergranulosis, cytolysis of suprabasal/granular layers, clumped tonofilaments (keratin intermediate filaments)
- Failure to thrive, hypernatremic dehydration, recurrent infections (bronchopneumonia, sepsis)

Harlequin Ichthyosis

- AR, ABCA12 mutation (ATP binding cassette A12)
- Presents at birth with encasement of hard, thickened restrictive stratum corneum with severe ectropion, eclabium, mitten-like hands and feet
- Death within few days of birth due to respiratory difficulties and sepsis
- Oral retinoid may prolong survival

Netherton Syndrome (Figure 2.35A)

- AR, SPINK5 gene defect (encodes serine protease inhibitor LEKT1)
- Presents at or near birth with generalized erythroderma and scaling, ± collodion membrane
- Triad of congenital ichthyosis (ichthyosis linearis circumflexa {ILC} or congenital ichthyosiform erythroderma {CIE}), trichorrhexis invaginata (TI, bamboo-like or ball-and-socket appearance of hair shaft), and atopy
- ILC: serpiginous or circinate erythematous plaques with double-edged scale
- TI: most specific hair finding (eyebrow with high yield), trichorrhexis nodosa is most common

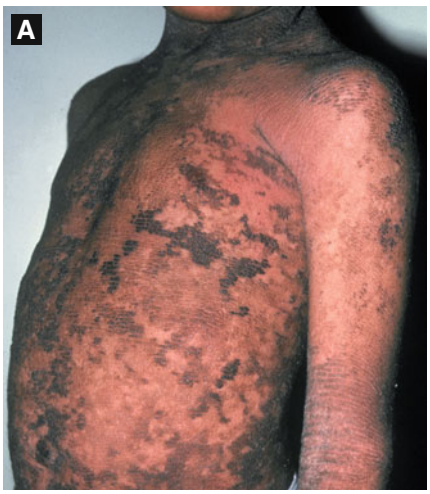
Sjögren–Larsson Syndrome

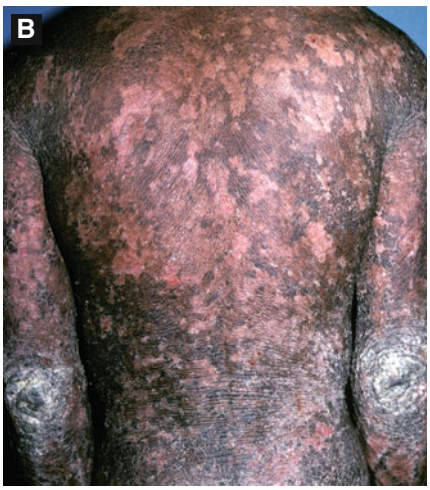
- AR, FALDH gene defect (encoding fatty aldehyde dehydrogenase) → involved in synthesis of epidermal lipids and catabolism of sphingolipids in the brain
- Presents at or near birth with erythema, generalized ichthyosis and pruritus → evolves into dark scales on lower abdomen, flexures, and neck with persistent pruritus, palmoplantar keratoderma (PPK)
- Ichthyosis, spastic ditetraplegia (scissor gait), MR, perifoveal "glistening white dots" in ocular fundus

SJO Gren – **Show**y **G**listening white dots
s**JOG**ren – think of trying to **JOG** with a spastic gait

CHILD Syndrome (Figure 2.35B)

- **C**ongenital **h**emidysplasia with **i**chthyosiform erythroderma and **l**imb **d**efects
- XLD, NSDHL gene defect, encodes NADPH steroid dehydrogenase-like protein (enzyme 3b-hydroxysteroid-dehydrogenase)
- Presents at or near birth with striking unilateral ichthyotic erythroderma (face typically spared); over time erythema fades while hyperkeratosis persists
- Ipsilateral alopecia, ipsilateral organ aplasia/agenesis, ± cleft palate
- Ipsilateral skeletal defects such as hypoplasia of digits or ribs to complete amelia, stippled epiphyses (seen in early infancy and resolves during childhood)





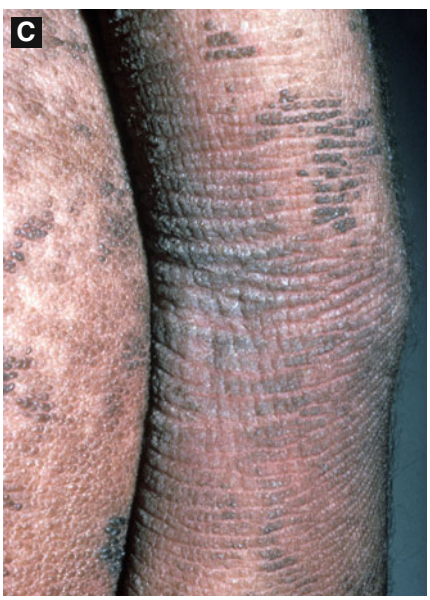


Figure 2.34
A: EHK*
B: EHK*
C: EHK*
* *Courtesy of Dr. Paul Getz*

Conradi–Hünermann–Happle Syndrome (XLD Chondrodysplasia Punctata) (Figure 2.35C)

- XLD (different from severe AR rhizomelic form), mutation in EBP gene, coding emopamil-binding protein (sterol isomerase activity) → accumulation of 8(9) cholesterol and 8-dehydrocholesterol (impaired cholesterol synthesis)
- Presents at birth with ichthyosiform erythroderma → hyperkeratosis replaced by linear/patchy follicular atrophoderma and ice pick–like scars
- Chondrodysplasia punctata: stippled or punctate calcification of the epiphyses or "stippled epiphyses" (detected during infancy)
- Cataracts, deafness, scarring alopecia, frontal bossing with flat nasal bridge

CONradi – think of a **CON** man who becomes crippled with **stippled** epiphyses

Chondrodysplasia Punctata (distinct from XLD CP)

- XR, arylsulfatase E defect, also can be AD

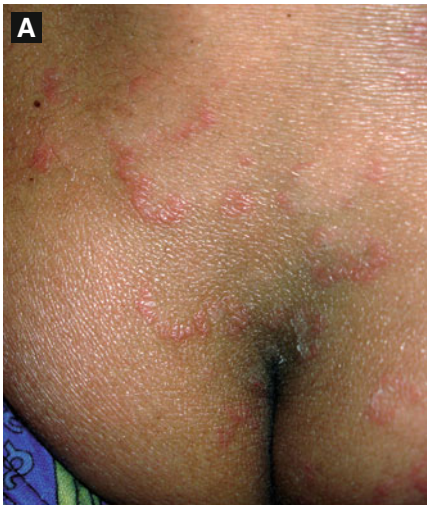
Rhizomelic Chondrodysplasia Punctata

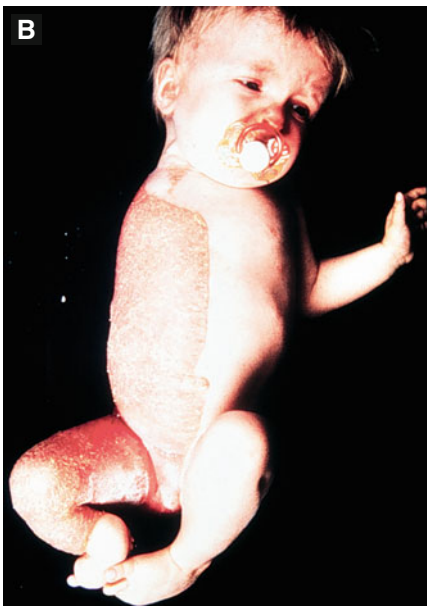
- AR, PEX7 gene defect (peroxisomal biogenesis disorder)
- Presents with diffuse fine scaling and erythema; alopecia
- Punctate chondrodysplasia, cleft vertebrate, respiratory compromise

KID Syndrome (Keratitis–Ichthyosis–Deafness Syndrome)

- AD (few AR), GJB2 gene defect (encoding connexin 26)
- Presents at or near birth with symmetric erythematous hyperkeratotic plaques on knees, elbows, and face; PPK with grainy or stippled appearance
- Congenital sensorineural deafness, vascularizing keratitis with secondary blindness, photophobia, abnormalities of teeth/nails, ↑ infections, ↑ risk (rare) of SCC

KID Syndrome – **K**onnexin 26





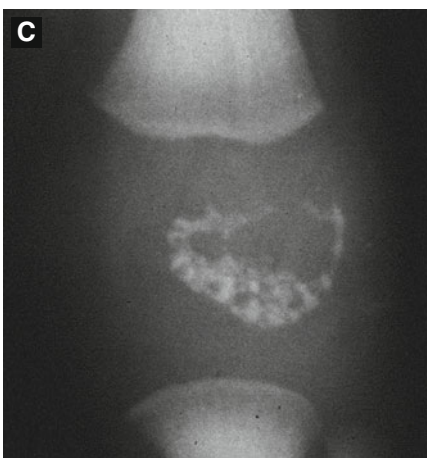


Figure 2.35
A: ILC in Netherton syndrome (*Courtesy of Dr. Michelle B. Bain*)
B: CHILD syndrome (*Reprint from Burgdorf WH, Plewig G, Wolff HH, Landthaler M, eds. Braun-Falco's Dermatology. 3rd ed. Heidelberg: Springer; 2009*)
C: Chondrodysplasia punctata (*Reprint from Laxer RM, ed. The Hospital for Sick Children: Atlas of Pediatrics. Philadelphia, PA: Current Medicine; 2005*)

Refsum Disease (Figure 2.36A)

- AR, mutation of PAHX (PHYH) gene (peroxisomal phytanolyl-CoA hydroxylase) or PEX7 gene (biogenesis factor 7) → excessive accumulation of phytanic acid
- Presents at childhood/adolescence with variable symptoms but typically mild ichthyosis (like ichthyosis vulgaris), cerebellar ataxia, peripheral neuropathy, "salt and pepper" retinitis pigmentosa, deafness
- **Infantile Refsum** (onset at birth): mutation in PEX1, PEX2, or PEX26
- Treat with dietary restriction of phytanic acid

Ref SUM – **RE**tinis pigmentosa, **SOME** salt and pepper please

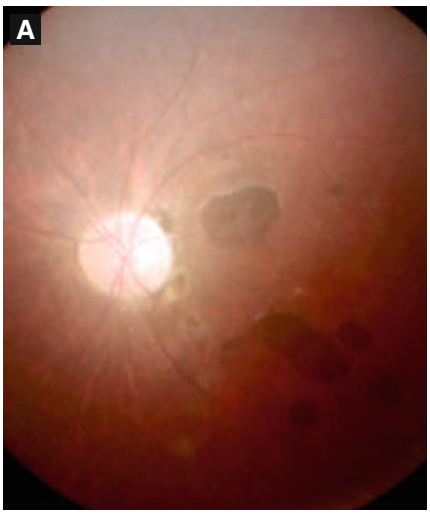
Darier Disease (Keratosis Follicularis) (Figure 2.36B, C)

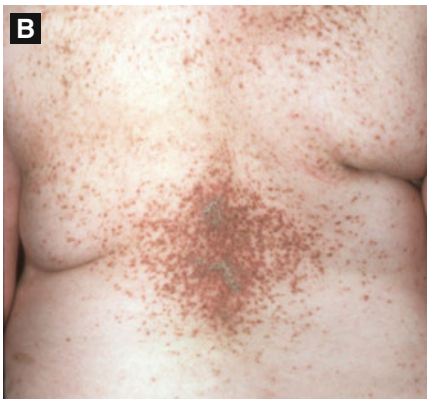
- AD, ATP2A2 gene mutation, encodes SERCA2 (sarcoendoplasmic reticulum calcium ATPase)
- Presents with hyperkeratotic papules coalescing into warty plaques in a seborrheic distribution
- Acrokeratosis verruciformis of Hopf: verrucous papules on dorsum of hands
- Palmar keratosis/pits
- Nails: red and white alternating longitudinal bands, V-shaped nicks at distal nail plate, subungual hyperkeratosis
- Oral: cobblestoning of oral and anogenital mucosa
- Histology: acantholysis with corp ronds and grains

d**A**rier – 2**A**2

K. OTHER CONDITIONS

Palmoplantar Keratodermas (see Tables 2-6, 2-7)
Ectodermal Dysplasias (see Table 2-8)
Metabolic and Enzyme Deficiency Diseases (Table 2-9)
Signs of Spinal Dysraphism (Table 2-10)
Keratinopathies (Table 2-11)





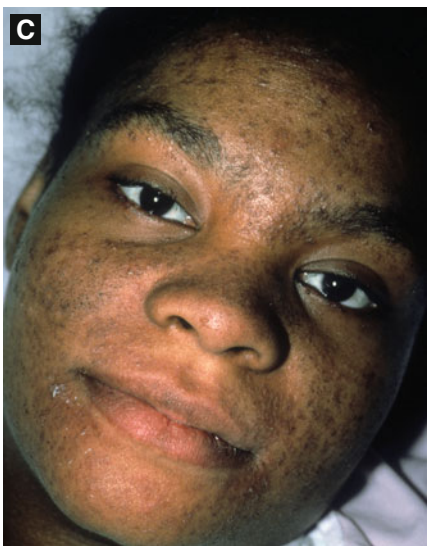


Figure 2.36
A: Retinitis pigmentosa
(*Reprint from Hoffman GF, Zschocke J, Nyhan WL. Inherited Metabolic Diseases. Berlin: Springer; 2010*)
B: Darier disease
(*Courtesy of Dr. Paul Getz*)
C: Darier disease
(*Courtesy of Dr. Paul Getz*)

Table 2-6 Diffuse Palmoplantar Keratodermas

Disease	Type	Inh	Mutation	Clinical Appearance
Non-epidermolytic PPK (Unna-Thost Syndrome)	Diffuse	AD	K1	PPK with erythematous border, hyperhidrosis, secondary tinea infections, pitted keratolysis, no transgrediens
Epidermolytic PPK (Vörner Syndrome)	Epidermolytic	AD	K1 or K9 (most common)	Clinically similar to non-epidermolytic PPK but histology shows epidermolytic hyperkeratosis
Mal de Meleda	**Transgredient**	AR	**SLURP-1** gene (encodes protein: **S**ecreted **L**y-6/**u**Par **r**elated **p**rotein)	Transgredient PPK (hands, feet, elbows, knees), hyperhidrosis with malodor and secondary infections, **perioral erythema**, thickened nails
Vohwinkel Syndrome, Classic (Keratoderma Hereditaria Mutilans)	**Mutilating keratoderma + deafness**	AD	**GJB2** (encodes connexin 26)	Diffuse honeycomb-like PPK, **pseudoainhum, starfish-shaped** keratoses of joints, sensorineural **deafness**, linear keratotic plaques of knees, scarring alopecia
Vohwinkel Syndrome, Variant	Mutilating + ichthyosis	AD	**Loricrin** (cornified envelope protein)	Similar to classic Vohwinkel, but no deafness and more generalized ichthyosis
Papillon–Lefèvre Syndrome	PPK + periodontitis	AR	**Cathepsin C** (lysosomal protease)	**Periodontitis**, early loss of teeth, transgredient erythematous PPK with psoriasiform lesions on extremities, **calcification of falx/tentorium**, hyperhidrosis
Haim–Munk Syndrome	PPK + periodontitis + onychogryphosis	AR	Cathepsin C	Papillon–Lefevre syndrome + **onychogryphosis**, arachnodactyly, acroosteolysis
Naxos Disease	PPK + woolly hair + cardiomyopathy	AR	**Plakoglobin**	**Woolly hair**, **right ventricular cardiomyopathy** with arrhythmias, PPK
Carvajal Syndrome	PPK + woolly hair + cardiomyopathy	AR	Desmoplakin	**Dilated cardiomyopathy**, PPK in first year of life, **woolly hair**
Olmsted Syndrome	Mutilating PPK + periorificial plaques	?	? (possible K5 and K14)	PPK (initially focal, then widespread) leading to flexion deformities, autoamputation, erythematous hyperkeratotic **perioral plaques**
Non-epidermolytic PPK with deafness	PPK + sensorineural deafness	?	Connexin 26 or A7445G (mitochondrial)	PPK, progressive sensorineural deafness

Table 2-7 Focal Palmoplantar Keratodermas

Disease	Inh	Mutation	Clinical Appearance
Howel–Evans Syndrome	AD	TOC gene (**t**ylosis-**o**esophageal **c**arcinoma)	Focal PPK over **pressure areas** (balls of feet > hands), oral leukokeratosis, ↑ **esophageal CA**
Richner–Hanhart Syndrome (Tyrosinemia Type II)	AR	Hepatic tyrosine amino-transferase (TAT)	Pseudoherpetic **keratitis**, dendritic corneal ulcers (tyrosine crystal deposition in eyes), **painful focal PPK**, progressive MR, treat with **diet restricted** in tyrosine and phenylalanine
Punctate PPK (Keratosis Punctata Palmaris Et Plantaris)	AD	?	Begins during or near adolescence, punctate keratoses on palms, can also occur in palmar creases of patients of African origin
Acrokeratoelastoidosis	AD		Skin-colored papules involving hands and feet
Striate PPK	AD	Desmoglein 1 and desmoplakin 1	Onset in teens/early adulthood, hyperkeratotic linear plaques on volar fingers, diffuse/focal plaques on proximal palms/soles
Erythrokeratoderma Variabilis (Mendes da Costa)	AD	**GJB3, GJB4** (connexin 30.3 and 31)	Erythematous migratory patches (may last minutes to days), fixed hyperkeratotic plaques, 50% with PPK, flexures spared
Progressive Symmetric Erythrokeratoderma	AD	Likely loricrin mutation or connexin 31	Fixed hyperkeratotic erythematous plaques over joints/extremities, 50% with PPK

Table 2-8 Ectodermal Dysplasias

Disease	Inh	Mutation	Clinical Appearance
Hidrotic Ectodermal Dysplasia (Clouston Syndrome)	AD	**GJB6** (connexin 30)	Hypotrichosis, diffuse PPK, **nail dystrophy, NORMAL teeth and sweating**, MR, ocular abnormalities
Hypohidrotic (Anhidrotic) Ectodermal Dysplasia (Christ-Siemens-Touraine)	XR	**EDA** (ectodysplasin A)	Hypotrichosis, **periorbital hyperpigmentation, ABSENT or conical teeth**, **sweating** with heat intolerance, NORMAL nails, saddle nose, everted thick lips, ↑ bronchopulmonary infections
	AD, AR	EDAR gene (ED-A receptor)	
Ankyloblepharon-Ectodermal Dysplasia-Clefting Syndrome (AEC) (Hay-Wells)	AD	p63	Chronic **erosive scalp dermatitis**, abnormal granulation tissue, recurrent bacterial infections, ankyloblepharon, hypotrichosis, 80% cleft lip/palate
Ectodermal Dysplasia-Ectrodactyly-Clefting Syndrome (EEC) (Split Hand-Split Foot-Ectodermal Dysplasia-Clefting)	AD	p63	Ectrodactyly (split hand/foot), hearing loss, nail dystrophy, ± PPK, 70% cleft lip/palate, sparse and dry hair, hypodontia
Rapp-Hodgkin Syndrome	AD		Mid facial hypoplasia, cleft lip/palate, scalp dermatitis, ↓ sweating, nail dystrophy, hypodontia
Ectodermal Dysplasia/Skin Fragility Syndrome	AR	Plakophilin-1	Trauma-induced bullae (most prominent during infancy), sparse hair, thick dystrophic nails

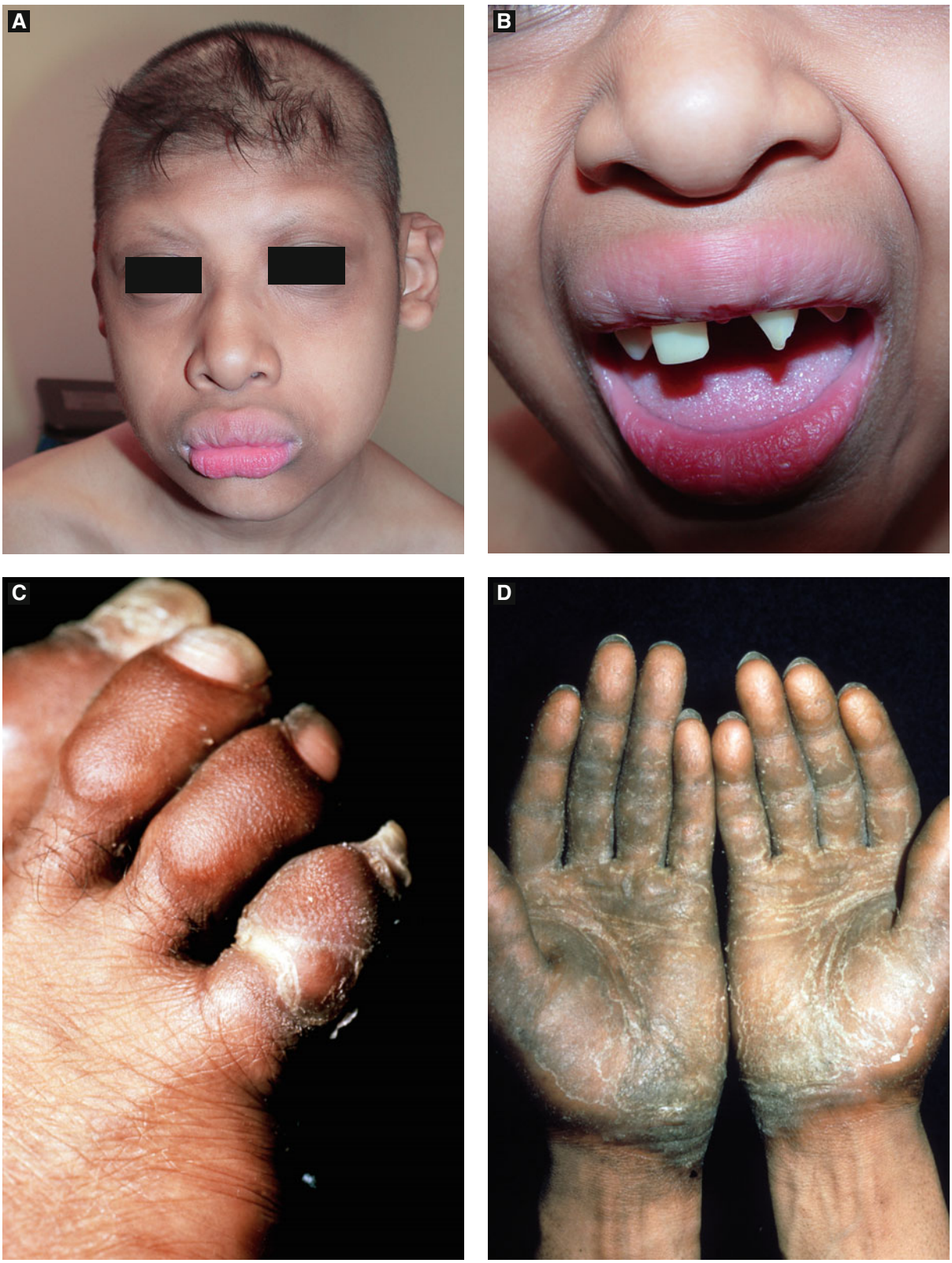


Figure 2.37
A: Anhidrotic ectodermal dysplasia
(*Courtesy of Dr. Michelle B. Bain*)
B: Anhidrotic ectodermal dysplasia
(*Courtesy of Dr. Michelle B. Bain*)
C: Pseudoainhum in Vohwinkel syndrome
(*Courtesy of Dr. Paul Getz*)
D: Palmoplantar keratoderma in Vohwinkel syndrome
(*Courtesy of Dr. Paul Getz*)

Table 2-9 Metabolic and Enzyme Deficiency Diseases

Disease	Inh	Defect	Clinical Findings
Alkaptonuria	AR	Homogentisic acid (HA) oxidase	Blue-gray pigmentation of cartilage (helices), sclera and skin (axilla); urine darkens on standing, arthritis
Biotinidase Deficiency	AR		Alopecia, periorificial dermatitis, developmental delay, seizures; treat with biotin
Fabry Disease	XLR	α-Galactosidase A	Glycosphingolipids in vascular endothelium: multiple angiokeratomas, extremity **pain/paresthesias**, **whorl-like corneal and lenticular opacities**, birefringent lipid globules in urine (**"maltese crosses"**), MI, cerebrovascular accident (CVA)
Fucosidosis	AR	α-Fucosidase	Multiple angiokeratomas, coarse facies, growth retardation, dysostosis multiplex, mental retardation
Gaucher Disease	AR	α-Glucosidase (Glucocerebrosidase)	Type I (adult): no CNS findings + diffuse brown skin pigmentation, thrombocytopenia, hepatosplenomegaly (HSM), bone pain, **ehrlenmeyer flask deformity** of femoral midshaft
			Type 2 (infant): no skin findings, severe, rapid death
			Type 3 (juvenile): chronic neuropathy
Hartnup Disease	AR	SLC6A19	↓ Renal reabsorption of neutral amino acids, pellagra-like dermatosis with photosensitivity, ataxia, tremors
Holocarboxylase Synthetase Deficiency	AR		Alopecia, perioral/perianal dermatitis, metabolic encephalopathy, metabolic acidosis; treat with biotin
Hunter Disease	XLR	Iduronidate sulfatase	Firm, flesh-colored to white papules coalescing over scapula
Hurler Disease	AR	α-L-iduronidase	Mental retardation (MR), HSM, hernia, opacities, gargoyle-like features
Lesch–Nyhan Syndrome	XLR	HGPRT deficiency	Self-mutilation, orange crystals in the diaper, gout, choreoathetosis, MR
Lipoid Proteinosis	AR	**ECM**1 defect	Pearly papules, hippocampal calcification, infiltration of deposits on lips and tongue (wooden), hoarseness
Neimann–Pick Disease	AR	Sphingomyelinase deficiency (SMPD1)	Type A: failure to thrive, HSM, neurologic deterioration Type B: minimal neurologic disease, xanthomas, histiocytic infiltration in viscera, psychomotor delay, muscle weakness, blindness (cherry red spots)
Phenylketonuria	AR	SLC39A4 (zinc transporter)	Diffuse hypopigmentation, eczema, MR, sclero-dermoid changes, blonde hair, blue eyes, urine and skin with mousy odor
Prolidase Deficiency	AR	Prolidase	Skin fragility, ulceration and scarring over lower extremities, photosensitivity, MR, recurrent infections
Wilson's Disease	AR	ATP 7B (ATPase copper transporting enzyme)	Copper accumulation in liver/brain/cornea, cirrhosis, blue lunula, Kayser–Fleischer rings, ataxia, dementia, hepatomegaly

Table 2-10 Signs of Spinal Dysraphism (High Risk for Dysraphism if ≥2 of the Following)

Hypertrichosis	Dimpling	Skin tags
Tails/pseudotails	Lipomas	Aplasia cutis
Hemangiomas	Dermoid cysts/sinuses	Telangiectasia, capillary malformation, nevi (less likely)

Table 2-11 Keratinopathies

Type II Keratin	Type I Keratin	Location of Expression	Associated Disease
1	10	Suprabasal keratinocytes	Epidermolytic hyperkeratosis (Bullous CIE) Unna-Thost PPK (K1) Ichthyosis hystrix of Curth-Macklin (K1)
1	9	**Palmoplantar**, supra-basal keratinocytes	Epidermolytic PPK (Vörner)
2 (2e)	10	Granular and upper spinous layer	Ichthyosis bullosa of Siemens
3	12	Cornea	Meesmann corneal dystrophy
4	13	Mucosal epithelium	White sponge nevus
5	14	**Basal keratinocytes**	Epidermolysis bullosa simplex (EBS) Dowling-Degos disease (K5 alone)
6a	16	Outer root sheath	Pachyonychia congenita I (Jadassohn Lewandowsky) Focal PPK
6b	17	**Nail bed**	Pachyonychia congenita II (Jackson-Lawler) Steatocystoma multiplex
8	18	Simple epithelium	Cryptogenic cirrhosis
K81 and K86		Hair	Monilethrix
	19	Simple epithelium, bulge cells	
6	16		Hyperproliferative keratinocytes

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